# Continuous EEG Monitoring

## Principles and Practice

Aatif M. Husain
Saurabh R. Sinha
*Editors*

Springer

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*Editors*
Aatif M. Husain
Neurology
Duke University Medical Center
Durham
North Carolina
USA

Saurabh R. Sinha
Neurology
Duke University Medical Center
Durham
North Carolina
USA

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*To my late parents, Mairaj and Suraiya Husain. Every day I am reminded of their wisdom, humility, generosity and love. I hope I can pass on the lessons I learned from them to my children.*

*Aatif M. Husain*

*To my wife, Vandita, and children, Varun and Sneha. Their love and encouragement is a constant in an ever-changing and challenging world.*

*Saurabh R. Sinha*

# Preface

It was only 20 years ago that when continuous EEG (cEEG) monitoring was discussed, it was in the context of monitoring patients in the epilepsy monitoring unit for spell characterization or epilepsy surgery evaluation. Certainly EEGs were performed in the intensive care units (ICU), and patients even underwent "prolonged monitoring." However, in the era of paper EEGs, prolonged monitoring often consisted of turning the EEG machine on for 5 min every hour or so. Interpretation of reams of paper was done the following day. Partly because of what now appears to be rudimentary methods, we did not appreciate the extraordinary prevalence of seizures in critically ill patients.

The last two decades have seen a remarkable change in our understanding of seizures in critically ill patients. Much of this change has been due to the availability of cEEG monitoring. The advent of digital EEG and advances in information technology have paved the way for the broad availability of cEEG monitoring, which has led to the realization that about 20 % of critically ill patients in whom cEEG monitoring is performed have seizures or status epilepticus (SE). The medical community has recognized the need for cEEG monitoring in large and small, university and community hospitals, and this has fueled a remarkable demand for these services.

Continuous EEG monitoring has now become a discipline in its own right. A few years ago, a handful of like-minded individuals set up the Critical Care EEG Monitoring and Research Consortium (CCEMRC); this consortium has grown to about 50 members. Many clinical neurophysiology fellowships have made cEEG monitoring education an essential part of their training. In fact, dedicated cEEG monitoring fellowships have also become available. Many clinical neurophysiologists and neurointensivists now complete their training with a special interest and expertise in cEEG monitoring. Professional societies throughout the world have also started offering education and training in this discipline at their annual meetings. The American Board of Clinical Neurophysiology now offers a subspecialty certification in critical care EEG monitoring.

This remarkable growth in cEEG monitoring was the impetus behind this book. The ever-expanding knowledge base, advances in recording and analysis, interpretation and treatment concerns, and implementation challenges can best be addressed in a textbook on this subject. In an effort to address these challenges and provide a state of the art of this field, we undertook editing *Continuous EEG Monitoring: Principles and Practice*.

With *Continuous EEG Monitoring: Principles and Practice*, we wanted to address all issues the practitioner may face in this field. With this in mind, we divided the text into four sections, "Clinical Aspects," "Special Situations," "Treatment," and "Technical and Administrative Considerations." Each chapter is written by authors who have been seminal to the advancement of cEEG monitoring. The "Clinical Aspects" section addresses the clinical issues of cEEG monitoring. Included are chapters detailing the history of the field, epidemiology of seizures and SE in critically ill patients, and classification of SE. Interpretative aspects of cEEG monitoring are also discussed in this section. Quantitative analysis of EEG is a vital aspect of this field, and several chapters are devoted to this. The "Special Situations" section addresses specific issues related to cEEG monitoring. Included are special situations that can lead to SE and warrant cEEG monitoring, such as anoxic encephalopathy, autoimmune SE, and medication-induced seizures. Critical care and prognostic issues in adults and children are also addressed in this section. The "Treatment" section has chapters detailing management options for acute seizure emergencies ranging from recurrent nonconvulsive seizures to super refractory SE. The final "Technical and Administrative Considerations" section deals with very important implementation issues for cEEG monitoring. The popularity of cEEG monitoring has not been without its challenges. EEG equipment, electrodes, staffing, billing, and information technology issues have all raised different challenges. These topics are addressed in this final section.

The four sections of this book provide a comprehensive "principles and practice" approach to cEEG monitoring. Readers will find that they not only learn the scientific and clinical aspects of this field but are aware of the practical challenges and potential solutions. As such many different types of professionals will find value in this book. Neurology, clinical neurophysiology, epilepsy, and neurointensive care trainees will benefit from reading this book in its entirety. Practicing neurologists, particularly neurohospitalists and others involved with hospital inpatients, clinical neurophysiologists, intensivists, neurosurgeons, and neuroscientists, will also find many sections of value. Technologists will find a lot of useful information that will help them care for these patients. Administrators and managers will find material that will help them run their departments more efficiently.

There are many individuals who have contributed to *Continuous EEG Monitoring: Principles and Practice*, and without them, this book would not have been possible. Foremost, we are extremely grateful to our colleagues who contributed chapters. They have spent many hours collating critical information to create this very useful textbook. Special thanks is due to the publisher, Springer Medicine Books, in particular, Sylvana Freyberg who recognized the need for such a book and encouraged us to put it together and Sowmya Ramalingam who kept us on task to make sure this project reached culmination. The technologists, residents, fellows, neurologists, neurosurgeons, nurses, and administrators we work with at Duke University Medical Center must be recognized and thanked for their unwavering dedication to patients, education, research, and each other. Without them, we could not do any of what we do. Of course, the most important group of individuals who have contributed is our

patients. It is through their illness that we learn. It is this learning that we hope will provide more effective treatment for these and other patients.

Finally, we must thank our families. Medicine is an extremely fulfilling and demanding profession. Our spouses and children endure our long work hours routinely; this book added many more hours away from them. Without their constant support, encouragement, and motivation, none of this would have been possible. For that, and a lot more, we are forever grateful.

Durham, NC, USA

Aatif M. Husain
Saurabh R. Sinha

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# About the Editors

**Aatif M. Husain, MD** is professor, Department of Neurology, Duke University Medical Center, and director, Neurodiagnostic Center, Veterans Affairs Medical Center, in Durham, North Carolina, USA. After completing medical school in Pakistan, he did an internship at the Henry Ford Hospital in Detroit, Michigan. He then completed a neurology residency at the Medical College of Pennsylvania in Philadelphia. After residency, Dr. Husain did fellowships in clinical neurophysiology, epilepsy and sleep medicine, and EMG/neuromuscular disorders at Duke University Medical Center. Since his fellowships, he has stayed at Duke University as faculty. He directs the clinical neurophysiology and sleep medicine fellowship programs at Duke University. His clinical interests include treatment of acute seizures and status epilepticus, neurophysiologic intraoperative monitoring, and general clinical neurophysiology. He has written many articles, chapters, and books on these topics. Dr. Husain is currently the editor in chief of the *Journal of Clinical Neurophysiology* and has been a past president of the American Clinical Neurophysiology Society and the American Board of Registration of EEG and EP Technologists.

**Saurabh R. Sinha, MD, PhD** is associate professor and vice-chair for education, Department of Neurology, Duke University Medical Center, and director of the Epilepsy Monitoring Unit, Duke University Hospital. After receiving his B.Sc. in biomedical engineering from Johns Hopkins University in Baltimore, Maryland, he completed his M.D., Ph.D. (in neuroscience), and internship (internal medicine) at Baylor College of Medicine in Houston, Texas. Dr. Sinha completed his residency in neurology and fellowships in clinical neurophysiology and advanced epilepsy at Johns Hopkins Hospital. After 4 years as medical director of the Epilepsy Program at Sinai Hospital in Baltimore, Dr. Sinha joined Duke University Medical Center where he currently also serves as program director for the Neurology Residency. His clinical and research interests include surgical epilepsy, quantitative EEG analysis, and neurophysiologic intraoperative monitoring. Dr. Sinha is currently on the board of directors for the American Board of Registration of EEG and EP Technologists and the American Board of Clinical Neurophysiology and on the council of the American Clinical Neurophysiology Society.

# Part I

# Clinical Aspects

# The History of Continuous EEG Monitoring

1

Raoul Sutter and Peter W. Kaplan

## Contents



R. Sutter, MD (✉)
Clinic of Intensive Care Medicine and Division of Clinical Neurophysiology, Department of Neurology, University Hospital Basel, Petersgraben 4, Basel CH – 4031, Switzerland
e-mail: raoul.sutter@usb.ch

P.W. Kaplan, MB BS, FRCP
Department of Neurology, Johns Hopkins Bayview Medical Care Center, 301 Building, 4940 Eastern Avenue, Baltimore, MD 21224, USA
e-mail: pkaplan@jhmi.edu



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## Introduction

The history of electroencephalography (EEG) began in the late 1800s and has increasingly led to clinical, experimental, and computational studies that have enabled the discovery, understanding, recognition, diagnosis, and treatment of a great number of neurophysiological abnormalities and critical illnesses of the brain and spinal cord. Currently, EEGs are often continuously recorded mostly using scalp or cortical electrodes with enough digital EEG memory to store extended recordings of several hours. Modern EEG machines are further equipped with fully computerized signal processing systems allowing rapid and multidimensional analyses that present many challenges to the managing physicians.

In this chapter, we provide an overview of the history of EEG and its clinical contributions toward the field of continuous EEG monitoring in critical care. Milestones in the history of EEG and the emergence of continuous EEG monitoring are presented in Fig. 1.

## From the Galvanometer to Scalp Electrodes

The introduction of the galvanometer with astatic needles has been mainly associated with Leopoldo Nobili, a physicist in Florence, and was further refined in 1858 by William Thompson (Lord Kelvin) in England. Galvanometers were able to faithfully demonstrate continuous electrical currents and their variations in intensity, but could not detect extremely brief electrical phenomena (Fig. 2). In 1875, Richard Caton, a scientist from Liverpool, England, placed two electrodes of a galvanometer over the scalp of a human and became the first to record brain activity in the form of electrical signals. Caton used a beam of light projected on the mirror of the galvanometer and reflected onto a large scale placed on the wall. With this type of visualization, Caton found that "feeble currents of varying direction pass through the multiplier when the electrodes are placed at two points of the external scalp

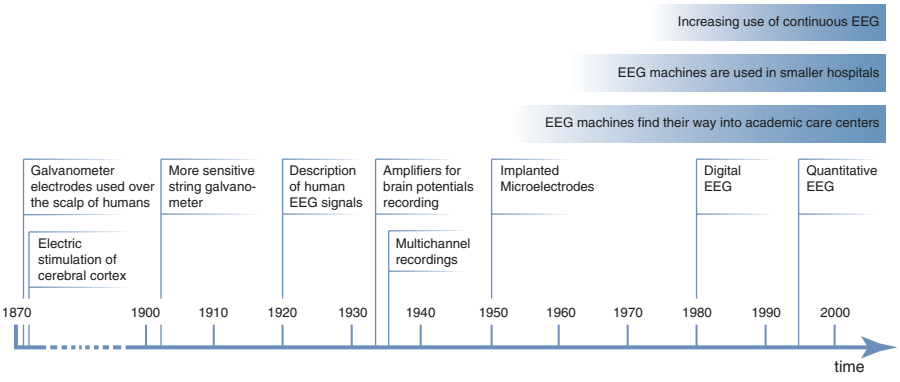


**Fig. 1** Technical electroencephalographic innovations over time. *EEG* electroencephalography

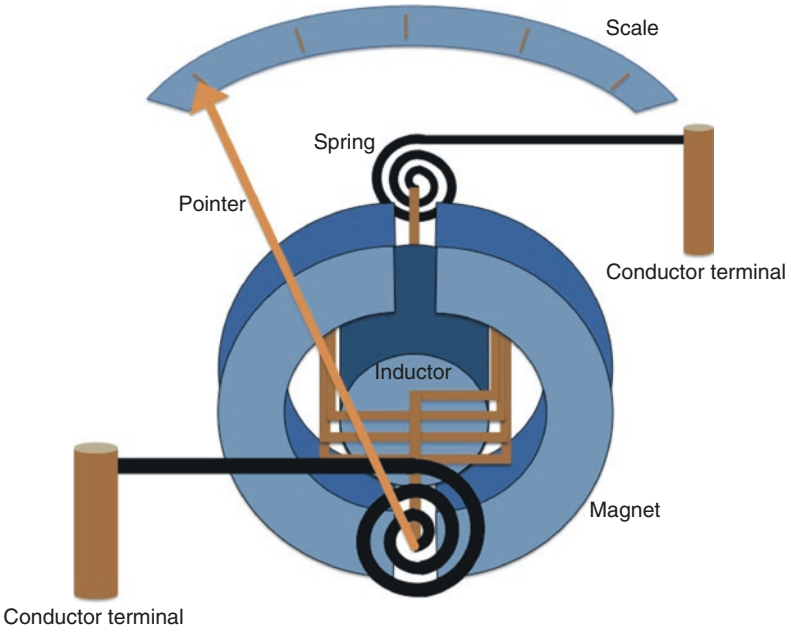


**Fig. 2** Scheme of a galvanometer

surface." This initial experiment led to the concept of the graphic recording of registered electrical brain signals, the technique that underlies present-day EEG. Caton noted that the surface of the gray matter was positively charged with respect to deeper structures in the cerebrum. He also noted that the electric currents of the cerebrum changed in relation to the underlying function with neurofunctional active regions exhibiting negative variations of electric current. Hence, Caton has also been credited with pioneering the work on evoked potentials.

Concurrent with Caton's work, physiologists in Eastern Europe began to report their observations on cerebral electrical activity with another discovery of greater impact on the neuroscientific world – the capability of the cerebral cortex to be electrically stimulated as described by Gustav Fritsch and Julius Eduard Hitzig in 1870. These discoveries were followed by several observations of spontaneous electrical activity in the brains of animals and the studies of electrical responses of the human brain after electrical stimulation. These included the first EEG evidence of epileptic activity during a seizure in a dog following electrical stimulation reported by Napoleon Cybulski, a Polish physiologist. Seven years after the study of Fritsch and Hitzig, Vasili Y. Danilevsky wrote his thesis on electrical stimulation and the spontaneous electrical activity of animal brains while working at the University of Kharkov. However, Danilevsky was disappointed as he had expected better correlation of the spontaneous regional electrical brain activity with psychic and emotional processes. Adolf Beck, a Polish physician and physiologist at the University of Lwów, Poland, further investigated the spontaneous electrical brain activity of

rabbits and dogs using nonpolarizable electrodes and observed the disappearance of rhythmical oscillations during illumination of the eyes (i.e., "alpha blocking").

In 1903, Willem Einthoven, a Dutch doctor and physiologist, invented a string galvanometer, an instrument with greater sensitivity of detection but which required photographic recording. The string galvanometer became the standard instrument for EEG at the turn of the century with Pravdich-Neminsky, a Ukrainian and then Soviet physiologist, reporting electrical activity recordings using this technique in animal brains in 1912.

## The First Human EEG

In the 1920s, Hans Berger, a German neuropsychiatrist and the discoverer of the human EEG, was the first to describe the existence of human EEG signals [1]. Berger first used a string galvanometer in 1910, to later migrate to an Edelmann model followed by a more powerful Siemens double-coil galvanometer. Unfortunately, it took more than 10 years for the scientific community to accept these scalp potentials as genuine brain signals.

In 1926, Berger started to use the more powerful Siemens double-coil galvanometer and published his first report of a human 3-min EEG recording in 1929. He described the alpha rhythm as the dominant component of human EEG signals and the alpha blocking response, a milestone in the history of clinical EEG [1]. For his one-channel EEG tracings, Berger used a bipolar recording technique with fronto-occipital leads along with a time marking line generated with a sine wave of 10 cycles/sec (Fig. 3). During the 1930s, Berger recorded the first EEG of human sleep, detecting sleep spindles. He followed this with the examination of human EEG patterns in hypoxic brain injury, in epilepsy, in the investigation of several diffuse and localized brain dysfunctions, and with the examination of changes in EEG signals with mental activities.

## Early Use of Multichannel EEG

While EEG provides very large-scale, robust measures of neocortical dynamic function, one single scalp electrode provided estimates of synaptic sources averaged over tissue masses containing between 100 million and 1 billion neurons.

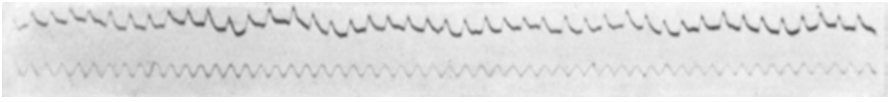

**Fig. 3** The first one-channel electroencephalogram in a human. One-channel electroencephalographic tracing with a bipolar recording technique with fronto-occipital leads (upper line) along with a time marking line generated with a sine wave of 10 cycles/sec (Reprinted with kind permission from Springer, Berger [1])

In 1932, a group of inventors in Berlin, Germany, lead by Jan Friedrich Tönnies, a German inventor and engineer, and investigators at the Rockefeller foundation in New York, USA, simultaneously built the first amplifiers designed to record cerebral potentials thus opening up the field of multichannel recordings that covered large brain regions [2]. By the 1940s, EEG technology was viewed as a genuine window on the mind, with important applications in neurosurgery, neurology, and cognitive science.

The first report of a prominent, transient, electrographic element termed an "epileptic spike" came from Fisher and Lowenbach in 1934 [3], inspiring further electrophysiological work in epileptology by Gibbs and Lennox, two neurologists and epileptologists from Harvard Medical School, USA. A few years later, Hallowell and Pauline Davis began the first investigations of EEG patterns during human sleep. This was followed by the first systematic studies of sleep EEG patterns and different stages of sleep in humans by Alfred L. Loomis and colleagues initiating EEG-based analyses of sleep disorders through the work of Kleitman in the 1940s at the University of Chicago, USA.

In the 1940s, the EEG started to become invasive, and the use of special implanted or "depth" electrodes and the exploration of deep intracerebral regions began. The space averaging of brain potentials resulting from extracranial recording is a random data reduction process forced by current spreading in the head volume conductor. In contrast, EEG electrodes implanted in brains provide more focal details but with very circumscribed spatial coverage that fails to provide a more global assessment of brain function. However, technical and ethical limitations of intracranial recording forced neurophysiologists to emphasize scalp recordings, which provide synaptic action estimates of larger scale sources that can be correlated to cognition and behavior.

Throughout the 1950s, clinical and experimental neurophysiological studies using EEG expanded rapidly worldwide with the discovery of cerebral recruiting responses, the effects of descending and mostly inhibitory influences of the brainstem reticular formation, and the use of EEG to locate brain regions that generated epileptic activity prior to surgical interventions. These studies were followed by EEG studies in newborns in the 1960s and investigations of evoked cortical potentials that became commonly used for prognosis and the monitoring of psychiatric and neurocritically ill patients in the late 1970s [4, 5]. Despite the large body and scientific impact of early investigations using EEG at that time, further discussion on this topic is beyond the focus of this chapter.

## From Paper to Digital Recording

Since the first human EEG recordings in the early 1920s and their widespread acceptance 20 years later, it has been known that the amplitude and frequency content of EEG patterns reveals substantial information about the neurofunctional state of the brain. For example, the voltage record during deep sleep has dominant frequencies in the delta range near 1 Hz, whereas the eyes-closed waking state is associated with

sinusoidal oscillations of an alpha frequency range near 10 Hz. Early in the history of EEG, it became clear that more standardized and automatic quantitative analyses would allow for reliable identification and correlation of EEG information to different neurofunctional states, such as distinguishing different sleep stages, determining the depth of anesthesia, identifying waxing and waning epileptic activity during seizures, and the analysis of encephalopathic states. Hence, in the 1950s, EEG became widely available, and almost every tertiary academic medical care center had at least one EEG machine. At the end of the decade, EEG was also in use in a large number of nonacademic hospitals and private practices in the 1960s.

This propagation of EEG significantly slowed in the 1970s, possibly explained by the advances in high resolution, structural neuroimaging techniques including computed tomography and magnetic resonance imaging. However, it soon became recognized that EEG provides real-time information on the neurofunctional status and its spatial development that cannot be assessed at bedside by neuroimaging techniques, and EEG regained interest in the 1990s.

Although in the 1980s technical advances allowed the EEG to be digitized and recorded on videotape, the number of channels and the resolution were limited at first. Electronic data storage volumes increased significantly in the 1990s, and computer networking enabled remote EEG reading and simultaneous video recording of the patients, making continuous EEG (cEEG) recordings over hours to days of many critically ill patients, possible. As manual review and interpretation of cEEG became increasingly labor-intensive, effective methods were developed to assist in rapid and accurate EEG interpretation, especially regarding seizure detection. In the late 1990s and early 2000s, complex algorithms enabling quantitative EEG analyses, such as the Wavelet analysis and Fourier analysis, with new focus on shared activity between rhythms including phase synchrony and magnitude synchrony, were developed. Automated spectral analysis was introduced to study spectral content through a spectrogram also known as a time-frequency plot, a color plot providing the temporal evolution of the EEG frequency spectrum. In this context, the color provides information about the power at a given instant of time for a given frequency band. These modern methods of EEG concerned with both temporal and spatial properties revealed robust electrographic correlations with cognitive processes, such as mental calculation, working memory, and selective attention further expanding the yield of EEG and increasing the diagnostic power of cEEG monitoring especially in epilepsy clinics and intensive care units (ICU) in the last several years.

## Diagnosis and Prognosis

Critically ill patients often become confused or obtunded from a variety of critical illnesses, including acute brain lesions, systemic metabolic derangements, seizures, or status epilepticus (SE). Nonconvulsive seizures (NCS) and nonconvulsive status epilepticus (NCSE) are states without visible convulsions and hence depend on EEG and cEEG to both make a diagnosis and ascertain treatment success. In recent

years, cEEG has been increasingly implemented in ICUs as a noninvasive tool to continuously assess dynamic real-time information of brain function, enabling immediate detection of changes in neurofunctional status, even if clinical examination of patients with altered mental status is limited or clinical seizure-related signs are subtle or nonspecific. Focal slowing of EEG background activity may indicate ischemia or the presence of other acute brain lesions, while global slowing suggests an encephalopathy. The loss of EEG variability and reactivity may indicate severe brain injury and poor prognosis [6].

Increasing use of cEEG reveals clinically undetected epileptiform activity in up to 80 % of critically ill patients with altered level of consciousness [7, 8] and results in heightened clinical awareness of treating physicians and greater detection rates than routine EEG, the latter because of the intermittent nature of occult seizures. Using cEEG, epileptic seizures have been detected in up to 15 % of non-neurocritically ill patients and in 10–50 % of neurocritically ill patients. Almost half of patients with traumatic brain injury monitored with cEEG reveal seizures [6]. SE is observed in up to 10 % of patients with ischemic stroke, in about 15 % with traumatic brain injury, in 20 % with intracerebral hemorrhage, in 10 % with subarachnoid hemorrhage, and in 30 % of patients after cardiac arrest [6]. Determining seizure type at SE onset and detecting interictal periodic discharges using cEEG monitoring provide pivotal prognostic information [9], and seizure detection with consecutive antiepileptic treatment has to be associated with improved outcome [10], further underscoring the importance of cEEG monitoring.

Aside from seizure detection, some EEG characteristics such as the degree of slowing of EEG background activity, the presence of non-epileptic episodic transients such as triphasic waves, and frontal intermittent rhythmic delta activity [11, 12], as well as sleep elements [13], alert clinicians to direct additional clinical investigations toward specific underlying etiologies of altered mental status and to improve prognostication in patients with acute non-epileptic encephalopathy. The prognostic importance of cEEG has further been demonstrated in patients suffering from hypoxic brain injury after cardiac arrest. While most studies indicate that somatosensory evoked potentials are the most reliable outcome predictor in this context [14], recent studies have revealed that the combination of clinical examination, EEG background reactivity, and serum neuron-specific enolase offers the best outcome predictive performance for prognostication of early postanoxic coma, whereas somatosensory evoked potentials may not add any complementary information [15]. However, although prognostication of poor outcome seems excellent, future studies are needed to further improve the prediction of good prognosis, which still remains inaccurate.

## Directing Treatment

While cEEG monitoring is routinely used in epilepsy clinics and in outpatients to guide antiepileptic treatment in patients with epilepsy, cEEG is mostly used to help in the management of patients with SE refractory to first- and second-line

antiepileptic drugs or to monitor frequency ranges of EEG background activity in patients treated for raised intracranial pressure or for impending vasospasm following subarachnoid hemorrhage. Antiepileptic and anesthetic agents can be titrated to achieve seizure suppression or to manage elevated intracranial pressure by the induction of EEG burst suppression. While these are common practices in ICUs, the optimal EEG endpoint and the duration of such suppression have not been determined.

The need to identify seizures and SE in critically ill patients is based on the assumption that certain types of persistent ictal activity damage the brain. In patients with brain trauma or intracerebral hemorrhage, NCSE or NCS may increase the risk of morbidity and mortality. In other clinical settings, the effect of seizures or SE is less clear except for refractory convulsive SE, which has a high mortality of up to 40 %. Therefore, current guidelines recommend close monitoring of SE refractory to first- and second-line antiepileptic treatment and a rapid treatment escalation guided by EEG, especially in some patients with NCS or nonspecific or subtle clinical signs of seizures. However, although the use of EEG for monitoring and directing treatment in patients with SE seems plausible, studies proving a reduction of morbidity and mortality by the use of cEEG in many of these clinical settings have not been conclusive.

## Interinstitutional Variability

The widespread and increasing use of cEEG in recent years calls for a standardized procedure to assure and enhance the quality of cEEG-related science. Data describing the current interinstitutional variability of cEEG practice in the critically ill are limited. In a recent study, a survey of cEEG indications and procedures was sent to intensivists and neurophysiologists responsible for ICU-cEEG at 151 institutions in the USA [16]. At some institutions only one physician could be identified. Of the 137 physicians from 97 institutions who completed the survey, cEEG was used by nearly all respondents to detect NCS or NCSE in patients with altered mental status following clinical seizures with in intracerebral hemorrhage, after traumatic brain injury and after cardiac arrest. It has also been used to characterize abnormal movements suspected of being seizures.

The majority of physicians monitor comatose patients for 24–48 h. However, in an ideal situation with unlimited resources, 18 % of respondents would increase cEEG duration. Eighty-six percent of institutions have an on-call EEG technologist available 24/7 for new patient hookups, but only 26 % have technologists available 24/7 in-house. There is substantial variability in who reviews EEGs and how frequently the record is reviewed as well as how often quantitative EEG is used. Although there is general agreement regarding the indications for cEEG in ICUs, there is substantial interinstitutional variability on how the procedure is performed. Future studies and guidelines in this context are warranted to justify the increased use of cEEG in the ICUs and to improve the art and science of this emerging field.

## Future Perspectives

Nowadays, EEGs in ICUs are recorded invasively and noninvasively using entirely computerized systems. The EEG machines are equipped with a variety of signal processing software and enough memory for long-term recordings lasting several hours or days. Delicate needle electrodes can be used for EEG recordings from the cortex without the attenuation and nonlinearity effects of the skull. In the future, EEG machines may be increasingly integrated with other dynamic neuroimaging systems such as functional magnetic resonance imaging. However, to what extent this development will target critical care is unclear and will face many obstacles including the transportation of vulnerable, critically ill patients to the radiologic units. New software for more complex investigations of neuronal network interaction and for automated seizure detection and artifact suppression will emerge, enhancing the scope and quality of application but also providing increasing analytic and technological challenges to neurophysiologists.

### Conclusions

Within the span of approximately 100 years, the value of EEG has evolved from a little accepted innovation to a vital procedure for monitoring critically ill patients. Though its origins were in the study of cognitive neurology, its value in epilepsy and seizures was quickly realized. Now, in addition to remaining an essential tool in the diagnosis of epilepsy, EEG is used for the assessment and prognostication of many different neurological conditions. With newer techniques in data analysis and interpretation, EEG promises to remain vital to the management of neurologically ill patients.

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# Epidemiology of Seizures in Critically Ill Adults

2

Jennifer M. Pritchard and Jennifer L. Hopp

## Contents



## Introduction

Seizures and status epilepticus (SE) are relatively common in critically ill adults, and manifestations may include convulsive status epilepticus (CSE), nonconvulsive status epilepticus (NCSE), and nonconvulsive seizures (NCS). Convulsive seizures that do not meet criteria for status are also seen in this patient population. SE is associated

J.M. Pritchard, MD (✉) • J.L. Hopp, MD
Neurology, University of Maryland School of Medicine,
22 South Greene Street, 12th floor, Room S12C09, Baltimore, MD 21201, USA
e-mail: JPritchard@som.umaryland.edu; JHopp@som.umaryland.edu



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with significant morbidity and mortality and should be diagnosed and treated appropriately. Some challenges in diagnosis and treatment center on the entity of NCSE. This group is now thought to be a heterogeneous patient population including different conditions and associated etiologies. In fact, the underlying etiology of seizures and status is felt to be a very important determinant of overall prognosis and outcome in this group of critically ill adult patients. In this chapter, the epidemiology, clinical features, and etiologies of the various SE types will be presented.

## Status Epilepticus: Overview

SE is a medical and neurologic emergency with a mortality of up to 20 % [1]. Significant morbidity has been reported as well [2]. SE was historically defined as continuous seizure activity of at least 30 min duration or a series of repetitive seizures without return of consciousness between seizures [3]. Currently, a working definition of SE is continuous seizure activity persisting greater than 5 minutes or 2 repetitive seizures without return to baseline level of consciousness between seizures [4]. This definition is now more widely accepted as it is considered more appropriate to guide treatment [5].

The incidence of SE across age groups is estimated on average as 7 [5, 6] to 41 cases per 100,000 annually, but there are several reasons why data can be discordant. Incidence in young adults has been shown to be 27 per 100,000 per year but 86 per 100,000 per year in the elderly [7]. Many of these population-based studies also use the International League Against Epilepsy (ILAE) 1993 definition of SE using the 30 minutes time period that is no longer in favor [3].

There appear to be ethnic differences in the incidence of SE with nonwhites reported as having a higher frequency of SE (13.7–57/100,000) compared to whites (6.9–20/100,000) [6–8]. Gender differences are also seen with higher rates in men than women [5, 6, 9]. This is typically attributed to higher rates of acute and remote symptomatic seizures in men [6]. There seems to also be a suggestion that the incidence of SE may be increasing over time. A recent review reports an increase in the frequency of SE from 3.5 to 12.5 per 100,000 cases from 1979 to 2010 [10], and prior large studies have suggested upward trends as well, which have been mostly attributed to increasing elderly populations [6].

Gastaut noted, “there are as many types of status as there are types of epileptic seizures” [11], and although classification of seizures and SE will be discussed in another chapter, the system continues to evolve and is utilized differently in many population-based studies. For the purpose of this chapter, SE will be categorized as CSE or NCSE, and NCS will also be briefly discussed.

## Convulsive Status Epilepticus

The term CSE is often used interchangeably with GCSE. CSE classically refers to SE with a predominant motor manifestation; when this is in the form of generalized convulsive seizures, it is best characterized as generalized CSE (GCSE). There are several other subtypes including focal motor SE and myoclonic SE (MSE).

## Generalized Convulsive Status Epilepticus

### Epidemiology

GCSE is one of the major categories of SE, and it remains a significant problem with regard to morbidity and mortality in adults. This is despite the fact that the definition of GCSE has changed over time to be defined as 5 minutes of convulsive seizures or recurrent seizures over this time period without return to baseline level of consciousness. The incidence of GCSE can sometimes be difficult to parse out from the rates of SE in general as many population-based studies include both GCSE and NCSE. Other inclusion criteria including age groups, definitions of SE, and other factors may differ, making the data somewhat variable.

GCSE accounts for the majority of cases of SE in most studies, and NCSE may account for only about 6 % [5]. The incidence of GCSE is age related, with highest rates in children under one year of age and adults over 60 years of age [5, 6]. A more detailed discussion of SE in children will be provided in another chapter.

### Clinical Features

GCSE is typically characterized by impaired consciousness as well as motor manifestations. It typically includes bilateral tonic stiffening followed by clonic (rhythmic jerking) of the limbs, and clinical features may include focal neurologic findings, such as hemiparesis, in the postictal period. Although GCSE includes both primary and secondarily generalized seizures, this differentiation may be difficult to discern in the critically ill adult. EEG can be useful in this classification, but the semiology can be quite similar, particularly if the clinical onset is not observed or if seizure and epilepsy history is not known. Asymmetric shaking and unilateral delayed cessation of clonic activity can be signs of focal onset, but this is not always a specific finding. Myoclonus prior to generalized tonic-clonic activity may suggest primary generalized epilepsy, but this can be challenging to gather from witness reports or even from direct observation.

## Focal Motor Status Epilepticus

### Epidemiology

The incidence of focal motor SE that does not secondarily generalize may be difficult to assess in the critically ill patient. CSE with focal onset may be common and incidence is typically included in the incidence of GCSE or NCSE in most population-based studies. Epilepsia partialis continua (EPC), described below, may be more commonly seen in children than in the adult population of critically ill patients.

### Clinical Features

Focal motor SE can vary greatly in terms of semiology and presentation that is largely referable to the area of epileptogenic onset. Many cases of generalized SE are actually focal in onset, but the signs may either not be recognized by observers or reported by patients, particularly in critically ill adults in an intensive care unit (ICU) setting. Focal motor SE with preserved consciousness may be the easiest to

recognize as it presents with jerking or clonus of the limb or face, which may spread to involve other areas. A refractory type of focal motor SE is EPC. This is characterized by repetitive focal jerking of typically one part of the body. It usually does not spread as with the "Jacksonian march" seen in other focal motor SE or secondarily generalized SE and may have a slower frequency than other focal motor SE types. Other "non-motor" types of focal SE are nonconvulsive and will be discussed below in the section on NCSE. These can be quite difficult to identify and classify in a critically ill patient with altered consciousness.

## Myoclonic Status Epilepticus

### Epidemiology

MSE is characterized by frequent myoclonic jerks that are typically generalized but can be focal and may be rhythmic or arrhythmic. This is a large group of heterogeneous disorders. In those associated with epilepsy syndromes, myoclonus may be a characteristic finding, such as juvenile myoclonic epilepsy (JME) or part of a broad variety of dysfunction (Lennox-Gastaut syndrome, LGS). MSE in these patient populations is less common than GCSE and may also have a more benign prognosis than secondary forms. It may also be associated with other neurologic or systemic dysfunctions that will be discussed later in this chapter, including hypoxia-anoxia.

### Clinical Features

Characteristic findings in MSE include frequent myoclonus that is often generalized but may also be focal. The jerking movements may be rhythmic or arrhythmic, and often there are characteristic EEG findings which will be discussed elsewhere. MSE that is epileptic in origin may be seen with other GCSE (as in JME) as well as other seizure types such as atonic or myoclonic-astatic seizures in LGS. These typically can be relatively easily distinguished from other forms of persistent myoclonus and MSE by history. While the former have a history of epilepsy, other nonepileptic types, sometimes termed "status myoclonus," are associated with an underlying diffuse etiology such as anoxia or other forms of encephalopathy. When seen in the setting of other medical conditions, the myoclonus is often nonrhythmic, prolonged, and continuous, with large amplitude jerking movements. These are classically described involving the face, trunk, and limbs, but may also be multifocal.

## Nonconvulsive Status Epilepticus

NCSE is an under-recognized form of SE that accounts for 20–50 % of all SE and is associated with significant morbidity and mortality. Approximately 8–10 % of critically ill patients have been found to be in NCSE [12]. NCSE is more widely diagnosed with the increasing use of continuous EEG (cEEG) monitoring. It remains difficult to determine the incidence of NCSE in the ICU, particularly as some studies make this diagnosis based on initial 30–60 min EEG, while others utilize cEEG

recordings. Some studies suggest that NCSE typically is diagnosed in the first hour, while others do not. Although SE has historically been easier to recognize by semiology with repeated or prolonged convulsions, recognition of NCSE followed later. In the early nineteenth century, some episodes of prolonged confusional states were thought to be due to seizures, but it was not until EEG was introduced in the 1940s that NCSE was conclusively established as a valid entity [13–15]. In 1956, Gastaut used the term "psychomotor status" to describe another type of NCSE associated with altered mental status [13]. In 1962, an international symposium codified SE by characterizing it as a term for a repeated or prolonged seizure as to create a fixed and lasting epileptic condition for at least 30–60 min [15, 16]. The same group also promoted the view that there were many types of SE.

There are several ways to think about categorization of NCSE, and the definition of the term remains controversial. The narrowest definition of the term refers only to two categories. They include absence (previously petit mal) status and focal or complex partial SE (previously psychomotor SE) [2, 11, 17, 18]. With wider use of EEG and cEEG monitoring, the stratification of this term has evolved.

Over time, other subtypes and classifications have been proposed, with the concept that there may be as many types of NCSE as there are seizure types or classifications. There are a variety of accepted definitions of NCSE, but in addition to a change in mental status, there is a common working definition that is often used for EEG criteria that also includes a "significant improvement in clinical state or baseline EEG after antiepileptic drug" [19]. These criteria can be problematic, however, in that one of the criteria establishes the definition by responsiveness to anticonvulsant treatment, which is not always the case in resistant NCSE [20].

Although semiology can be broadly divided between CSE and NCSE as those forms of status with or without convulsions, there may be more subtle features of partial or focal status that are increasingly recognized. Typically, the lack of major motor manifestations delineates the difference between CSE and NCSE, but many patients with NCSE have minor abnormal motor findings. These may include nystagmus, facial twitching, or tonic eye movements [18]. As might be expected, the findings typically correspond to the origin of onset of the localization-related epilepsy.

While on one hand findings in temporal lobe NCSE may be characterized as confusion, parietal lobe NCSE, which is much less common, may be manifest by findings referable to the areas involved. The most common types of parietal lobe seizures arise from the postcentral gyrus and are typically described as a positive or negative sensation. Patients describe sensations in NCSE as prolonged paresthesias, pain, sexual phenomenology, or a widespread body "aura" [21]. Pain and perceptions of heat or cold are less common, as are seizures with sexual phenomenology or psychiatric phenomena, or disturbances of body image, but they have also been associated with seizures of parietal lobe origin and also those of parietal NCSE. Prolonged ictal sensory changes are thought to be rare and are uncommonly reported. Recognition of somatosensory SE requires that patients report symptoms and this may be hindered when patients are amnestic for the auras or sensory symptoms during the seizure or if the area of ictal onset has spread to lead to confusion, thus impairing patient report.

It is more common for these patients to have had a witnessed seizure or GCSE, but it is notable that there is a large portion of critically ill patients who may not have had a clinically evident seizure. The diagnosis can be difficult, particularly as patients in the ICU setting may be thought to be postictal after clinically evident seizures. It has also, and still is, often mistaken for other reasons for change in mental status [22].

There are several ways to think about NCSE, and it is useful to understand that the categories and divisions that are utilized are not mutually exclusive. NCSE has been divided into different types by semiology, EEG patterns, and association with varied levels of consciousness. Traditionally, NCSE was thought to primarily be associated only with epilepsy syndromes, as in the "wandering confused" patient with epilepsy who has a relatively good prognosis, now other presentations are recognized. These are often seen in the critical care setting and are seen in acutely ill patients with impaired mental status. Motor manifestations may or may not be seen. Clinicians should be attuned to the possibility of NCSE, even in patients without clinically evident seizures, although NCSE that follows uncontrolled SE is the more common presentation.

By EEG criteria, NCSE is typically categorized as generalized or lateralized. There are often blurred lines in patients with altered consciousness or coma who have periodic or continuous patterns on EEG that may resemble those typical in NCSE patients. It is not yet fully clear whether treating these patterns may improve outcome or is then diagnostic of NCSE. Some groups advocate categorizing NCSE into "NCSE proper" and "comatose NCSE" to delineate these patient populations [23].

## Etiology

Among critically ill adults, causes of seizures and SE are diverse, and this contributes to the notion that not all such patients can be approached in the same manner. Furthermore, the underlying etiology of seizures and SE has increasingly been recognized as a critical determinant of prognosis and outcome in this patient population. Thus, prompt recognition of the root cause(s) of seizures and SE, along with its subsequent evaluation and treatment, is crucial.

In critically ill adults, etiologies are varied. Important causes of acute seizures and SE include insufficient dosages or low levels of antiepileptic drugs (AEDs) in patients with known epilepsy, cerebrovascular disorders, traumatic brain injury (TBI), hypoxia-anoxia, and infectious etiologies including sepsis, brain tumors, and toxic-metabolic disorders [24, 25]. Less common, but also important, etiologies including inflammatory and immune-mediated conditions are garnering increasing interest. Such disorders include paraneoplastic syndromes and autoimmune encephalitides such as anti-N-methyl-D-aspartate (NMDA) receptor encephalitis. Many of these important causes will be discussed individually in greater detail in the sections that follow. Given the broad spectrum of associated underlying conditions, critically ill patients with seizures and SE are, in many ways, a very heterogeneous group (Table 1).

**Table 1** Etiologies of seizures and status epilepticus in critically ill adults

| |
|---|
| Preexisting epilepsy |
| Insufficient doses of AEDs |
| Low levels of AEDs |
| Sleep deprivation, stress, nonspecific illness |
| Cerebrovascular disorders |
| Ischemic stroke |
| SAH |
| ICH |
| Traumatic brain injury |
| Hypoxic-anoxic injury |
| CNS infection |
| Viral, bacterial, less common infectious etiologies |
| Sepsis |
| Brain tumors |
| Toxic-metabolic disorders and drugs |
| Electrolyte disturbances |
| Intoxication and withdrawal states (alcohol and illicit drugs) |
| Medications |
| Inflammatory and immune-mediated conditions |
| NORSE |
| Paraneoplastic or non-paraneoplastic limbic encephalitis |

In the literature, some studies seek to emphasize the importance of the underlying etiology of NCSE and NCS by dividing or categorizing patients into groups based on the associated diagnosis or precipitant. For example, acute symptomatic causes of NCSE are defined by acute neurologic or medical disorders causally related to the status, independent of a prior epilepsy diagnosis. Such conditions can include strokes, head trauma, hypoxia-anoxia, central nervous system (CNS) infections, or brain tumors [18]. Alternatively, patients with a preexisting diagnosis of idiopathic epilepsy who present in NCSE without having one of the acute symptomatic conditions would comprise an idiopathic group. Lastly, cryptogenic patients would be those without an idiopathic epilepsy diagnosis or an acute symptomatic cause of NCSE [18]. Thinking about NCSE in this manner helps to highlight the variations between these patient groups and the significance and influence that etiology can potentially have on factors such as treatment, prognosis, and outcome.

The expanding use of cEEG monitoring has aided in the evaluation of seizures and SE, especially NCSE, in critically ill adults. It has also lead to greater focus on identifying seizures in comatose patients who may be admitted to the ICU for reasons initially unrelated to epilepsy or seizures. Patients may undergo evaluation with cEEG in a variety of intensive care unit settings, including the medical ICU (MICU) or neurologic ICU (NICU). Often, cEEG monitoring is requested to evaluate impaired level of consciousness or altered mental status in such patients with multiple

neurologic and medical comorbidities, which may put them at increased risk for seizures. Literature has suggested that the admission diagnoses and etiologies of seizures and SE may vary between patients admitted to a MICU as opposed to NICU [26]. For example, recent work has found a higher rate of toxic-metabolic, infectious, and substance-related etiologies in a MICU population and a higher rate of stroke in the NICU [26]. Overall, cEEG monitoring is a valuable tool in the detection and management of seizures and SE of varied etiologies in critically ill patients.

## Preexisting Epilepsy

Adults with a preexisting diagnosis of epilepsy, either of focal or generalized onset, can present with an acute worsening of their seizures or with SE. This can occur due to one of the acute symptomatic etiologies discussed in detail in the following sections, such as an acute stroke, CNS infection, or a metabolic disturbance exacerbating the underlying epilepsy. However, in the case of preexisting epilepsy, alternate etiologies may include nonadherence to an AED regimen, low AED levels, or treatment with an inappropriate medication for a particular epilepsy type [24]. A potential example of the latter would be treatment of a primary generalized epilepsy syndrome, such as JME, with a medication such as carbamazepine that can actually exacerbate the underlying seizure disorder. In individuals with epilepsy, estimates in the literature suggest that around 15 % have developed SE at least once during the course of their illness [24]. Additionally, SE can also be the initial presentation of seizures in patients who will ultimately go on to develop epilepsy [6].

The particular presenting features of acute seizures and SE in epilepsy patients will vary based on the principal epilepsy diagnosis. For example, patients with an underlying primary generalized epilepsy may present with nonconvulsive, absence SE, or potentially GCSE, while those with a focal epilepsy syndrome can develop focal NCSE or GCSE [24]. MSE can also occur in the setting of preexisting epilepsy and in this case certainly represents a unique clinical scenario, as opposed to myoclonic status in patients with anoxic brain injury and cardiac arrest, which will be reviewed later. Examples of syndromes in which myoclonic status can develop include JME and secondary generalized epilepsies such as LGS.

In the setting of epilepsy, there are additional factors which can lower the threshold for seizures and possibly contribute to acute breakthrough seizures or SE in particular clinical scenarios. Such factors include significant sleep deprivation, alcohol or drug intoxication or withdrawal, stress, fatigue, nonspecific illness, or metabolic abnormalities [27]. These circumstances may precipitate acute seizures or SE in individuals with an underlying predisposition to seizures, and clinicians can often provide important education to patients on avoidance of at least some of these potential triggers.

## Acute Cerebrovascular Injuries

Acute cerebrovascular injuries, including subarachnoid hemorrhage (SAH), ischemic stroke, and intracerebral hemorrhage (ICH), are common etiologies of seizures

and SE in critically ill adults. In addition, remote hemorrhagic and ischemic strokes have also been recognized as frequent precipitants, especially in older adults [28]. A study that looked at causes of hospital-onset seizures found stroke to be one of the most common etiologies, accounting for 23 % of cases in those patients without a prior history of seizures [29]. Patients with acute cerebrovascular disorders may have convulsive seizures; nonconvulsive, electrographic seizures; or a combination of the two categories. In this patient population, seizures and SE can occur as part of the initial presentation of the brain injury or may be detected during the subsequent hospital course. The expansion of cEEG monitoring has aided in the detection of NCS and NCSE in patients with strokes and brain hemorrhages that may frequently be encephalopathic or comatose or may require prolonged sedation.

Recent work has demonstrated electrographic seizures in up to one third of patients with nontraumatic ICH undergoing cEEG monitoring, and over half of these seizures were not associated with any clear clinical findings [30]. Another group investigating rates of NCSE among patients referred for EEG testing found that out of 451 study subjects, ICH, including traumatic ICH, was the etiology in 18 % of cases [18]. In addition to electrographic seizures, periodic EEG patterns can also be seen in patients with ICH, including lateralized periodic discharges (LPDs), generalized periodic discharges (GPDs), and rhythmic delta activity (RDA). Periodic patterns have been noted to have an association with cortical, as opposed to deep, hemorrhages. Similarly, an expanding ICH volume (30 % expansion at 24 h follow-up CT scan) has been associated with electrographic seizures [30]. An ongoing challenge in this patient group, as is the case with many critically ill populations, lies in determining the impact of treating seizures and periodic patterns on overall prognosis and patient outcome.

Acute clinical seizures, as well as NCS and NCSE, are recognized complications of SAH and felt to be generally associated with poor outcomes. As noted, a high clinical index of suspicion is often needed to diagnose nonconvulsive ictal activity in these patients. Recent estimates of the frequency of electrographic seizures in SAH patients undergoing cEEG monitoring range from 7 to 19 % [31, 32]. Reports have additionally suggested that SAH patients at higher risk for NCSE include those with poor neurologic grade (Hunt and Hess grade 4 or 5 and Fisher grade 3 or 4) and older age [33]. Treatment of NCS and NCSE in these patients is aimed at prevention of secondary brain injury and associated complications. Quantitative EEG analysis has also shown promise as an additional tool for evaluation of delayed cerebral ischemia in SAH and is increasingly utilized at academic and other centers performing high volumes of cEEG monitoring. Details of quantitative EEG techniques will be reviewed in a later chapter.

## Traumatic Brain Injury

Following TBI, seizures and SE can occur, and cEEG monitoring can assist in the detection of these events, especially in patients with altered mental status or coma. Important factors contributing to the occurrence of seizures include brain injury severity and the existence of hemorrhagic contusions [34]. In a series of twenty

moderate-severe TBI patients with non-penetrating head injuries monitored prospectively with cEEG and cerebral microdialysis, ten were found to have electrographic seizures [34]. Of those ten patients, seven had SE. In this group, seizures were also found to be linked to persistent elevations in intracranial pressure as well as increases in the lactate/pyruvate ratio in cerebral microdialysis measurements [34], suggesting that seizures can have multifaceted effects on the brain in this population. In another large cohort of critically ill adults undergoing cEEG monitoring, 18 % of the included patients with a diagnosis of TBI had electrographic seizures [32]. In the TBI population, as with many of the other patient groups discussed here, the effect treatment of seizures has on overall patient outcomes, and neurologic function remains unknown. However, treatment of identified seizures does at least provide a potential mechanism to help in prevention of further brain injury and metabolic distress [34].

## Central Nervous System Infections

Electrographic and clinical seizures can occur with CNS infections of various types in critically ill adults, including cases of viral and bacterial infections, as well as with less common infectious diseases. A well-recognized example is that of herpes simplex encephalitis (HSE), a potentially life-threatening condition in which seizures are common during the course of the illness. EEGs performed in patients with HSE often demonstrate lateralized findings, such as lateralized periodic discharges (LPDs) [35], which can be highly epileptogenic. cEEG monitoring can be useful in identifying electrographic seizures and periodic patterns in patients with various CNS infections [36].

In a study of critically ill adults admitted with CNS infections who were monitored with cEEG, 48 % had either electrographic seizures or PDs [36]. The largest group of patients had a viral etiology (68 %), followed by bacterial and then fungal or parasitic causes. As has been discussed with other etiologic groups, only a fraction of the patients with electrographic seizures (36 %) had an appreciable clinical correlate, again highlighting the concept that a high index of suspicion along with the use of cEEG monitoring is often necessary to detect these seizures [36].

There are additional rare infectious causes of SE that have been described, including uncommon bacterial and viral infections and prion diseases, about which less is known. Some examples of atypical bacterial infectious agents include *Bartonella*, *Coxiella burnetii* (Q fever), and neurosyphilis [24, 37]. Less common viral causes that have been reported can include West Nile encephalitis, *JC virus*, *Parvovirus B19*, and measles encephalitis, among others; and prion diseases such as Creutzfeldt-Jakob disease are also noted [24, 37]. Such atypical infectious causes of SE should be considered in the appropriate clinical context and in cases where standard initial work-up is unrevealing.

## Toxic-Metabolic Disorders and Drug-Related Causes

Toxic-metabolic disorders are an additional cause of acute seizures and SE in critically ill adults. There are a number of metabolic disturbances that can be associated

with seizures, including hyponatremia, hypoglycemia or hyperglycemia, hepatic encephalopathy, uremia and renal failure, and less commonly hypomagnesemia and hypocalcemia [24, 29, 38]. While such metabolic abnormalities are recognized as seizure precipitants, precise cut points for serum values below or above which seizures may occur have yet to be fully delineated [38]. In patients with seizures or SE related to metabolic disturbances, there may be an additional underlying cerebral lesion that may be remote, such as a prior stroke. In this case, the metabolic abnormality would further lower the threshold for acute seizures in patients who may already be predisposed. A study evaluating the etiologies, treatment, and outcomes of hospital-onset seizures found metabolic abnormalities to be one of the most commonly observed causes of seizures (20 % of cases). It was an especially prevalent etiology among those without a prior existing history of seizures [29]. An interesting link between metabolic disorders and SE is that of EPC and hyperosmolar nonketotic hyperglycemia. EPC has multiple, varied causes, and among them metabolic disorders, such as nonketotic hyperglycemia, are relatively common [24, 39]. As mentioned previously, there is most often a co-occurring structural brain lesion in addition to the metabolic abnormality in these cases of EPC [39].

Alcohol and drug intoxication and withdrawal states are also accepted as precipitants for acute symptomatic seizures in adults [38]. If alcohol withdrawal is to be implicated as the etiology, then the seizure must take place within 7–48 h of the patient's last drink [38]. Withdrawal from certain medications, such as benzodiazepines, can also cause acute seizures. Drugs of abuse that can precipitate acute symptomatic seizures include cocaine and crack cocaine, certain stimulants and inhalants, and potentially hallucinogens such as phencyclidine (PCP) [38].

In critically ill, hospitalized patients, certain medications have also been linked to seizures and SE. One important, representative example to consider is that of cephalosporin antibiotics, such as cefepime. Periodic discharges, such as atypical triphasic waves, as well as NCSE have been reported to occur in association with cefepime, typically in patients with renal impairment [40]. An awareness of medication-induced seizures and NCSE is important for practitioners treating critically ill patients, as the use of such broad-spectrum drugs is common and often necessary.

## Sepsis

Sepsis is a frequent ICU admission diagnosis and/or complication in critically ill patients and has been shown to be an additional, important risk factor for acute brain dysfunction as well as electrographic seizures and periodic discharges (PDs) [41]. A recent study evaluating cEEG monitoring in the MICU found that 60 % of their subjects had an admission MICU diagnosis of sepsis, and of these patients, 10 % were found to have electrographic seizures, while 17 % had PDs [41]. As is the case with other conditions that may result in encephalopathy or potentially a comatose state, cEEG monitoring can be very valuable in diagnosing electrographic seizures, NCSE, and PDs in patients with sepsis [41]. Again, these electrographic seizures are often associated with no detectable clinical signs or only subtle findings.

## Inflammatory and Immune-mediated Disorders

Immune-mediated and inflammatory etiologies of seizures and SE are increasingly entertained in patients presenting without a prior history of epilepsy and without a clear alternate etiology identified after initial work-up. Additionally, such conditions may be included in the differential diagnosis for known epilepsy patients with an acute worsening of their seizures or those who have been previously thought to have an idiopathic epilepsy. New onset refractory status epilepticus (NORSE) is a relatively newly described entity characterized by superrefractory status epilepticus in patients without a preexisting epilepsy diagnosis, often following a nonspecific febrile illness and with a potential early CSF pleocytosis [42]. The precipitating cause of NORSE remains uncertain, despite an extensive work-up, in many cases. However, given the frequent preceding mild febrile illness, a post-viral or autoimmune/inflammatory etiology is often hypothesized [42]. NORSE is associated with significant morbidity and mortality, and the time course of the status can be weeks to months or more.

Patients with a paraneoplastic or non-paraneoplastic limbic encephalitis can also present with a focal NCSE, in addition to other features such as psychiatric symptoms or movement disorders. Examples of such syndromes include limbic encephalitis associated with antibodies against voltage-dependent potassium channels (VGKC) or glutamic acid decarboxylase (GAD) and anti-NMDA receptor encephalitis [24]. Certain forms of limbic encephalitis can interestingly be associated with a specific seizure type. For example, faciobrachial dystonic seizures have been described as a unique seizure type seen with VGKC-complex/leucine-rich glioma-inactivated 1 (LGI1) antibodies [43]. Hashimoto's encephalopathy can also potentially present with seizures and SE, or alternately EEG monitoring can demonstrate nonspecific markers of encephalopathy such as slowing or "triphasic waves" (GPDs with triphasic morphology) [44]. This area presents exciting opportunities for future research and exploration, as new autoantibodies and their associated syndromes are regularly identified and characterized. Neurologists and intensivists may therefore be able to better diagnose and appropriately treat some groups of patients with seizures and status previously felt to be cryptogenic or due to an uncertain encephalitis.

## Hypoxia-Anoxia and Cardiac Arrest

Acute seizures and SE, including MSE, occur commonly following cardiac arrest. In this critically ill patient population, there is ongoing debate as to whether seizures represent a marker of the underlying hypoxic-anoxic brain injury or independently contribute to poor neurologic outcomes and recovery. Many centers now perform cEEG monitoring on post-cardiac arrest patients undergoing therapeutic hyperthermia (TH) as part of standard protocol, if the resources are available. These patients are often sedated and paralyzed while undergoing TH, making the diagnosis of NCS and NCSE especially challenging. Recent studies have found electrographic seizures on cEEG in between 23 and 33 % of post-cardiac arrest patients undergoing

TH, similar to prior estimates [45, 46]. Neurologic outcome was generally poor in these patients. Seizures can occur both during the cooling phase of TH as well as during or after rewarming. This time course should be taken into account when determining the appropriate duration of cEEG monitoring in this population. In addition to NCS and NCSE, periodic patterns such as GPDs can commonly be seen with post-cardiac arrest patients undergoing cEEG. These patterns themselves are potentially associated with evolution into NCS [47]. While the use of cEEG monitoring facilitates earlier identification of seizures and interictal epileptiform activity in this population, the prognostic value and optimal approach to treatment of these findings is yet to be fully established.

**Conclusions**

In summary, seizures and SE are common occurrences among critically ill adults. Manifestations include GCSE, focal motor SE, MSE, and NCS or NCSE. Acute seizures and SE can occur in patients with preexisting epilepsy or de novo. CEEG monitoring is an important tool in the evaluation of these conditions, especially NCSE which may present with subtle clinical manifestations or be identified predominantly through electrographic findings. Causes are varied, and in critically ill adults often relate to an acute symptomatic etiology. The underlying etiology confers important information regarding the prognosis and outcomes in this population.

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# Epidemiology of Seizures in Critically Ill Children and Neonates

3

Nicholas S. Abend and Courtney J Wusthoff

## Contents



N.S. Abend, MD (✉)
Departments of Neurology and Pediatrics, Perelman School of Medicine at the University of Pennsylvania, The Children's Hospital of Philadelphia, Philadelphia, PA, USA
e-mail: abend@email.chop.edu

C.J. Wusthoff, MD
Stanford Division of Child Neurology, Lucile Packard Children's Hospital Stanford, Palo Alto, CA, USA



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## Introduction

Over the last few decades, much has been learned about the epidemiology of seizures in critically ill children and neonates. Seizures are often difficult to identify in this patient population by clinical observation alone so continuous EEG (cEEG) monitoring is needed. Because cEEG monitoring is a relatively new technique and is necessary to accurately detect seizures in the intensive care unit (ICU), the data on epidemiology of seizures in critically ill children and neonates is still emerging. This topic is covered in three sections in this chapter: (1) epidemiology of seizures in children in the pediatric ICU, (2) epidemiology of seizures in children in the cardiac care unit (CCU), and (3) epidemiology of seizures in the neonatal ICU.

## Seizures in the Pediatric Intensive Care Unit

### Seizure Incidence

Studies of critically ill children undergoing cEEG monitoring in pediatric ICUs have reported that 10–50 % experience electrographic seizures, and about one-third of children with electrographic seizures have a sufficiently high seizure exposure to be categorized as electrographic status epilepticus (SE) (Fig. 1) [1–19]. The exact indications for monitoring varied across these studies, but most included a primary indication related to an acute encephalopathy or altered mental status. The largest study of cEEG monitoring in the pediatric ICU retrospectively evaluated 550 children who underwent clinically indicated cEEG monitoring at 11 tertiary care pediatric ICUs in the United States and Canada. Electrographic seizures occurred in 30 % of monitored children. Further, among those children with seizures, electrographic SE occurred in 33 %. Consistent with other single-center studies which demonstrated a high occurrence of EEG-only (also termed subclinical or nonconvulsive) seizures [3, 6, 8–10, 12, 14–16, 18], 35 % of children with electrographic seizures had exclusively EEG-only seizures [13]. Several studies have demonstrated that EEG-only seizures occur even in children who have not received any or recent paralytics [15, 18], indicating clinically evident changes were not being simply masked by paralytic administration, but that electromechanical uncoupling occurred, referring to a dissociation of electrical brain activity and outward mechanical signs.

### Seizure Risk Factors

Identifying children at higher risk for electrographic seizures is complex since electrographic seizures have been reported in both large heterogeneous cohorts [13] and smaller more homogeneous cohorts of children with single brain insult etiologies [7, 11, 12, 16]. Several risk factors have been reported including younger age (infants as compared to older children) [8, 11, 13, 16, 18], the occurrence of convulsive seizures [9, 13, 14] or convulsive status epilepticus (CSE) [8] prior to initiation

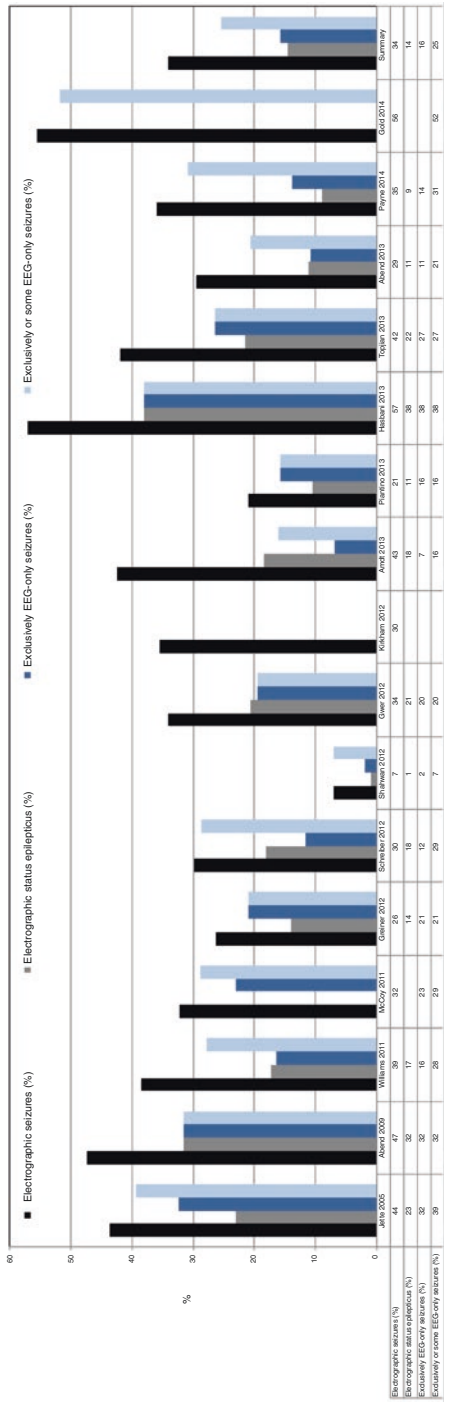


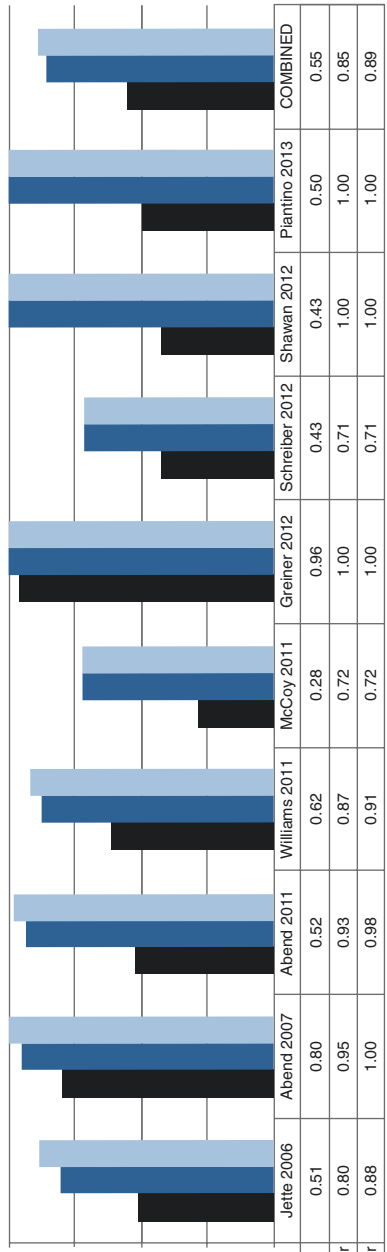

**Fig. 1** Proportions of subjects with electrographic seizure, electrographic status epilepticus, and EEG-only seizures from studies in which critically ill children underwent cEEG monitoring

of monitoring, the presence of acute structural brain injury [7–9, 11, 12, 14, 16], and the presence of interictal epileptiform discharges [8, 12–14] or periodic epileptiform discharges [3]. Although the reported risk factors are statistically significant, the absolute difference in the proportion of children with and without electrographic seizures based on the presence or absence of a risk factor is often only 10–20 %, so these risk factors may have limited clinical utility in selecting patients to undergo monitoring.

EEG monitoring is resource intense, and seemingly small changes in utilization may have substantial impacts on equipment and personnel needs [20, 21]. Seizure prediction models combining multiple known seizure risk factors could allow targeting of EEG monitoring to children with the highest risk for experiencing electrographic seizures within the resource limitations of an individual medical center. A recent study derived a seizure prediction model from a retrospectively acquired multicenter dataset and validated it on a separate single-center dataset. Both datasets were derived from clinically indicated EEG monitoring performed for critically ill children with heterogeneous etiologies for their acute encephalopathy. The model had fair to good discrimination including the validation dataset, indicating that most (but not all) patients were appropriately classified as having or not having electrographic seizures. The model could be applied clinically in three steps. First, the clinician would obtain two clinical variables (age and whether there were clinically evident seizures) and two EEG variables (background category and interictal epileptiform discharge presence). Second, using these variables, the clinician could determine a model score. Third, patients with model scores above an institutional cutoff score would be selected to undergo cEEG monitoring. Individual institutions could select different model cutoff scores based on center-specific criteria. A center with substantial EEG monitoring resources might perform EEG monitoring for any patient with a model score >0.10. At this lower cutoff, 14 % of patients with electrographic seizures would not undergo EEG monitoring, so the seizures would not be identified and managed. However, 58 % of patients without electrographic seizures would be identified as not needing EEG monitoring, so limited resources would not be expended. Given a seizure prevalence of 30 %, this cutoff would have a positive predictive value of 47 % and negative predictive value of 91 % [22]. Further development might yield improved predictive models by incorporating additional variables or focusing on more homogeneous cohorts.

## Continuous EEG Monitoring Duration

Decisions regarding the duration of EEG monitoring must balance the goal of identifying electrographic seizures with practical concerns regarding the substantial and limited resources required to perform EEG monitoring. Observational studies of critically ill children undergoing clinically indicated EEG monitoring have reported that about 50 % and 90 % of patients with electrographic seizures are identified with 1 h and 24–48 h of EEG monitoring, respectively (Fig. 2) [3, 6, 8, 9, 12, 14, 15, 18]. Thus, 1 h of EEG will fail to identify many children who will subsequently




| | Jette 2006 | Abend 2007 | Abend 2011 | Williams 2011 | McCoy 2011 | Greiner 2012 | Schreiber 2012 | Shawan 2012 | Plantino 2013 | COMBINED |
|---|---|---|---|---|---|---|---|---|---|---|
| Probability at 1 hour | 0.51 | 0.80 | 0.52 | 0.62 | 0.28 | 0.96 | 0.43 | 0.43 | 0.50 | 0.55 |
| Probability at 24 hour | 0.80 | 0.95 | 0.93 | 0.87 | 0.72 | 1.00 | 0.71 | 1.00 | 1.00 | 0.85 |
| Probability at 48 hour | 0.88 | 1.00 | 0.98 | 0.91 | 0.72 | 1.00 | 0.71 | 1.00 | 1.00 | 0.89 |

**Fig. 2** Proportion of subjects in whom electrographic seizures were identified by cEEG monitoring for 1 h, 24 h, and 48 h

experience electrographic seizures, while 48 h of monitoring identifies most children with electrographic seizures.

There are two important limitations regarding the electrographic seizure timing data described above. First, most of the studies providing the data above calculated timing at the onset of EEG monitoring and not the onset of the acute brain insult. However, in clinical practice patients may present at varying durations after the onset of acute brain insult. Furthermore, patients may experience clinical changes potentially producing additional brain injury while in the ICU, and it is unclear if the timing considerations should restart with each of these clinical occurrences. Second, most of the studies providing the data above were observational studies in which patients underwent 1–3 days of clinically indicated EEG monitoring. Thus, some patients may have experienced electrographic seizures after EEG monitoring was discontinued. In specific circumstances electrographic seizures are known to occur later in time, such as following cardiac arrest resuscitation [7].

Based on the data described above, the Neurocritical Care Society's Guideline for the Evaluation and Management of Status Epilepticus strongly recommends performing 48 h of EEG monitoring to identify electrographic SE in comatose children following an acute brain insult [23]. The American Clinical Neurophysiology's Consensus Statement on Continuous EEG Monitoring in Critically Ill Children and Adults recommends performing EEG monitoring for at least 24 h in children at risk for seizures [24].

## Outcome

Several studies in critically ill children have reported associations between high seizure exposures and worse outcomes. However, the extent to which electrographic seizures are actually producing secondary brain injury versus serving as biomarkers of more severe acute brain injury remains unknown. Further, the extent to which seizures produce secondary brain injury is likely dependent on a complex interplay between acute brain injury etiology, seizure exposure, seizure characteristics, and seizure management strategies. As summarized below, a number of recent studies have reported an association between electrographic seizures, particularly with high electrographic seizure exposures, and worse outcomes even after adjustment for potential confounders related to acute encephalopathy etiology and critical illness severity.

Several studies have described an association between electrographic seizures and unfavorable short-term outcome. A prospective observational study of 1–3 channel EEG in 204 critically ill neonates and children found that the occurrence of electrographic seizures was associated with a higher risk of unfavorable neurologic outcome (odds ratio 15.4) in a multivariate analysis that included age, etiology, pediatric index of mortality score, Adelaide coma score, and EEG background categories [10]. Several other studies aimed to evaluate the effect of seizure burden

and classified children as having no seizures, electrographic seizures, or electrographic SE. A single-center study of 200 children in the pediatric ICU with outcome assessed at discharge identified an association between electrographic SE and higher mortality (odds ratio 5.1) and worsening pediatric cerebral performance category scores (odds ratio 17.3) in multivariate analyses including seizure category, age, acute neurologic disorder, prior neurodevelopmental status, and EEG background categories. Electrographic seizures not classified as electrographic SE were not associated with worse outcomes [25]. A larger multicenter study of 550 children in the pediatric ICU reported an association between electrographic SE and mortality (odds ratio 2.4) in a multivariate analysis that included seizure category, acute encephalopathy etiology, and EEG background categories. Electrographic seizures not classified as electrographic SE were not associated with worse outcomes [13]. A single-center prospective study evaluated 259 critically ill infants and children who underwent EEG monitoring described electrographic seizures in 36 % of subjects which constituted electrographic SE in 9 % of subjects. Seizure burden was calculated as the proportion of the hour containing seizures, and the maximum hourly seizure burden was identified for each subject. The mean maximum seizure burden per hour was 15.7 % in subjects with neurological decline versus 1.8 % in subjects without neurological decline. In a multivariate analysis that adjusted for diagnosis and illness severity, for every 1 % increase in the maximum hourly seizure burden, the odds of neurological decline increased by 1.13. Maximum hourly seizure burdens of 10, 20, and 30 % were associated with odds ratios for neurological decline of 3.3, 10.8, and 35.7. In contrast to some of the other studies described above, electrographic seizures were not associated with higher mortality [17].

A study addressing long-term outcome obtained follow-up data at a median of 2.7 years following pediatric ICU admission from 60 children who were neurodevelopmentally normal prior to admission and underwent clinically indicated EEG monitoring. Multivariate analysis including acute neurologic diagnosis category, EEG background category, age, and several other clinical variables identified an association between electrographic SE and unfavorable Glasgow Outcome Scale (Extended Pediatric Version) category (odds ratio 6.36), lower Pediatric Quality of Life Inventory scores (23.07 points lower), and an increased risk of subsequently diagnosed epilepsy (odds ratio 13.3). Children with electrographic seizures not classified as electrographic SE did not have worse outcomes [26].

Together, these studies suggest there may be a dose-dependent or threshold effect of seizures upon outcomes, with high seizure burdens having clinically relevant adverse impacts. This threshold may vary based on age, brain injury etiology, and seizure characteristics such as the extent of brain involved and electroencephalographic morphology. While further study is needed, these data suggest that at least in some patients and at high seizure exposures, electrographic seizures may be producing secondary brain injury, and identifying and managing those seizures might mitigate such injury.

## Clinical Practice and Guidelines

A recent survey of EEG monitoring use in the pediatric ICUs of 61 large pediatric hospitals in the United States and Canada reported that the median number of patients who underwent cEEG monitoring per month increased about 30 % from 2010 to 2011 [27]. Indications for EEG monitoring included determining whether events of unclear etiology were seizures in 100 % of centers and identifying electrographic seizures in patients considered "at risk" in about 90 % of centers. Patients considered "at risk" included those with altered mental status following a convulsion, altered mental status in a patient with a known acute brain injury, and altered mental status of unknown etiology. About 30–50 % of centers reported using EEG monitoring as part of standard management for specific acute encephalopathy etiologies within a clinical pathway (i.e., following resuscitation from cardiac arrest or with severe traumatic brain injury) [27].

The Neurocritical Care Society's Guidelines for the Evaluation and Management of Status Epilepticus recommends the use of EEG monitoring to identify electrographic seizures in at-risk patients including those with persisting altered mental status for more than 10 min after convulsive seizures or SE or encephalopathic children after resuscitation from cardiac arrest, with traumatic brain injury, with intracranial hemorrhage, or with unexplained encephalopathy. The guideline strongly recommends 48 h of EEG monitoring in comatose patients. If SE occurs (including electrographic SE), then the guideline recommends that management should continue until not only the clinical seizures are halted, but until all electrographic seizures are halted [23].

The American Clinical Neurophysiology Society's (ACNS) Consensus Statement on Continuous EEG Monitoring in Critically Ill Children and Adults recommends EEG monitoring for 24–48 h in children at risk for seizures. Monitoring indications include recent convulsive seizures or CSE with altered mental status, cardiac arrest resuscitation or with other forms of hypoxic-ischemic encephalopathy, stroke (intracerebral hemorrhage, ischemic stroke, and subarachnoid hemorrhage), encephalitis, and altered mental status with related medical conditions. Detailed recommendations are provided regarding personnel, technical specifications, and overall workflow [24].

## Quantitative EEG

Increasing EEG monitoring use among critically ill children [27, 28] is resource intense and would benefit from improved seizure identification efficiency. Quantitative EEG (qEEG) techniques separate the complex EEG signal into components (such as amplitude and frequency) and compress time, thereby permitting display of several hours of EEG data on a single image that may be interpreted more easily than conventional EEG. QEEG techniques may facilitate more efficient EEG monitoring review by encephalographers and perhaps even earlier identification of seizures by

non-encephalographer clinicians providing bedside care. These techniques are still being developed and their test characteristics are still being established.

Several studies have examined the utility of qEEG in critically ill children. In the first study, 27 color density spectral array (CDSA) and amplitude-integrated EEG (aEEG) tracings were reviewed by three encephalographers. The median sensitivity for seizure identification was 83 % using CDSA and 82 % using aEEG, but for individual tracings the sensitivity varied from 0 to 100 %. A false positive occurred about every 17–20 h [29]. In the second study, 84 CDSA images were reviewed by eight encephalographers. Sensitivity for seizure identification was 65 %, indicating that some electrographic seizures were not identified. Further, only about half of seizures were identified by six or more raters. Specificity was 95 %, indicating some non-ictal events were misdiagnosed as seizures [30]. A study of CDSA and envelope trend EEG found that seizure identification was impacted by both modifiable factors (interpreter experience, display size, and qEEG method) and non-modifiable factors inherent to the EEG pattern (maximum spike amplitude, seizure frequency, and seizure duration) [31].

Critical care providers have expertise at screening multiple monitoring modalities and are generally continually available within the ICU. Thus, if critical care clinicians are able to use qEEG, then electrographic seizures might be identified more rapidly. A study provided 20 critical care physicians (attendings and fellows) and 19 critical care nurses with a brief training session regarding CDSA and then asked them to determine whether each of 200 CDSA images created from conventional EEG derived from critically ill children contained electrographic seizures. The true seizure incidence was 30 % based on electroencephalographer review of the conventional EEG tracings. The CDSA seizure identification sensitivity was 70 %, indicating that some electrographic seizures were not identified. The specificity was 68 %, indicating that some images categorized as containing EEG seizures did not contain seizures. These errors may be problematic since they could lead to exposure of non-seizing children to antiseizure medications with potential adverse effects. Given the 30 % seizure incidence used in the study, the positive predictive value was 46 % and negative predictive value was 86 % [32].

These data indicate that commercially available qEEG techniques permit identification of many but not all seizures. Since seizures often occur early during EEG monitoring recordings and EEG technologists may not be readily available when EEG monitoring is needed [18], rapid bedside implementation may be an important advantage of these qEEG techniques. Seizure identification may improve with user training and experience, further development of qEEG trends, and implementation of qEEG panels with multiple trends. However, since qEEG leads to misclassification of some non-ictal events as seizures, potentially leading to unnecessary antiseizure mediation administration, confirmation by conventional EEG review may be indicated for when qEEG techniques suggest seizures are present. With further development these synergistic methods could make use of the efficiency and bedside availability of qEEG methods and the accuracy of conventional EEG tracings.

## Seizures in the Cardiac Intensive Care Unit

### Seizure Incidence

A number of studies have evaluated the incidence of clinically evident and EEG only seizures and their association with outcomes among neonates with congenital heart disease, as recently reviewed [33]. Neonates and infants undergoing surgery for congenital heart disease often experience clinically evident seizures in the postoperative period. A study of infants who survived newborn cardiac surgery requiring deep hypothermic circulatory arrest for defects other than hypoplastic left heart syndrome reported seizures in 18 % of 164 infants, with most seizures occurring within 2 days of surgery [34]. Similarly, a study of infants undergoing repair of D-transposition of the great arteries reported convulsions in 6 % of 171 infants during the initial 2 days [35].

EEG-only seizures may be even more common than convulsions in neonates with congenital heart disease [35–41]. A recent study described implementation of the ACNS Guidelines on Continuous EEG Monitoring in Neonates which recommend EEG monitoring in neonates with congenital heart disease [42]. EEG monitoring was performed for 161 of 172 eligible neonates over an 18-month period. Electrographic seizures occurred in 13 neonates (8 %). Among neonates with seizures, 85 % had exclusively EEG-only seizures and 62 % had SE [41]. In a second study of neonates with D-transposition of the great arteries, 136 of 171 infants underwent EEG monitoring for 48 h. Electrographic seizures occurred in 20 % of infants, most seizures had no clinical correlate, and most seizures occurred 13–36 h after surgery [35]. Similarly in a third study, EEG-only seizures occurred in 12 % of 183 children who underwent 48 h of EEG monitoring after cardiac surgery. None of the seizures had a clinical correlate, and the median seizure onset time was 21 h [37]. In a fourth study of infants with congenital heart disease, electrographic seizures in 6 % of 93 children, and all seizures occurred within 1 week of surgery [38]. A fifth study of 36 children who underwent cardiac surgery with cardiopulmonary bypass and underwent EEG from intubation until 22–96 h after bypass reported electrographic seizures in 8 % of children [39]. Finally, a study of 39 infants undergoing Norwood-type operations and aEEG identified intraoperative and postoperative seizures in 23 % and 18 % of infants, respectively [40].

### Seizure Risk Factors

Several risk factors for seizures among patients with congenital heart disease have been identified. In one study, variables associated with an increased risk of clinical seizures included coexisting genetic defects, aortic arch obstruction, and deep hypothermic circulatory arrest duration greater than 60 min [34]. In another congenital heart disease population, electrographic seizures occurred in 24 % of 58 children with deep hypothermic circulatory arrest duration of 40 min or longer, 7 % of 59 when duration was less than 40 min, and only 3 % of 61 who did not undergo deep hypothermic circulatory arrest. Electrographic seizures occurred in 14 % of the

neonates but only 7 % of the older infants [36]. In the Boston circulatory arrest trial of infants with transposition of the great arteries, risk factors associated with electrographic seizures included treatment with deep hypothermic circulatory arrest rather than continuous cardiopulmonary bypass, longer duration of deep hypothermic circulatory arrest, and the presence of a ventricular septal defect [35]. In a study of neonates with multiple types of congenital heart disease requiring cardiopulmonary bypass, risk factors for seizures were delayed sternal closure or longer deep hypothermic circulatory arrest duration [41].

## Outcome

Several studies in infants and children with congenital heart disease have explored their association with subsequent outcome. A cohort of children with D-transposition of the great arteries who underwent perioperative EEG monitoring and subsequent serial neurodevelopmental assessments found that perioperative electrographic seizures were associated with lower developmental scores, higher risk of definite MRI abnormalities, and higher risk of abnormal neurologic examination [35, 43–46]. Among 139 subjects available for follow-up at adolescence, multivariable analysis found postoperative seizures as infants (electroclinical seizures or EEG-only seizures) were the medical variable most consistently associated with worse outcome, including lower scores on reading and math composites, general memory index, executive function, and visual-spatial testing. These differences were substantial, with scores falling at approximately two-thirds of a standard deviation below age-defined means [46]. In a second cohort of 178 infants with complex congenital heart disease, early postoperative seizures had occurred in 11 %, and all seizures were EEG only. Outcome assessment was performed at 1 year in 114 of 164 survivors. There was a nonsignificant trend toward worse outcome in patients with postoperative seizures, and this difference was significant in a subgroup with frontal-onset seizures [47]. A follow-up study reported neurodevelopmental testing among 132 of 151 survivors at 4 years. Multivariate analysis included clinical and operative factors, and the presence of postoperative seizures (which were all EEG-only seizures) was associated with worse executive function and impaired social interactions/restricted behavior but no difference in cognition, language, or motor skills [48]. In a study of 161 neonates with congenital heart disease who underwent EEG monitoring, mortality was higher among neonates with than without seizures (38 % vs 3 %) [41].

Although electrographic seizures have been associated with worse outcomes, further study is needed to determine whether electrographic seizure identification and management improves neurodevelopmental outcomes among children with congenital heart disease.

## Guidelines

The ACNS's Guideline on Continuous EEG Monitoring in Neonates lists congenital heart defects that require early surgery using cardiopulmonary bypass as a clinical

scenario conferring a high risk for seizures in which EEG monitoring should be considered [42]. As described above, one study which implemented this recommendation for 161 of 172 eligible neonates identified electrographic seizures in 13 neonates (8 %) [41].

## Seizures in the Neonatal Intensive Care Unit

### Seizure Incidence

Studies of neonatal seizures have been limited by the difficulty diagnosing seizures in this age group. When outward clinical signs of seizures are present, they are often subtle and difficult to distinguish from other movements in critically ill newborns, such as clonus or benign myoclonus. Additionally, even if clinical signs are initially present, administration of antiseizure medications can result in electroclinical dissociation: EEG-only seizures may persist despite resolution of outward clinical signs. Furthermore, in the majority of neonatal seizures, there are no clinical signs. In a study of 393 neonatal seizures recorded on EEG, only 21 % of seizures were accompanied by clinical signs, while 79 % were "occult" or subclinical [49]. These findings have since been replicated in multiple intensive care nurseries and with multiple neonatal seizure etiologies. Thus, while population-based studies of neonatal seizures relying on clinical signs describe an incidence of 1–5 per 1000 live births, these are likely underestimates.

More recent work has employed the gold standard of EEG monitoring to diagnose seizures in high-risk neonates. A recent multicenter cohort study prospectively applied EEG monitoring to 90 term neonates with hypoxic-ischemic encephalopathy during therapeutic hypothermia [50]. In this cohort, 48 % of neonates had seizures on EEG monitoring [50], in agreement with prior smaller studies that also used EEG to define incidence of seizures among neonates with hypoxic-ischemic encephalopathy [51]. Increasingly, seizures are also reported in preterm newborns: a cohort of 95 preterm neonates born at 24–30 weeks' gestation found 48 % had seizures on aEEG [52].

### Seizure Risk Factors

The vast majority of neonatal seizures are symptomatic of acute injury or illness. A 2011 World Health Organization Guideline on Neonatal Seizures summarized available evidence regarding the prevalence of seizures in at-risk neonates. Among neonates with seizures, 38–48 % have hypoxic-ischemic encephalopathy, 3–8 % have hypoglycemia, 2–9 % have hypocalcemia, and 5–50 % have central nervous system infections [53]. A study using MRI to identify etiology in a cohort of neonates with seizures similarly found hypoxic-ischemic encephalopathy and stroke were the most common etiologies [54]. Thus, neonates presenting with seizures should always be evaluated for acute brain injury and systemic illness; very few neonates with seizures have a neonatal onset epilepsy.

Among neonates with brain injury, some groups are at particularly high risk for seizures. As described above, about half of neonates receiving therapeutic hypothermia for hypoxic-ischemic encephalopathy have electrographic seizures identified when EEG monitoring is performed [50, 51]. When acute ischemic stroke is identified in neonates, it is almost always in the setting of seizures [55]. However, the true incidence of seizures in perinatal stroke is unknown, as many strokes are only diagnosed in retrospect, without recognition of signs in the perinatal period. Intracranial hemorrhage is a relatively common cause of neonatal seizures, present in up to 18 % of patients [56]. As discussed in the section above, neonates with congenital heart disease are also at risk for seizures.

## Continuous EEG Monitoring Duration

For the majority of neonates, EEG monitoring should be continued for a minimum of 24 h [42]. Across heterogeneous populations, the majority of seizures begin within 24 h of EEG monitoring onset [42]. Thus, 24 h is often adequate when using EEG monitoring to screen for EEG-only seizures. There are no published data to guide duration of recording after neonatal seizures are identified and controlled, and the common practice of continuing EEG monitoring until achieving 24 h of seizure freedom is largely based on convention.

Longer EEG monitoring durations may be indicated in select patients. Notably, neonates receiving therapeutic hypothermia for hypoxic-ischemic encephalopathy remain at risk for seizures beyond the first 24 h of life. A case series of 26 neonates undergoing EEG monitoring throughout therapeutic hypothermia for hypoxic-ischemic encephalopathy identified electrographic seizures in 66 %. Of those neonates with seizures, 47 % had seizure onset after the initial 24 h of age [51]. Similarly, 19 % overall had temporary resolution of seizures for over 24 h on EEG monitoring, only to have seizures return at a later point during monitoring. Overall, approximately 5 % of neonates receiving therapeutic hypothermia for hypoxic-ischemic encephalopathy are described as having seizures onset after hypothermia is complete during the return to normothermia [50, 51]. For these reasons, it may be appropriate to continue EEG monitoring beyond 24 h and up to the entire period of hypothermia and rewarming, particularly if the initial EEG background is abnormal.

## Outcome

Outcome data is available from series of neonates with seizures due to specific causes, as recently reviewed.[57]. While these studies do not allow outcome comparisons between those with and without seizures, they offer useful data regarding outcomes. The best prognosis is among newborns with seizures symptomatic of an acute metabolic derangement, such as hypoglycemia. In these cases, death is quite rare, and neurodevelopment is often normal. Conversely, neonates with seizures and hypoxic-ischemic encephalopathy have historically had mortality rates above 25 %,

with moderate or severe neurodevelopmental impairments in the majority of those who survive. Overall, preterm babies with seizures have worse outcomes, though further research is needed to fully define this risk. Following neonatal seizures, the majority of babies do not develop subsequent epilepsy. Because neonatal seizures are usually symptomatic, as the acute period of injury passes the seizures often resolve. Multiple studies have reported associations between electrographic seizures and worse clinical outcomes [58–61] or worse MRI-evident brain injury [62].

There is uncertainty regarding the impact of neonatal seizures on neurodevelopmental outcome. Because the majority of neonatal seizures are symptomatic of brain injury, studies of long-term outcomes struggle to delineate the relative contributions of seizure versus underlying condition toward later neurodevelopmental outcomes. While it is clear that the underlying etiology is often the most important factor, there is debate about how much seizures may produce secondary brain injury that adds to the risk for later neurodevelopmental impairment. Several studies have indicated that electrographic seizures or SE are associated with worse outcomes even after adjusting for variables thought to reflect acute brain injury severity [63, 64]. A prospective study of 77 term neonates with hypoxic-ischemic encephalopathy found that full-scale intelligence quotients at 4 years were lower among subjects with more severe seizures as neonates even after adjusting for severity of initial injury on MRI [63]. Similarly, in a longitudinal study of 129 children with neonatal encephalopathy, neonatal SE remained associated with increased risk for subsequent epilepsy (hazard ratio 35.8) even after adjusting for the initial degree of clinical encephalopathy and for severe/near-total brain injury on MRI [64]. A study of 106 neonates reported that SE was associated with increased risk for adverse neurologic outcomes (odds ratio 20.3) and postneonatal epilepsy (odds ratio 6.5) even within a multivariable model including cerebral ultrasound findings [65]. Finally, a study of 218 term neonates with neonatal encephalopathy reported that the absence of aEEG-identified seizures was associated with better 18-month outcome (odds ratio 0.46) in a multivariable analysis including hypothermia group, birth weight, Apgar scores, and encephalopathy grade [66].

## Clinical Practice and Guidelines

Given the data above, there is increasing use of conventional EEG monitoring or aEEG in neonatal ICUs. Surveys within the United States and internationally indicate 60–90 % of neonatologists have access to EEG or aEEG, and these modalities are often used for seizure identification and management [67–69]. Concerning, despite widespread aEEG use, many neonatologists report a lack of confidence in their ability to interpret aEEG [68].

The World Health Organization (WHO) identifies EEG as the most accurate method for diagnosis of neonatal seizures and notes EEG carries little risk. The WHO recommends EEG be used to confirm all clinical seizures in the neonatal period. Their guideline does acknowledge that not all settings will have the resources to adhere to this recommendation [53].

The ACNS has provided a detailed guideline on EEG monitoring in neonates [42]. The guideline recommends EEG monitoring for all neonates with suspected seizures in order to confirm that clinical events are truly electrographic seizures. Further, it recommends that EEG monitoring should continue for at least 24 h in an effort to capture clinical events of unclear etiology or until multiple typical events are captured and determined not to be seizures. If seizures are identified, the guideline recommends that EEG monitoring should be continued in order to assess response to treatment until the neonate has been seizure-free for 24 h. In addition to EEG monitoring for neonates with suspected or known seizures, the guideline suggests EEG monitoring be used to screen for EEG-only seizures in neonates known to be at high risk, such as those with acute neonatal encephalopathy, with cardiorespiratory risk factors for brain injury (such as requiring extracorporeal membrane oxygenation or presence of congenital heart disease), with stroke, or other neurological conditions.

## Quantitative EEG

Neonatal intensive care units increasingly use bedside qEEG trends for near real-time diagnosis of neonatal seizures. In particular, aEEG is widely used. As discussed above, observing for clinical signs may fail to diagnose many neonatal seizures, yet many centers do not have access to conventional EEG monitoring, and even in centers with EEG monitoring availability, it is seldom reviewed continuously. Thus, aEEG is employed. Variations of aEEG include: (1) recording of full-array conventional EEG, processed by software at the bedside to be displayed as aEEG in real time, (2) postrecording processing of conventional EEG to be displayed as aEEG to facilitate efficient review of recordings by encephalographers, and (3) reduced array (typically single- or dual-channel) EEG displayed at the bedside as aEEG. Many aEEG devices are marketed to and used by neonatologists independent of encephalographer involvement.

aEEG is generated by selecting a limited number of channels of "raw" or source EEG, which is then processed through proprietary software algorithms to generate a time-compressed trend display of the amplitude of the EEG signal. aEEG may be generated from any channel recorded as part of conventional cEEG. More often, neonatal intensive care units use stand-alone aEEG machines that rely upon one to three channels of EEG (recorded through four scalp electrodes plus one ground electrode). Electrodes are typically placed at the central and parietal locations, for channels recording from the left hemisphere, right hemisphere, and cross-hemispheric (Fig. 3). Signals recorded from these limited channels of EEG is then filtered to remove high-frequency activity that is more likely to be artifact (typically >60 Hz). The waveforms are rectified, smoothed, and then displayed as graphical output with amplitude represented logarithmically on the y-axis and time represented in compressed fashion on the x-axis. aEEG is most commonly used for neonatal seizure detection. This relies on the principle that seizures often are characterized by an increase in waveform amplitude. On aEEG, this is reflected as a transient elevation of signal along the y-axis, as activity temporarily is higher in amplitude. aEEG does

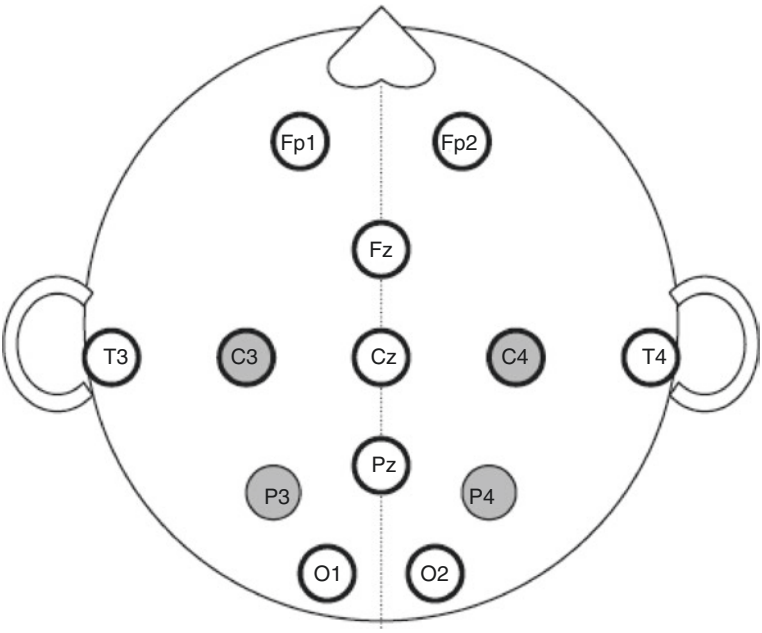



**Fig. 3** Neonatal EEG electrode placement. *Open circles* represent typical electrode placement in conventional EEG; *shaded circles* represent typical electrode placement for aEEG

not incorporate information about frequency or power; it only reflects amplitude. Whereas typically displayed conventional EEG might show 15 s of EEG on a single screen, typical aEEG displays 3–6 h on a single screen. Newer systems provide the option of displaying simultaneously the "raw" EEG signal for a selected time within the longer aEEG period on the same screen (Fig. 4).

The sensitivity and specificity of aEEG for seizure detection have been well documented in term neonates, particularly in those with hypoxic-ischemic encephalopathy. Among published data, there is some variation in reported accuracy that likely reflects both differences in aEEG methods used and in the expertise of the aEEG reviewers in individual studies. For example, aEEG systems which allow simultaneous review of multiple channels, and of raw EEG alongside aEEG, have better accuracy. Overall, aEEG has limited sensitivity for detecting individual seizures, with over half of seizures present on conventional EEG missed when relying on aEEG alone. Seizures are more likely to be missed on aEEG if they are low amplitude, are brief in duration, or occur in a location away from the limited electrodes used [70]. Furthermore, aEEG may overdiagnose seizures by as much as 50 % [71]. However, because aEEG does identify some seizures, it has reasonable sensitivity as a screening tool for determining whether a neonate has had *any* seizures. In this capacity, aEEG may identify up to 85 % of neonates having seizures when interpreted by expert users [72]. While aEEG does not have the accuracy of the gold standard, conventional EEG monitoring, it is superior to clinical observation alone in diagnosing neonatal seizures.

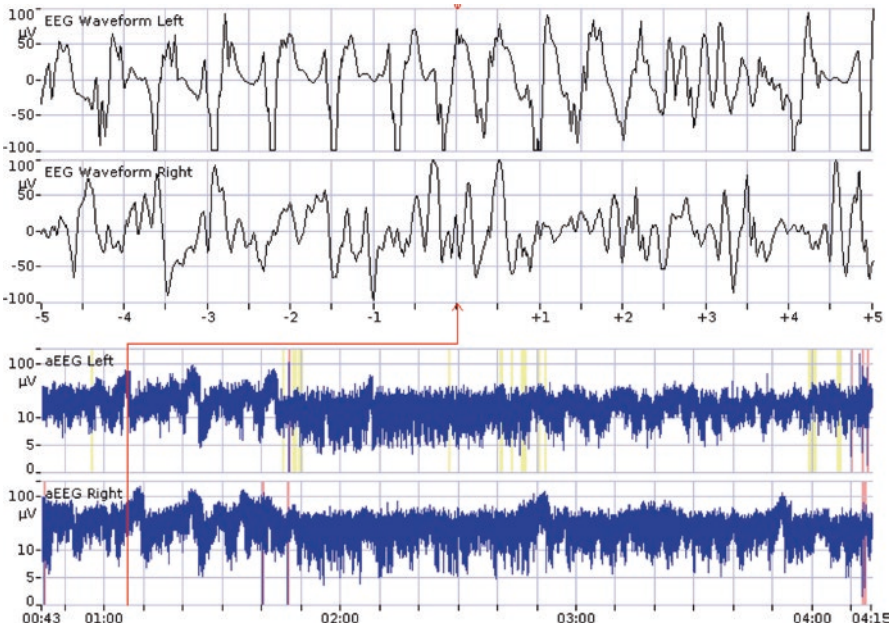



**Fig. 4** Example of amplitude-integrated EEG (*bottom*) with concurrent raw EEG (*top*). The arches on amplitude-integrated EEG represent EEG-only seizures

Ideally, aEEG is used in combination with conventional EEG monitoring. This allows the most complete data to be obtained through recording full-array conventional EEG, which can be reviewed by encephalographers to provide definitive information regarding seizures, localization, and background features, while concurrently aEEG can be displayed at the bedside allowing the care team to continuously visualize the overall trend in real time. With practice, nurses and non-neurologists can monitor aEEG in real time for early identification of changes in brain activity concerning for seizure, and subsequently, targeted review of the EEG by an encephalographer can then confirm whether or not aEEG changes are seizures. While new conventional EEG monitoring systems have this capacity, implementing dual aEEG and conventional EEG into practice requires coordination among the neonatal and neurology teams.

## Conclusions

Seizures in critically ill children and neonates are common. With appropriate EEG monitoring supplemented with qEEG analysis, many of seizures can be identified. EEG monitoring for 24–48 h is often appropriate to identify seizures, and an additional 24 h of monitoring should be considered after control of seizures. Detecting these seizures may be important, as there is growing evidence that the seizures are associated with worse outcomes, independent of the underlying etiology. Hopefully in the near future, data will emerge that demonstrates that optimally treating these seizures improves outcome.

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# Status Epilepticus Classification

4

David Gloss

**Contents**



## Introduction

Classifications of epileptic seizures and epilepsies have been developed by the International League Against Epilepsy (ILAE). Since the early classifications, there has always been a recognition that the classification scheme will change as more is learned about these disorders. The ILAE has also classified status epilepticus (SE), and this classification, too, has evolved over the last few decades. However, the latest ILAE classification of epilepsy from 2010 does not talk discuss SE, although it

D. Gloss
Geisinger Health System, 100 N Academy Drive,
Danville, PA 17822, USA
e-mail: davy.gloss@gmail.com



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**Table 1** Classification of status epilepticus

| |
|---|
| 1. Epilepsia partialis continua (EPC) of Kojevnikov |
| (a) Rasmussen syndrome |
| (b) Focal lesions |
| (c) Inborn errors of energy metabolism |
| 2. Supplementary motor area status epilepticus |
| (a) Individual tonic motor seizures, without impairment of consciousness |
| (b) Tonic motor seizures which involve into generalized seizures, with impairment of consciousness |
| 3. Aura continua |
| 4. Dyscognitive focal status epilepticus |
| (a) Mesial temporal origin |
| (b) Neocortical origin |
| 5. Tonic-clonic status epilepticus |
| 6. Absence status epilepticus |
| (a) Typical and atypical absence status epilepticus |
| (i) Absence status epilepticus |
| (ii) Atypical absence status epilepticus |
| (iii) Absence status epilepticus with focal features |
| (iv) De novo absence status epilepticus in the elderly |
| (b) Myoclonic absence |
| 7. Myoclonic status epilepticus |
| (a) Negative myoclonic status epilepticus |
| 8. Tonic status epilepticus |
| 9. Subtle status epilepticus |
| 10. Nonconvulsive status epilepticus |
| 11. Febrile status epilepticus |

does address the definition of seizures [1]. The penultimate report from 2006 on the classification of epilepsy does discuss SE [2]. The older document will be used in this chapter with those definitions of SE [3], but with updated language to reflect the newer terminology related to seizures. The older document divided SE into nine areas. There are some additions to the 2006 classification system that have been included in this chapter, since new information has come out in the last 10 years. Please see Table 1 for a classification of SE.

The 2010 ILAE terminology excludes some terms as they may lead to confusion and were not clearly defined. Some examples of such terms are idiopathic epilepsy, symptomatic epilepsy, and complex partial seizure. These have been replaced with terms that are meant to be more clearly defined. As the newer terms appear in the text, where there might be confusion, they will be concretely defined. In addition, the 2006 ILAE report on the classification of SE gives sparse details on some of the types of SE. When the details are so sparse as to be potentially misleading, additional details have been added, and they are identified as not appearing in the ILAE classification system.

## Definition of Status Epilepticus

The definition of SE is an area of controversy. The 1993 ILAE guidelines for epidemiologic studies define SE as a seizure lasting more than 30 min or more than one epileptic seizure where function has not been regained for more than 30 min [4]. In certain animal models, 30 min is the time in which there is neuronal injury, so the 30-min time does make certain sense. Unfortunately, none of the American Academy of Neurology Class I trials on SE use the 30-min criteria for defining SE. The Veterans Affairs SE Cooperative Study, for example, used 10 min as the inclusion criteria. Others have suggested other times, such as 15 min, 5 min, etc. [5]. Moreover, another study found no significant differences between episodes of SE lasting more or less than 30 min [6]. An operational SE definition has been suggested in which SE is treated as if it were SE after 5 min, even if it cannot be formally diagnosed until 30 min.

## Classification Scheme

The various types of SE that are recognized in the 2006 ILAE classification are discussed in the section below. As noted above, additional information is provided to add clarity where needed.

### Epilepsia Partialis Continua

Epilepsia partialis continua (EPC) is a combination of focal seizures with ongoing twitching. The site of twitching represents the area of the motor cortex from where the seizure originates. There are three subtypes of EPC.

#### Rasmussen Syndrome

EPC with Rasmussen syndrome has focal myoclonus and focal seizures emanating from the same hemisphere. There is variability regarding the presence of an EEG correlate of the myoclonic jerks. The jerks persist during sleep. Over time, the EEG shows progressive background slowing of the affected hemisphere.

#### Focal Lesions

Focal lesions such as tumors and dysplastic cortex can lead to seizures and EPC. The jerking seen with EPC affects the same area as the focal seizures, but it does not persist in sleep. There is often an EEG correlate. It can last for days to months. This type of EPC is also seen with nonketotic hyperglycemia.

#### Inborn Errors of Metabolism

EPC with inborn errors of metabolism have uni- or bilateral rhythmic jerks that persist in sleep, and they typically have an EEG correlate. These inborn errors of metabolism are the ones affecting energy metabolism, like myoclonic epilepsy with ragged red fibers (MERRF) or Alpers syndrome.

## Supplementary Motor Area

### With Preserved Consciousness

In this type of supplementary motor area (SMA) SE, there are recurrent focal tonic seizures with preserved consciousness. The individual tonic seizures occur every few minutes during wakefulness and sleep.

### With Impaired Consciousness

SMA SE can also result in secondarily generalized, bilateral, convulsive seizures. These can become repetitive asymmetric, tonic motor seizures with impairment of consciousness.

## Aura Continua

Aura continua is an episode with symptoms that depend on localization wax and wane, often for hours, without impairment of consciousness. A full seizure with alteration of consciousness does not occur. Symptoms may include a motor component, dysesthesia, painful sensations, or visual changes. Perhaps the most common form is limbic aura continua, which may include fear, epigastric rising sensation, or other limbic features that recur every few minutes for hours or longer. EEG correlation is variable.

## Dyscognitive Focal

Dyscognitive focal SE has recurrent focal seizures with impairment of consciousness or awareness leading to SE. There are two types.

### Mesial Temporal

Mesial temporal dyscognitive focal SE arises, as the name implies, from mesial temporal structures. It manifests as a series of dyscognitive focal seizures without clear return of consciousness between events. Electrographic onset can be unilateral or can alternate sides.

### Neocortical

The semiology of neocortical dyscognitive focal SE is unpredictable, as its manifestation depends on the cortical area involved. It can appear similar to absence SE or generalized tonic-clonic SE if arising from the frontal lobe. Persistent language or vision changes may occur if the SE arises from the temporal or occipital cortices, respectively.

## Tonic-Clonic

Tonic-clonic SE can appear as a primary generalized event from genetic and structural/metabolic generalized epilepsy. More commonly, however, this type of SE

evolves into bilateral, convulsive seizures from focal epilepsies. Sometimes is remains unilateral, providing a clue regarding site of onset. Tonic-clonic SE can occur as part of an acute event.

There are a few important features of tonic-clonic SE that are not specifically stated in the ILAE classification. (1) There is always profound impairment of consciousness. (2) There can be variable combinations of tonic, clonic, or both types of motor activity in an episode of SE. (3) It is important to note that at least focal-onset tonic-clonic seizures appear to be a dynamic state. As the SE continues to be untreated, the motor manifestations wane, until there are only subtle movements, termed subtle SE (discussed below). (4) Before the motor manifestations wane, there is a clear ictal EEG component that ends abruptly when the seizure ends. (5) If the patient does not fully return to baseline before the next tonic-clonic seizure starts, it is tonic-clonic SE.

## Absence

Absence SE, like absence seizures, is the term used for a particular type of SE in which the patient has reduced responsiveness and may appear to be staring. Often confused with other types of SE in which there is a paucity of motor activity, absence SE has typical clinical and EEG characteristics as discussed below. There are several types of absence SE.

### Typical and Atypical Absence

Typical and atypical absence SE is the term applied to several different types of SE that have a similar semiology. There are several subtypes of typical and atypical absence SE.

#### Typical

Typical absence SE is considered to be part of a genetic epilepsy with impairment of consciousness. The level of impairment is variable and may depend on the individual. About 20 % of patients have slight clouding of consciousness, about 60 % having a confusional state where they are typically calm but do not interact with their environment, and about 20 % with more severe impairment [5]. At times there are accompanying subtle jerks of the eyelids during the event. The EEG correlate is bilateral and symmetric, typically bifrontally predominant, spike or polyspike, and wave complexes occurring at a frequency of at least 2.5 Hz. This type of SE responds well to antiepileptic drugs (AEDs). Most commonly intravenous benzodiazepines will terminate the event.

#### Atypical

Atypical absence SE is more commonly encountered in patients with structural/metabolic (generalized symptomatic) epilepsy. There is a fluctuating level of consciousness. This fluctuating confusional state is different than typical absence SE, which usually has a certain consistent level of impairment. The ictal semiology is quite different than typical absence SE, because it can include tonic, atonic, myoclonic, or

lateralized phenomena. The EEG consists of spike and polyspike and wave complexes that are irregular and occur at a frequency of less than 2.5 Hz. These episodes of SE may recur, and they are not generally amenable to treatment with benzodiazepines. In patients with recurrent atypical absence SE, who have an underlying genetic epilepsy, valproic acid may be particularly helpful in reducing recurrences.

#### With Focal Features

Absence SE with focal features is typically encountered in frontal lobe localization-related epilepsy. There is impairment of consciousness, but the level of impairment may depend on the individual. The EEG typically demonstrates a bilateral ictal pattern, but it is asymmetric. Later in the episode, the EEG may start to look like other types of absence SE. Treatment responsiveness varies with the individual.

#### Late-Onset De Novo

Late-onset de novo absence SE occurs in older adults that have an underlying toxic or metabolic derangement leading to seizures. Such patients can have repeated episodes with recurrent toxic/metabolic problems causing further episodes of SE. The preferred treatment is prevention of the underlying toxic/metabolic cause.

### Myoclonic Absence

Myoclonic absence SE has proximal, predominantly upper extremity myoclonic jerks that are synchronized to the 3 Hz spike and wave pattern seen on the EEG. It can last for hours or days and is most commonly refractory to treatment with AEDs.

## Myoclonic

In myoclonic SE there is irregular, typically bilateral myoclonic jerking which persists for hours without impairment of consciousness. It is usually seen in conjunction with Dravet syndrome, myoclonic-astatic epilepsy, nonprogressive myoclonic epilepsy in infancy (especially Angelman syndrome), and incompletely controlled juvenile myoclonic epilepsy. While not specifically mentioned in the ILAE terminology report, it is also seen with Lennox-Gastaut syndrome and epilepsy with myoclonic absences.

The ILAE report does not mention negative myoclonic SE, such as may be seen in epileptic encephalopathy with continuous spike-wave during slow wave sleep. In this kind of SE, a limb, often one of the upper extremities, becomes paralyzed but continues to have brief atonic episodes. There can be alteration of consciousness with these events and that may persist after the episode ends.

## Tonic

With tonic SE patient has recurrent, brief tonic spasms that can continue for hours. Most typically, if the patient is lying down, the neck and arms flex. It can occur with both structural/metabolic and genetic epilepsies; with structural/metabolic epilepsies the duration can be longer than hours.

**Table 2** Diagnostic criteria for NCSE

| |
|---|
| 1. In patients without a known epileptic encephalopathy |
| A. Rhythmic spikes, polyspikes, sharp waves, sharp and slow wave complexes of > 2.5 Hz, OR |
| B. Rhythmic spikes, polyspikes, sharp waves, sharp and slow wave complexes of < 2.5 Hz or rhythmic delta/theta activity of > 0.5 Hz with one or more of the following: |
| (i) Intravenous antiepileptic drug causes improvement of both clinical status and EEG |
| (ii) During EEG pattern above, there is subtle clinical ictal phenomena |
| (iii) Increase in voltage and change in frequency at onset, change in frequency by > 1 Hz and/or change in location/spread during event, or change in voltage or frequency on termination of the event |
| 2. In patients with known epileptic encephalopathy |
| A. Increase in prominence or frequency in the features mentioned above, with both an observable change in clinical status and a change from baseline at the same time, OR |
| B. Intravenous antiepileptic medication causes improvement of both clinical status and EEG |

## Subtle

Subtle SE is of the end result of uncontrolled tonic-clonic SE, with focal or multifocal myoclonias, coma, lateralized periodic discharges (previously called periodic lateralized epileptiform discharges, PLEDs), and a slow suppressed background EEG. The myoclonias may not be epileptic in nature. The ILAE guidelines do not provide details of the myoclonias, but they typically occur in the form of subtle twitches of the trunk or extremities or as nystagmus. The EEG has an epileptic pattern that includes generalized but asymmetric bilateral rhythmic discharges. As the subtle SE continues, eventually there is complete loss of the motor component, and there is only ongoing EEG epileptic activity. This is often also called nonconvulsive status epilepticus (NCSE).

## Nonconvulsive

NCSE is not formally included as part of the ILAE classification, but it is probably more frequently encountered in patients undergoing continuous EEG (cEEG) monitoring in an intensive care unit than all other forms of SE. While it can appear as the end stage of tonic-clonic SE, it is far more frequently found with patients with unexplained changes in mental status. While this is an area of ongoing investigation, frequently quoted diagnostic criteria of NCSE are presented in Table 2 [7].

## Febrile

Febrile SE was included in the 1993 ILAE report, but was not mentioned in the 2006 report, where the SE is explicitly classified. It is included here for completeness. Febrile SE is defined as 30 min of continuous seizure activity or intermittent seizure activity lasting at least 30 min without return to baseline consciousness in

the setting of a febrile illness. The febrile illness is not due to a central nervous system infection and there is no acute electrolyte imbalance. The child is older than 1 month of age and does not have a history of previous febrile seizures.

**Conclusions**

The ILAE has provided a framework for the classification of SE that reflects the classification of seizures. This provides a reasonable way to understand this complex condition and describe it in a way that can be universally understood. It is important to appreciate that with the evolution in the understanding of SE, particularly as new information about NCSE becomes available, this classification will change to incorporate additional aspects of pathophysiology, genetics, semiology, response to treatment, and prognosis.

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# Criteria for Continuous EEG Monitoring

5

Keith E. Dombrowski

**Contents**



## Introduction

The use of continuous EEG (cEEG) monitoring has grown significantly over the last 15 years. Monitoring for nonconvulsive seizures (NCS) and nonconvulsive status epilepticus (NCSE) is currently driving most cEEG utilization, but other uses are recognized and are becoming common indications. As with other areas in health care, the growth of EEG and information technology (IT) is increasing the capabilities of this century-old technology. As cEEG monitoring evolves, there is a small but growing base of evidence on how to use it. With time, that evidence base will become larger and provide better guidance on the most efficient and effective way to monitor patients. At this time though, institutions must rely on consensus statements, expert opinion, and their own resources to determine how cEEG will be deployed in their practice. Many institutions develop their own guideline such as the truncated example seen in Table 1 from Duke University Hospital. It is critical that any such service line has some form of guideline or service agreement to direct the use of this important resource.

K.E. Dombrowski, MD
Department of Neurology, Duke University Medical Center, Durham, NC 27710, USA

Durham VA Medical Center, Durham, NC, USA
e-mail: Keith.dombrowski@duke.edu



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**Table 1** Duke University Hospital Guidelines for the use of continuous video/EEG monitoring (truncated)

| |
|---|
| *Management of status epilepticus* |
| 1. In patients that present with clinical status epilepticus and do not have an improving mental status after treatment, a minimum of a routine EEG should be obtained |
| 2. In patients with persistent alteration or fluctuation in mental status 1 after clinical seizures have stopped, continuous EEG monitoring is indicated |
| (a) If no ictal or interictal abnormalities are noted after 24 h, cEEG monitoring can be discontinued |
| (b) If seizures or epileptiform abnormalities are seen during the first 24 h, monitoring should be continued for an additional 24 h |
| *Monitoring for NCSE* |
| 1. Patients with altered mental status of any cause, particularly those in coma or with a waxing-waning exam, should undergo a minimum of 24 h of cEEG monitoring |
| (a) For those without known neurologic injury, consider extending the monitoring period to 48 h |
| *Monitoring for seizures following cardiac arrest* |
| 1. CEEG monitoring should be started on all post-cardiac arrest patients undergoing therapeutic hypothermia as soon as possible |
| (a) Monitoring should continue for 24 h after normothermia is reached |
| 2. CEEG monitoring should be considered in comatose cardiac arrest patients for up to 48 h in those who are not undergoing therapeutic hypothermia |
| 3. Though there is no data to guide treatment, the presence of ictal activity or status epilepticus should be treated like other types of seizures beginning with phenytoin or levetiracetam, particularly in those receiving therapeutic hypothermia |
| 4. Consider SSEPs within 24 h of cardiac arrest for any patient that has not regained consciousness within 2–3 h of return of spontaneous circulation |
| *Monitoring for seizures in patients with traumatic brain injury* |
| 1. All patients with TBI who have a Glasgow Coma score (GCS) of <9 or fluctuating mental status should receive 24 h of cEEG monitoring within 24–48 h of admission |
| *Monitoring of patients with subarachnoid hemorrhage* |
| 1. For all patients with subarachnoid hemorrhage and a GCS <9, cEEG monitoring is indicated for at least 24 h |
| 2. Currently, monitoring for ischemia from cerebral vasospasm is not indicated |

## Criteria for Starting Continuous EEG Monitoring

The most common reason for initiating a cEEG study in the intensive care unit (ICU) is for the detection of subclinical or NCS. CEEG is the only type of monitor capable of detecting these types of seizures and, therefore, uniquely suited to this job. The most important population to monitor are those patients who are encephalopathic and were known or strongly suspected to have experienced generalized convulsive status epilepticus (GCSE). The time to recovery of a normal level of consciousness varies greatly, but if the patient does not appear to show improvement within 30 min, cEEG monitoring will almost certainly be needed. Multiple studies in adults and

children have shown high rates of NCS (43–57 %) and NCSE (13 %) after clinical seizure activity has stopped with or without the use of abortive medications [1, 2]. In clinical practice, these patients should take precedence over others that will require cEEG monitoring. If cEEG resources are limited and monitoring cannot be initiated promptly, it may be necessary to transfer the patient to an institution with these capabilities. If cEEG is not available, an emergency 30 min EEG may be helpful, but it is likely to not meet the needs of the patient. The American Clinical Neurophysiology Society (ACNS) and Neurocritical Care Society recommend initiating the study as soon as possible and within 60 min, if possible [1, 3]. CEEG monitoring will be required for multiple days or longer if NCS or NCSE is detected after GCSE. Though the technique for monitoring and review does not change, the purpose of cEEG is now directed at terminating seizure activity and ensuring that it does not recur.

Refractory (RSE) and super refractory status epilepticus (SRSE) require IV anesthetic agents such as midazolam, propofol, and pentobarbital. Once RSE or SRSE has been diagnosed and IV anesthetics started, cEEG monitoring is required not only to monitor for the termination of seizure activity but also to titrate to the desired depth of anesthesia whether it is seizure, burst, or total EEG suppression. During the withdrawal of IV anesthetics, cEEG monitoring is needed to ensure that NCSs do not reemerge. In SRSE, the rate of seizure reoccurrence is unfortunately high (greater than 50 %), and close monitoring is necessary to confirm that treatment has been effective [4]. If monitoring is anticipated to last for many days, different tools could be used if they are available. Computed tomography (CT) and magnetic resonance imaging (MRI) compatible electrodes, like disposable plastic, subdermal needle, and wire electrodes, may be used in place of non-disposable gold-plated electrodes if neuroimaging is needed. Quantitative EEG (qEEG) software can be used to facilitate review of long periods of data particularly if a reproducible seizure pattern is found.

CEEG for the detection of seizure activity should not be limited to those with GCSE. In the setting of supratentorial brain injury, many encephalopathic patients are at risk for NCSs. Though clinical seizure activity noted prior to the onset of encephalopathy increases the risk, the rates of detecting subclinical seizure activity in this population remain relatively high. The patients most likely to experience NCS include those with prior epilepsy, intracranial hemorrhage (ICH), moderate-severe traumatic brain injury (TBI), central nervous system (CNS) infections, hypoxic-ischemic-related injury, and brain tumors and those who have undergone a recent neurosurgical procedure [1]. If there is suspicion for NCS, early application of cEEG is critical to identify and treat seizures as they become refractory to abortive agents without prompt recognition and treatment. Though little outcome data is available, it is likely that detection and treatment of seizures may reduce any secondary brain injury that may occur as a result of the NCS [5]. As with patients after GCSE, routine EEG will be inadequate. Therefore, patients with known brain injury and an unexplained encephalopathy should be considered “high risk” and undergo cEEG monitoring as soon as possible.

Though high rates of NCS and NCSE are well recognized in those with brain injury and encephalopathy, acutely ill medical and surgical patients with altered

mental status may also be at high risk for seizures. Many acute illnesses, especially sepsis, with single or multi-organ failure and encephalopathy are associated with NCS and NCSE. Similarly, patients who are found to have epileptiform patterns, such as lateralized or generalized periodic discharges, on routine EEG are also at high risk for seizures. Therefore, in these cases cEEG should be strongly considered if resources are available [1, 6].

CEEG has proven critical in the ICU for spell characterization. Similar to studies performed outside the ICU, characterizing paroxysmal events is a common use for cEEG. Stereotyped motor movements presumed to represent seizure are a frequent request for a routine EEG. However, cEEG with audio and video has the advantage of detecting multiple events over several hours and is crucial for determining the etiology of these events. Many such movements are seen that resemble seizure activity but are not epileptic in nature, including clonus, tremors, and intermittent posturing from herniation. This is a common and expected use for cEEG monitoring. When monitoring for spell characterization, capturing several events is encouraged to properly define their etiology and determine their clinical significance. However, once the desired events have been captured, monitoring may no longer be needed.

Routine EEG has been used for several decades as a prognostication tool, particularly after cardiac arrest, but cEEG is becoming useful for this purpose as well. Though there is no evidence as of yet to suggest that cEEG would necessarily be more helpful than a routine study, compelling information has been gained from experience with cEEG monitoring. In most patient populations studied, a lack of EEG reactivity in the absence of significant sedation is consistently associated with a poor prognosis [1, 6]. EEG reactivity has been defined as a change in background frequency and/or amplitude when an external stimulus is applied [6, 7]. EEG reactivity is best determined using a standardized stimulation protocol, but a combination of auditory and tactile stimulation is probably all that is needed in most circumstances. The association between poor prognosis and a lack of reactivity is best documented in comatose post-cardiac arrest patients, but it is present in those with TBI, SAH, and sepsis as well. Though less well studied, a wide range of other prognostic findings can be found during cEEG monitoring. In cardiac arrest, burst suppression patterns are associated with a poor outcome, whereas a continuous reactive record is associated with a good outcome. In sepsis, the appearance of lateralized periodic discharges (LPD) and seizures may be associated with a poor outcome, but this association is less robust [1, 6, 8].

CEEG is also commonly used to measure the depth of anesthesia in circumstances outside of RSE. Refractory intracranial hypertension may require titration of anesthetics to burst suppression. Reducing EEG activity to that of burst suppression correlates well with maximal reduction in cerebral metabolic oxygen ($CMRO_2$) demand, thereby decreasing cerebral blood volume. The anesthetics can be titrated to a desired intracranial pressure (ICP), but monitoring the depth of anesthesia is important for avoiding dose-dependent side effects. Treatment to total EEG suppression does not correlate with improved ICP control but risks over treatment. In many institutions, pentobarbital remains the agent of choice for controlling

refractory intracranial hypertension. As serum levels do not correlate well with either effectiveness or toxicity, cEEG is required to titrate the effective dose of pentobarbital. Avoidance of electrocerebral inactivity may reduce the possibility of causing cardiac suppression and other harmful side effects including a gastrointestinal ileus and hypothermia. Though there may be alternatives to cEEG monitoring such as Bispectral index, familiarity with these modalities in the ICU is limited, and the available data to promote its use is sparse [9]. QEEG processing may assist in rapid review but requires the same equipment and resources as standard cEEG monitoring.

Throughout its development, cEEG has functioned chiefly as a seizure detector and secondarily as a neuromonitor. It provides information on a patient's level of sedation and can reveal global or focal insults when imaging is unavailable and the clinical exam is unhelpful. A more recent and novel use for cEEG is the detection of cerebral ischemia [10]. Developments in quantitative trending tools now allow EEG to be a sensitive, real-time detector of cerebral ischemia and other forms of secondary brain injury. Though currently feasible with the aid of qEEG tools, the evidence base for cEEG in this role is limited. CEEG can provide data on the development or worsening of slowing or suppression suggestive of ischemia. However, given that slowing and suppression are not specific for ischemia, EEG should be used in combination with other data including imaging, transcranial ultrasound, brain parenchymal oxygen monitors, or cerebral microdialysis. This function of cEEG monitoring is also the most difficult to perform effectively and should only be used when an EEG laboratory is able to support it. Very frequent or real-time review is needed to relay information in a time frame that will allow intervention. Other options include training bedside providers to interpret qEEG trends. As this is a developing role, this should not be considered a routine use for cEEG in most institutions [1].

## Duration of Continuous EEG Monitoring

The duration of cEEG monitoring is determined by the indication and goals of performing the study. CEEG started for spell characterization, in many instances, can be a short recording as long as the events of interest are satisfactorily captured. On the other hand, cEEG for ischemia monitoring will need to continue for a few days during the time when the patient is at highest risk for neurologic deterioration such as vasospasm in SAH. For determining prognosis in the setting of hypoxic-ischemic injury, there is no clear duration for EEG monitoring. Many institutions will perform cEEG during therapeutic hypothermia or targeted temperature management both to detect NCS as well as to assist in prognostication. This monitoring will often last for 3 or 4 days. If the study is restricted to assisting in prognostication, cEEG may not be necessary. If adequate samples of both baseline and post-stimulation EEG can be captured, intermittent routine EEGs are a reasonable alternative.

When monitoring for NCS, the most common use of cEEG, the proper length of an EEG study is less clear. For patients with RSE on continuous IV anesthetics,

monitoring will typically be required until they are off of the infusion for at least 24 h. If the patient has been on IV anesthetics for several days or has SRSE, the duration of monitoring will often need to be a few days after anesthetic agents have been stopped. Due to either active metabolites (i.e., midazolam) or the volume of distribution (i.e., propofol), the effects of the drugs may be seen long after the infusion is stopped. This is a principle called context sensitive half time. In this circumstance, the patient effectively remains on the anesthetic until those effects have dissipated. The duration of this period is unpredictable and depends on many factors including age, renal and hepatic function, and temperature. In cases of RSE and SRSE, monitoring will need to continue until it is deemed safe to stop monitoring by the treating provider.

For both adults and children undergoing monitoring for NCS without known GCSE, the minimum duration of cEEG monitoring should be at least 24 h and perhaps 48 h in the pediatric population [1, 11]. It is likely that a single 30 min or 60 min study will not accurately identify a patient who is experiencing intermittent NCS. Increasing the duration of monitoring will almost certainly increase the likelihood of detecting seizures and epileptiform discharges if they are present. However, it has been difficult to determine how long the cEEG monitoring must be. Most studies have found 80–85 % seizure detection in the first 24 h and a yield of over 90 % when monitoring is extended to 48 h [2, 12]. Most of this data comes from a diverse neurocritical care population with a variety of different pathologies such as TBI, SAH, stroke, and CNS infections. No one population has been studied in large enough numbers to make a disease-specific monitoring duration recommendation. However, recent studies are beginning to provide some guidance on the duration of cEEG monitoring. For example, the first 30 min epoch of EEG data can provide a great deal of information and may predict which patients are likely to have seizures and those that will not. A recent study found that the majority of seizures detected in a neuro-ICU population are found within the first 30 min [12]. When seizures are not seen during this time, the background of the EEG can be predictive of seizures as well. With the possible exception of patients with known epilepsy, those with epileptiform findings in the first 30 min may be more likely to develop NCS than those without [12–15]. Similarly, the patient is much less likely to have NCSs if the first 2–4 h of EEG data shows only diffuse slowing without evidence of epileptiform discharges [12–14]. In a recent study of a large neuro-ICU population, the temporal dynamics of seizure risk were examined and showed a precipitous drop in seizure occurrence based on early EEG features [12]. When no epileptiform features are found within just 15 min, the likelihood of detecting a seizure falls below 10 %. With epileptiform features, the likelihood of detecting seizures drops below 10 % at 7 h.

Though the growing body of literature has been helpful to determine the adequate length of a cEEG study, many questions still remain. How long should EEG monitoring be when a patient's brain injury is in evolution or the susceptibility to further insult remains high for several days. Examples of this include vasospasm in SAH or worsening ICP in TBI or ICH. In these circumstances, there is susceptibility to further brain injury for several days and the likelihood of subsequent seizures could be high as well. Therefore, it may be wise to monitor a particularly tenuous

patient for a longer period of time even if seizures are not seen early in the monitoring period.

**Conclusions**

Although clinical research data on seizure detection and prediction is helpful to determine the duration of monitoring, cEEG resources are a critical element in determining who will be monitored and for how long. Maintaining a cEEG service line is expensive and labor intensive. An EEG laboratory capable of maintaining cEEG services requires a large amount of capital expense for EEG acquisition and review equipment as well as robust network and IT services. IT infrastructure is critical both for recording a study as well as review, as remote viewing of cEEG is typically necessary. Without it, an interpreting provider will need to be present in the hospital or be easily able to come to the hospital to ensure timely review and communicate the findings. An equally, if not more important, element to maintaining an effective cEEG service is technologist staffing. Adequately trained and registered technologists are the lynchpin of an effective service line, and their availability will frequently determine how many patients can be monitored and how quickly a study can be performed. Most EEG laboratories capable of high volume cEEG monitoring require 24 h staffing either with in-house or on-call technologists. As many of these elements are not universally available, a hospital-specific service agreement or guideline that emphasizes appropriate triage of studies is critical. CEEG requires a great deal of resources. Therefore, judicious ordering and appropriate triage are always necessary.

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# Periodic Complexes: Classification and Examples

6

Jessica W. Templer and Elizabeth E. Gerard

**Contents**



## Introduction

Continuous electroencephalography (cEEG) is an important diagnostic tool, frequently used to assess brain function and detect nonconvulsive seizures (NCS). The expansion of cEEG monitoring has led to the realization that rhythmic and periodic patterns are commonly seen in critically ill patients. Unfortunately, the significance and implications of many of these patterns remain poorly defined, making it difficult for the electroencephalographer to clearly communicate their meaning to the clinical team. For some of these patterns, there has been an association with increased risk of seizures and morbidity [1–4]. However, decision regarding if and how aggressively to treat these patterns remains controversial. Furthermore, the

J.W. Templer, MD (✉) • E.E. Gerard, MD
Department of Neurology, Feinberg School of Medicine, Northwestern University, 675 N. St. Clair, Suite 7-104, Chicago, IL 60611, USA
e-mail: jessica.templer@northwestern.edu; e-gerard@northwestern.edu



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distinction between ictal and interictal can become blurred, making this decision even more challenging. Debate continues about whether these patterns intrinsically have potential for neuronal injury or whether they exist as an epiphenomenon of acute brain injury or encephalopathy [5]. A helpful conceptualization is to consider that each of these patterns lie on an ictal-interictal continuum (IIC), implying varying degrees of cortical irritability and need for treatment [6].

In the past 10 years, there has been a great deal of research dedicated to periodic and rhythmic patterns. The true incidence of these patterns remains unknown because some accounts of incidence are based on routine electroencephalography (EEG) that likely underestimate the incidence seen on cEEG monitoring. In addition, it is important to keep in mind that prior to the widespread use of cEEG, the patients undergoing cEEG monitoring were a selected population thought to be at greatest risk for seizures [7]. However, despite the limitations of this research, there is a developing understanding of the etiology of these patterns and their relationship to prognosis and outcome.

## ACNS Terminology

The American Clinical Neurophysiology Society (ACNS) has created and revised a version of critical care EEG terminology with the goal of standardizing terminology to describe EEG patterns frequently encountered in critically ill patients [8, 9]. The aim of standardizing the terminology is to facilitate communication and allow multicenter research to attain a better understanding of the meaning of these patterns. This classification system was designed to avoid using terms that have become attached to certain clinical connotations (i.e., "triphasic waves"). In addition, the terminology does not include the terms "ictal," "interictal," and "epileptiform" in order to avoid the implication that these patterns definitively lie on one side of the IIC [8].

Excluding unequivocal electrographic seizures (i.e., generalized spike-and-wave discharges at 3 per second or faster and clearly evolving discharges that reach a frequency of more than 4 per second), the ACNS subcommittee divided the remaining EEG patterns into periodic discharges (PDs) or rhythmic delta activity (RDA). In addition, the most recent version of the guidelines introduced the category of spike-and-wave or sharp-and-wave (SW) [8]. To be characterized as a periodic or rhythmic pattern by ACNS terminology, the waveform must repeat for a minimal duration of six cycles (i.e., 1 per second for 6 s or 2 per second for 3 s) [9].

Two main terms are included in the description, term one which describes the location (ie, generalized (G), lateralized (L), bilateral independent (BI), or multifocal (Mf)) and term two which identifies the type of pattern (PDs, RDA, or SW) [8, 9]. Additionally, there are several modifiers as well as "minor" modifiers that further describe EEG patterns (see Table 1). One of the modifiers commonly used is the "plus" (+) descriptor. This descriptor implies an additional feature is present which suggests that the pattern is more ictal-appearing. The modifier "+F" can be used with PDs or RDA to describe superimposed fast activity only seen when the

**Table 1** Main terms including some additional modifiers included in the American Clinical Neurophysiology Society's Standardized Critical Care EEG Terminology (2012 version)

| Main term 1 | Main term 2 | Plus modifiers | |
|---|---|---|---|
| *Generalized* (*G*) | *Periodic discharges* (*PDs*) | +F | Superimposed fast activity (PDs and RDA only) |
| *Lateralized* (*L*) | | +R | Superimposed rhythmic activity (PDs only) |
| *Bilateral independent* (*BI*) | | +FR | Both superimposed fast and rhythmic (PDs only) |
| *Multifocal* (*Mf*) | *Rhythmic delta activity* (*RDA*) | +F | Superimposed fast activity (PDs and RDA only) |
| | | +S | Superimposed sharp waves or spikes or sharply contoured (RDA only) |
| | | +FS | Both superimposed fast and sharp waves or spikes or sharply contoured (RDA only) |
| | *Spike-and-wave or sharp-and-wave* (*SW*) | No plus modifiers | |

Additional modifiers

| Prevalence (% of record) | Rare <1 % | | Occasional 1–9 % | | Frequent 10–49 % | | Abundant 50–89 % | | Continuous ≥90 % |
|---|---|---|---|---|---|---|---|---|---|
| Duration (s) | Very brief <10 s | | Brief 10–59 s | | Intermediate 1–4.9 min | | Long 5–59 min | | Very long ≥1 h |
| Frequency (cycle/s) | <0.5 | 0.5 | 1 | 1.5 | 2 | 2.5 | 3 | 3.5 | ≥4 |
| Sharpness (ms) | Blunt >200 | | Sharply contoured >200 with sharp morphology | | Sharp 70–200 | | Spiky <70 | | |
| Stimulus-induced | Stimulus induced (SI-) | | Spontaneous (Sp-) | | | | Unknown | | |

Adapted from Gerard [10]

pattern is present. The modifier "+R" can only be used with PDs and connotes superimposed rhythmic or quasi-rhythmic delta activity. Finally, the modifier "+S" is used exclusively with RDA, when there are frequent intermixed sharp waves, spikes, or sharply contoured RDA.

The revised 2012 ACNS terminology included changes made based on solicited feedback and studies of inter-rater agreement on the use of the terminology. The first assessment found that inter- and intra-observer agreement for the presence/absence of rhythmic or periodic patterns and for localization of these patterns was moderate and agreement for the modifiers was slight to fair [11]. After initial changes were made to the criteria, an assessment was conducted using the interim version. Inter-rater agreement for the main terms was almost perfect, but agreement on modifiers was more variable [12]. In the most recent assessment, the inter-rater

agreement using the revised 2012 ACNS terminology was found to be almost perfect for the two main terms (i.e., pattern location (91 %) and pattern type (85 %)). Modifiers including sharpness, absolute amplitude, frequency and number of phases, and the + S modifier also had an "almost perfect" agreement (greater than 80 %), while the + F and + R modifiers had "substantial agreement." However, agreement for triphasic morphology and evolution were "moderate" (58 %) and "fair" (21 %), respectively [5]. While further work may need to be done to improve the understanding and reproducibility of some of the modifiers, main terms one and two seem to be easily recognized and reliable. As a result, they have now largely replaced older terminology in both clinical reports and cEEG literature.

An overview of each of the periodic patterns, alternative terminology, characteristics, prevalence, association with seizures, mortality rate, and common etiologies is listed in Table 2.

## Periodic Discharges

PDs are discharges with both a uniform morphology and duration that repeat with a definable and quantifiable interval between consecutive waveforms [8]. These waveforms recur at nearly regular intervals [7]. The discharges can be generalized, lateralized, bilateral independent, or multifocal [8]. Common etiologies include infectious and toxic-metabolic etiologies.

### Lateralized Periodic Discharges

Lateralized periodic discharges (LPDs) are discrete repetitive discharges that are lateralized to one hemisphere and have a consistent morphology that recur at periodic intervals, most frequently, between 0.5 and 3 Hz (Fig. 1). This pattern was first termed "periodic lateralized epileptiform discharges" (PLEDs) by Chatrian et al. in 1964 [18]. The term was then changed to LPDs as part of the new ACNS terminology [9]. Traditionally, the discharges are sharp waves or sharp wave complexes ranging from 50 to 300 μV. The new ACNS terminology proposes that the term applies to all PDs regardless of morphology. The discharges must be lateralized to one hemisphere but can be maximal in any focal area of the brain [18]. Most frequently, the field of discharges is broad, including the parasagittal chains and temporal chains of the ipsilateral hemisphere, though focal PDs are still considered LPDs. LPDs can involve the contralateral hemisphere; this is commonly seen if the discharges are maximal in the frontal or occipital regions; however, the discharges must have higher amplitude over one hemisphere [18]. It is important to exclude periodic artifacts that can mimic LPDs, most commonly electrocardiographic or pulse artifact.

LPDs are typically associated with ipsilateral cerebral dysfunction. As such, there is usually focal slowing or loss of the posterior dominant rhythm in that hemisphere. The contralateral hemisphere may show evidence of an encephalopathy, although it may also be unaffected.

**Table 2** Overview of periodic discharges and rhythmic delta activity patterns

| Consortium terminology | Other names | Characteristics | Prevalence | Association with seizures | Mortality rate | Common etiologies |
|---|---|---|---|---|---|---|
| *LPDs*<br>Lateralized periodic discharges | PLEDs | Lateralized repetitive discharges recurring at 0.5–3 Hz; typically with broad field but may be focal | 0.4–1 %<br>(rEEG)<br>8 % (cEEG)<br>[4, 13, 14] | 49–100 %<br>[4, 15–17] | 24–53 %<br>[13, 15] | Ischemic stroke [13, 15, 18]<br>Neoplastic lesions [14]<br>Viral encephalitis, ICH, SAH, and anoxic encephalopathy [18] |
| *BIPDs*<br>Bilateral independent lateralized periodic discharges | BIPLEDs | Asynchronous periodic discharges occur independently but simultaneously over both hemispheres | 0.1 %<br>(rEEG)<br>[15] | 70 % [15] | Up to 61 %<br>[15, 19, 20] | CNS infection, anoxia, chronic epilepsy, stroke, tumor, metabolic abnormalities, bilateral structural lesions[2,29] |
| *GPDs*<br>Generalized periodic discharges | GPEDs | Synchronous discharges that are relatively symmetric in amplitude across homologous regions | 0.01–1 %<br>(rEEG)<br>4–8 %<br>(cEEG)<br>[3, 21, 22] | 46 % [3] | 36 % in one study [3] | Hypoxic ischemic injury (e.g., cardiac arrest), metabolic disorders, rarely SSPE or sCJD [15, 19], drug toxicities [2], late stages of status epilepticus [23] |
| *GPDs-TW*[a]<br>Generalized periodic discharges<br>Triphasic morphology | Triphasic Waves | Discharges consisting of three phases, each longer than the preceding one with a surface positive high-amplitude wave preceded and followed by negative waves with a smaller amplitude | 20–57 %<br>(rEEG) [1] | 0–4 %<br>[24, 25] | 20–77 %<br>[26, 27] | Metabolic encephalopathy, steroid responsive encephalopathy, toxic encephalopathy, postictal stupor [28] |
| *LRDA*<br>Lateralized rhythmic delta activity | | Rhythmic delta pattern as a repetitive waveform with relatively uniform morphology and duration; lateralized to one hemisphere | 4.7 %<br>(cEEG)<br>[4] | 63 % [4] | NR | CNS neoplasm, subarachnoid hemorrhage, subdural hemorrhage, intracerebral hemorrhage, ischemic stroke [1] |
| *GRDA*<br>Generalized rhythmic delta activity | | Rhythmic delta pattern with a generalized distribution | NR | NR | NR | Non-specific, including focal and diffuse processes, limbic encephalitis, toxic-metabolic encephalopathy |

Abbreviations: *cEEG* continuous EEG, *CNS* central nervous system, *NR* not reported, *rEEG* routine EEG, *sCJD* sporadic Creutzfeldt-Jakob disease, *SSPE* subacute sclerosing panencephalitis, *PLEDs* Periodic lateralized epileptiform discharges, *BIPLEDs* Bilateral independent periodic lateralized epileptiform discharges, *GPEDs* Generalized periodic epileptifom discharges

[a]TW modifier can also be used with generalized spike-and-wave or sharp-and-wave term (GSW-TW)

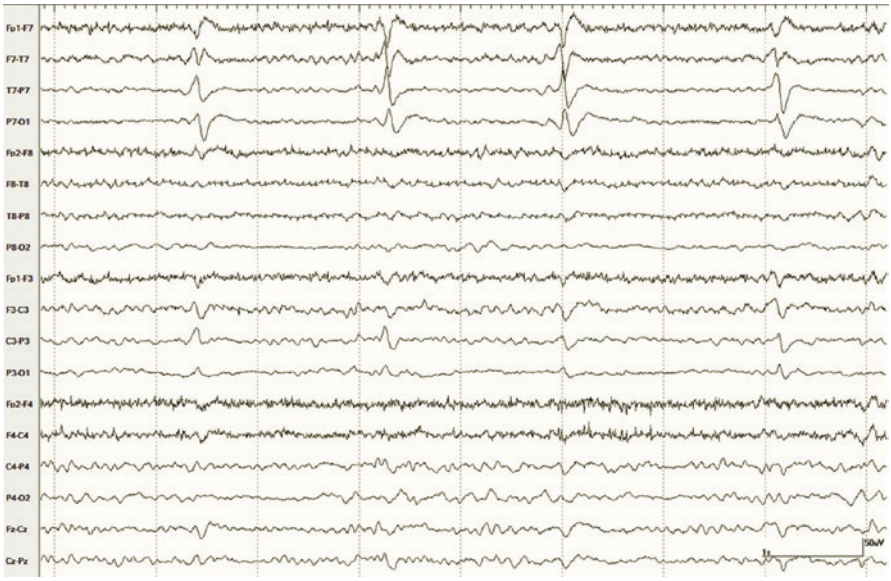


**Fig. 1** Lateralized periodic discharges (LPDs) in a 61-year-old man with history of alcohol abuse initially presenting after a witnessed generalized tonic-clonic convulsion. In the emergency department, he was noted to have fever and right hemiparesis. CT of the brain demonstrated multifocal infarcts, including the left MCA territory and bilateral PCA infarcts, thought to be cardioembolic in etiology. LPDs seen here later evolved to discrete seizures

The overall incidence of LPDs was previously estimated to be 0.4–1 % based on routine EEG studies; however, a more recent study evaluating cEEG has reported an incidence as 8.6 % in patients with cEEG monitoring [4, 13, 14]. Classically, this pattern has been considered a transient phenomenon, usually seen within the first days of an acute brain insult and often resolving within days to weeks [13].

In historic literature based on routine EEGs, the most common etiology associated with LPDs is an acute or subacute structural lesion involving the cortex, typically caused by an ischemic stroke [13, 15, 18]. In the authors' series, neoplastic lesions were the most common cause of LPDs on cEEG, possibly reflecting a difference in monitoring practices [14]. Other etiologies include viral encephalitis (i.e., herpes encephalitis), intracranial hemorrhage, tumors, subarachnoid hemorrhage, and anoxic encephalopathy. LPDs have been described in posterior reversible encephalopathy syndrome, migraine, demyelinating diseases, Creutzfeldt-Jakob disease (CJD), and mitochondrial encephalopathy with lactic acidosis and stroke-like episodes (MELAS) [29]. While stroke and hypoxic-ischemic encephalopathy are common etiologies for LPDs among neonates, an infectious etiology is more common in the rest of the pediatric population. One study found that 2/3 of pediatric patients with LPDs had central nervous system infections [30].

The majority of patients with LPDs do not have a prior history of epilepsy; however, seizures occur in the majority of patients with LPDs during their

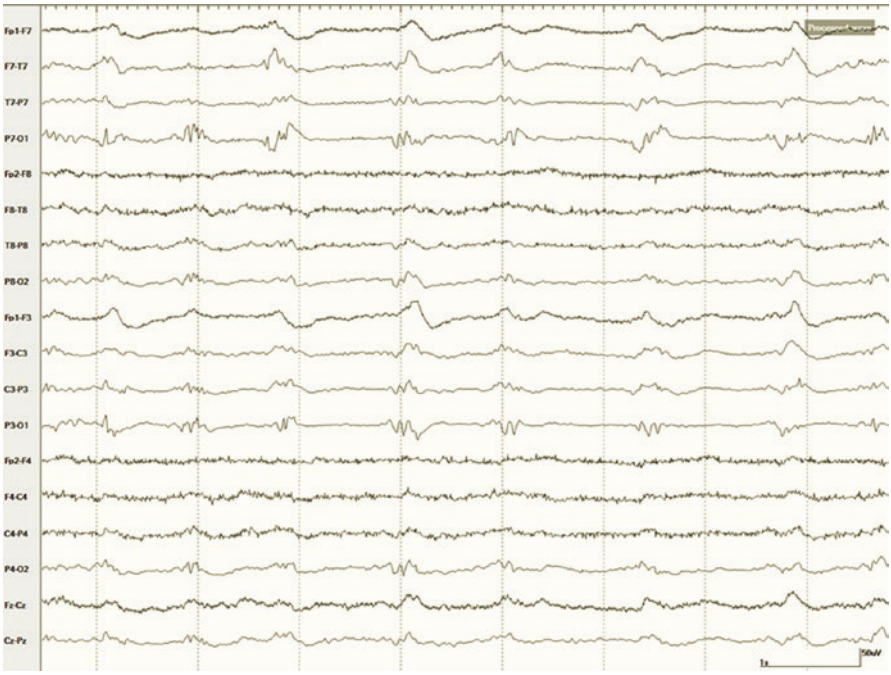


**Fig. 2** Lateralized periodic discharges with fast activity (LPDs + F) in a 55-year-old woman with history of diabetes presenting with hyperglycemia and altered mental status. Continuous EEG demonstrated 1 Hz left hemispheric LPDs + F as well as frequent electrographic seizures arising from the left parieto-occipital region

hospitalization, seen in 49–100 % of patients with LPDs [4, 15–17]. The most common seizure type associated with LPDs is focal motor seizures [13, 16, 18]. Both clinical and nonconvulsive seizures are associated with LPDs. One study found that of all patients with seizures identified during continuous monitoring, 40 % had LPDs. The majority of the seizures identified were nonconvulsive. Furthermore, approximately 20 % of patients with LPDs had their first seizure after the first 24 h of continuous monitoring, compared to 8 % of patients without LPDs [31].

A subtype of LPDs, namely, LPDs + F (or previously PLEDs+), were first described as LPDs with superimposed rhythmic discharges, typically low-voltage fast activity. This pattern has been reported to be more frequently associated with clinical or electrographic seizures compared to LPDs alone (74 % vs. 6 %, respectively, in one study) [32] (Fig. 2).

LPDs are typically considered ictal if the PDs are time locked to electromyographic recordings demonstrating clonic activity. This pattern is frequently associated with LPDs arising from the hemisphere contralateral to the focal clonic seizures (Fig. 3).

In most studies, LPDs have been associated with a high mortality rate in adults, ranging from 24 to 53 % [13, 15]. LPDs have been found to be an independent

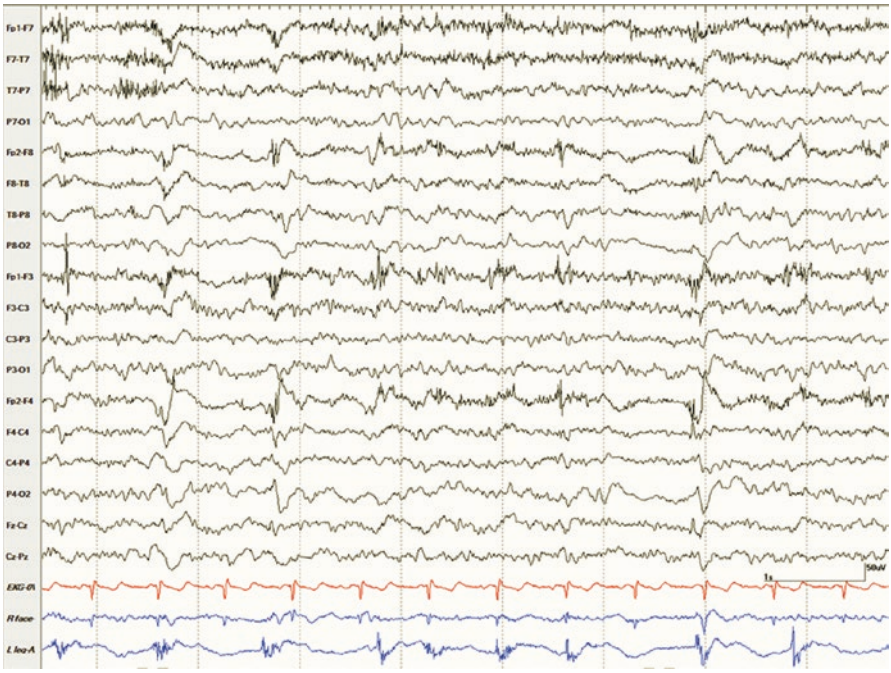

**Fig. 3** Ictal lateralized periodic discharges (LPDs) in an 87-year-old woman who presented with altered mental status and rhythmic clonic movements of her left face, arm, and leg after probable convulsion at home. EEG demonstrates lateralized periodic discharges, maximal over the right frontocentral region, time locked with focal movements of the left lower extremity (i.e., EMG lead, "L leg"). MRI of the brain was negative for a focal lesion. Etiology cryptogenic, suspected to be infectious vs. inflammatory

predictor of poor outcome (moderate to severe disability or death) in patients with subarachnoid hemorrhage, intracerebral hemorrhage, and patients in the medical intensive care unit [33–35]. Interestingly, in one study of adult patients, the occurrence of seizures in patients with LPDs was associated with a lower likelihood of death as a clinical outcome compared to LPDs that occurred without seizures [15]. In one study of 44 pediatric patients with LPDs, the mortality rate was 23 % and morbidity rate was 50 % [30]. Of the patients with LPDs, a better prognosis is seen among patients with a prior history of epilepsy or children with acute infections.

On account of the strong association with seizures, most experts agree that if LPDs are seen on EEG, the patient should be treated with at least one antiepileptic drug (AED) to prevent further seizures. Whether or not to "treat" LPDs to resolution of the pattern remains highly controversial. A common practice has been to "treat" LPDs when the pattern has a clear clinical correlate. However, the most commonly recognized clinical correlate is clonic motor jerking, which has been shown to be principally a manifestation of the location of LPDs or underlying lesion in or near the motor cortex [36]. LPDs in other locations may have subtle clinical correlates such as aphasia, eye deviation, or cognitive changes, which are subtle and

particularly hard to recognize when a patient is in coma [29]. For example, evaluating whether frontopolar or occipital LPDs have a clinical correlate in a patient in iatrogenic coma is not feasible. This does not necessarily mean that all LPDs should be treated aggressively. LPDs can often be seen following clinical seizures or resolution of status epilepticus (SE). They may also be very resistant to escalating medications and can take days to weeks to resolve; thus, it is unclear if aggressive treatment with sedating medications or anesthesia is always warranted [13, 37]. Ultimately, the decision to treat must account for the underlying etiology and overall clinical context including the progression of the patient's EEG patterns. While there is no agreed-upon prescription for treating LPDs, a common approach in a patient who has had nonconvulsive status that converted to complex LPDs is to watch the LPDs for at least 1–2 days and continue the observation without intervention as long as there is progressive improvement in the complexity and frequency of the LPDs (Fig. 4).

LPDs can also be associated with corresponding regional increases in cerebral perfusion or glucose metabolism on single-photon emission computed tomography (SPECT) or positron emission tomography (PET) [38, 39]. Whether these functional imaging studies should have a role in determining the appropriate degree of intervention has not been established.

## Bilateral Independent Lateralized Periodic Discharges

Bilateral independent lateralized periodic discharges (BILPDs) are asynchronous PDs that occur independently but simultaneously over both hemispheres. Discharges are typically sharp waves, spikes, or polyspikes, though epileptiform morphology is not required under ACNS criteria [2, 9]. The independent left and right complexes seen in BILPDs usually differ in morphology, amplitude, repetition rate, and site of maximal involvement (Fig. 5) [19].

BILPDs are much less common than other rhythmic and periodic patterns. They have been reported in 0.1 % of routine EEGs [15]. The etiologies associated with this pattern include CNS infection, anoxia, chronic epilepsy, stroke, tumor, metabolic abnormalities, and bilateral structural lesions [2, 19]. The bilateral involvement of the discharges likely reflects more diffuse disease, and as such, these patients have a higher likelihood of associated coma compared to unilateral discharges [15, 19].

BILPDs are seen much less frequently than unilateral LPDs, and therefore, the data regarding the significance of this pattern is limited. While both LPDs and BILPDs are associated with a high frequency of seizures, generalized seizures are more common with BILPDs compared to focal seizures seen in LPDs [19]. More recent studies have found that patients with BILPDs were less likely to have seizures compared to LPDs (43 % vs. 70 %, respectively) [15]. However, interestingly, in one series of patients with CNS infections, 100 % of patients with BILPDs (4/4) had electrographic seizures compared to 57 % (8/14) of patients with LPDs with seizures.

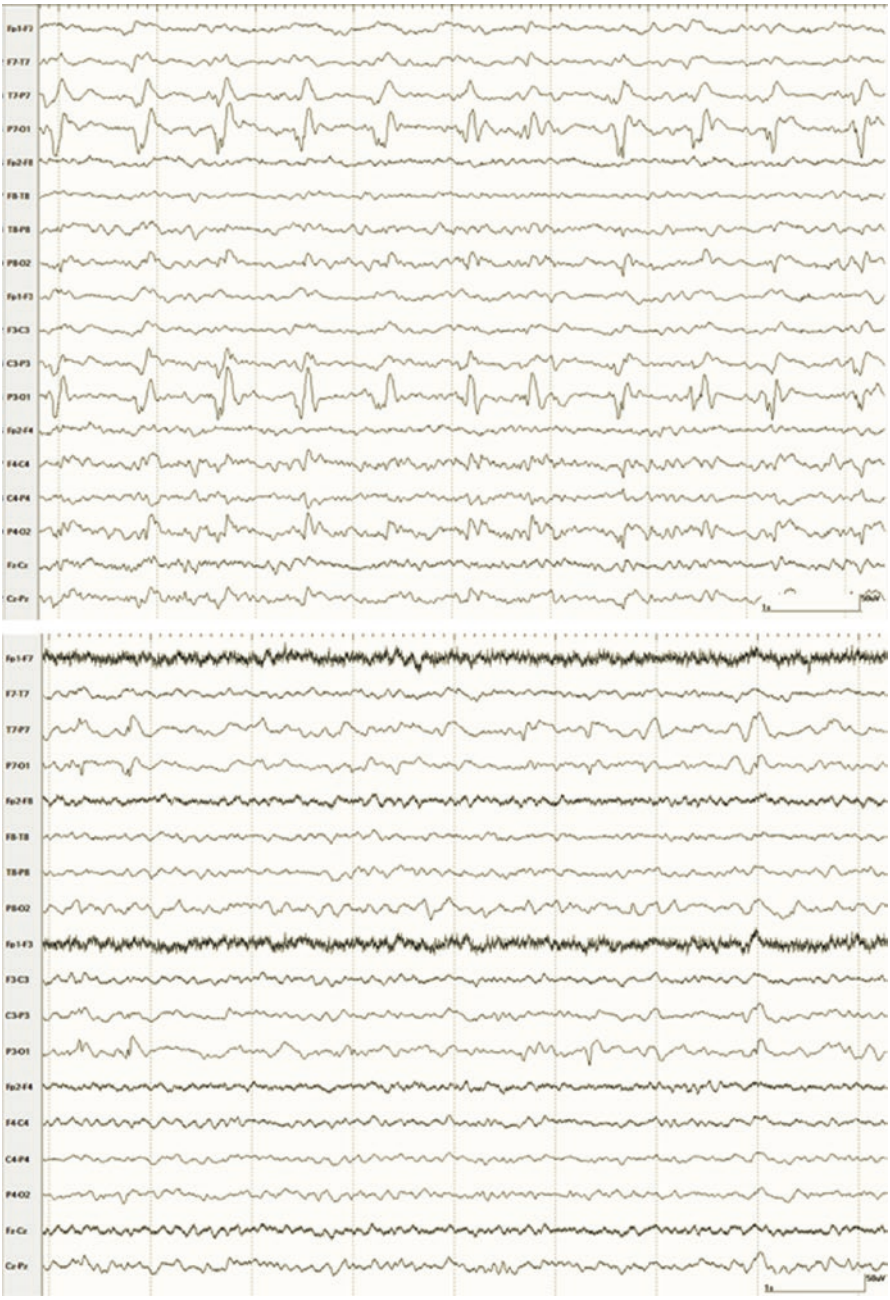

**Fig. 4** Evolution of lateralized periodic discharges with fast activity (LPDs + F) in a 65-year-old woman over the course of 1 month. The patient has a history of monoclonal gammopathy of unknown significance (MGUS), HTN, and lupus who initially presented with confusion and gait instability. MRI revealed posterior reversible encephalopathy syndrome (PRES) involving the left occipital region. Frequent focal left occipital seizures and persistent LPDs were present on initial 24 h continuous EEG record. Seizures responded to multiple antiepileptic medications (valproic acid, levetiracetam, lacosamide, and clonazepam) but LPDs + F persisted. Periodic discharges improved in frequency, complexity, and morphology over the course of a month, while the patient continued the same antiepileptic medication regimen

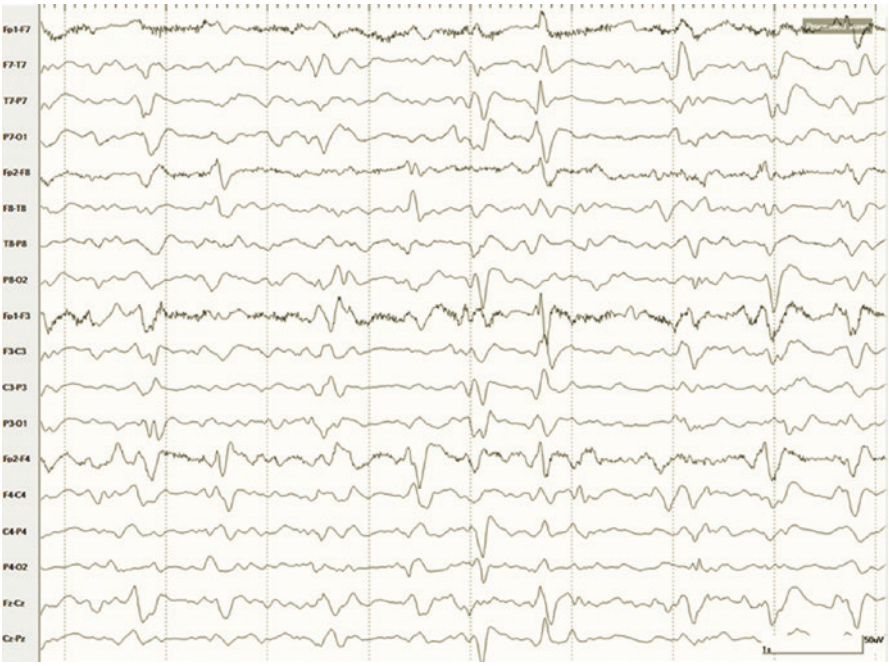

**Fig. 5** Bilateral independent lateralized periodic discharges (BILPDs) in a 94-year-old woman who presented with Non-ST segment elevation myocardial infarction (NSTEMI) followed by pulseless electrical activity (PEA) arrest. Hypothermia protocol was performed. Patient remained comatose, and EEG was obtained to evaluate for subclinical seizures. Continuous EEG demonstrated LPDs, arising independently from the bifrontal regions (BILPDs)

Compared to LPDs, the mortality rate for patients with BILPDs is higher, up to 61%; however it does not appear that functional outcomes among survivor are significantly different [15, 19, 20]. It does not appear that functional outcomes among survivors are significantly different [15].

As with LPDs, vigilance with cEEG monitoring is recommended for patients with BILPDs given the increased risk of seizures, and at least one prophylactic AED is often started though this practice is less well-described and likely less uniform than that for LPDs. Again, it is unclear if there is value in attempting to "treat" BILPDs to resolution. If possible, correcting the underlying etiology is an important part of treatment. In some cases, BILPDs may represent nonconvulsive status epilepticus (NCSE), and attempts should be made to treat the pattern, especially if there is no alternative explanation for the patient's mental status.

## Generalized Periodic Discharges

Prior to the new ACNS terminology, generalized periodic discharges (GPDs) were referred to as generalized periodic epileptiform discharges (GPEDs) [8, 9]. GPDs are synchronous discharges that are relatively symmetric in amplitude across homologous regions of the brain [7]. Discharges may be frontally or occipitally predominant. According to the ACNS criteria, discharges are most frequently

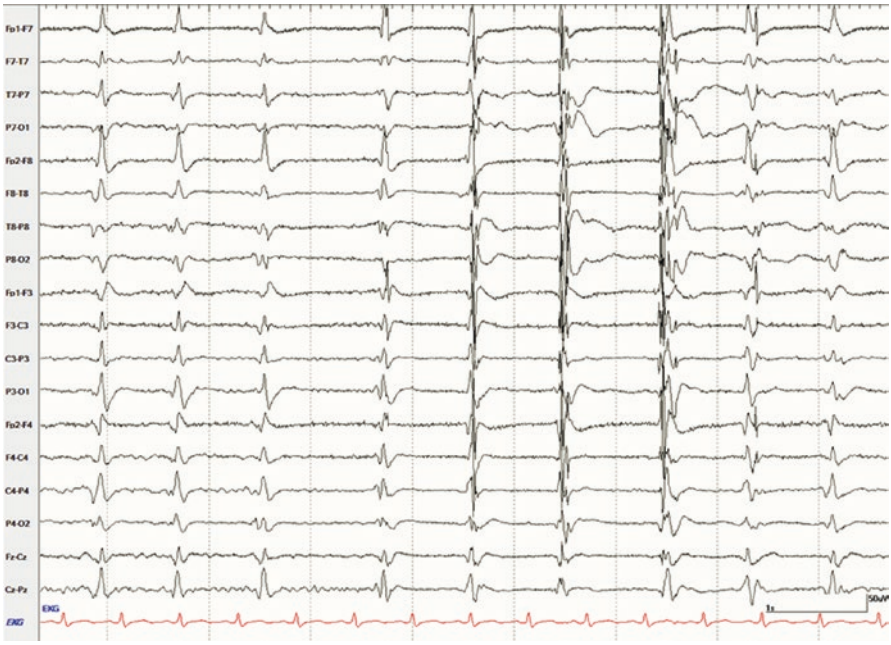


**Fig. 6** Generalized periodic discharges (GPDs) seen in a 63-year-old man with a history of hypertension with asystole in the setting of profound hypoglycemia. The patient underwent hypothermic protocol. EEG demonstrates generalized periodic discharges intermittently time locked with whole-body myoclonus

spikes, polyspikes, or sharp waves and have a negative polarity, although blunt PDs can also be considered GPDs [2, 15]. Between runs of PDs, typical patterns include diffuse delta slowing or attenuation (Fig. 6) [7].

GPDs have been reported in 4–8 % of patients undergoing cEEG and 0.01–1 % of routine EEGs [3, 6, 23]. This pattern can be seen in up to 20 % of patients in coma with severe postanoxic encephalopathy after cardiac arrest [40].

It has been hypothesized that GPDs may result from disruption of the thalamocortical pathway with diffuse or multifocal cerebral dysfunction or systemic disease [3]. Common etiologies include hypoxic ischemic injury (i.e., cardiac arrest), metabolic disorders, sporadic CJD, and subacute sclerosing panencephalitis [15, 41]. Drug toxicities associated with GPDs include cefepime, baclofen, lithium, phencyclidine, ketamine, barbiturates, and anesthetics [2, 21, 41]. GPDs may also be seen in the late stages of generalized convulsive SE and after the SE has resolved [22]. The pattern can also represent NCSE, even without preceding convulsions. In particular, GPDs occurring at a frequency greater than 2.5 Hz should raise suspicion for NCSE, although this is not the only criteria [42].

The presence of GPDs in an EEG record has been associated with seizures [23]. The most comprehensive study to date included 200 patients with GPDs with matched controls and found that almost one half of patients with GPDs had a

seizure at some point during their hospital stay (although this was not statistically different than matched controls). Of note, there was no difference in outcome or mortality between the patients with GPDs and the matched controls. However, NCSE was found to be associated with worse outcome for patients both with and without GPDs [3].

Given the common association between NCS and GPDs, it is important to continue careful monitoring in patients with GPDs in order to detect and treat NCSE. Treatment of the underlying etiology is of the utmost importance in patients with GPDs. The use of AEDs in patients with GPDs is even less understood and more controversial than it is in the setting of other patterns. In general, many experts do not start AEDs for GPDs where a correctable toxic or metabolic etiology is suspected, though some feel it may hasten recovery and prevent seizures in the brain's transient period of increased irritability. On the other hand, if there is no explanation for the patient's mental status and/or the pattern meets criteria for NCSE, treatment should be considered [3, 6, 23]. A "trial" of a benzodiazepine or another antiepileptic drug can be considered in uncertain cases. In order for such a trial to be considered positive, both the electrographic pattern and the patient's mental status must improve [43].

The treatment of GPDs in the setting of anoxia, particularly if associated with myoclonus, is especially controversial. Some consider the threshold to treat GPDs associated with myoclonia lower than GPDs with nonconvulsive symptoms; however, in postanoxic encephalopathy, it is thought that the treatment may be futile given a higher incidence of neuronal necrosis and a greater risk of poor outcome [44]. Some authors have suggested that the background between individual discharges may be useful in prognosis and the utility of antiepileptic drug treatment [1, 44].

## Generalized Periodic Discharges: Triphasic Morphology

The triphasic wave (TW) pattern was first described in the context of hepatic coma in 1955 [45]. Over time, this term has become pathognomonic of a metabolic encephalopathy. In fact, electroencephalographers have been found to choose to report triphasic waves rather than GPDs based on the clinical history when classifying an EEG pattern [46]. In order to extract clinical implications from EEG terminology, the revised ACNS proposed standard terminology considers triphasic waves to be a type of PDs (GPDs-TW) or occasionally a sharp-and-wave subtype (GSW-TW) [9].

The TW modifier is used to define repetitive electrographic discharges consisting of three phases, each longer than the preceding one; a surface positive high-amplitude (typically greater than 70 μV) wave preceded and was followed by negative waves with smaller amplitude [9, 47]. GPD-TWs are typically diffuse, although may have an anteroposterior or a posteroanterior time lag seen in bipolar montages and may show a frontocentral or frontoparietal predominance. Typically, individual complexes exceed 0.3 s (Fig. 7).

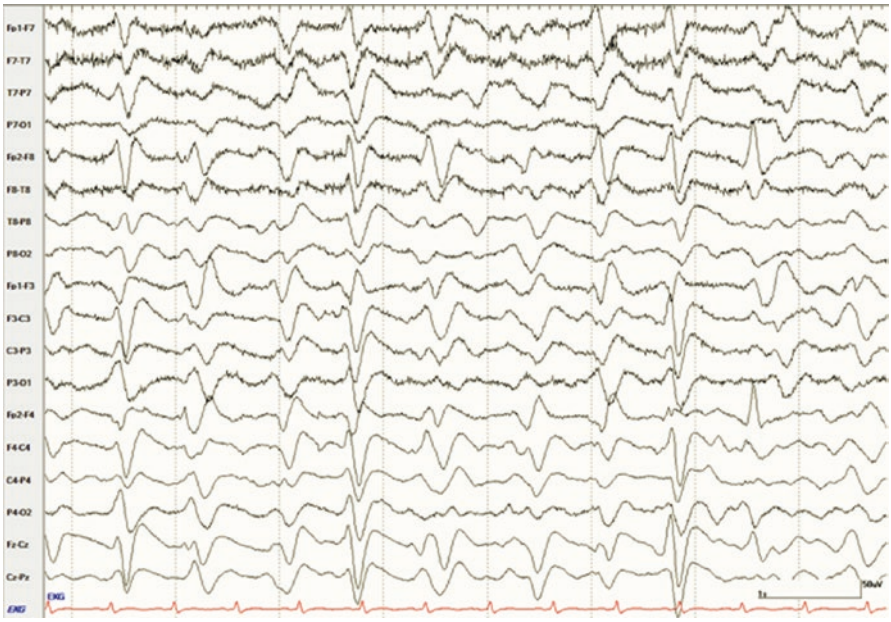

**Fig. 7** Generalized periodic discharges with a triphasic morphology (GPDs-TW) seen in a 47-year-old woman with history of epilepsy, depression, anxiety, and polysubstance abuse who presented with fulminant hepatic failure after an acetaminophen overdose

Traditionally, GPD-TWs have been associated with metabolic encephalopathy. They are highly characteristic of hepatic encephalopathy but not pathognomonic [48]. Other possible etiologies include renal failure, toxic encephalopathies, steroid-responsive encephalopathy, sepsis-associated encephalopathy, and postictal stupor [28]. Studies have shown that the majority of patients with GPD-TWs have a combination of at least two pathologic conditions and/or neuroradiologic abnormalities, and over one quarter of patients have been found to have elements of all three abnormalities [28]. It has been general consensus that GPD-TWs represent the overall derangement of thalamocortical circuits that result from metabolic, toxic, infectious, and structural cerebral abnormalities, rather than being considered intrinsically epileptogenic [28, 49]. Rarely have they been found to be associated with seizures, estimated at 0–4 % [24, 25].

GPD-TWs may be seen as an ictal pattern which can be difficult to differentiate from NCSE [28]. It has been suggested that GPD-TWs typically disappear with sleep, and this is one method to distinguish between them and an ictal pattern [50]. It was previously thought that only epileptiform discharges would respond to benzodiazepines; however, GPD-TWs of metabolic origin also respond temporarily to benzodiazepines, making it difficult to distinguish between the two entities [51]. For this reason, as discussed above, a positive benzodiazepine trial requires both improvement in the EEG pattern and the patient's mental state [43].

The presence of GPD-TWs has been associated with high mortality, in the range of 20–77 % [26, 28]. However, a recent study evaluated encephalopathic patients GPD-TWs, and matched controls (encephalopathic patients without GPD-TWs) found that when the EEG background activity and GCS were matched, GPD-TWs were not specifically associated with death [27]. Therefore, this pattern likely does not intrinsically impact mortality, rather the comorbid conditions associated with it affect outcome.

It is still not clear whether GPD-TWs represent a distinct entity from GPDs or GSWs. Treatment of GPD-TWs (or GSW-TWs) should be similar to the approach to GPDs. Again, a focus on addressing the underlying pathologic conditions that may predispose the patient to this pattern is especially important. However, it is important to keep in mind that the triphasic morphology does not in and of itself predict a metabolic cause, and the possibility that this represents a potentially ictal pattern should be considered.

## Rhythmic Delta Activity

Intermittent rhythmic delta activity (IRDA) was first described by WA Cobb in 1945 [52]. The ACNS terminology defines RDA as a repetitive waveform with relatively uniform morphology and duration. In contrast to PDs, RDA occurs without an interval between consecutive waveforms. In order for the pattern to be considered rhythmic, the duration of one cycle should vary by less than 50 % from the duration of the subsequent cycle for the majority of the cycle pairs. In addition, the rhythmic activity must be less than or equal to 4 Hz [9]. There are two basic patterns of RDA, namely, lateralized and generalized.

### Lateralized Rhythmic Delta Activity

Lateralized rhythmic delta activity (LRDA) is a rhythmic delta pattern lateralized to one hemisphere (Fig. 8). A recent study described the largest cohort of patients with LRDA to date [4]. Using the same definition of LRDA as described above, they found 27 subjects with LRDA out of 558 individuals older than 1 month of age who had cEEG or an urgent EEG over the course of 1 year (i.e., 4.7 %). Typically, the duration of LRDA was brief or very brief (less than 1 min and less than 10 s, respectively), made up of runs of monomorphic, 50–200 μV sinusoidal or sharply contoured delta activity. Most often, the frequency was 1–2 Hz or 2–3 Hz. Most commonly, the foci of LRDA are anterior (typically frontal or temporal). When the morphology of LRDA was compared to LPDs, LPDs were typically slower (less than or equal to 1 Hz) and occurred in longer runs (greater than 1 min, often between 5 min and 1 h).

In terms of associated pathology, similar to LPDs, LRDA is most commonly associated with an acute or remote cerebral injury, frequently involving the cortex, juxtacortical white matter, and/or deep gray structures. If a patient has a single focal lesion, LRDA is typically localized in the same region as the lesion [4, 52]. In the

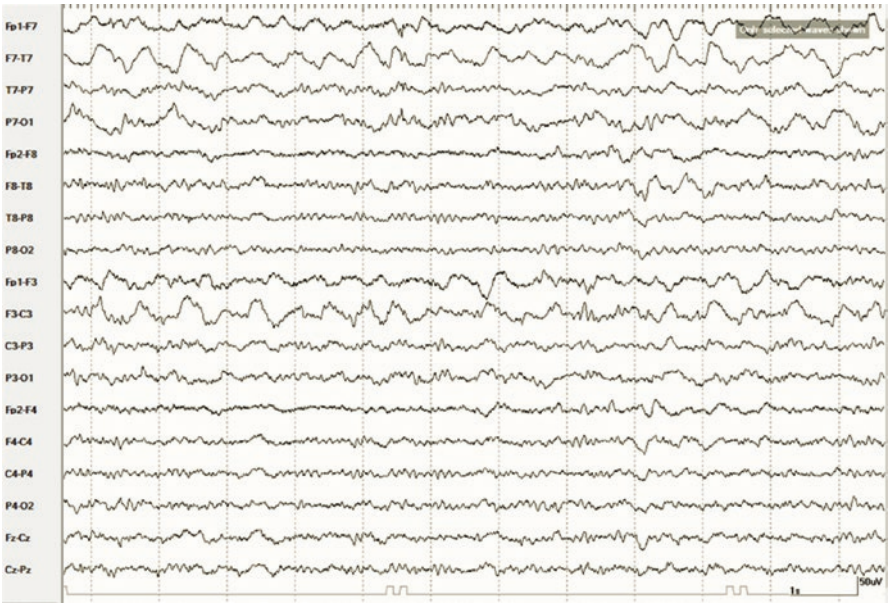


**Fig. 8** Lateralized rhythmic delta activity (LRDA), maximal in the left frontal region, in a 61-year-old man with history of focal epilepsy and a left frontotemporal glioblastoma multiforme s/p resection who presented with intermittent aphasia

aforementioned study, almost one quarter of patients had a history of epilepsy [4]. The authors found that approximately 60 % of the patients with LRDA were found to be stuporous or comatose; otherwise, LRDA was not associated with obvious clinical manifestations.

Over half of patients (63 %) with LRDA were found to have acute seizures during their hospital stay. This is similar to patients with LPDs, although is significantly higher than in patients with focal nonrhythmic slowing and controls. Of note, if patients have both LRDA and LPDs, the incidence of seizures has been found to be 84 % [4].

Given the shared implications of LPDs and LRDA, it is reasonable to approach LRDA in a fashion similar to LPDs. As discussed, there is a high incidence of seizures seen in association with LRDA; starting an AED to prevent further seizures is reasonable. In the case of frequent or continuous LRDA, more aggressive treatment may be merited in specific clinical situations where the pattern may represent an ictal pattern even in the absence of clear evolution.

## Generalized Rhythmic Delta Activity

RDA seen diffusely is classified as generalized rhythmic delta activity (GRDA). GRDA is a relatively new term, and as such, there is limited data in the literature.

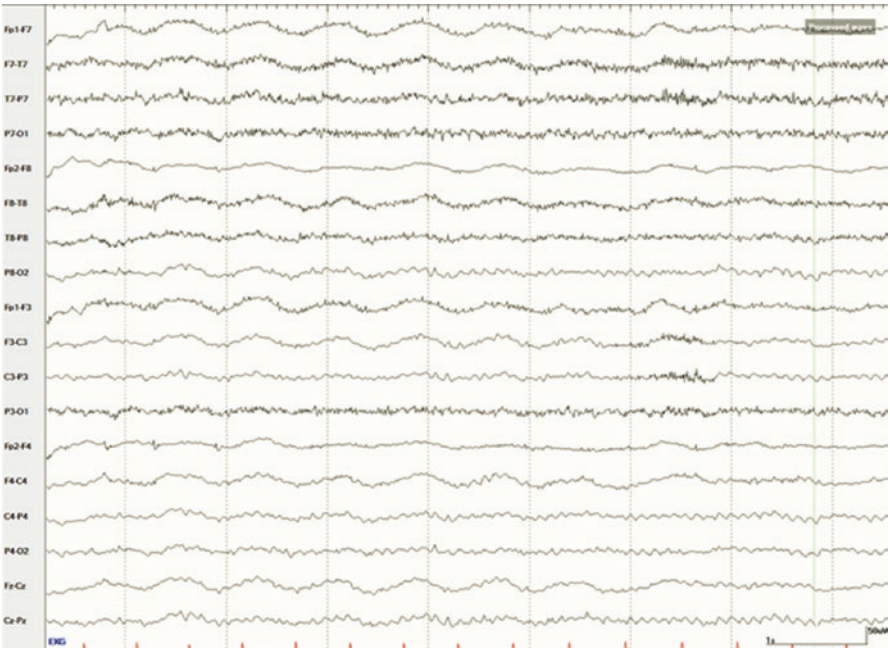

**Fig. 9** Generalized rhythmic delta pattern (GRDA) seen in a 26-year-old woman with NMDA receptor antibody limbic encephalitis

Intermittent GRDA is associated with a broad range of neurologic abnormalities, both diffuse and focal processes, including inflammatory, vascular, neoplastic, degenerative, or traumatic disorders [53–56]. As such, its significance is typically considered relatively non-specific. This pattern is more frequently seen in older patients and inpatients, and it has a higher rate of comorbidity compared to controls [56]. Interestingly, in one series evaluating EEG features seen in anti-N-methyl-D-aspartate (NMDA) encephalitis, almost one half of patients (47.8 %) had GRDA (Fig. 9) [57].

The majority of the literature addressing rhythmic delta patterns focuses on frontal intermittent rhythmic delta activity (FIRDA). FIRDA was first described by Cobb in 1945 and, over time, has been thought to be a possible indicator of deep midline lesions and increased intracranial pressure [55]. This pattern can be considered bilateral independent lateralized rhythmic delta activity (BILRDA) or GRDA, depending on the maximal location and field involved in the rhythmic activity.

FIRDA can be seen as a normal response to hyperventilation, although should be limited to hyperventilation alone. In other contexts, this pattern is rarely seen on EEG; FIRDA has been reported in less than 1 % up to 6 % of EEG recordings [56, 58]. There is a reportedly low incidence of seizures in patients with FIRDA (i.e., 9 % of all patients with this pattern in one study) [4].

When GRDA is seen on EEG, treatment should usually be guided by the underlying etiology and comorbid conditions.

## Spike-and-Wave and Sharp-and-Wave

This pattern was a new addition to the 2012 version of the ACNS nomenclature. It is defined as a polyspike, spike, or sharp wave with an after-going slow wave that occurs in a regular alternating pattern with no interval between the discharges. Given the recent addition of this terminology, there is limited research on this pattern. Therefore, incidence and treatment implications have not yet been established.

### Conclusions

While there remains much to be understood about rhythmic and periodic patterns on cEEG, understanding the common means of characterizing them allows for better communication of difficult to describe findings. In doing so, it is important to acknowledge both what is and is not known about the meaning and treatment implications of these patterns. Future prospective studies will hopefully help clinicians gain an understanding of the pathophysiology underlying these patterns, the impact on neuronal injury, and their effect on functional outcome and, ultimately, use them as a tool to guide treatment decisions to improve prognosis and outcome.

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# Electrographic Seizures in Adults: Recognition and Examples

7

Jonathan Halford

**Contents**



## Introduction

Continuous EEG (cEEG) monitoring is used increasingly to assess brain function in critically ill patients. One of the main indications for CEEG is to detect electrographic seizures. Seizures are frequently detected by continuous EEG monitoring in the intensive care unit (ICU) setting, particularly in the neurological ICU. Most of these seizures are nonconvulsive and clinically subtle [1]. The reported risk of

J. Halford, MD
Medical University of South Carolina, Charleston, SC, USA
e-mail: halfordj@musc.edu



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seizures as a complication or as the principal reason for ICU admission is only 3.3 % [2]. But the frequency of seizures in ICU patients is considerably higher. The frequency of seizures detected by EEG monitoring in adult ICU patients is in the range of 8–34 % [3–5], depending on which patient population is studied.

## Causes of Seizures

Causes of seizures and status epilepticus (SE) in the ICU include antiepileptic drug (AED) withdrawal or noncompliance, alcohol withdrawal, hypoxia/anoxia, stroke, infection, head trauma, metabolic disorders, subarachnoid hemorrhage, and tumors [4]. In the medical ICU, the most common etiology for seizures is sepsis [1].

### Cerebrovascular Disease

#### Subarachnoid Hemorrhage

Seizures are a well-recognized complication of subarachnoid hemorrhage (SAH) with studies demonstrating clinical seizures in 4–9 % of patients during hospitalization based on EEG monitoring [5]. In comatose patients with SAH, electrographic seizures are more common. In a series of 108 comatose patients with SAH, 19 % were found to have electrographic seizures, most of which were purely subclinical [4]. Additionally, when intracranial EEG and other modalities are monitored, seizures were found to occur in 38 % of patients with SAH [6]. Therefore, clinicians should have a high degree of suspicion for seizures in patients with SAH.

#### Intracerebral Hemorrhage

Similar to SAH, intracerebral hemorrhage (ICH) has also been associated with a high rate of clinical seizures ranging from 3 to 19 % of patients [5]. Two studies found a high incidence of seizures in patients with ICH undergoing EEG monitoring. In one of these studies, 28 % (18/63) of patients with ICH experienced nonconvulsive seizures (NCS), which were associated with an increase in midline shift, higher NIH stroke scale scores, and a trend toward worse outcome compared with ICH patients without seizures [7]. Seizures occurred after both cortical and subcortical ICH, although they were more common after cortical ICH, which makes sense because seizures are generated by the gray matter. A similar rate of seizures was found in a series of 102 patients with ICH, in which seizures were detected in 31 % and over half were purely electrographic [8]. Perhaps more importantly, seizures were associated with an increase in the volume of hemorrhage and a trend toward worse outcomes.

#### Ischemic Stroke

Ischemic stroke is a common cause of seizures and the leading cause of epilepsy in the elderly population. In ICU ischemic stroke patients, the rate of clinical seizures is less than in patients with SAH or ICH, but still high in the range of 6–26 % [7].

As with SAH and ICH, cEEG monitoring uncovers more seizures than would be found by clinical monitoring alone.

### Anoxic Brain Injury

Seizures are a common complication following hypoxic/anoxic brain injury due to cardiac arrest and can have a variety of clinical presentations from myoclonus to generalized convulsions. Many studies have shown a very poor prognosis for patients with myoclonic status epilepticus (MSE) within the first day of cardiac arrest, although this may not be the case if patients are treated with therapeutic hypothermia [9]. The frequency of NCS during treatment with therapeutic hypothermia has been found to be 9–33 %, and seizures are associated with a poor prognosis for recovery. These seizures can occur at during normothermia, hypothermia, or rewarming.

## Traumatic Brain Injury

Many studies have evaluated the incidence of clinical seizures (both acute and chronic) following traumatic brain injury (TBI). Approximately 20–30 % of patients have acute seizures in the ICU after TBI. More than half of these seizures are nonconvulsive. Seizures following TBI have also been associated with increased intracranial pressure and abnormal neuronal metabolism (transient elevation in lactate/pyruvate ratio on cerebral microdialysis). A recent study showed that TBI patients who have seizures are at greater risk for hippocampal atrophy 6 months after the head trauma, suggesting that the seizures themselves may lead to greater brain injury [10].

## Infection

### Brain Infection

Clinical seizures are commonly associated with acute central nervous system (CNS) infections, both bacterial and viral. Clinical seizures complicate 17 % of bacterial meningitis cases, particularly pneumococcal meningitis, and patients with seizures have a much higher mortality. Seizures are frequent in patients with viral meningitis as well and prior studies have shown that approximately half of all patients with confirmed herpes encephalitis experience clinical seizures. A study of cEEG monitoring in 42 ICU patients demonstrated electrographic seizures in 14 (33 %) with only 5 (36 %) associated with a clinical correlate. Electrographic seizures were also independently associated with poor outcome, such as severe disability, vegetative state, or death [11].

### Sepsis

Sepsis is associated with several serious systemic complications, which include effects on the nervous system. The presence of encephalopathy as well as

polyneuropathy is quite prevalent in this patient population, and seizures are a cause of encephalopathy [12]. Several studies have shown that 10–16 % of patients with sepsis undergoing cEEG monitoring have seizures [13]. A lower number seizures are found in septic patients if only a routine EEG is recorded. Although sepsis-related seizures are still poorly understood, these findings underscore the importance of monitoring for seizures in septic patients.

## Brain Tumor

Brain tumors are also a common cause of seizures, and patients often undergo neurosurgical procedures that leave them at even higher risk for seizures. The postoperative period is a particularly vulnerable time when seizure risk is high. Electrographic seizures can go completely undetected during this period and contribute to prolonged encephalopathy and increased mortality. There have been few studies evaluating the incidence of subclinical seizures in patients with brain tumors with or without recent surgical resection. A recent study of all EEG studies recorded on a large group of brain tumor patients showed that 24 out of 259 patients (9 %) were in nonconvulsive status epilepticus (NCSE) [14]. CEEG monitoring should be strongly considered for brain tumor patients with unexplained or prolonged encephalopathy, especially following any neurosurgical procedure.

## Uncommon Causes

### Autoimmune/Inflammatory

Paraneoplastic and autoimmune limbic encephalitis is characterized by acute or subacute mood and behavioral changes, short-term memory problems, complex partial seizures, and cognitive dysfunction [15]. Antineuronal antibodies are invaluable in directing the search for occult malignancy and guiding treatment, although up to 30–36 % of patients with limbic encephalitis have negative antibody studies [15]. Seizures often precede the onset of other symptoms, and therefore maintaining a high index of suspicion provides for the opportunity for early diagnosis and treatment. Clinical seizures are seen in approximately two-thirds of patients, which are usually complex partial seizures of temporal lobe onset [15]. However, patients may have very brief, subtle seizures that can be difficult to distinguish from concomitant encephalopathy and often go unrecognized. The most common cancers associated with paraneoplastic limbic encephalitis include lung (usually small cell lung cancer), seminoma and other testicular tumors, thymoma, breast cancer, and Hodgkin lymphoma. Neurologic symptoms typically precede discovery of the tumor by weeks or months.

Limbic encephalitis with antibodies against N-methyl-D-aspartate (NMDA) receptor causes a predictable set of symptoms that combine to make up a characteristic syndrome. Patients often have a prodromal headache, fever, or a viral-like process, followed in a few days by a multistage progression of symptoms that include (1) prominent psychiatric manifestations including anxiety, agitation, bizarre

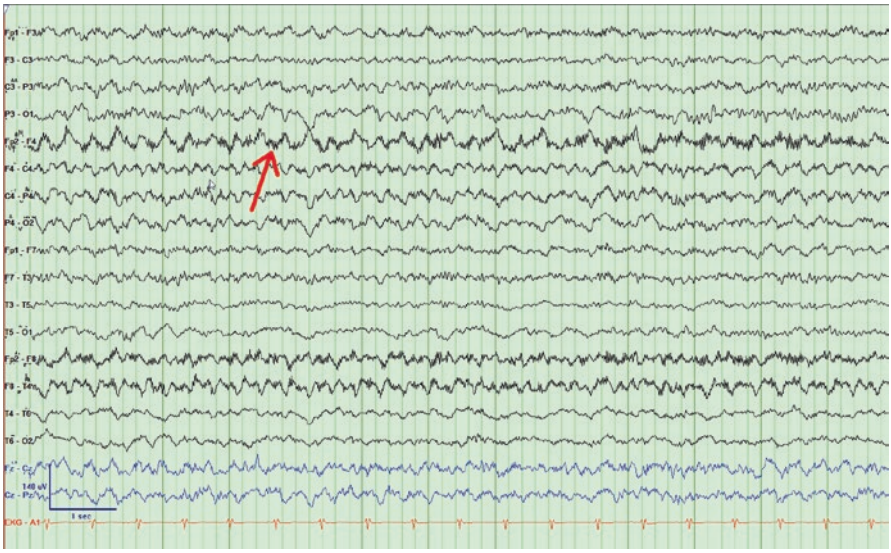

**Fig. 1** Extreme delta brush pattern (*arrow*) and seizure onset in a patient with NMDA encephalitis

behaviors, hallucinations, and disorganized thinking, (2) insomnia, (3) memory deficits, (4) seizures, (5) decreased level of consciousness, (6) dyskinesias, (7) autonomic dysfunction, and (8) language dysfunction. This is a paraneoplastic syndrome seen most commonly in young women. In a series of 100 patients, 76 % had clinical seizures and 60 % were found to have an underlying tumor, most commonly an ovarian teratoma [16]. Early recognition is important, as many patients respond to immunomodulation with corticosteroids or intravenous immunoglobulin (IVIg) in addition to tumor resection. The interictal EEG of patients with NMDA receptor encephalitis often shows an extreme delta brush pattern with delta activity with superimposed beta activity. Figure 1 is a page of EEG with an extreme delta brush pattern and showing ongoing seizure activity in the right posterior frontal parietal region.

Patients with antibodies to the leucine-rich glioma-inactivated 1 (LGI1) protein component of the voltage-gated potassium channel (VGKC) have typical limbic encephalitis symptoms and develop memory disturbances, confusion, and seizures. Memory and cognitive deficits may be preceded by short faciobrachial dystonic seizures. These seizures often do not respond to AED therapy. Patients may develop hyponatremia or rapid eye movement sleep behavior disorders. Only 20 % of cases are paraneoplastic; the most common associated tumors are thymoma or lung cancer. Early diagnosis is important to prevent progression from seizures to other symptoms of encephalitis and because these patients have a dramatic response to corticosteroid treatment [17].

There are several other causes of autoimmune encephalopathy in which seizures play a significant role that are not associated with underlying malignancy or limbic encephalitis. One type of presentation of Hashimoto's encephalopathy includes seizures, acute deterioration of consciousness, and stroke-like episodes with the

presence of antithyroid antibodies but with normal or slightly abnormal thyroid function. The most common seizure pattern includes generalized tonic-clonic seizures followed by complex partial seizures, with or without secondary generalization [18]. Other systemic autoimmune diseases associated with seizures that usually respond to steroid therapy include systemic lupus erythematosus, Sjogren's syndrome, Wegener's granulomatosis, and neurosarcoidosis [12].

### Posterior Reversible Encephalopathy Syndrome

Posterior reversible encephalopathy syndrome (PRES) is characterized by altered mental status, seizures, and visual changes accompanied by characteristic neuroimaging changes in a posterior symmetrical distribution, interpreted as edema. Altered mental status, headache, and visual disturbances are the classic clinical findings and seizures are frequently reported. Most seizures are single short grand mal seizures but multiple grand mal seizure and focal seizures can sometimes occur [19]. It is associated with a variety of underlying clinical conditions that may cause seizures and encephalopathy such as electrolyte disturbances. Treatment of the underlying cause is paramount and rapid initiation of AEDs may help to prevent further neuronal injury from seizures.

### Subacute Encephalopathy with Seizures in Chronic Alcoholism

Subacute encephalopathy with seizures in chronic alcoholism (SESA) is a rare clinical syndrome which describes alcoholic patients presenting with confusion, seizures, and focal neurologic deficits. The occurrence of SESA may be underestimated, as many patients may be misdiagnosed with alcohol withdrawal seizures. It has recently been proposed that this syndrome may be a type of NCSE because these patients have focal seizures between which they have PEDs and do not return to baseline mental status [20]. Therefore, cEEG monitoring is recommended for alcoholic patients with encephalopathy and focal neurologic deficits. An accurate diagnosis is critical because these patients require long-term treatment with antiepileptic medications to prevent recurrence [12].

### Other Rare Causes

There are a variety of other systemic diseases that can contribute to both encephalopathy and seizures, including hepatic failure, uremia, human immunodeficiency virus (HIV) infection, and drug intoxication (both prescription as well as recreational) [12].

## Clinical Significance of Seizures

The detection of seizures in ICU patients is associated with poor prognosis as defined by death or severe disability at hospital discharge [1]. It is unclear if the seizures themselves worsen prognosis or if seizures are simply found more often in patients who are more seriously ill. Therefore, it is unclear if the treatment of intermittent seizures improves prognosis. Generalized convulsive status epilepticus

(GCSE), on the other hand, if not controlled almost certainly leads to irreversible neuronal injury, and therefore treatment of GCSE almost certainly improves prognosis.

If we are not sure that treatment of seizures changes prognosis, why should we monitor patients? At this point, most monitoring is done with the assumption that the treatment of seizures improves patient care. The detection of seizures in patients in the ICU certainly affects their medication management. A study of 300 consecutive monitoring studies of 287 adult and pediatric inpatients demonstrated that cEEG monitoring led to a change in AED prescribing in 52 % of cases. There was initiation of an AED in 14 %, modification of an AED regimen in 33 %, and discontinuation of AED therapy in 5 % [3]. Many of these changes were due to the detection of seizures. A similar study in children reported the CEEG monitoring affected the care of children of 59 % of cases, again mostly by affecting AED management [21].

It is important to accurately recognize electrographic seizures. There are many non-epileptic events, either clinical or electrographic, which can be difficult to distinguish from epileptic seizures on EEG or video. Treatment of non-epileptic events with AEDs can cause harm to patients by increasing sedation in an already susceptible patient population. Lorazepam, for instance, is routinely used to abort seizures and has been shown to be an independent risk factor for delirium in ICU patients. Increased risk of delirium may translate to increased morbidity and mortality, prolonged hospital stay, and increased health-care costs [22].

## Electrographic Criteria for Labeling Seizures

### Definition of Electrographic Seizure

Although there is reasonable general acceptance of what constitutes a clinical seizure, the variety of electrographic and clinical events observed during the care of critically ill patients make it difficult to define a specific electrographic criterion for seizures. For non-seizure periodic and paroxysmal activity, a committee of the American Clinical Neurophysiology Society (ACNS) has recently established research terminology for some of the more frequently encountered electrographic patterns for ICU monitoring based on whether they are generalized or localized and their periodicity, persistence, duration, frequency, inducibility by external stimuli, and evolution [23]. Although there is no equivalent established terminology for electrographic seizures, the EEG terminology developed for NCSE may be adapted to cover most types of seizures seen in the ICU. In this terminology [24], an event would meet criteria for a seizure if it consisted of epileptiform discharges at a frequency of greater than 2.5 Hz or if it contained epileptiform discharges or rhythmic delta/theta activity at less than 2.5 Hz accompanied by one of the following three criteria: (1) EEG and clinical improvement after an IV AED, (2) subtle clinical ictal phenomena during the EEG patterns, or (3) typical spatiotemporal evolution. Spatiotemporal evolution refers to a characteristic of most seizures

whereby the EEG pattern "evolves" or changes over time in either its frequency or in its spatial distribution. In the case of a typical seizure, this usually involves a gradual increase or decrease in the frequency of the EEG rhythm accompanied by spread of the EEG activity to a greater number of EEG electrodes. The 2012 ACNS Standardized Critical Care EEG Terminology lists definite seizure activity to be generalized spike and wave patterns of a frequency greater than 3/s and evolving discharges that are of a frequency equal or greater than 4/s. Patterns that do not meet this criteria are not ruled out as seizure activity, only deserving of greater scrutiny [23]. The Pediatric Critical Care Terminology lists the minimum duration for a seizure to be 10 s, and this is a generally accepted criterion for adult seizures as well.

## Borderline Seizure Patterns

### Brief Ictal Rhythmic Discharges

Most electroencephalographers use a definition of seizures that includes a minimal duration of 10 s, which reflects the typical lower limit to the duration of focal seizures in patients with chronic epilepsy. Rhythmic ictal-appearing patterns lasting less than 10 s have been described in neonates under multiple different acronyms including brief ictal rhythmic discharges (BIRDs). In neonates, these patterns encompass discharges of any frequency, including less than 4 Hz, because they are common in this age group. Brief bursts of rhythmic delta activity and periodic discharges with a frequency of less than 4 Hz are common in critically ill patients but are usually not considered to be ictal. Ictal discharges in children and adults often have a higher frequency than those in neonates. The occurrence of BIRDs with a frequency higher than 4 Hz has recently been reported in 20 out of 1135 CEEG recordings [25]. The typical frequency for BIRDs was in the theta, alpha, and beta frequency bands in 14 (70 %), 3 (15 %), and 3 (15 %) cases, respectively. Typical duration was 1–3 s. Most (17 of 20 [85 %]) BIRDs were sharply contoured except in the theta frequency band in two patients (10 %) and the beta frequency band in one patient (5 %), which were sinusoidal. None of the BIRDs showed obvious evolution. Most of the patients with BIRDs had acute brain injuries such as tumor and stroke, and most patients were comatose or stuporous. BIRDs were present in the first hour of the recording in most patients and recordings with BIRDs were more likely to also contain seizures than recording without BIRDs. Figure 2 shows an example of two BIRDs in one page of EEG.

### Lateralized Periodic Discharges

Lateralized periodic discharges (LPDs) (previously known as periodic lateralized epileptiform discharges (PLEDs) in older nomenclature [23]) are associated with nearly any type of structural abnormality including those due to infection, neoplasm, ischemia, hemorrhage, and anoxia. They are associated with poor prognosis, particularly in patients with neoplasms. They are not generally considered to

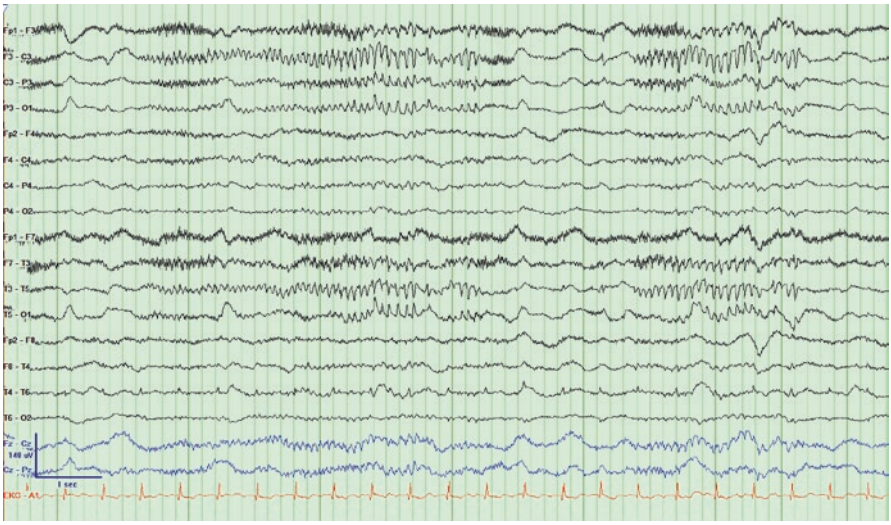

**Fig. 2** Two brief ictal rhythmic discharges (BIRDs) in the left hemisphere

indicate seizure activity, although this is debated. Evidence indicating that LPDs may indicate ongoing focal seizure include reports of altered mental status in the elderly patients associated with LPDs and increased metabolic activity present in regions with LPDs in positron emission tomography (PET) and single-photon emission computed tomography (SPECT) scans. But most LPDs are not considered seizures because many patients have LPDs chronically, and in patients with both LPDs and seizures, the seizures appear distinct from the LPDs and the LPDs stop during the seizures. Some types of LPDs are considered more likely to indicate focal seizure activity, and these have been termed "PLEDs-plus" [26] in older terminology, now probably known as "LPDs-plus." The periodic discharges which make up the LPDs-plus pattern include brief focal rhythmic activity, and/or the patient has physical manifestations which correlate with these LPDs such as rhythmic movements or myoclonus. Figure 3 shows left central LPDs which are accompanied by right facial twitching, so they are considered LPDs-plus and therefore evidence of focal seizure activity. Figure 4 shows a LPDs-plus pattern which is not accompanied by clinical manifestation of seizure but should be considered evidence of focal seizure activity because the EEG pattern of LPDs is combined with rhythmic alpha and theta activity.

### Stimulus-Induced Rhythmic Periodic or Ictal Discharges

Stimulus-induced rhythmic, periodic, or ictal discharges (SIRPIDs) are found in approximately 20 % of patients undergoing cEEG monitoring. These are rhythmic frontally predominant generalized periodic discharges which occur when a patient is stimulated. They are considered to fall somewhere along the ictal-interictal continuum. Clinical or subclinical/electrographic seizures are found in about half of

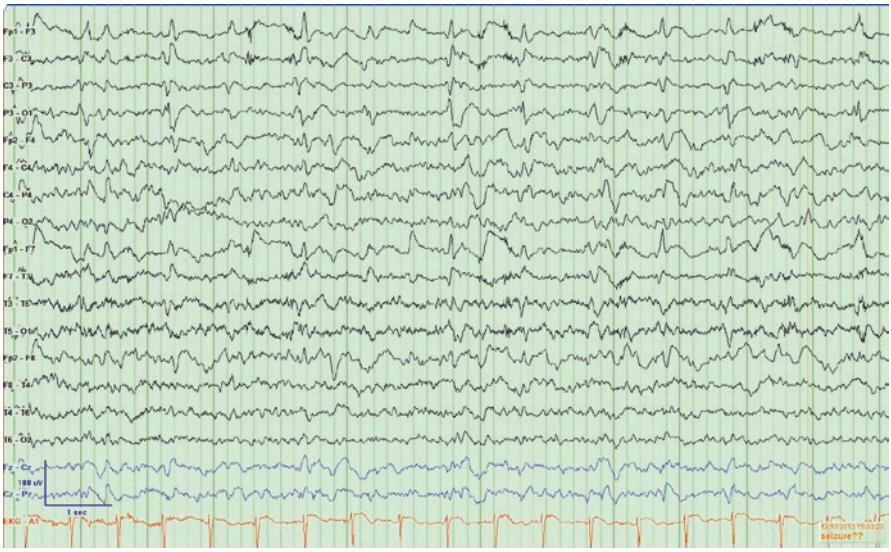

**Fig. 3** Left central LPDs which are accompanied by right facial twitching, consistent with the LPDs-plus pattern and therefore evidence of focal seizure activity

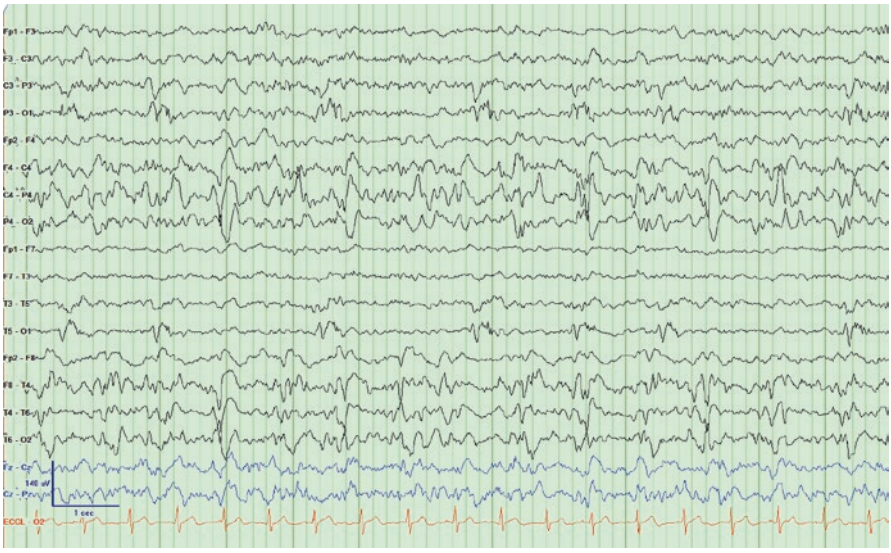

**Fig. 4** LPDs-plus pattern in the right temporal-parietal region which can be considered to be evidence of focal ongoing seizure activity

these patients; SE is found more frequently in focal or ictal-appearing SIRPIDs [27]. As such, treatment with a conventional AED is advisable. But studies have shown no increase in regional cerebral blood flow to indicate that they may represent seizure activity, and as a result aggressive treatment is not recommended. After

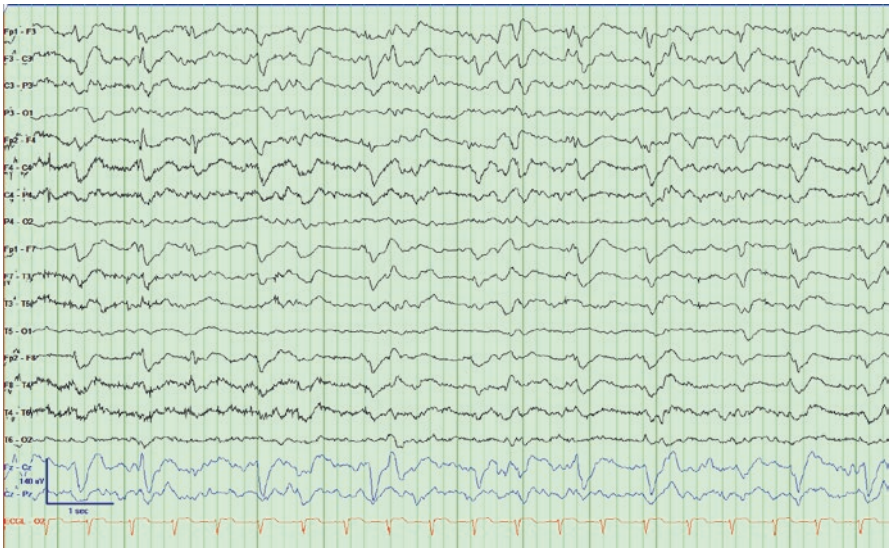

**Fig. 5** An episode of SIRPIDs, as manifested on EEG by GPDs

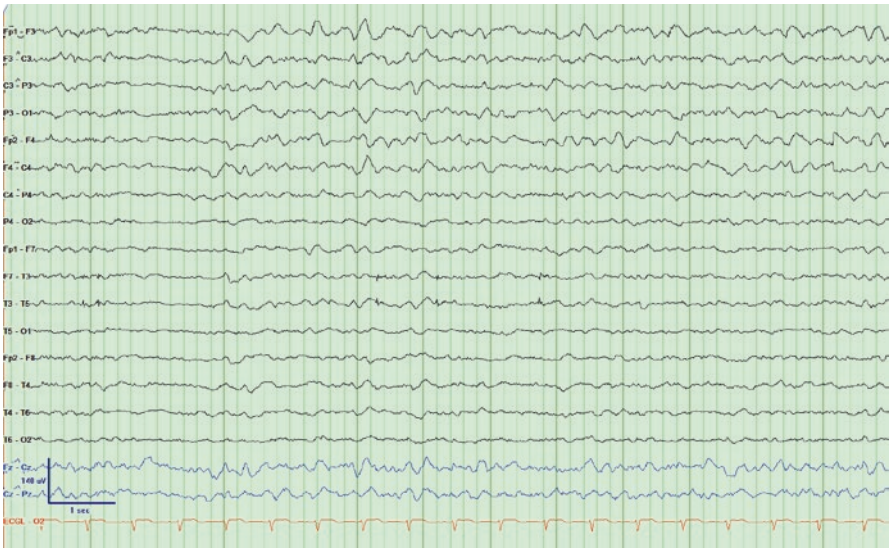

**Fig. 6** EEG of the same patient as pictured in Fig. 5, at a time when SIRPIDs are not present

cardiac arrest, SIRPIDs are associated with poor outcome, especially during hypothermia, but in other instances, outcome is yet to be defined. Figure 5 shows EEG from a patient during a SIRPID episode, and Fig. 6 shows EEG from the same patient during a period without SIRPIDs.

## Predictors of Electrographic Seizures

There are multiple elements of the past medical history, neurological exam, and interictal EEG that predict the presence of electrographic seizures in cEEG recordings. Predictors in the past medical history include young age, a history of epilepsy, and remote risk factors for seizures including brain injury. Elements of the history of present illness which predict seizures are a report of convulsive seizures before the EEG recording is begun, sepsis, and recent cardiac or respiratory arrest. Findings on the neurological exam which predict seizures include oculomotor abnormalities including nystagmus, hippus, and eye deviation. Electrographic features which predict seizures include epileptiform discharges including spikes, sharp waves, LPDs, and generalized periodic discharges (GPDs) [1, 28]. Patients without epileptiform discharges in the first 30 min of an EEG recording have approximately a 10 % chance of developing seizures in the subsequent cEEG recording. If patients have epileptiform discharges in the first 30 min, the changes of recording a seizure are significantly elevated to around 25 %. Patients with no epileptiform discharges in the first 2 h of the EEG recording have less than a five percent change of developing subsequent seizures. More than 95 % of seizures are recorded in the first 24 h of EEG monitoring, so if a patient does not have a seizure in 24 h of monitoring, it is unlikely (less than 5 % chance) that seizures will be recorded with further EEG monitoring, even if epileptiform discharges are present [29].

## Inter-rater Agreement for Labeling Seizures

Because the performance of automated seizure detection programs has not been verified in sizable studies, it is not consistently used in clinical practice. Therefore, seizures are usually identified by visual inspection of the unprocessed EEG recordings. This is a significant challenge because these recordings can be quite long and seizure patterns can be subtle. Inter-rater performance for experts in labeling seizures is not perfect. In a recent study of eight board-certified EEG experts who independently identified seizures and periodic discharges (PDs) in 31-h ICU EEG segments from three medical centers, the inter-rater correlation between the experts was only moderate. But the correlation of experts for labeling of seizures was considerably higher than for the labeling of periodic discharges. Improved performance in labeling seizures and PDs was seen in experts who had received specific training by the Critical Care EEG Monitoring Research Consortium [30].

## Automated Detection of Seizures

The first general-purpose seizure detection methods were introduced in the 1980s. However, none of the seizure detection software currently available on the market has been shown to be as accurate as a human for reviewing long-term cEEG recordings. For example, Reveal (by Persyst Development Corporation), one of the most

advanced seizure detection products, offers an average sensitivity of 85 % with a false detection rate of about 14 per day for adult epilepsy monitoring unit (EMU) patients [31]. Reveal's false detection rate often becomes extremely high (>40/day) when an EEG recording contains high number of recording artifacts, a problem common in EMU scalp EEG monitoring and more frequently seen in ICU studies. Due to this high false detection rate, most centers do not utilize or rely on seizure detection software in the long-term EEG study review process. In addition to insufficient detection performance, another major problem is that all commercially available seizure detection software is marketed for use across all patient populations, but has not been clinically validated for each patient population. These substantially different patient populations include adult and pediatric EMU patients (with scalp and intracranial recordings), adult and pediatric in home (ambulatory) EEG patients, and neonatal, pediatric, and adult ICU patients. It has been well documented that, despite of some underlying similarities, there exist significant differences in both ictal and background EEG patterns among these patient populations. Therefore, it is very difficult, if not impossible, for one algorithm to perform well enough in all cEEG patient populations to be clinically useful. An ideal seizure detection system must include different modules for use in different patient populations, and the performance of each must be clinically validated using patient data collected from the respective patient population. In the recent US Food and Drug Administration (FDA) Workshop on Seizure Detection, the agency instructed that, in "Indication for Use," it has to include "In whom the device is intended to be used – specify intended population (age, patient group, seizure type)." Hopefully, advances in commercial seizure detection software over the next few years will improve performance and provide algorithms specific to different patient populations.

## Examples of Seizures

A typical electrographic seizure has an amplitude greater than the baseline EEG amplitude, shows evolution in both frequency and spatial distribution, and lasts greater than 10 s. Figures 7, 8, and 9 illustrate a typical seizure which begins in the left temporal region with a sharply contoured 8 Hz rhythm which slows in frequency down to around 3 Hz and spreads to involve also the left posterior temporal and occipital region. Unfortunately, not all electrographic seizures demonstrate this typical appearance. Some seizures are obscured by electromyographic (EMG) artifact and cannot be easily recognized. EMG is a common contaminate of ICU EEG recordings and many seizures go unrecognized because of it. The Persyst automated EEG analysis software recently added an EMG artifact removal feature which makes it easier to see seizures like this and improves the performance of the Persyst seizure detector. Figures 10, 11, and 12 show a right temporal seizure which is similar in morphology to the typical seizure in Figs. 7, 8, and 9, but it is obscured by EMG artifact. Figures 13, 14, and 15 show the same EEG recording with the high-frequency (low-pass) filter set at 30 Hz which allows the seizure to be seen.

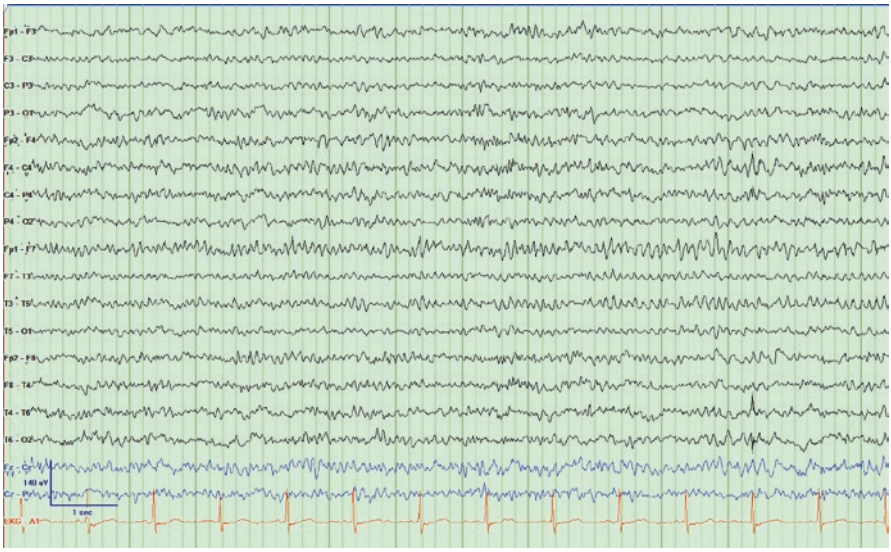

**Fig. 7** Figures 7, 8, and 9 picture consecutive 10-s epochs of a typical electrographic seizure which begins in the left temporal region

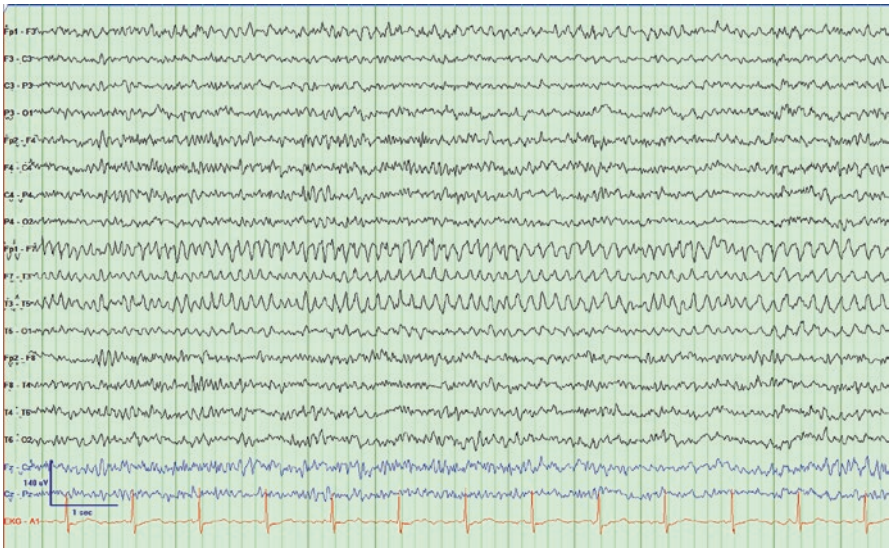

**Fig. 8** Figures 7, 8, and 9 picture consecutive 10-s epochs of a typical electrographic seizure which begins in the left temporal region

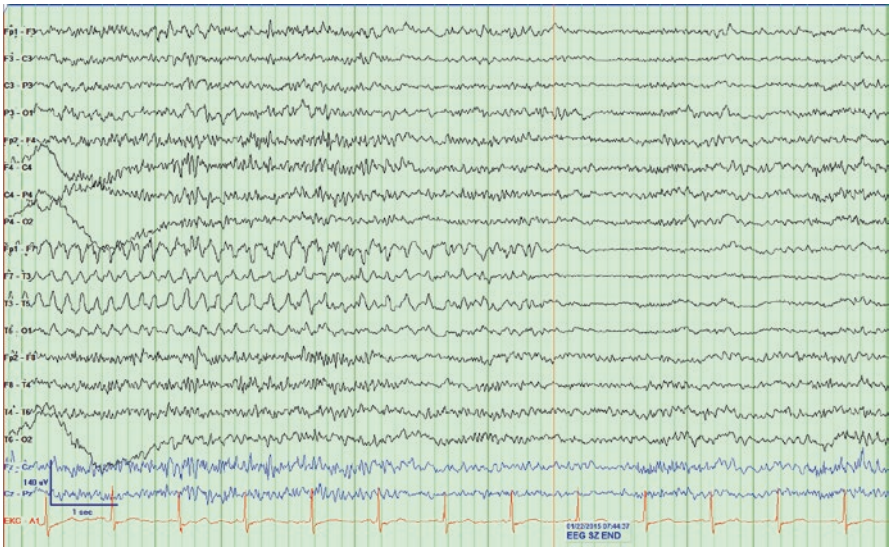


**Fig. 9** Figures 7, 8, and 9 picture consecutive 10-s epochs of a typical electrographic seizure which begins in the left temporal region

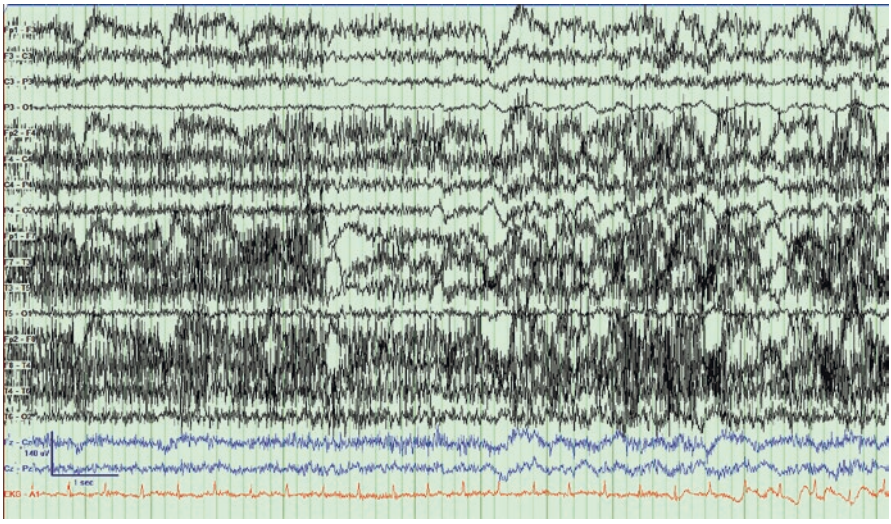

**Fig. 10** Figures 10, 11, and 12 picture consecutive 10-s epochs of a right temporal seizure but it is obscured by EMG artifact

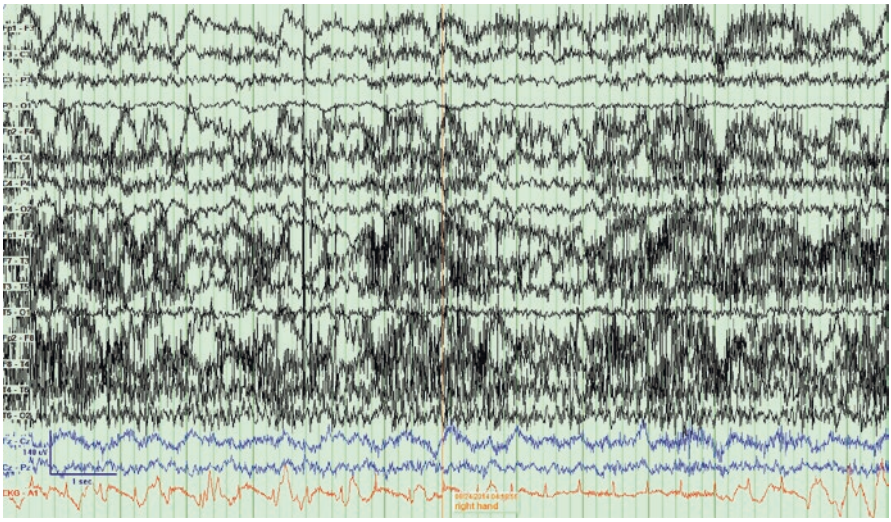

**Fig. 11** Figures 10, 11, and 12 picture consecutive 10-s epochs of a right temporal seizure but it is obscured by EMG artifact

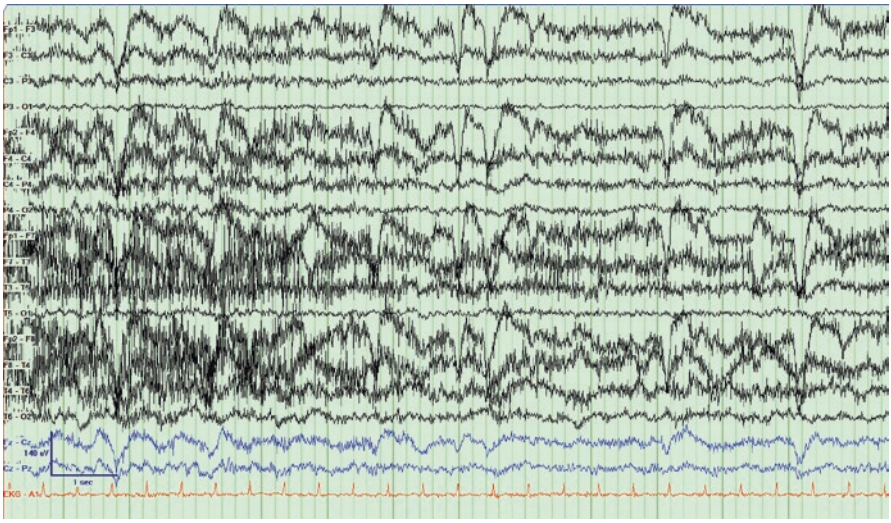

**Fig. 12** Figures 10, 11, and 12 picture consecutive 10-s epochs of a right temporal seizure but it is obscured by EMG artifact

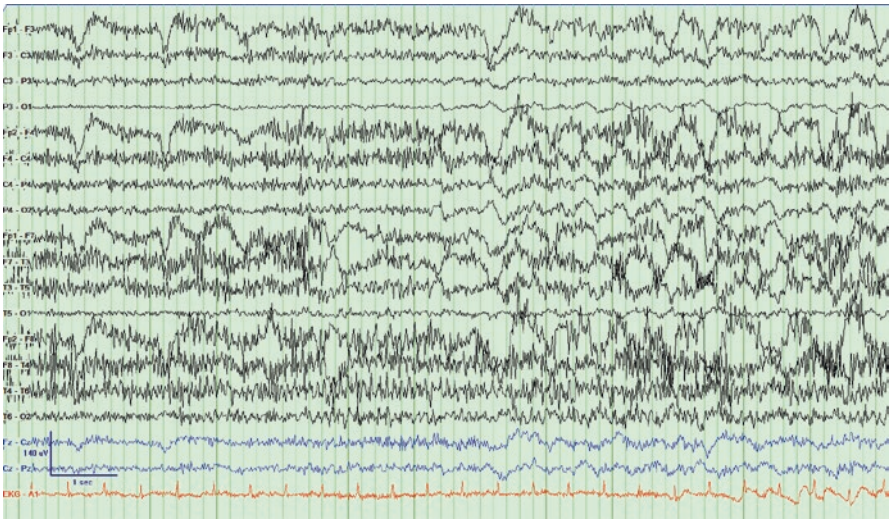

**Fig. 13** Figures 13, 14, and 15 picture consecutive 10-s epochs of the same EEG recording as in Figs. 10, 11, and 12 but with the high-frequency (low-pass) filter set at 30 Hz which allows the seizure to be seen

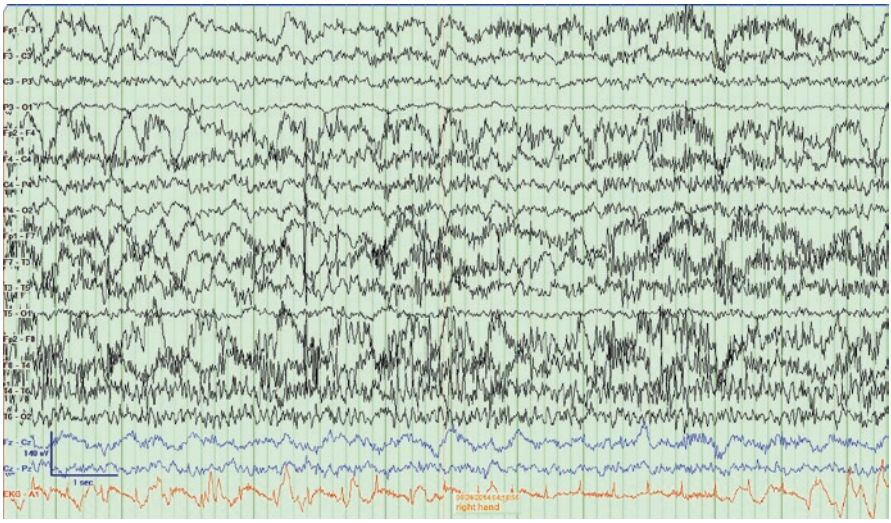

**Fig. 14** Figures 13, 14, and 15 picture consecutive 10-s epochs of the same EEG recording as in Figs. 10, 11, and 12 but with the high-frequency (low-pass) filter set at 30 Hz which allows the seizure to be seen

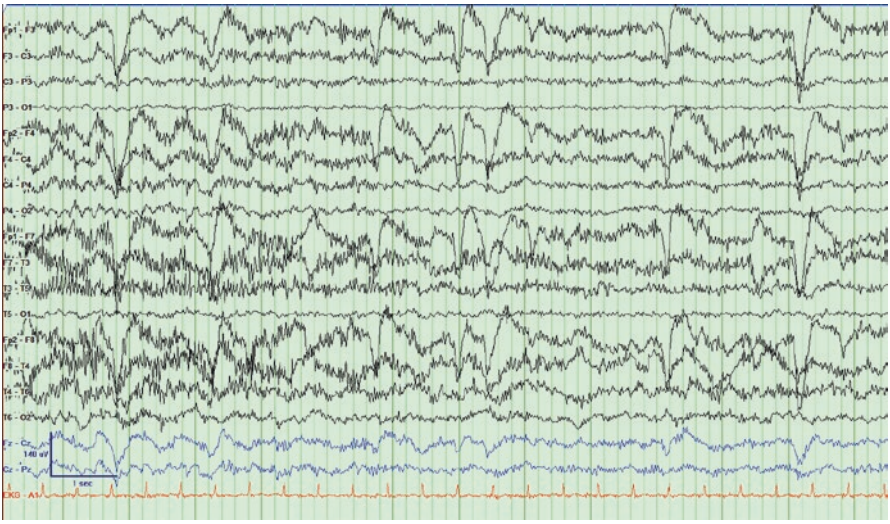

**Fig. 15** Figures 13, 14, and 15 picture consecutive 10-s epochs of the same EEG recording as in Figs. 10, 11, and 12 but with the high-frequency (low-pass) filter set at 30 Hz which allows the seizure to be seen

Some seizures may be difficult to recognize because they involve delta activity that is of a frequency less than 2.5 Hz. Figures 16 and 17 show an EEG recording with a right central 2 Hz sharply contoured delta activity that is an electrographic seizure because the spatial extent of the seizure increases between Fig. 16 and approximately 1 min later in Fig. 1 Some seizures are of relatively low amplitude and do not stand out well from the background EEG activity. The right temporal seizure in Figs. 18, 19, and 20 has an amplitude which is equivalent or slightly above the background activity and begins at a frequency around 2 Hz. Later in the seizure, the frequency increases to around 4–5 Hz (Fig. 19) but the amplitude does not increase significantly.

Seizures often occur in patients with periodic discharges. Sometimes the transition from a periodic discharge to a seizure can be subtle. In Figs. 21 and 22, left central LPDs stop and a subtle left central seizure begins in the middle of the page in Fig. 21. Figure 22 demonstrates how approximately 30 s later the seizure involves both hemispheres. Figures 23, 24, and 25 demonstrate left parietal LPDs which stop and are replaced with a very subtle low-amplitude high-frequency (beta-range) seizure in the left parietal region. It is more obvious that it is an electrographic seizure toward the end (Fig. 25) when it has spread to involve both hemispheres and the amplitude has increased. GPDs can also transition into seizures. Figures 26, 27, and 28 show GPDs at approximately 1 Hz which transition into being a seizure at the end of Fig. 26 as the amplitude increases and the frequency increases. On the EEG page of Fig. 28, the seizure ends and the GPDs return.

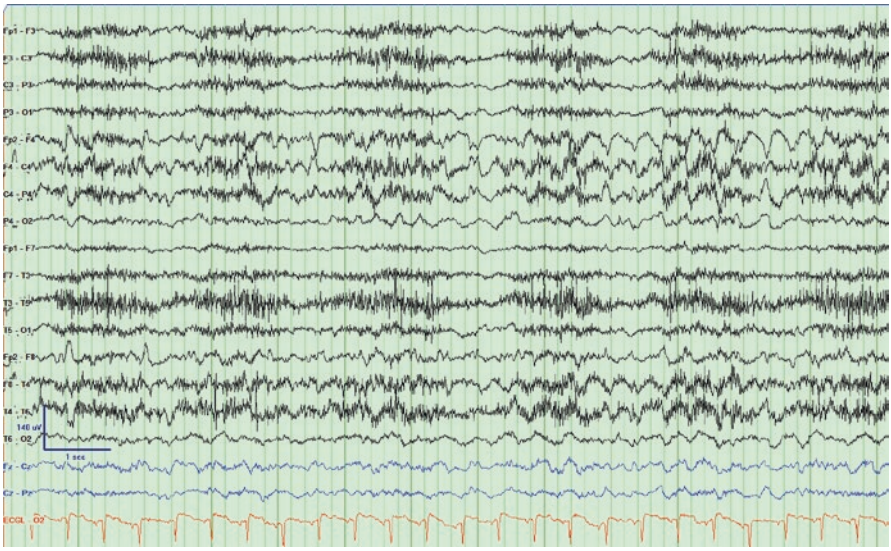

**Fig. 16** Figures 16 and 17 picture consecutive 10-s epochs which show a subtle right central electrographic seizure

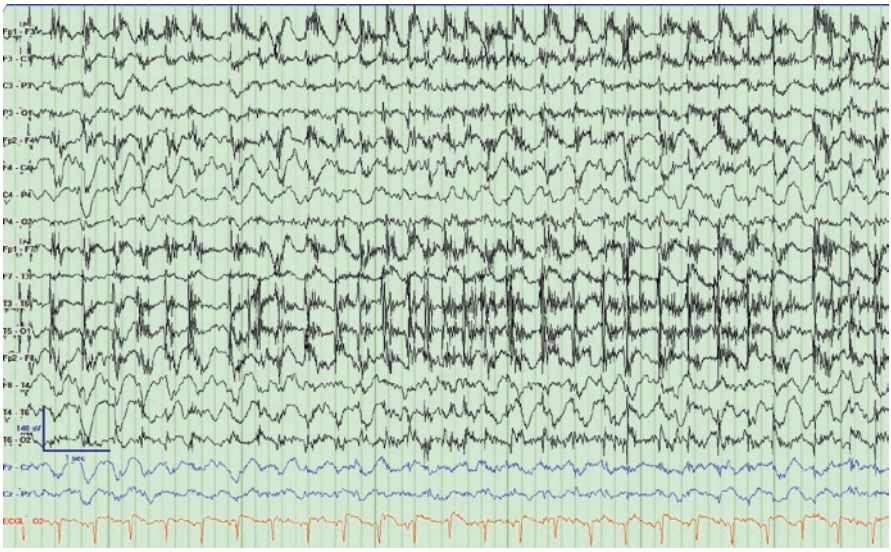

**Fig. 17** Figures 16 and 17 picture consecutive 10-s epochs which show a subtle right central electrographic seizure

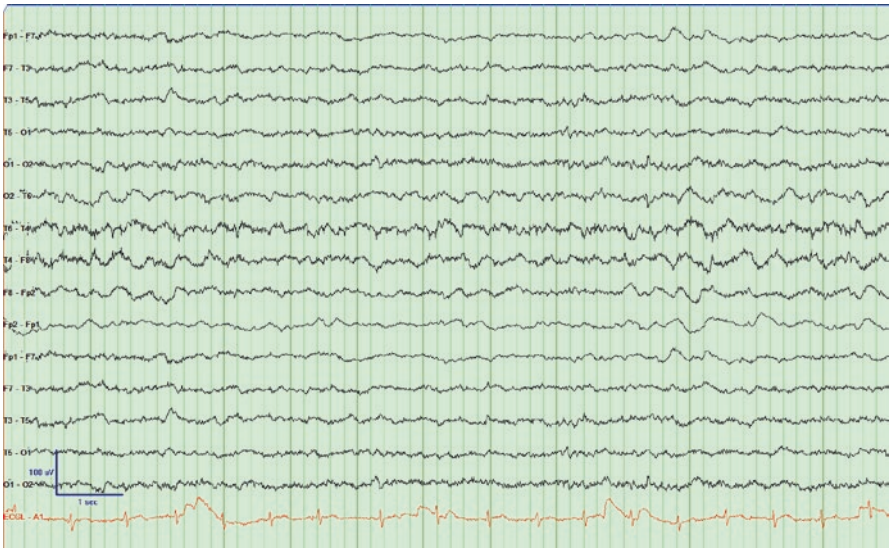

**Fig. 18** Figures 18, 19, and 20 picture consecutive 10-s epochs of a subtle low-amplitude right temporal seizure which begins at a 2 Hz and evolves to a higher frequency of 4–5 Hz

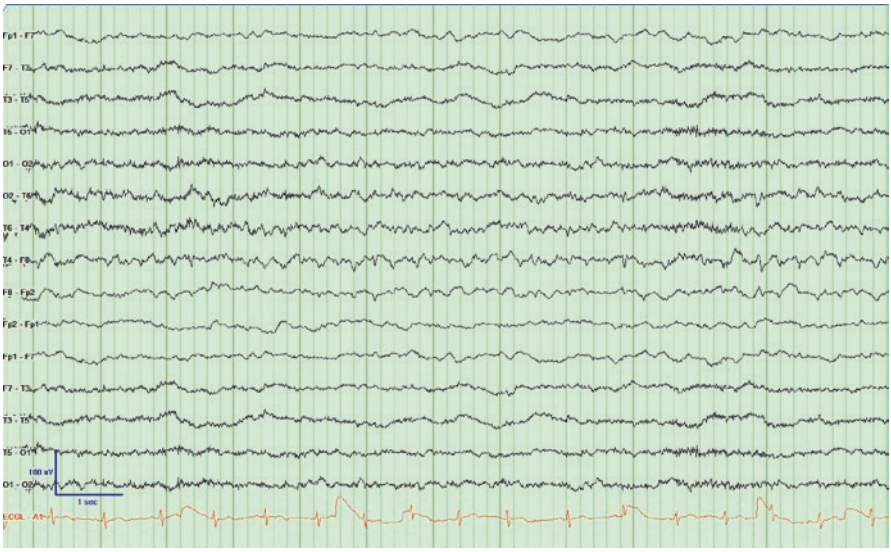

**Fig. 19** Figures 18, 19, and 20 picture consecutive 10-s epochs of a subtle low-amplitude right temporal seizure which begins at a 2 Hz and evolves to a higher frequency of 4–5 Hz

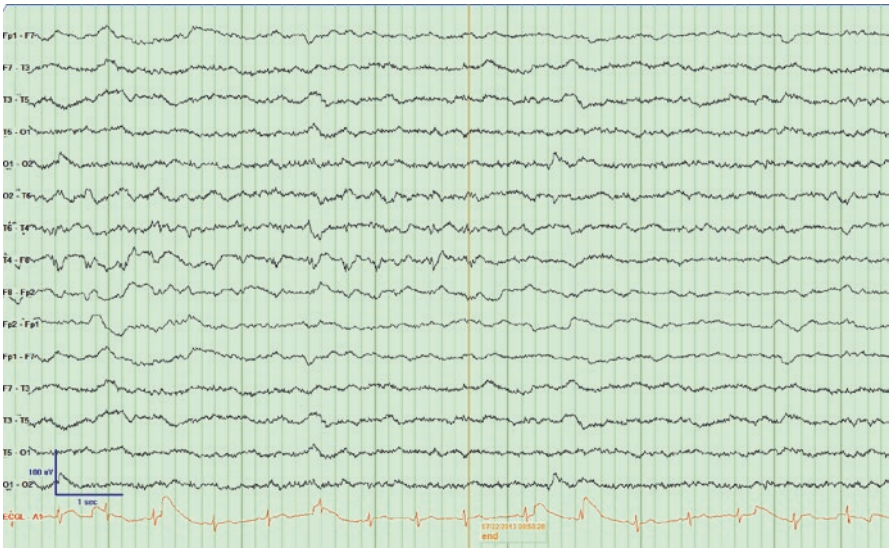

**Fig. 20** Figures 18, 19, and 20 picture consecutive 10-s epochs of a subtle low-amplitude right temporal seizure which begins at a 2 Hz and evolves to a higher frequency of 4–5 Hz

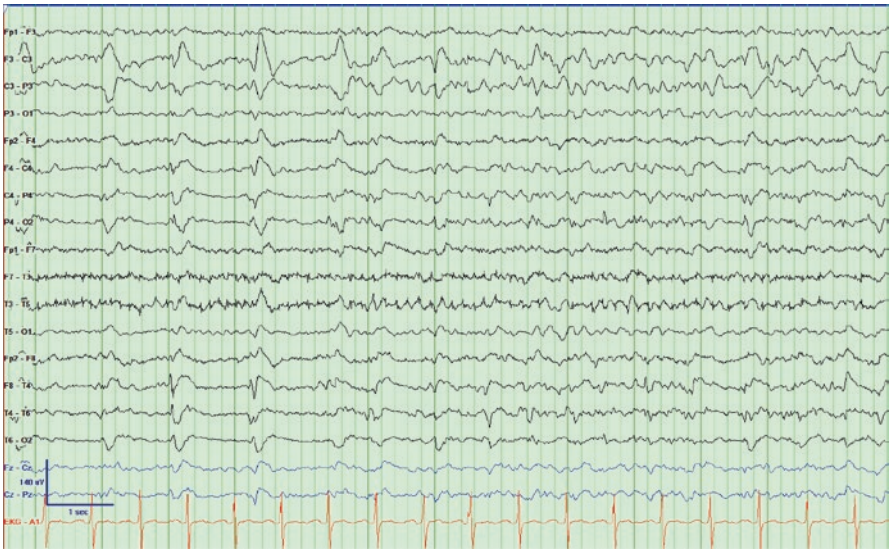

**Fig. 21** The transition from left central LPDs to a subtle left central seizure

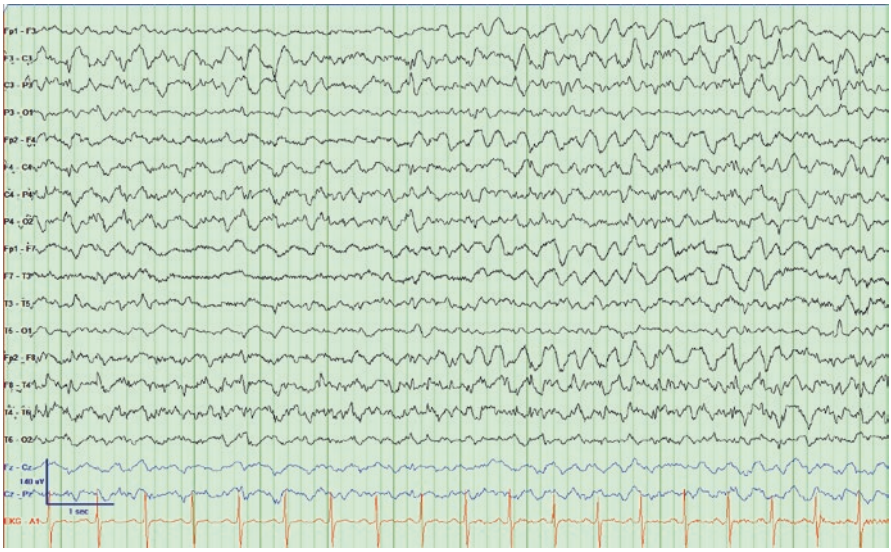

**Fig. 22** The left central seizure in Fig. 21 spreads spatially to involve both hemispheres 30 s later

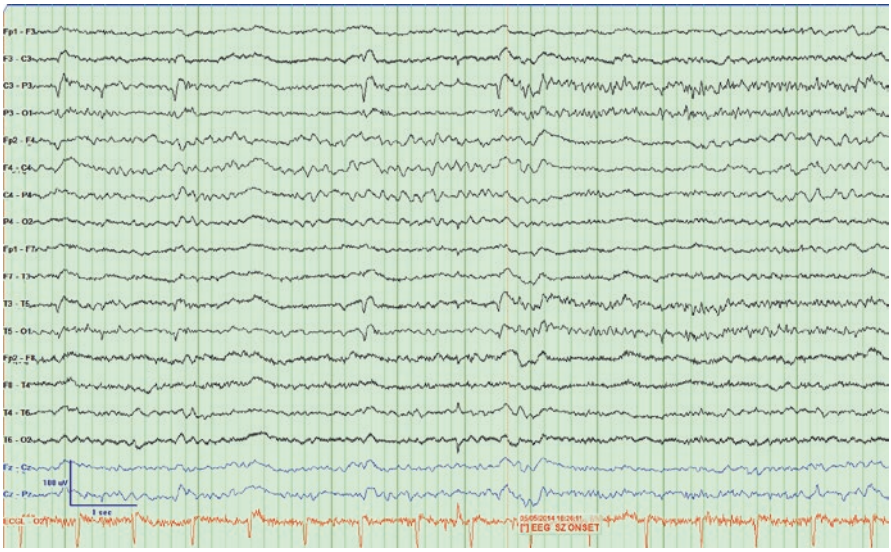


**Fig. 23** Figures 23, 24, and 25 picture consecutive 10-s epochs which show left parietal LPDs which stop and are replaced with a very subtle seizure in the left parietal region

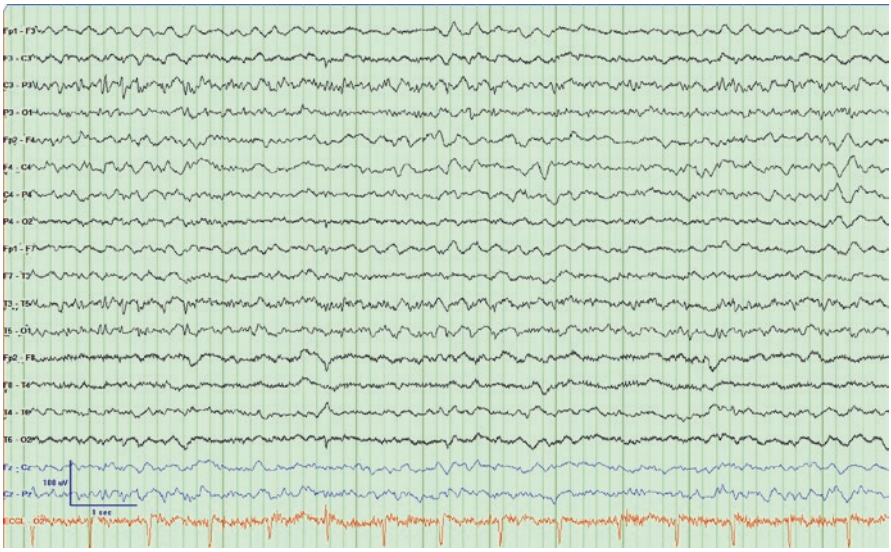

**Fig. 24** Figures 23, 24, and 25 picture consecutive 10-s epochs which show left parietal LPDs which stop and are replaced with a very subtle seizure in the left parietal region

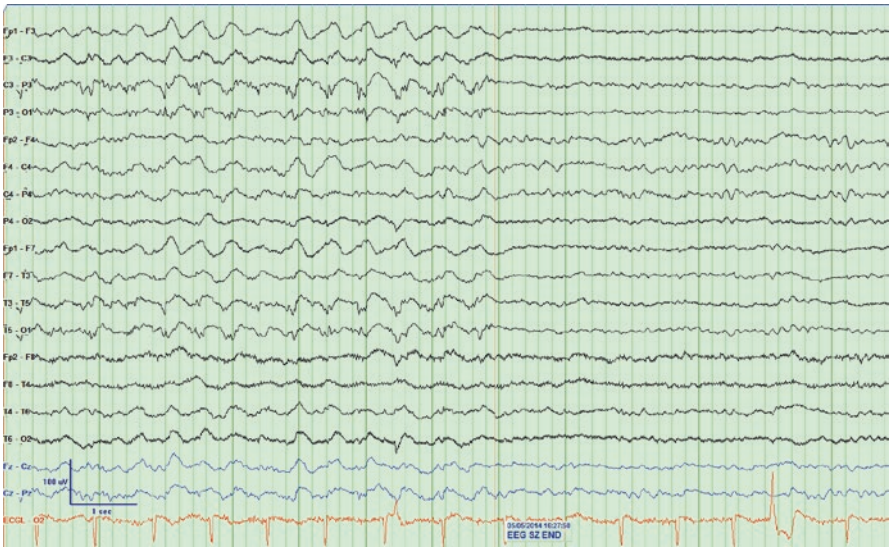


**Fig. 25** Figures 23, 24, and 25 picture consecutive 10-s epochs which show left parietal LPDs which stop and are replaced with a very subtle seizure in the left parietal region

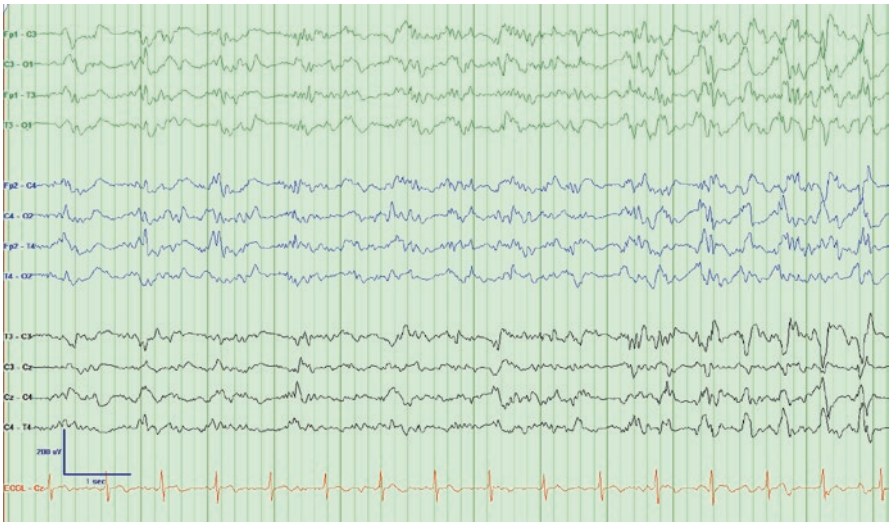

**Fig. 26** Figures 26, 27, and 28 picture consecutive 10-s epochs which show GPDs which transition into being a seizure at the end of Fig. 26 and then by Fig. 28 back to GPDs

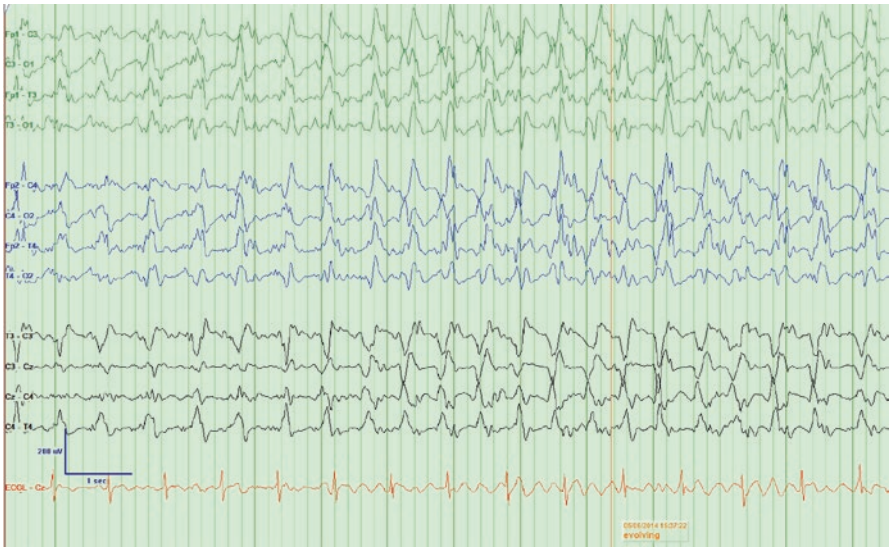

**Fig. 27** Figures 26, 27, and 28 picture consecutive 10-s epochs which show GPDs which transition into being a seizure at the end of Fig. 26 and then by Fig. 28 back to GPDs

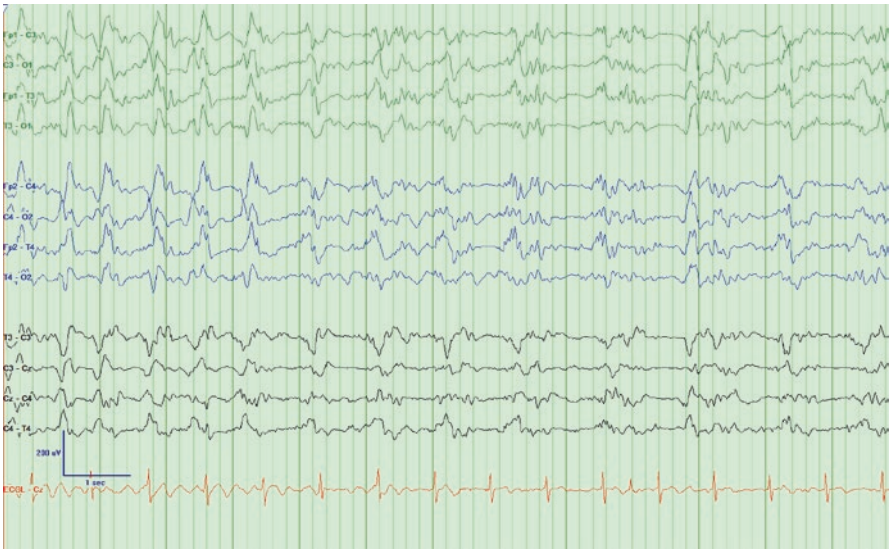

**Fig. 28** Figures 26, 27, and 28 picture consecutive 10-s epochs which show GPDs which transition into being a seizure at the end of Fig. 26 and then by Fig. 28 back to GPDs

**Conclusion**

The detection of seizures is the most important function of cEEG monitoring. Seizures can be seen in many different neurological and medical conditions in a large fraction of critically ill patients. Many of these seizures are subclinical and electrographically subtle. It is important to recognize the risk factors for seizures in critically ill patients including interictal EEG signs such as epileptiform discharges, which can help in the decision of which patients to monitor. There are no automated detection systems that perform well enough to reliably do the work of searching for seizures in cEEG monitoring studies. When reviewing long EEG recordings, human experts also sometimes miss electrographic seizures. Further research is needed to improve automated seizure detection systems and to determine whether the cEEG monitoring improves patient outcomes.

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# Electrographic Seizures in Pediatrics: Recognition and Examples

8

Jessica L. Carpenter, N. Mehta, and T.N. Tsuchida

**Contents**



## Introduction

Increased use of continuous EEG (cEEG) monitoring over the last decade has led to recognition of a relatively high prevalence of electrographic seizures in neonates and children with critical illness. Definitions of seizures and status epilepticus (SE) have evolved along with the increased availability of monitoring. While there are some differences in the frequency of seizures and seizure types in neonates and

J.L. Carpenter (✉) • T.N. Tsuchida
Departments of Neurology and Pediatrics, Children's National Health System, George Washington University School of Medicine and Health Sciences, Washington, DC, USA
e-mail: jcarpent@childrensnational.org

N. Mehta
Floating Hospital for Children at Tufts Medical Center, Department of Pediatrics, Division of Neurology, Tufts University School of Medicine, Boston, MA, USA



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children, both benefit from cEEG. Rates of electrographic-only seizures in these populations are high, and recent studies suggest that electrographic seizures have a negative impact on outcome. This chapter will discuss current definitions of electrographic seizures and SE, as well as indications for cEEG monitoring. The timing and duration of monitoring necessary to obtain the highest yield for seizure detection will also be presented. Examples of electrographic seizures encountered in the intensive care unit are also featured with discussion of strategies to facilitate accurate identification.

## Definitions

### Seizures

In neonates and older children, seizures can be classified as electroclinical, electrographic only, or clinical only.

- Electroclinical seizures are seizures with definite clinical signs coupled with a simultaneous EEG correlate.
- Electrographic-only (nonconvulsive) seizures are abnormal, paroxysmal, encephalographic events that differ from background activity and evolve in frequency, morphology, voltage, or spatial distribution on EEG with duration of at least 10 s [1, 2]. Seizures can consist of evolving epileptiform activity (Fig. 1) or rhythmic theta or delta activity (Fig. 2). There are additional criteria for electrographic seizures in the neonate. Neonatal seizures must have a minimum voltage

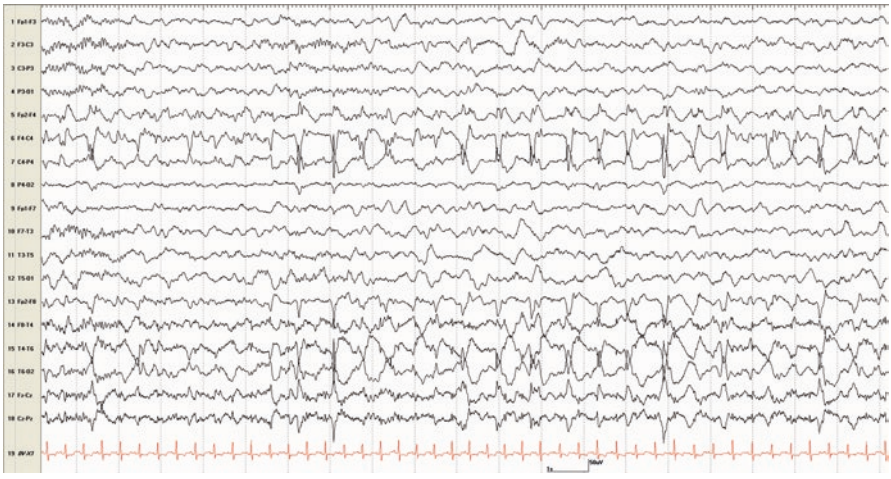

**Fig. 1** A 4-month-old male with presumed abusive head trauma presenting with clinical seizures consisting of clonic movements of the left face and arm. EEG later with focal electrographic seizure without clinical correlate

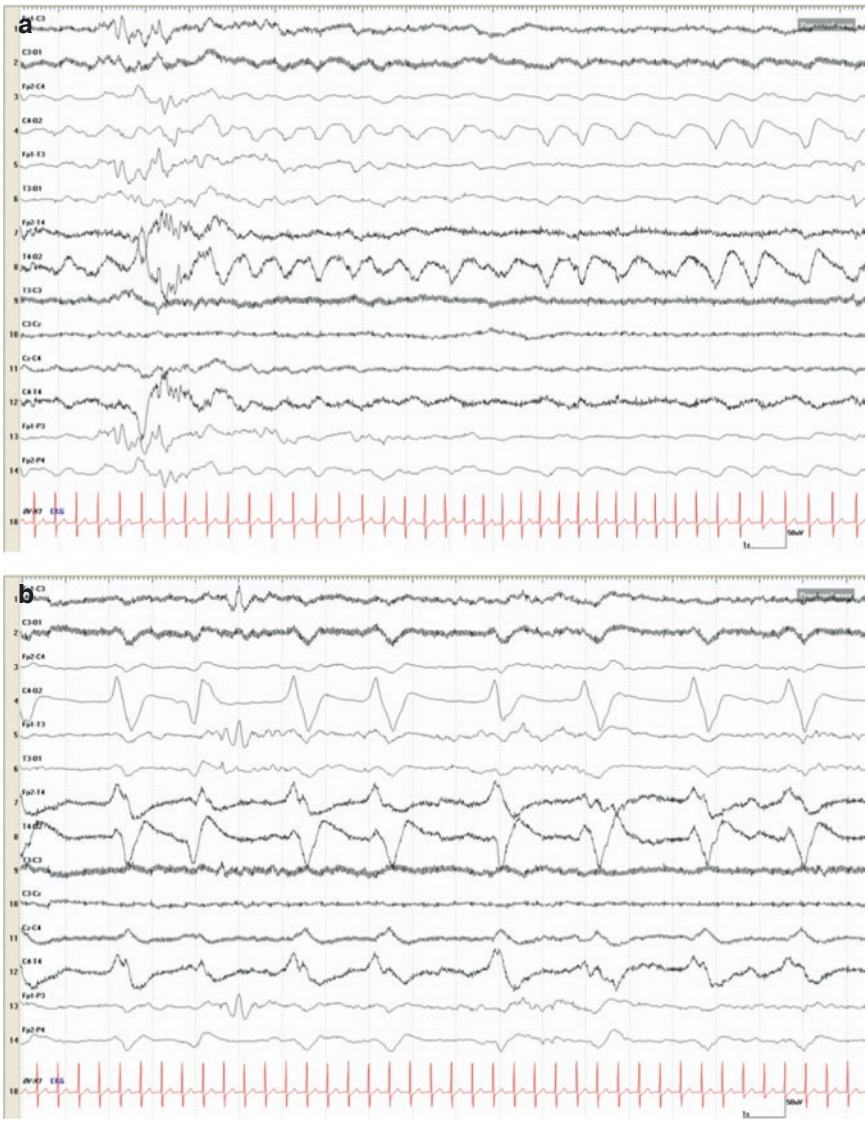


**Fig. 2** Full-term (FT) neonate with HIE, hypothermia, asleep. Seizure consists of evolving RDA rather than spike wave over 3 min. (**a**) first part of seizure, (**b**) towards end of seizure

of 2uV [3]. Additionally there must be 10 s or more between each seizure to characterize them as two separate seizures.

- Clinical-only seizures are abnormal, paroxysmal movements *with no* EEG correlate. These have historically only been described in neonates. Neonatal literature historically has determined outcomes after clinical seizures. Since mortality, epilepsy, and neurodevelopmental outcomes are worse for electrographic

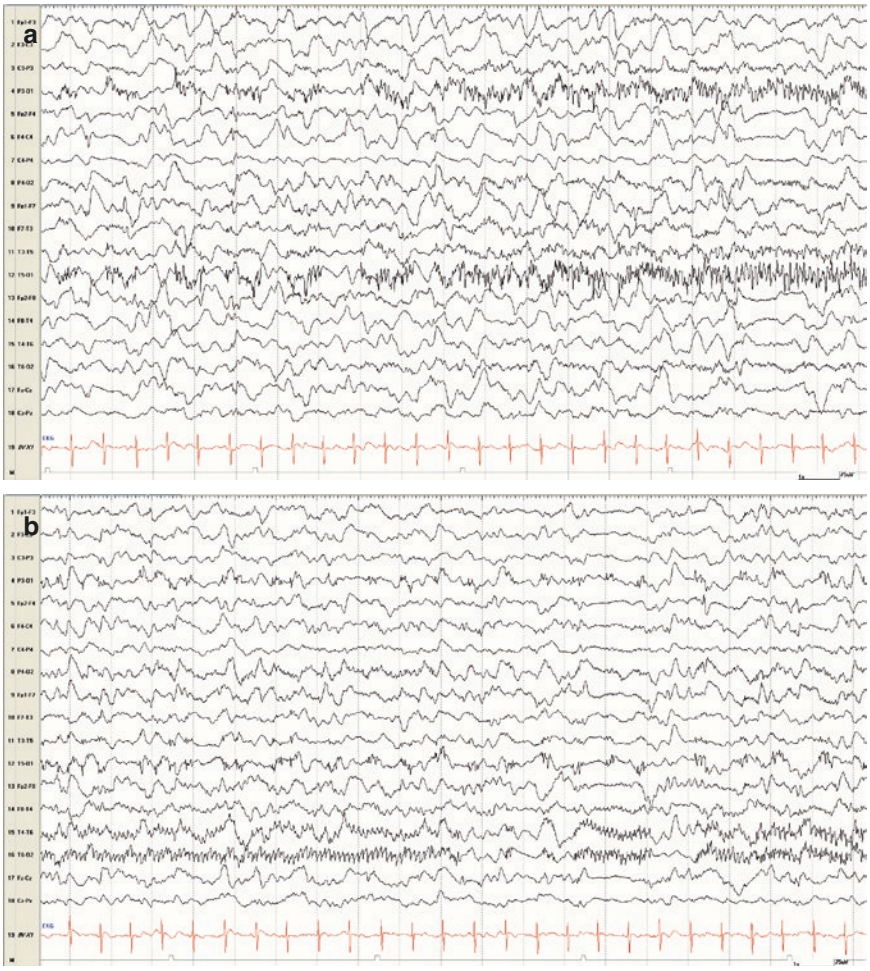


**Fig. 3** (**a**) Atypical initial morphology of intermittent left occipital sharply contoured rhythmic alpha activity in a patient with FIRES. (**b**) Later seizure in the same patient with atypical morphology of rhythmic right temporal alpha activity

compared to clinical seizures, current studies focus primarily on neonates with electrographic and electroclinical seizures [3].

Both neonates and children can have unusual seizure morphology [4] (Fig. 3a, b). To enhance detection of electrographic seizures, it can be useful to display 20–30 s per page (Fig. 4a, b) rather than the typical 10–15 s per page (Fig. 4c–e). If the paroxysmal activity still does not meet full criteria for a seizure (Fig. 5a) or there are unusual features (Fig. 5b–c), review of more cEEG is needed. Either no further concerning paroxysmal activity will occur or features more typical for a seizure will occur (Fig. 5d, e). Since neonates typically have many seizures [5, 22, 32], it is not necessary to make a treatment decision based on a few seizures.

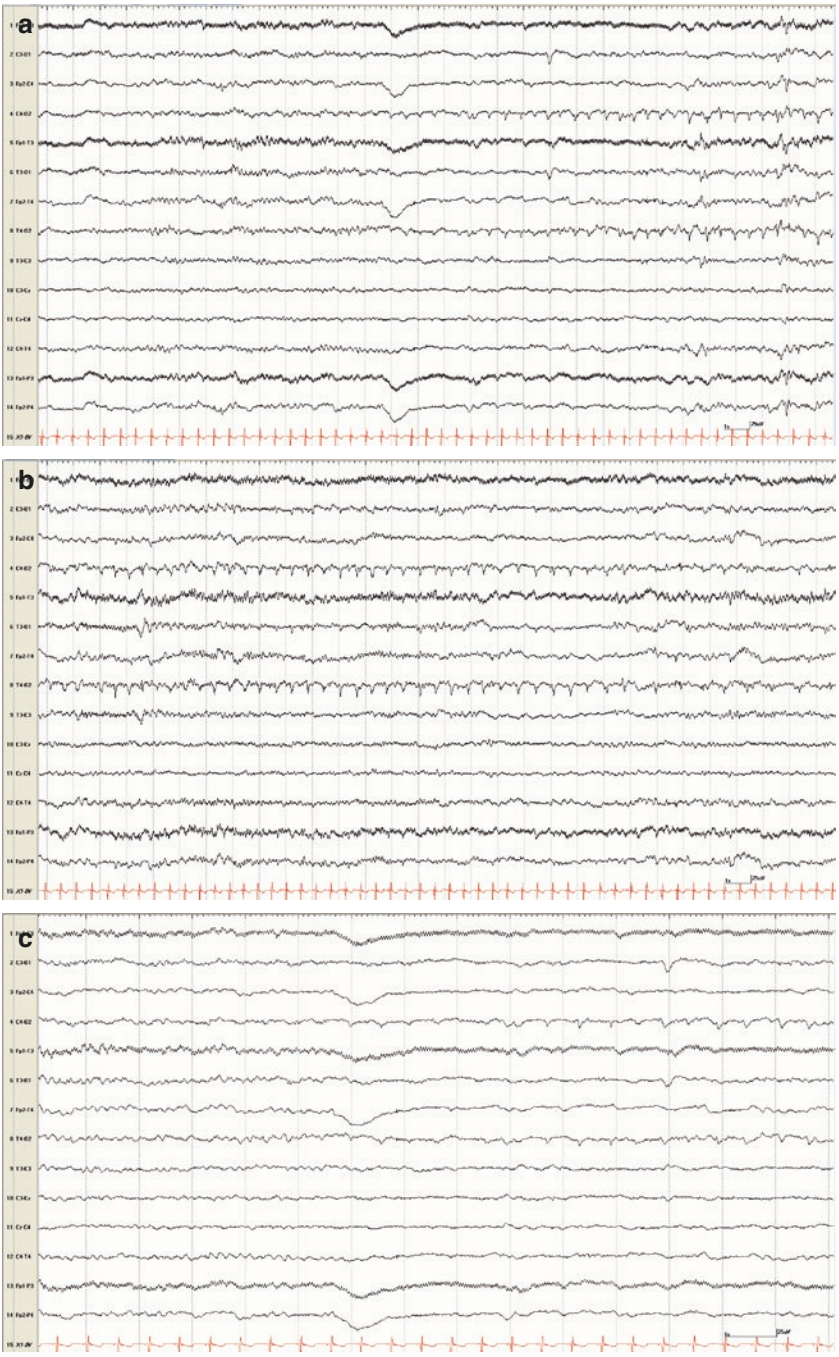


**Fig. 4** A 3-week-old FT neonate with apnea, cyanosis after feeding, and 2–3 min behavior arrest. Initial cEEG no seizure with apnea. Eye flutter, upper body shake 6 days later and put back on cEEG. (**a**, **b**) 30 sec/page. (**c**, **d**, **e**) Seizure looks more like periodic discharges at 15 sec/page

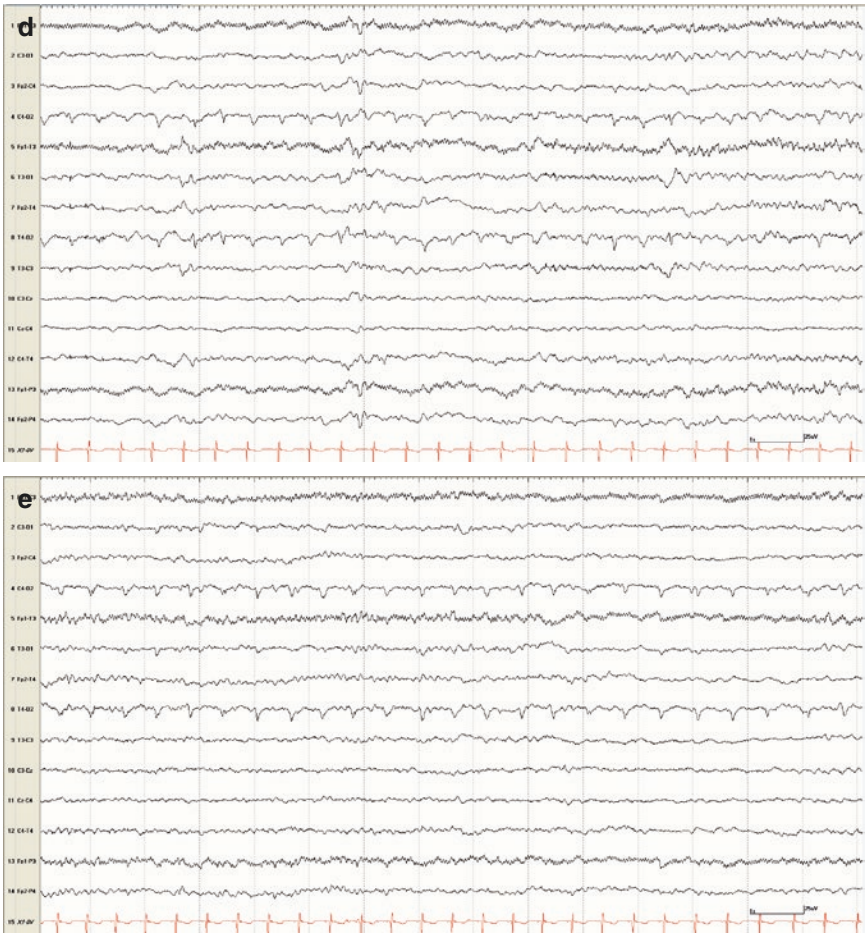


**Fig. 4** (continued)

After administration of medications such as sedatives, paralytics, and antiepileptic drugs (AEDs), patients with initially electroclinical seizures may no longer have clinical correlations to their electrographic seizures. When present, clinical changes can be infrequent and/or subtle, such as paroxysmal changes in heart rate, blood pressure, and/or oxygen saturation [5–7]. Subtle motor movements can be difficult to distinguish from normal movements related to circumstance and age (e.g., intubated infant sucking on an endotracheal tube) and/or abnormal movements not ictal in etiology (e.g., clonus or gaze palsy). CEEG monitoring provides the highest yield when there is video and audio accompaniment. Family members and bedside caregivers should be encouraged to document clinical events of concern, and feedback should be provided when events are or are not correlated with an electrographic seizure.

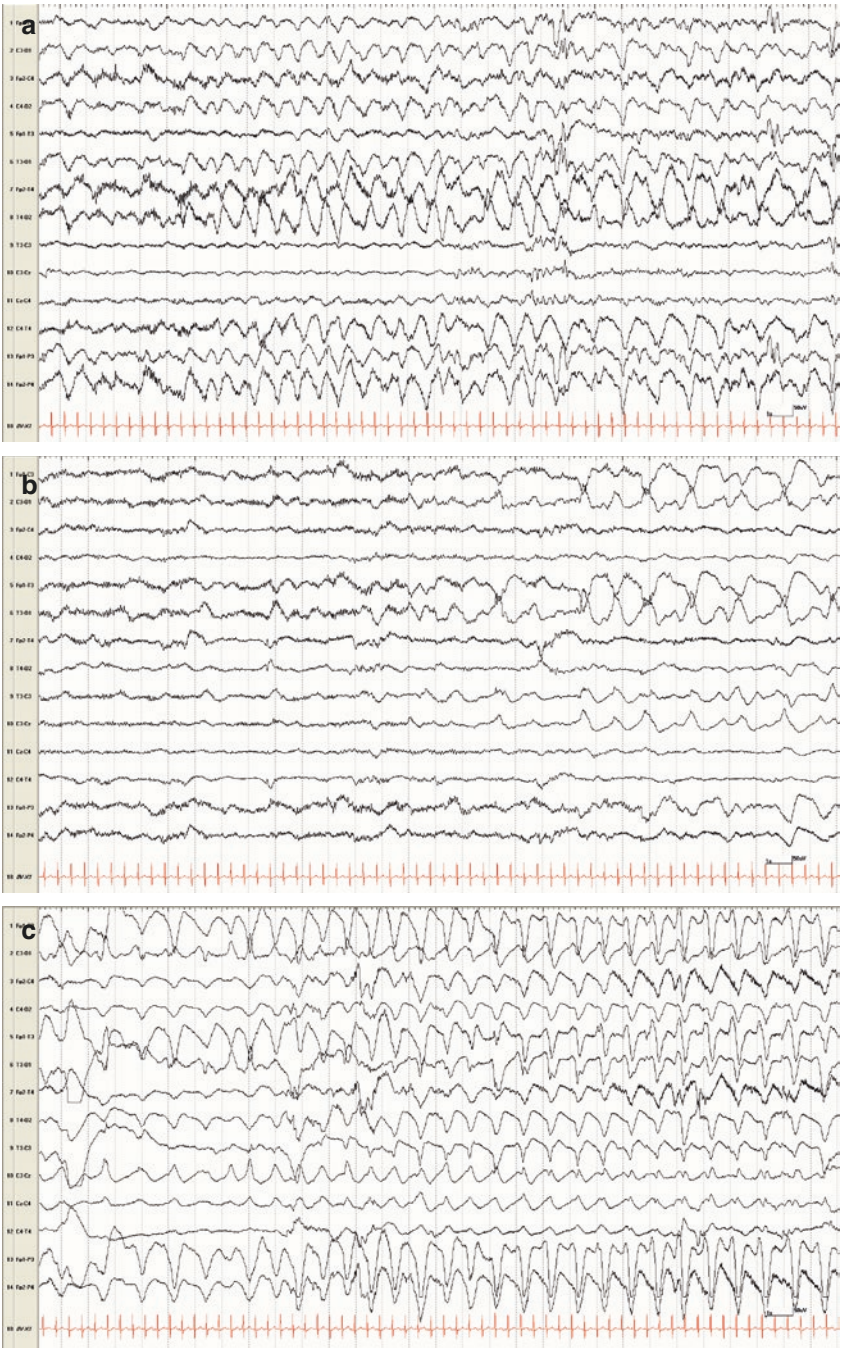


**Fig. 5** (**a**) FT neonate with slightly evolving right posterior quadrant rhythmic delta activity that does not fully meet criteria for seizure. (**b**–**c**) Same neonate later has a seizure with unusual morphology. Initial left centrotemporal rhythmic delta activity (**b**) evolving to left central sharply contoured rhythmic delta activity and left frontal notched rhythmic delta activity (**c**). (**d**, **e**) Same neonate has a seizure with evolving left centrotemporal sharply contoured rhythmic delta activity (**d**) followed by left frontal sharply contoured rhythmic delta activity (**d**) evolving to left frontal spike and wave discharges (**e**)

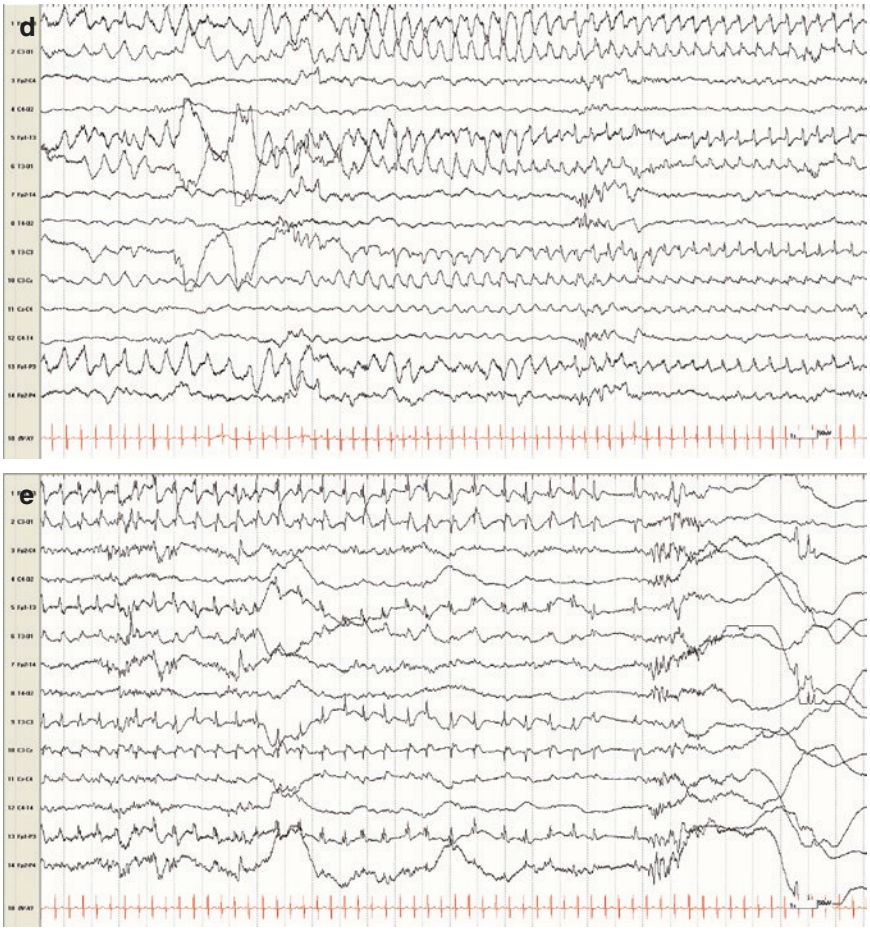


**Fig. 5** (continued)

## Status Epilepticus

SE was classically defined as a clinical event of 30 min duration or multiple events without return to baseline between over 30 min. In 2012, the Neurocritical Care Society (NCS) proposed modifying the above definition by reducing the duration to 5 min [8]. Clinical manifestations of SE are varied but typically include alteration of consciousness, focal motor movements, generalized convulsions, or some combination thereof. The variability of clinical manifestations often makes it difficult to determine the duration of a seizure. Increased availability of EEG monitoring has led to the recognition of subclinical seizures in many patients previously thought to have resolution of their seizure with cessation of motor movements [9–11].

Electrographic SE is defined by EEG characteristics alone. In neonates SE can be classified when the electrographic seizure lasts at least 30 min or when recurrent seizures last more than 50 % of total summed duration of an arbitrary 1-h epoch. In

infants and older children, SE is diagnosed if electrographic seizure activity lasts at least 5 min or if recurrent seizures last at least the same duration without return to clinical baseline in between [8].

## Indications for Continuous EEG

Increased use of cEEG over the last decade has led to recognition of a relatively high prevalence of electrographic seizures in neonates and children with critical illness. Multiple single-center studies and one large multicenter study report similar rates of electrographic seizures in critically ill neonates and children (~30%) of which, up to a third are electrographic only [9–12, 14, 15]. Seizures often occur in the setting of an acute encephalopathy with and without a known central nervous system pathology [11]. Several risk factors for electrographic seizures have been identified and can be used as a guide to determine whom to monitor with EEG and for how long (Table 1). Neonates and infants seem to be at higher risk than older children [9, 11]. Following major neonatal cardiac surgery, the majority of seizures are electrographic only [17]. Neonates with acute encephalopathy and inborn errors of metabolism such as hyperammonemia or glycine encephalopathy or extensive dysgenesis also are at high risk of seizures [12].

The risk of electrographic seizures in those with convulsive SE is greater than 30%, and up to a third of the patients with electrographic seizures have electrographic-only seizures [9, 12, 19]. Once a seizure medication is started, the majority of seizures are electrographic. Some types of neonatal clinical seizures are more likely to be associated with electrographic seizures: focal or multifocal clonic, focal tonic, generalized myoclonic or subtle seizure with gaze deviation in term infants, and subtle seizures like sustained eye opening with visual fixation in preterm infants [20]. There is a less consistent association between electrographic seizures and clinical subtle seizures such as blinking, behavior arrest, nystagmus, and motor automatisms.

There are EEG patterns that suggest a higher risk for seizure. These include interictal epileptiform discharges, periodic discharges and rhythmic patterns in children, and runs of spike and wave discharges in neonates (Fig. 6) [9, 12, 21]. Seizures are less likely with a normal EEG background but can still occur in

**Table 1** Populations at increased risk for electrographic seizures

| |
|---|
| Age less than 24 months [11] |
| Acquired brain injury<br>Stroke [14, 15]<br>Intracranial hemorrhage [16]<br>Traumatic brain injury [13]<br>Hypoxic-ischemic injury<br>Meningitis/encephalitis |
| Cardiopulmonary bypass/ECMO [18, 19] |
| Epilepsy [9] |
| Clinical seizures/status epilepticus [9, 19] |
| Acute encephalopathy [10, 11] |

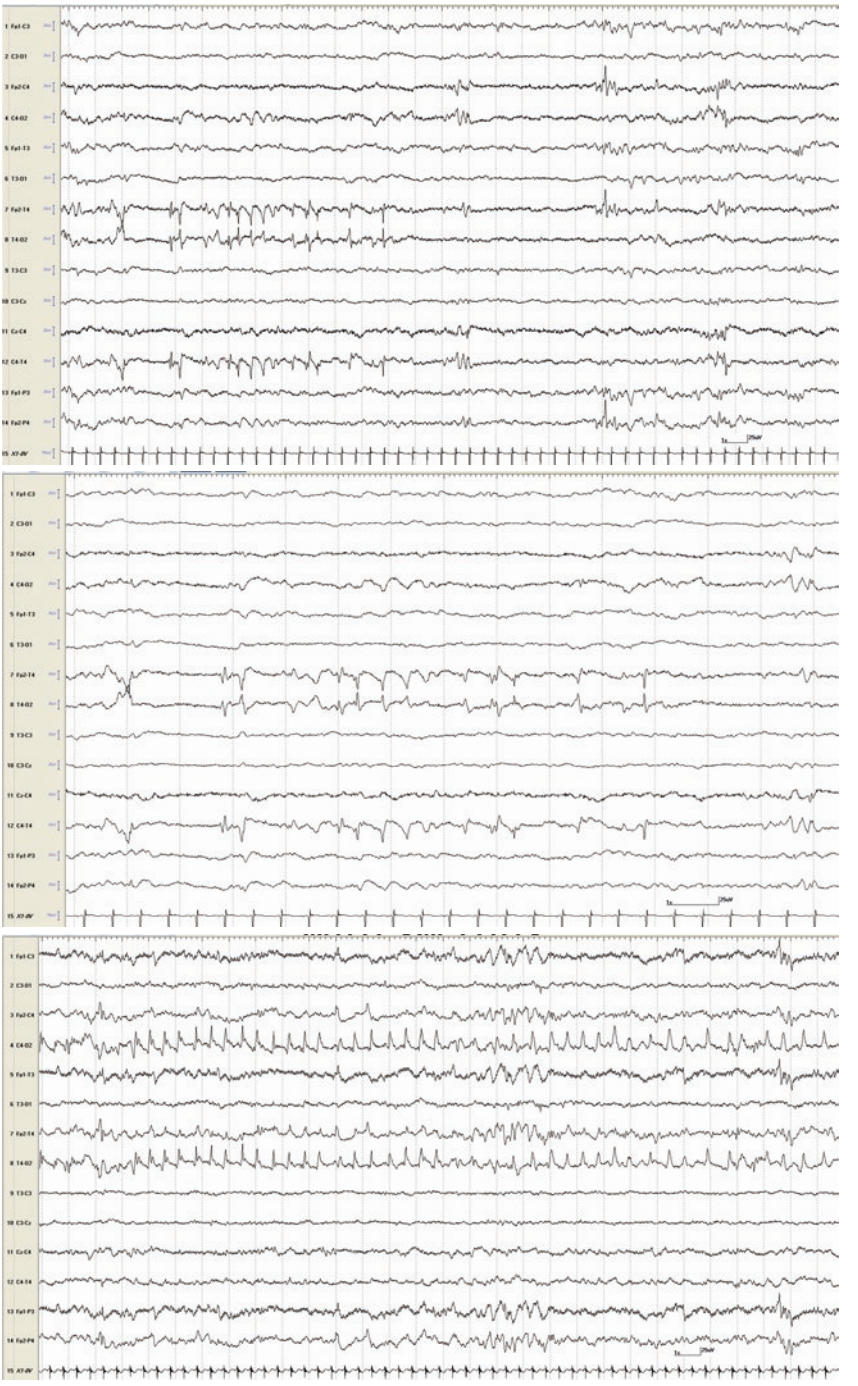

**Fig. 6** FT neonate with runs of right temporal spike wave (top panel at 30 sec/page, middle panel 15 sec/page) prior to seizure (last 2 panels)

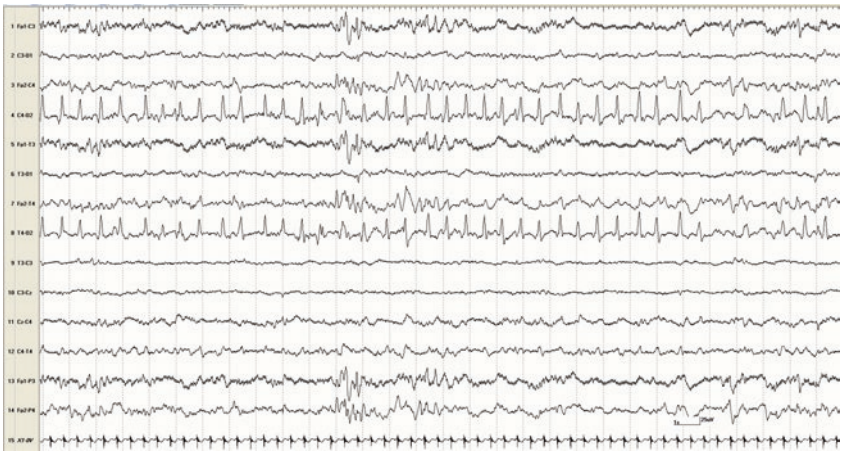

**Fig. 6** (continued)

neonates and children with clinical risk factors for seizures [6, 9, 12]. One study in children suggests there is a greater likelihood for seizures with initial EEG background patterns of burst suppression and attenuated/featureless, but seizures are also more likely to occur with other abnormal patterns such as discontinuous and slow/disorganized [9]. In neonates, an excessively discontinuous background without state changes, burst suppression, or inactive patterns are more likely to occur in seizure patients [23].

Until recently, there was little knowledge on how the presence of electrographic seizures impacted the outcome. Early studies revealed an association with seizures and poor outcome but were not designed to determine if the seizures themselves negatively impacted the outcome or were a marker of more severe disease. Several recent studies suggest worse outcomes in children and neonates with a larger electrographic seizure burden [22, 24–26]. This suggests that using cEEG for early identification and treatment of electrographic seizures may improve outcome.

## Duration of Continuous EEG

CEEG is readily available in many tertiary care centers but is costly and labor intensive and thus not available at all centers. Nonconvulsive seizures were first described in several papers using serial routine EEGs, but since then multiple studies have demonstrated the advantages of cEEG over routine EEGs for seizure detection. Since seizures can occur more than an hour apart, routine EEGs may not detect all neonates with seizures [27]. In addition, seizures occur in the first hour of recording in 60 % or less of neonates and children [11, 12]. Finally, since the majority of seizures are electrographic, especially after starting seizure treatment, more seizures are detected on cEEG compared to routine EEG [11, 12, 19].

Optimal duration of cEEG to ensure adequate seizure detection may vary by clinical scenario. The literature is fairly consistent in reporting more than 85 % of electrographic seizures are captured in the first 24 h of cEEG [11, 12, 28]. If cEEG is started at or near the time of a neonatal insult, up to 36 hours of monitoring may be needed [29–32]. Most clinical guidelines recommend 24–48 h of monitoring for high-risk populations [12].

Duration of cEEG during therapeutic hypothermia for hypoxic-ischemic encephalopathy has not been well established. Neonates may need to be monitored for at least 78 h, as seizures can occur in neonates during the rewarming period [33, 34]. Children undergoing therapeutic hypothermia should also have cEEG until rewarmed since electrographic seizures present both during the 24 h of hypothermia and the rewarming period [35].

There is less consensus on how long patients should be monitored once seizures are controlled. Neonatal and pediatric consensus guidelines suggest that cEEG should be continued for 24 h following the cessation of seizures [12]. Decisions should be tailored to the resources available for EEG recording and the individual patient's risk of seizure recurrence based on seizure etiology and EEG features.

In some patients, it may be difficult to tell whether the seizures have resolved after use of a seizure medication. The appearance of the seizure can change, such that definitive spike and wave discharges are no longer present (Fig. 7). Sometimes the seizures are replaced by low-voltage poorly evolving runs of spike and wave discharges. When they are at the same location as the prior seizures, additional seizure treatment may be considered. In other children, a seizure (Fig. 8a) may be replaced by periodic discharges that wax and wane but do not clearly evolve (Fig. 8b, c). Unless there is also clinical accompaniment, this pattern would not typically prompt escalation of seizure management.

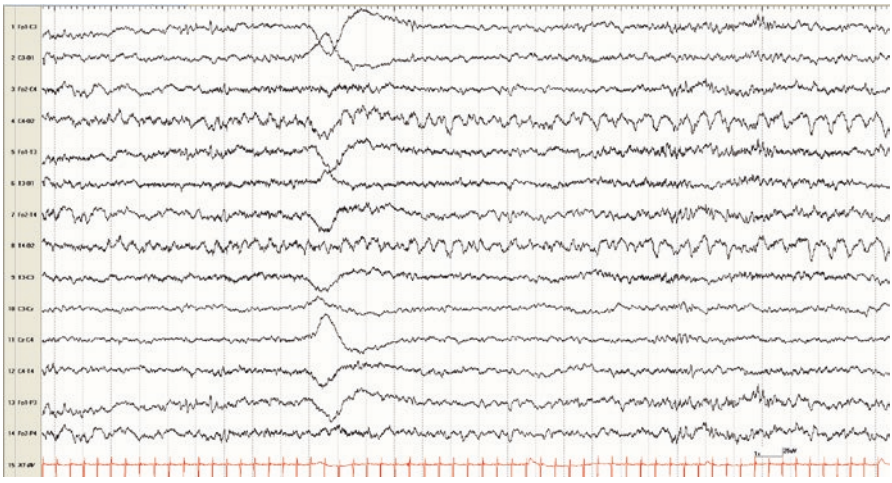

**Fig. 7** Same neonate in Fig. 4a, b. After Keppra 30/kg, seizure consists of evolving rhythmic delta activity rather than spike wave. Left arm clonic jerking in last 10 sec of seizure

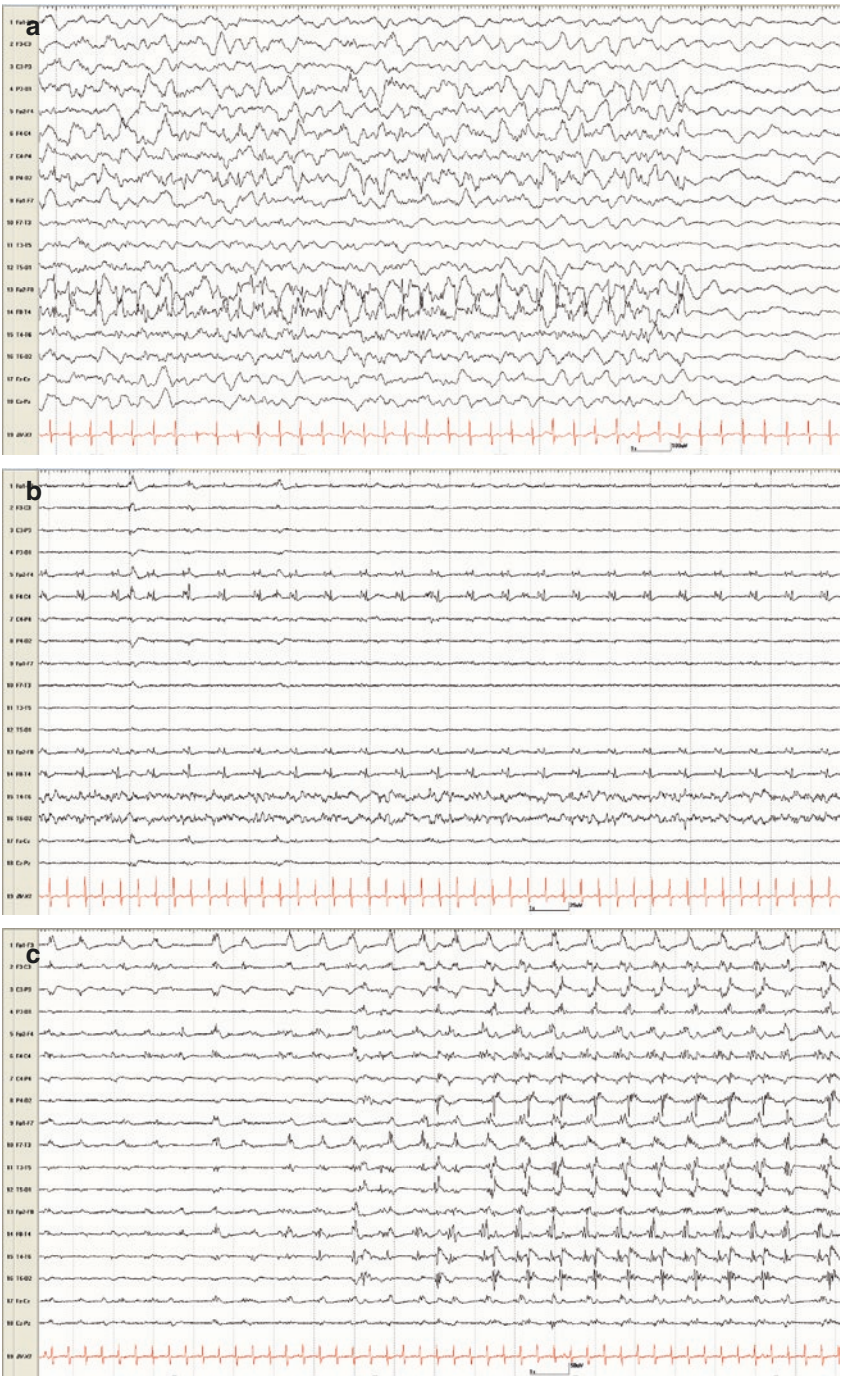


**Fig. 8** (**a**) A 7-year-old female with superrefractory status epilepticus treated with pentobarbital infusion. Right frontal seizure with clinical correlate prior to treatment with anesthetics. (**b**) After initiation of pentobarbital, electroclinical seizure consisting of right frontal periodic discharges. (**c**) Electroclinical seizure consisting of generalized discharges after initiation of pentobarbital

## Accurate Identification of Electrographic Seizures

CEEG can be used to characterize clinical events not associated with an electrographic seizure, thus minimizing the unnecessary use of AEDs. In one pediatric study, 21 % of children with events concerning for seizure did not have confirmed electrographic seizures on cEEG [36]. Neonates whose seizures are not causing hemodynamic instability and are not in SE should have cEEG to confirm the presence of seizures prior to treating with an AED. Multiple studies indicate that neonates thought to have seizures can later be found to have abnormal movements and no seizures on EEG [20, 37, 38]. In one study, 73 % (129/177) of behaviors thought to be seizures were actually generalized muscle clonus, jitteriness, or subtle movements (mouthing, fisting) [37]. In another study, utilizing 11 seizures and nine non-seizure video EEG clips, physicians ($n=91$) and nurses ($n=46$) identified seizures correctly 54 % and 48 % of the time. Behaviors incorrectly identified as seizure included nonspecific movements (44 % of reviewers), sleep myoclonus (44 %), and clonus (70 %) [38].

## Artifacts Mimicking Epileptiform Activity and Seizures

The intensive care unit (ICU) setting there are many different sources of artifact that can mimic rhythmic activity, epileptiform activity, and seizures. Artifacts from the environment include patting, ventilators, sequential compression devices (SCD), and oscillating beds (Fig. 9a–c). Patient-generated artifacts include ECG and body movements such as sucking and respirations that are seen at all ages. Patting artifact mimicking rhythmic or epileptiform activity is common in neonates and infants (Fig. 10) and usually can be distinguished from an electrographic seizure by lack of evolution. In addition, activity due to artifact will often appear in a single electrode (in non-neonates) or lack a physiologic field. Neonate sucking and chewing movements can create artifact at the temporal electrodes that look like muscle artifact or spikes. Pulse artifact can be seen at the vertex in neonates and young infants due to the open fontanelle. Synchronous video is always helpful to determine whether the abnormal activity is artifact, epileptiform, or seizure and should be reviewed if there are atypical features such as no physiologic field, unusual morphology, and/or atypical evolution.

## CEEG and Seizure Etiology

The cEEG background pattern in isolation is not diagnostic of a particular seizure etiology. However, the cEEG combined with clinical risk factors and seizure semiology can be helpful. Localization of seizures may suggest a particular etiology such as posterior reversible encephalopathy syndrome (PRES) in children with hypertension, encephalopathy, and posterior seizures. In neonates, a normal or mildly abnormal background suggests benign familial neonatal convulsions in

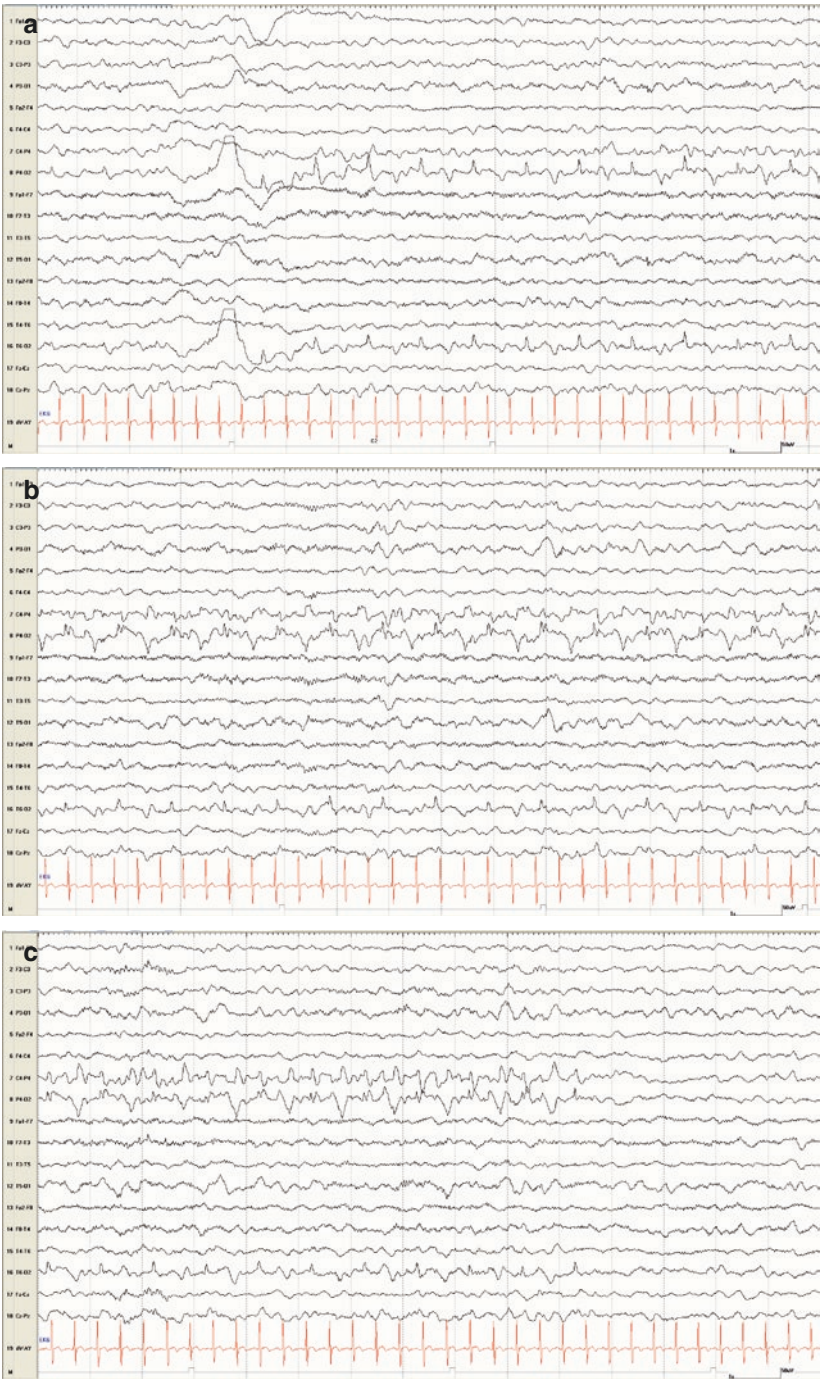


**Fig. 9** Bed rocking artifact with evolution mimics an electrographic seizure. (**a**) onset of rocking (**b**) middle. (**c**) end

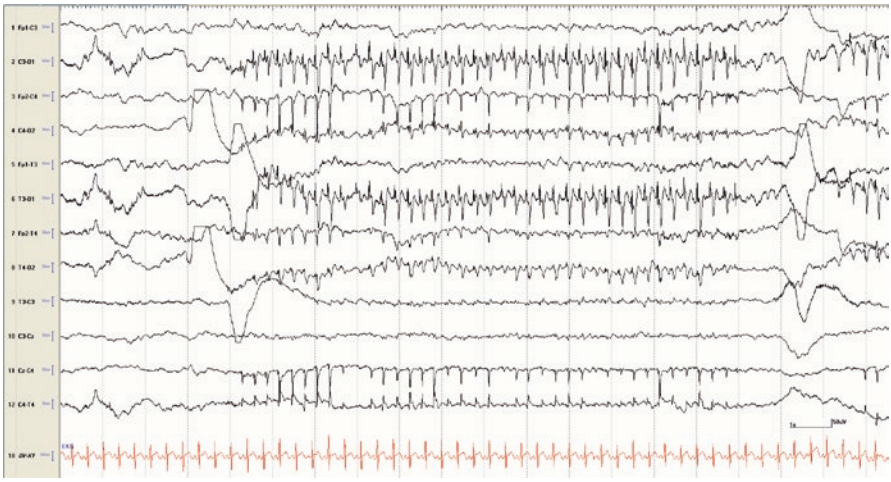

**Fig. 10** A 11-day FT neonate from Fig. 6 after seizure treatment. Pat artifact rather than seizure identifiable on EEG due to lack of evolution and physiologic field

contrast to high-amplitude, slow, and multifocal spike wave and random suppression that can have a burst suppression appearance in KCNQ2 encephalopathy. In contrast, CDKL5 and migrating partial seizures of infancy can have an interictal EEG background pattern that is normal or slow when the infant or child is having daily multifocal or generalized seizures.

A burst suppression pattern that is sustained and not due to a neuroactive medication has a limited number of neonatal etiologies including severe hypoxic ischemic encephalopathy (HIE), pyridoxine dependency, and the syndromes of early myoclonic epileptic encephalopathy and early infantile epileptic encephalopathy, also called Ohtahara syndrome [39]. Evolution of the burst suppression pattern can be helpful since the burst suppression pattern resolves within weeks to a month after HIE. In contrast, the burst suppression pattern is sustained for infants with epileptic encephalopathies.

The presence of electrographic seizures in critically ill neonates and children without a history of epilepsy should prompt an evaluation for acute brain injury [40, 41]. When multifocal seizures are present there could be to a diffuse process such as meningitis/encephalitis. When unifocal seizures occur, a focal process such as intracranial hemorrhage or ischemic arterial stroke is more likely [42].

## CEEG and Changes in Cerebral Physiology

Neonates and older children with seizures can benefit from cEEG in ways other than seizure detection and management. Other chapters in this book discuss EEG background patterns that are useful for predicting mortality and neurologic morbidity. While this can be done with a short segment of EEG, cEEG is needed to

detect dynamic changes in cerebral activity. As with adults, the cEEG can be used for titrating pentobarbital to induce pharmacologic burst suppression for intracranial pressure management. Changes in cEEG background patterns over time can indicate changes in brain physiology that prompt new diagnostic evaluations and/or treatments. A new asymmetry in cEEG background activity can indicate an acute focal injury. A significant change in the background pattern, such as changing from excessively discontinuous to inactive over a few hours, may indicate acute severe cerebral injury [40]. Increasing interburst interval duration in an EEG showing burst suppression in neonates with citrullinemia is a sign of increasing ammonia levels [43]. Both neonates and children have increased discontinuous activity with decreasing blood flow [44, 45]. The ability of cEEG to indicate changes in cerebral activity makes it a useful adjunct for clinical management of neonates and children in the ICU.

**Conclusion**

There are minor differences in the definition of seizures and SE in neonates as compared to children. The most commonly used ICU EEG definition of SE is shared by neonates and children, and there are similarities in seizure detection and management in these patients. EEG at all ages is useful for both management of seizures and other conditions that commonly occur in the ICU setting.

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# Patterns of Uncertain Significance

9

Aneeta R. Saxena and Lawrence J. Hirsch

**Contents**



A.R. Saxena, MD (✉)
Comprehensive Epilepsy Center, Yale University, New Haven, CT, USA
e-mail: aneetasax@gmail.com

L.J. Hirsch, MD
Comprehensive Epilepsy Center, Yale University, New Haven, CT, USA

Division of Epilepsy and EEG, Comprehensive Epilepsy Center, Critical Care EEG Program, Yale University School of Medicine, LLCI-714, 208018, New Haven, CT 06520-8018, USA
e-mail: lawrence.hirsch@yale.edu



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## Introduction

With increasing use of continuous EEG (cEEG), patterns of uncertain significance are being recognized, and they can complicate treatment decision making. In this chapter, several of these patterns of uncertain significance are discussed. Some (but not all) are defined by the formal American Clinical Neurophysiology Society (ACNS) nomenclature, readily available at www.acns.org, including a self-teaching training module.

Specifically, this chapter will discuss the following patterns: stimulus-induced rhythmic, periodic, or ictal discharges (SIRPIDs), lateralized rhythmic delta activity (LRDA), brief potentially ictal rhythmic discharges (B(I)RDs), the concept of the ictal-interictal continuum (IIC), and generalized rhythmic delta activity (GRDA). These patterns will be identified and discussed, prevalence and clinical associations will be described, and a reasonable approach to patient management will be presented.

## Stimulus-Induced Rhythmic, Periodic, or Ictal Discharges

### Description and Definition

Stimulus-induced epileptiform patterns or seizures have been noted for some time in the field of epilepsy. From a critical care standpoint, it was initially described in the postanoxic population as it pertains to stimulus-induced or exacerbated myoclonus, usually with a burst-suppression pattern on EEG. Traditionally, it has been thought that periodic or rhythmic patterns induced by alerting stimuli were similar to arousal patterns and therefore not considered worrisome or potentially ictal. With the increasing use of video with cEEG monitoring, it was recognized that seizures and other highly epileptiform patterns were commonly induced by a variety of alerting stimuli. In 2004, these patterns were formally described (by one of the authors) as "periodic, rhythmic, or ictal appearing discharges that were consistently induced by alerting stimuli such as auditory stimuli, sternal rub, examination, suctioning, turning and other patient-care activities" [1]. Ictal-appearing was defined as "any rhythmic discharge or spike and wave pattern with definite evolution in frequency, location or morphology; evolution in amplitude alone was not considered evidence of ictal appearing" [1]. In the formal ACNS nomenclature, any pattern that is induced by alerting stimuli receives an "SI-" prefix for "stimulus induced."

Patients with SIRPIDs of any type may also have the same pattern at times without obvious stimulation, due to internal stimuli, unrecognized stimuli, or other reasons for sudden alerting. As long as the pattern can be reproducibly caused by alerting stimulation, it qualifies as SIRPIDs or can receive the "SI-" prefix. Similarly, a pattern that is present but becomes much more prominent with stimulation (often higher amplitude and frequency, sometimes developing a clinical correlate) falls under the umbrella of SIRPIDs or the "SI-" prefix. See Figs. 1 and 2 for example of SIRPIDs.

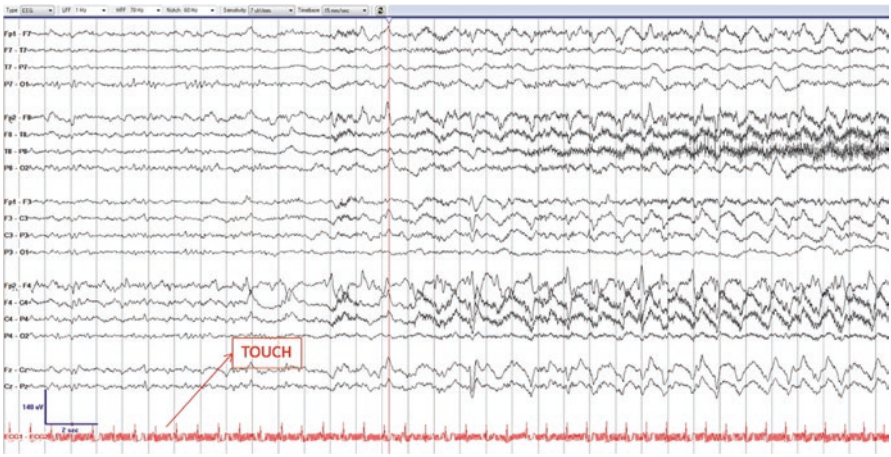


**Fig. 1** SI-LRDA+S: A 64-year-old female with subarachnoid hemorrhage, status post clipping and placement of right frontal external ventricular drain. EEG shows stimulus-induced lateralized rhythmic delta with embedded sharps (SI-LRDA+S) after nurse touches patient; there was no visible clinical response. Sensitivity 7 uV/mm, low frequency filter 1 Hz, high frequency filter 70 Hz, notch 60 Hz, 15 mm/s

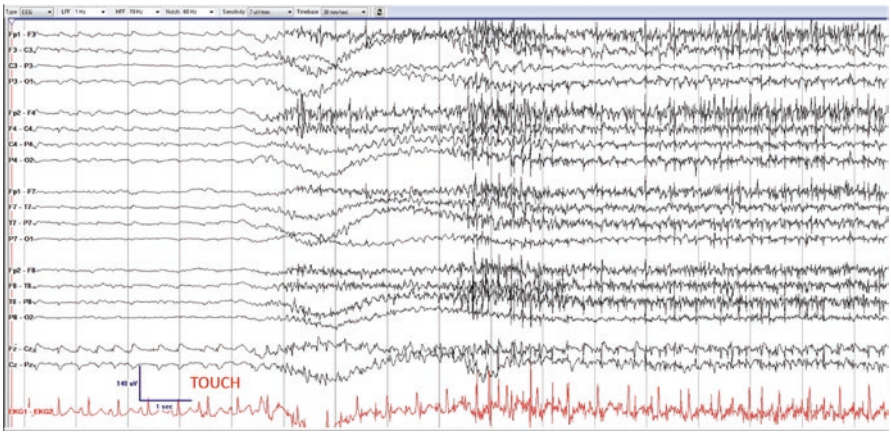


**Fig. 2** SI seizure. A 52-year-old man status post pulseless electrical activity cardiac arrest and history of alcoholism. EEG shows a stimulus-induced seizure with clinically associated jerking of trunk more than limbs. Sensitivity 7 uV/mm, low frequency filter 1 Hz, high frequency filter 70 Hz, notch 60 Hz, 30 mm/s

Stimulus-induced seizures or periodic discharges likely arise from activation of arousal pathways, including thalamocortical projections, in conjunction with hyperexcitable cortex. Stimulation acts upon normal arousal circuitry, initiated in the upper brainstem reticular activating system and projecting through the reticular nucleus of the thalamus and widespread thalamocortical connections. A highly

epileptiform or ictal pattern is thought to occur when hyperexcitable cortex is activated through normal arousal circuitry.

Clinical manifestations are rare with SIRPIDs but may be present, partially depending on the location of the area of cortical hyperexcitability. In a case series from 2008, slightly more than half of the patients with clinical seizures induced by alerting stimuli had lesions in the primary motor region, which may explain the stimulus-induced focal motor seizures [2]. Clinical seizures imply a well-organized propagation of ictal discharges through the cerebrum and brainstem generating clinical motor activity. In some cases, patients' brains are probably too impaired to generate this type of synchronous, organized, and propagating electrical activity, even if motor pathways are involved.

## Prevalence and Clinical Context

The prevalence of SIRPIDs in the intensive care unit (ICU) population was found to be approximately 22 % of patients placed on cEEG [1]. Although most commonly seen with intracerebral hemorrhage (ICH), SIRPIDs were seen with a variety of acute brain injuries such as subarachnoid hemorrhage (SAH) and cerebral infarction. Clinical status epilepticus (SE) was more common in patients with focal or "ictal-appearing" SIRPIDs than non-ictal-appearing SIRPIDs. In addition, patients often had more than one type of SIRPID. The type of SIRPID, ictal versus non-ictal, did not correlate with clinical outcome. Most patients were found to be comatose on the days they showed SIRPIDs. Rarely (probably less than 5 %), SIRPIDs are associated with a clinical manifestation as shown in the case series mentioned above [2]. In this series, nine comatose or encephalopathic patients had clear stimulus-induced focal clinical seizures typically involving clonic hand, face, or upper arm movements. These focal clinical motor seizures were consistently seen after a stimulus, removing any doubt about the ictal nature of these events [2].

## Treatment and Management

There are no guidelines on treatment of SIRPIDs. At this time the authors advocate treatment of a pattern that is stimulus-induced in the same manner as spontaneous patterns. There is no inherent reason and no experimental data to suggest that seizures or other patterns are more or less harmful or important due to the fact that they are stimulus induced. For example, a photic-induced convulsive seizure has the same pathophysiology and adverse effects as a spontaneous convulsion. Minimizing patient stimulation by bundling clinical care (i.e., nursing, exams, and procedures) and possibly even premedicating bundled clinical care with short-acting benzodiazepines (or other similar agents) remain unstudied but could be helpful. If there was a reliable measure of acute seizure-related neuronal injury, the value of this intervention could be determined.

Stimulus-induced periodic discharges can be treated (as we recommend with most periodic discharges) with the use of a prophylactic antiepileptic drug (AED) in hopes of preventing seizures and monitoring with cEEG to identify and treat electrographic seizures as quickly as possible. The authors do not advocate attempting to eliminate the periodic discharges, especially if 1 Hz or slower, except in rare circumstances.

Imaging studies have been used to look at SIRPIDs to determine if there are metabolic or blood flow effects that may help decide whether or not to treat SIRPIDs. The authors, however, do not find single-photon emission computed tomography (SPECT) to be useful for this purpose. For example, in 2011, SPECT imaging was used to study a patient who had both stimulus-induced periodic discharges and stimulus-induced evolving LRDA [3]. There was no evidence of increased cerebral blood flow (CBF) over the left hemisphere when the patient was injected 5 s after SI-LRDA at 2–3 Hz over the left temporal lobe, which the authors considered a possible ictal pattern. The authors concluded that this finding implied that the pattern was not ictal, and they did not initiate further treatment with AEDs. However, lack of visible increased cerebral blood flow (a subtraction study comparing a time when the pattern was not present may show a relative increase that is not apparent on a single study) does not necessarily imply a pattern is not ictal or that it is not causing harm. In an acutely injured brain, seizures may not generate the necessary increase in CBF needed to match the energy requirement resulting in neuronal injury without any increased CBF. Of note, in the above case study, the patient had a further decline and was treated with additional AEDs. Subsequent to AED treatment, the patient had a stuttering course of recovery.

This case brings to light an ongoing conundrum relating to patterns of uncertain significance. The EEG may demonstrate a pattern that can now be defined; however, it is not clear what to do with this information and further neuroimaging may or may not aid in determining management [3]. SIRPIDs remain poorly understood and require additional research to determine when they cause neuronal damage, when they contribute to the patient's poor mental status, when they require treatment, and if they have independent prognostic significance.

## Lateralized Rhythmic Delta Activity

### Description and Definition

LRDA is defined by the ACNS guidelines as unilateral, or bilateral asymmetric, rhythmic delta activity. Per the guidelines for any pattern to be defined as rhythmic, it must recur regularly for at least 6 cycles in duration, e.g., 1/s for 6 s or 2/s for 3 s. Typically, lateralized rhythmic delta activity (LRDA) is 1–3 Hz in frequency and very brief (more than half were less than 10 s in the only study of LRDA, and almost all were less than 1 min in duration). In contrast, lateralized periodic discharges (LPDs) are typically slower (~1 Hz) and longer in duration (several minutes to hours); however, LRDA seems to carry similar clinical implications as LPDs [4]. See Fig. 3a,b for an example of LRDA and seizures arising from LRDA.

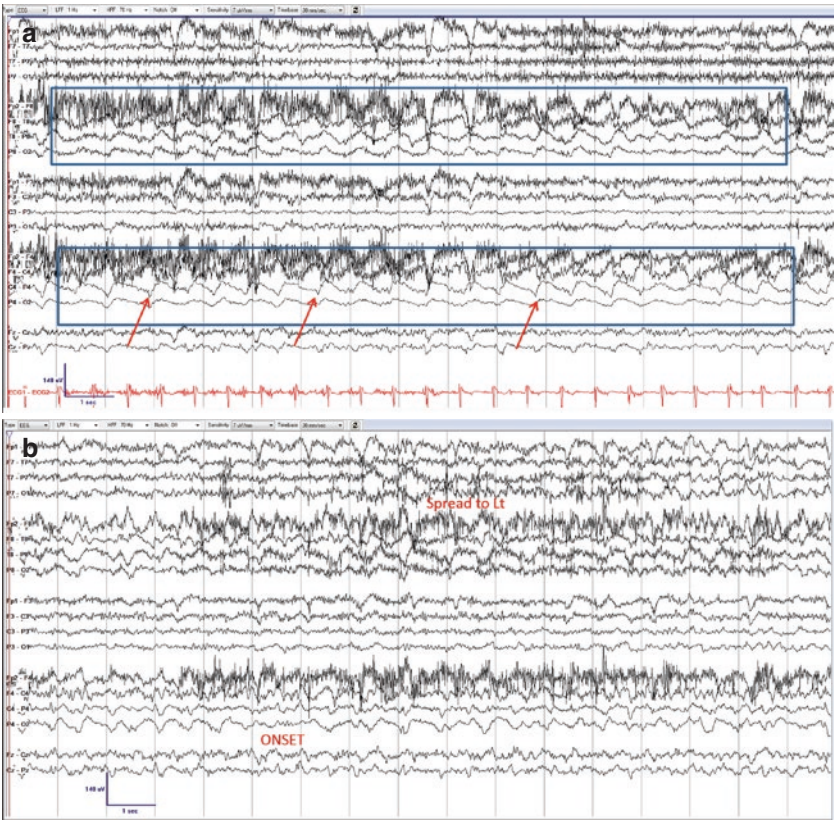


**Fig. 3** (**a**) LRDA: A 60-year-old man with epilepsy, hypertension, and traumatic subdural hematoma, presents with epilepsia partialis continua with continuous jerking of his left side, including during this EEG clip. EEG shows lateralized rhythmic delta (in boxes) with superimposed sharp waves (examples highlighted with *arrows*) (LRDA+S), which suggests a highly epileptogenic focus and high chance of seizures in the near future or past. Sensitivity 7 uV/mm, low frequency filter 1 Hz, high frequency filter 70 Hz, notch off 30 mm/s. (**b**) Seizure in same patient: Above patient with electroclinical seizure arising from LRDA, now spreading to the left and associated with head and arm jerking seen on video, Sensitivity 7 uV/mm, low frequency filter 1 Hz, high frequency filter 70 Hz, notch off, 30 mm/s. (**c**) Evolution of seizure. Sensitivity 7 uV/mm, low frequency filter 1 Hz, high frequency filter 70 Hz, notch off, 30 mm/s. (**d**) Seizure ends (note return of nearly normal EEG activity on the left, in box) and LRDA+S continues over the right (ellipse). Sensitivity 7 uV/mm, low frequency filter 1 Hz, high frequency filter 70 Hz, notch off, 30 mm/s

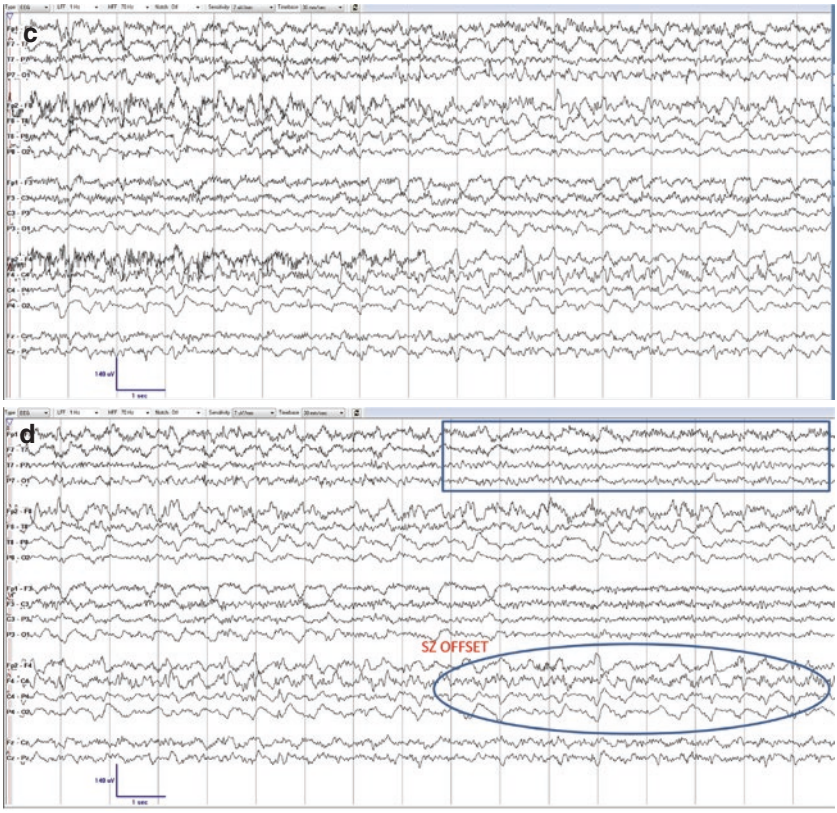


**Fig. 3** (continued)

## Prevalence and Clinical Context

There is only one manuscript published on LRDA in the critically ill [4]. LRDA was uncommon, but, when present, was highly associated with seizures: 63 % of patients with LRDA had seizure(s) during the acute illness. Seizures were most often nonconvulsive in nature (90 %), and all but one arose from the same region as the LRDA. LRDA was associated with seizures just as often as LPDs (63 % vs. 57 %). If both LPDs and LRDA were seen, seizures were even more likely (84 %). This is in contrast to clinically matched control patients with only nonrhythmic slowing, in whom only 20 % had seizures. LRDA is commonly seen in conjunction with other patterns such as LPDs.

LRDA developed within the first 24 h in 80 % of cases, but 10 % emerged after 48 h of recording. This was a bit more delayed in appearance than LPDs, which were noted within the first 24 h in 91 % of patients and always within 48 h. There was a trend toward even higher association with seizures if the LRDA had embedded sharp waves (LRDA + S) or lasted greater than 10 s, but sample sizes were small and further confirmation is needed.

### Treatment and Management

Based on the above study, the authors treat LRDA as a highly epileptogenic pattern, identical to LPDs in its association with seizures. The goal of treatment is to prevent definite seizures with AED prophylaxis and not to abolish the pattern, as LRDA is likely to persist despite treatment with AEDs. In addition, it is recommended that cEEG (at least 24–48 h) be performed to identify seizures whether AEDs are given or not. LRDA typically involved a lesion of the cortex or juxtacortical white matter and/or deep gray structures; therefore, its presence should warrant neuroimaging, as with any prominent focal EEG finding [4]. There is some evidence from simultaneous intracranial recordings of LRDA seen on scalp EEG that intracranially there are periodic epileptiform discharges or bursts while LRDA is seen on the overlying scalp EEG [5].

Temporal intermittent rhythmic delta activity (TIRDA) has been described previously in ambulatory patients and is highly associated with temporal lobe epilepsy. TIRDA is a temporal lobe subtype of LRDA that is seen in awake and alert patients with temporal lobe epilepsy.

## Brief Potentially Ictal Rhythmic Discharges

### Description and Definition

In the neonatal literature, brief discharges were described referring to potentially ictal patterns that were shorter than the arbitrary standard of 10 s required to qualify as an electrographic seizure [6, 7]. These patterns have been termed brief rhythmic discharges (BRDs) or brief electroencephalographic rhythmic discharges (BERDs). These rhythmic patterns are controversial as to whether they are seizures themselves or represent an interictal phenomenon in patients with similar seizure patterns. A similar pattern in the adult population has been described and referred to them as B(I)RDs [8]. The term is left intentionally ambiguous (“potentially ictal”) to demonstrate the difficulty in knowing if the pattern is representative of seizure activity or an interictal phenomenon. Although this may seem like semantics, the terminology may have treatment implications for the clinical team.

One study evaluated neonates with brief (less than 10 s) rhythmic discharges (BRDs) and longer rhythmic discharges (LRDs) and compared them to patients without any rhythmic discharges [7]. They found that any rhythmic discharge was more often seen in healthy “preterm” (less than 38 weeks) newborns and “high-risk” newborns. In addition, in long-term follow-up, BRDs and LRDs both conferred a risk for abnormal neurological development; however, this risk was greater with LRDs than BRDs. In this study, “high-risk” newborns were not clearly defined but predominantly had prematurity, hypoxic-ischemic encephalopathy, neonatal infection, intra- and periventricular hemorrhage, respiratory distress syndrome, CNS malformation, hypoglycemia, leukomalacia, congenital infection, or metabolic defects.

B(I)RDs in adults were described as "very brief (<10 s) lateralized runs of rhythmic activity with a frequency greater than 4 Hz with or without evolution" [8]. These discharges were typically within the theta range, sharply contoured, and 1–3 s in duration. See Fig. 4a,b for typical examples of B(I)RDs and seizures arising from B(I)RDs.

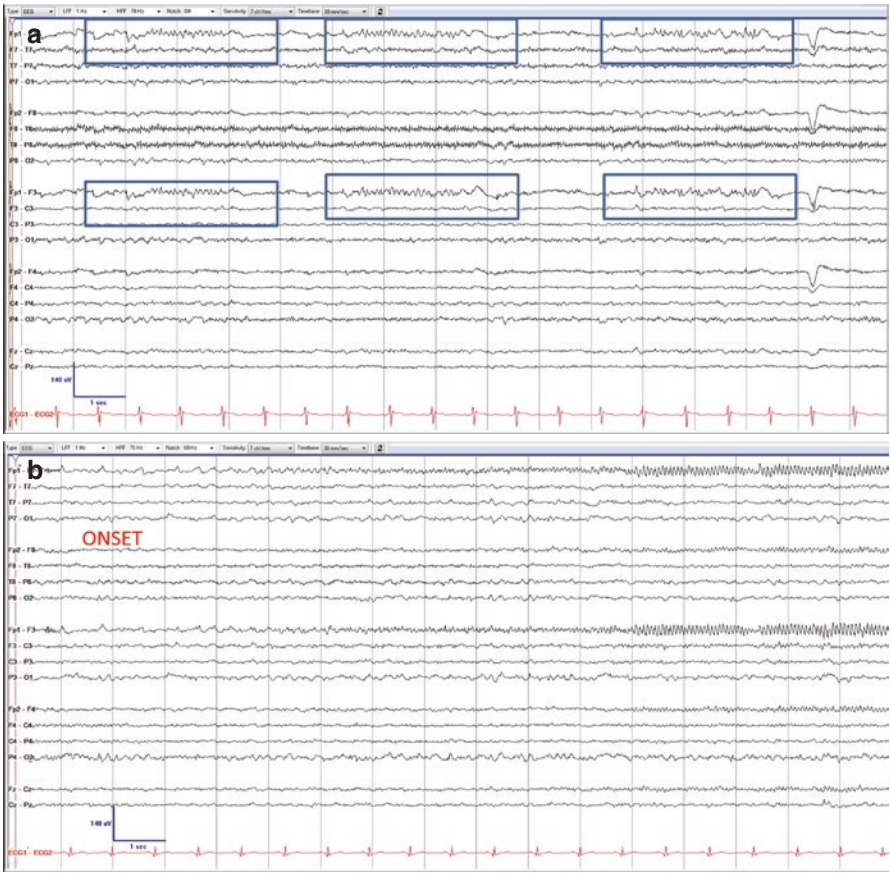


**Fig. 4** (**a**) B(I)RDs: A 45-year-old man with hypertension and diabetes presenting with 2 generalized tonic-clonic seizures, previously found to be in subclinical focal electrographic status epilepticus with 10–12 seizures/hour. Above EEG shows runs of rhythmic alpha/beta for about 2–3 s (brief potentially ictal rhythmic discharges, or B(I)RDs). Sensitivity 7 uV/mm, low frequency filter 1 Hz, high frequency filter 70 Hz, notch off 30 mm/s. (**b**) Seizure in same patient: Above patient with nonconvulsive seizures over the left frontal region, maximal at Fp1 (same location as the B(I) RDs). Sensitivity 7uV/mm, low frequency filter 1 Hz, high frequency filter 70 Hz, notch 60 Hz 30 mm/s. (**c**) Evolution of seizure. Sensitivity 7 uV/mm, low frequency filter 1 Hz, high frequency filter 70 Hz, notch off 30 mm/s. (**d**) Evolution of seizure and offset. Sensitivity 7 uV/mm, low frequency filter 1 Hz, high frequency filter 70 Hz, notch 60 Hz 30 mm/s

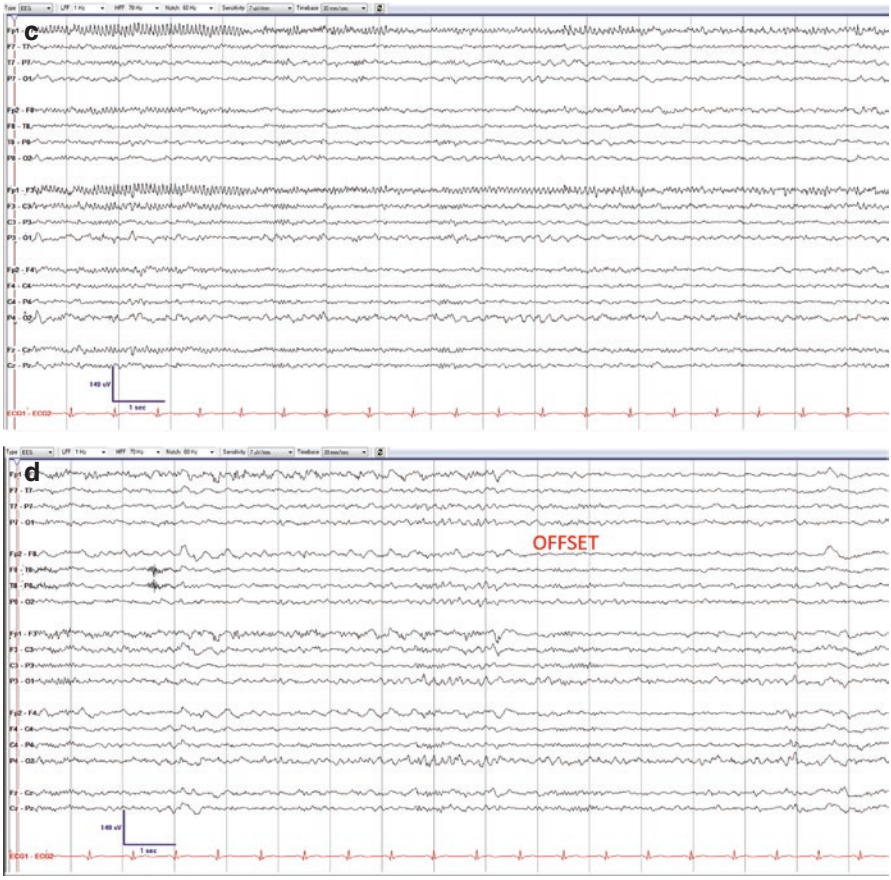


**Fig. 4** (continued)

## Prevalence and Clinical Context

In the only study of B(I)RDs in a large cohort of critically ill patients, B(I)RDs were only seen in 20/1135 (2 %) patients [8]. Similar to other patterns of uncertain significance, these patients often had acute or chronic cerebral injury, more commonly acute. Of those with acute brain injury, stroke and tumor were the most common etiologies of B(I)RDs; about 2/3 of these patients were comatose or stuporous. B(I)RDs were usually (but not always) localized in the same region as the focal injury on imaging. Patients with B(I)RDs were more likely to have seizures (75 %) than patients without B(I)RDs (25 %). Typical of critically ill patients with seizures, these were predominantly nonconvulsive seizures (NCS). B(I)RDs usually occurred within the first hour of recording (in 75 % of cases).

### Treatment and Management

There are no guidelines for the treatment of B(I)RDs. Although in the study discussed above patients with B(I)RDs tended to have worse outcome, this finding was not statistically significant. Due to their high association with NCS, the authors advocate initiation of AED treatment when B(I)RDs are seen and continue monitoring with cEEG to ensure there is no progression to definite electrographic seizures.

## Interictal-Ictal Continuum

### Description and Definition

The IIC has no standard definition and is not part of the ACNS nomenclature. The first mention of this phrase was in 1996 in reference to periodic lateralized epileptiform discharges (PLEDs; now referred to as LPD), stating that there is a "dynamic pathophysiological state in which unstable neurobiological processes create an ictal-interictal continuum" [9]. Over time, the concept of this continuum has evolved to include other highly epileptiform and potentially ictal patterns. This pathophysiological concept is reflected through dynamic patterns on EEG that are not clearly defined. One of the authors has previously noted "[A] clear division of EEG patterns as either ictal or interictal is elusive or nonexistent, and interpretation varies considerably among different electroencephalographers" [10]. Typically the EEG shows fluctuating activity that is rhythmic or periodic as defined in the ACNS nomenclature. This activity can be a combination of both or fluctuating between the two. Frequency is usually between 1 and 2.5 Hz, and there is often no discrete onset or offset. See Fig. 5 for an example of the ictal-interictal continuum.

### Prevalence and Clinical Context

There is sparse literature looking at the prevalence of the IIC in the acute brain injury population. The pattern can be interpreted as ictal by some and interictal by others. This pattern may be seen after treating generalized convulsive status epilepticus or in the setting of acute brain injury such as intracerebral hemorrhage, CNS infections, brain tumors, severe head trauma, and SAH or in the setting of exacerbation of preexisting epilepsy [10, 11].

### Treatment and Management

There are no guidelines on how to treat EEGs with patterns that lie on the IIC. The authors believe that these patterns usually warrant a diagnostic treatment trial to attempt to determine whether or not it is ictal; this is often equivocal (see Table 1

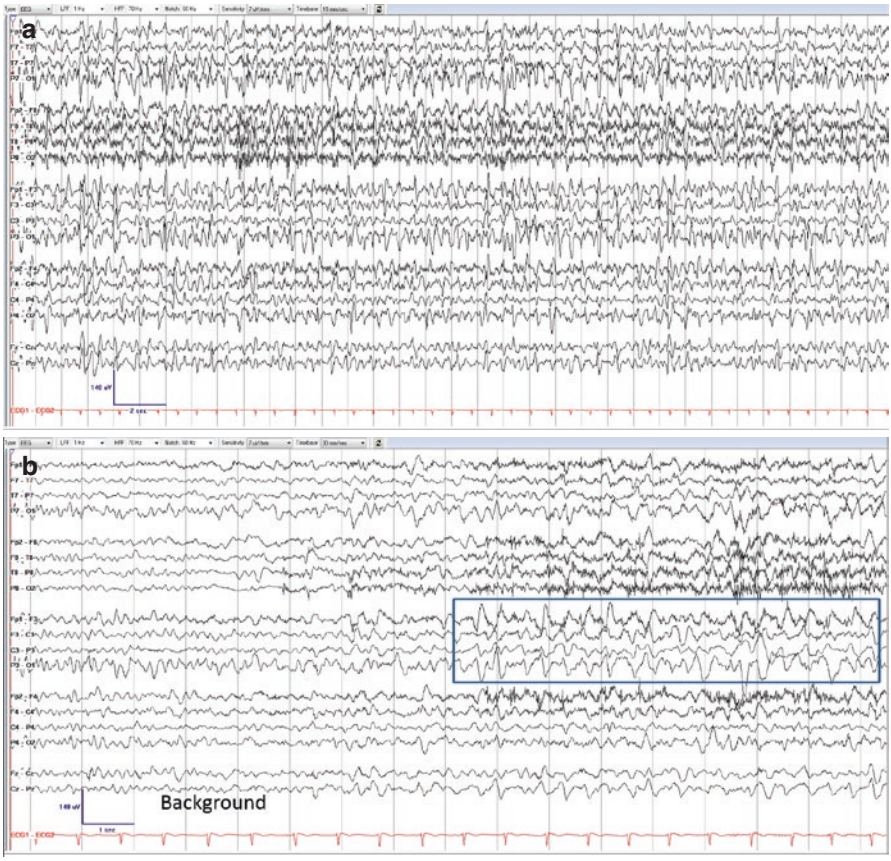


**Fig. 5** (**a**) This is the same EEG from same patient on a compressed time scale. Looks more ictal on 15 mm/s display, but still no definite evolution. Sensitivity 7 uV/mm, low frequency filter 1 Hz, high frequency filter 70 Hz, notch 60 Hz. 15 mm/s. (**b**) Ictal-interictal continuum (IIC): A 70-year-old woman with chronic lymphocytic leukemia presents with altered mental status and GI bleed. EEG shows fluctuating rhythmic delta maximal in the left parasagittal region, sometimes sharply contoured (most prominent in the box). Sensitivity 7 uV/mm, low frequency filter 1 Hz, high frequency filter 70 Hz, notch 60 Hz 30 mm/s. (**c**) No definite evolution and usually slower than 3 Hz, but highly epileptiform, fluctuating, and potentially ictal. Sensitivity 7 uV/mm, low frequency filter 1 Hz, high frequency filter 70 Hz, notch 60 Hz, 30 mm/s

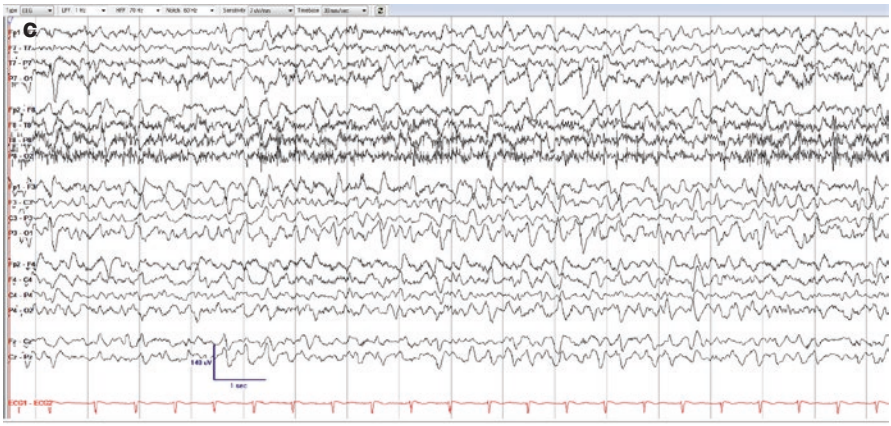


**Fig. 5** (continued)

**Table 1** AED drug trial for the diagnosis of nonconvulsive status epilepticus

| |
|---|
| *Indication* |
| Rhythmic or periodic focal or generalized epileptiform discharges on EEG with neurologic impairment |
| *Contradiction* |
| Patients who are heavily sedated/paralyzed |
| *Monitoring* |
| EEG, pulse oximetry, blood pressure, electrocardiography, respiratory rate with dedicated nurse |
| *Antiepileptic drug trial* |
| Sequential small doses of rapidly acting short-duration benzodiazepine such as midazolam at 1 mg or nonsedating IV antiepileptic drug such as levetiracetam, valproate, fosphenytoin, or lacosamide |
| Between doses, repeated clinical and EEG assessment |
| Trial is stopped after any of the following: |
| Persistent resolution of the EEG pattern (and examination repeated) |
| Definite clinical improvement |
| Respiratory depression, hypotension, or other adverse effect |
| A maximum dose is reached (such as 0.2 mg/kg midazolam, although higher may be needed if on chronic benzodiazepines) |
| *Interpretation* |
| The test is considered positive if there is resolution of the potentially ictal EEG pattern and either an improvement in the clinical state or the appearance of previously absent normal EEG pattern (e.g., posterior-dominant "alpha" rhythm). If EEG improves but patient does not, the result is equivocal |
| Non-ictal patterns may disappear after administration of benzodiazepine (always without clinical improvement) |
| Administration of too high a dose of benzodiazepine might improve the EEG but also leads to sedation, preventing the ability to detect clinical improvement |
| A negative or equivocal result does not rule out nonconvulsive status epilepticus |

Copied from Table 12.6 of Hirsch and Gaspard [12] ©2013 with permission from Wolters Kluwer Health, Inc.

as an example of a diagnostic treatment trial protocol) [12]. When equivocal, we usually recommend treatment with an AED, partly to prevent development of more definitive seizures and partly to attempt to treat the pattern itself. In part, this is related to the belief that subclinical ictal activity, if present, is associated with adverse physiologic effects, especially in the acutely injured brain. Furthermore, it is quite possible that more definitively ictal activity would be seen with simultaneous intracranial recordings [5]. On the other hand, we attempt to avoid the use of anesthetic doses or high doses of multiple AEDs for equivocal patterns to minimize the chance of doing more harm than good. This can be a difficult balance.

Other authors describe a three-step approach to managing EEG patterns in the IIC [11]. These three steps are (1) comparing clear electrographic seizures of the patient to the IIC pattern seen in the same patient, (2) characterizing physiologic measures during the IIC (e.g., changes in cerebral blood flow) as well as AED response trials to see if the pattern behaves like seizures, and (3) attempting to quantify ongoing neuronal injury during the IIC using measures such as serial neuron-specific enolase (NSE) and invasive multimodality monitoring when available (e.g., brain tissue oxygen, intracranial pressure, and cerebral microdialysis for measurement of lactate, pyruvate, glucose, glycerol, and glutamate).

Neuroimaging such as positron emission tomography (PET), SPECT, and magnetic resonance imaging (MRI) may help to determine escalation of treatment. When PET studies can be obtained, an area of increased metabolism comparable to that seen during established seizures may encourage more aggressive treatment. SPECT scans may show hyperperfusion during these periods, suggesting they are similar to seizures in that regard. However, as discussed above, hyperperfusion does not necessarily mean the pattern is ictal or causing neuronal injury and therefore may not clarify if more aggressive treatment is warranted. In addition, a negative SPECT image may not have any utility (see prior SPECT discussion in Sect. 2.3 above). PET and SPECT imaging must also be interpreted in terms of the overall clinical context of the patient. The interpretation can change based on the overall clinical picture in patients with brain injury, i.e., increased blood flow in a patient with LPDs, and brain injury may signify that the underlying tissue is healthier than in a patient with LPDs and decreased blood flow. In addition, although these metabolic studies have been used to evaluate findings in patients with chronic epilepsy, not much is known about the changes in metabolism and perfusion during patterns on the IIC. There are some data to suggest that nonconvulsive seizures in the critically ill population may be associated with a drop in tissue oxygenation rather than an increase in tissue oxygenation that is typically seen in healthy patients with seizures [13]. MRI showing restricted diffusion in the gray matter (especially the cortical ribbon or hippocampus) corresponding to the area of the abnormal pattern, especially without other explanation, tends to make the authors be more aggressive with treating equivocal patterns (and definite NCS) since this may be a sign of ongoing potentially irreversible neuronal injury.

## Generalized Rhythmic Delta Activity

### Description and Definition

GRDA is often seen in critically ill patients and patients with altered mental status. In most of the literature regarding EEG and coma, higher voltages and slower frequencies are associated with coma. One study found that the "variety and complexity of possible rhythms is inversely related to the severity of the dysfunction" [14]. The typical features of GRDA are 1–1.5 Hz, monomorphic, and medium to high voltage. See Fig. 6 for an example.

### Prevalence and Clinical Context

Many series have discussed that intermittent rhythmic delta activity ranging from 1 to 2 Hz is often nonspecific and is seen most commonly in metabolic and toxic encephalopathies and less commonly in hemispheric lesions, increased pressure on the third ventricle, and conditions affecting cortical and subcortical regions diffusely [15, 16].

A common subset of GRDA is known as frontal intermittent rhythmic delta activity (FIRDA); in the ACNS nomenclature, this is more cumbersomely described as "very brief, frontally predominant GRDA." FIRDA has been described as a nonspecific finding associated with bi-frontal predominance in adults and most often seen in encephalopathies and less commonly associated with lesions. FIRDA is not predictive of seizures or epilepsy. In 2011, a group looked prospectively at all EEGs recorded at a tertiary care facility over 3 months to determine the clinical correlations

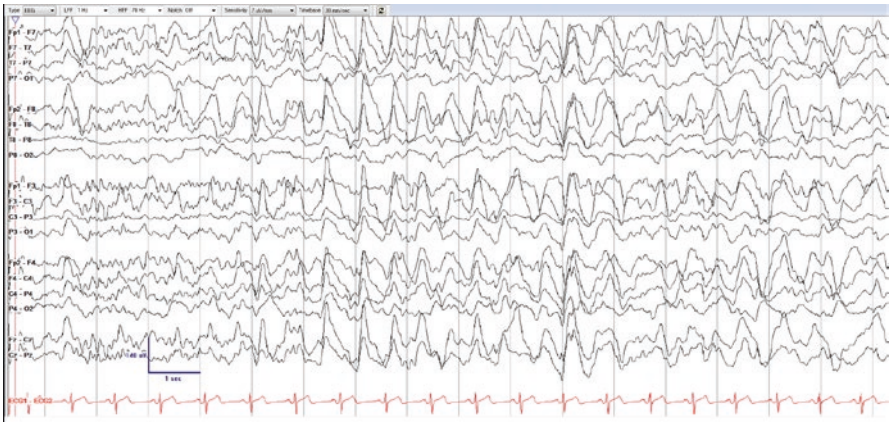

**Fig. 6** GRDA: A 48-year-old male with Stage IV chronic kidney disease, cerebral palsy, spina-bifida admitted with sepsis. EEG shows generalized rhythmic delta activity (GRDA). No definite electrographic or clinical seizures occurred. Sensitivity 7 uV/mm, low frequency filter 1 Hz, high frequency filter 70 Hz, notch 60 Hz, 30 mm/s

of FIRDA. They found that FIRDA was more common than previously reported, noting it was present in about 6 % of all EEGs recorded and was most associated with an encephalopathy (63 %), followed by a structural brain lesion (55 %) [17].

A rare subset of GRDA in the ICU population is the "extreme delta brush" pattern, which is associated with anti-*N*-methyl-D-aspartate (NMDA) receptor encephalitis. A case series from 2012 looked at the typical characteristics of anti-NMDA receptor encephalitis. They found that 17 % had GRDA as defined above without extreme delta brush. Another 30 % demonstrated the extreme delta brush pattern: medium- to high-voltage GRDA pattern with overriding beta activity, often with a burst of beta with each delta wave, which bears a resemblance to the delta brush pattern seen in neonates [18]. Patients with the extreme delta brush pattern tended to be more severely affected than those without.

## Treatment and Management

At the authors' institution, GRDA is believed to be a representation of an ongoing encephalopathy or coma and almost always non-ictal in nature. Correction of the underlying process is encouraged without the use of AEDs unless a pattern more closely tied to seizures is also present. That being said, GRDA that is sustained at a frequency greater than 2.5 Hz is occasionally seen in the setting of nonconvulsive status epilepticus (NCSE) [12]. Thus, a diagnostic treatment trial is reasonable in selected cases.

**Conclusions**

Patterns of uncertain significance lie along a spectrum from underlying encephalopathy to frank seizures. Clinically, this means that not all patterns of uncertain significance warrant the same level of AED therapy. In fact, the authors often advocate for prophylactic use of AEDs for patients with these patterns, without trying to ablate the patterns themselves. When the ictal nature of a pattern of uncertain significance is in question, a trial of a loading dose of an AED and monitoring the clinical response in order to help answer this question is recommended (see Table 1) [12]. Unfortunately, there are many clinical questions left unanswered at this time. Due to a lack of reliable biomarkers, it is not known when or if these patterns are causing acute neuronal injury or if there are long-term effects of these patterns. Further studies are needed to help clinicians manage patients with these controversial patterns more effectively.

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# Artifacts Resembling Seizures

10

Sarah Schmitt

**Contents**



## Introduction

One of the greatest challenges in the evaluation and interpretation of EEG data is distinguishing between signals generated from the cerebral cortex and signals generated from extracerebral sources. In EEG, the term "artifact" can refer to any electrical potential that is recorded on an EEG but which does not originate in the brain. Artifacts can be both physiologic (i.e., originating within the patient's body but not within the brain) and nonphysiologic (i.e., originating from areas outside the patient's body).

S. Schmitt, MD
Medical University of South Carolina, Charleston, SC, USA
e-mail: sarahschmittmd@gmail.com



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EEG recordings from the intensive care unit (ICU) are particularly prone to artifacts. This is even more so the case with continuous EEG (cEEG) monitoring that can last hours to days. Ideally, EEG should be recorded in a room with little or no electrical equipment outside of the EEG machine and in an environment with minimal patient, staff, or personnel movement. Unfortunately, in the ICU, movement from visitors, staff, and patients within rooms is commonplace, and most patient rooms include a wide variety of electrical devices, many of which can create artifacts on EEG recording. Many artifacts are sharply contoured or rhythmic, which can lead to the misinterpretation of these artifacts as periodic discharges, seizures, or epileptiform activity. Some artifacts can obscure underlying EEG activity so markedly that actual seizure activity cannot be reliably detected. Although research algorthims have been developed to minimize some physiologic artifacts, these algorithms are not commonly in use outside of the research setting. Learning to appropriately identify artifacts is one of the cornerstones of accurate EEG interpretation in the ICU environment. This chapter will review the common artifacts seen during cEEG monitoring that have the potential to be mistaken for seizures and other abnormal brain rhythms.

## General Principles

Several steps can be taken by the EEG technologist and ICU team to aid in the appropriate evaluation of artifacts. EEG technologists should perform an impedance check in order to ensure that electrode impedance is less than 10,000 Ohms, and efforts should be made at EEG onset to identify and eliminate any potential sources of artifact [1, 2]. Unfortunately, many individuals in the ICU will have disruptions of their underlying scalp or skull as a consequence of surgery, trauma, drain, or device placement. This may limit the ability to secure an electrode to the scalp, which may result in high-impedance electrodes [3]. High-impedance electrodes can generate their own artifacts but can also result in increased artifact recording from extracerebral sources, such as 60 Hz artifact, device-related artifacts, or movement artifacts.

Concurrent synchronized video should be recorded with EEG whenever possible to aid in the identification of artifacts. In order to allow appropriate visualization of the patient, cameras should be adjusted to allow a full view of the patient's body; this can often be assisted by mounting the camera on a tall pole or wall [2]. Finally, efforts should be made to document abnormal movements or other potential sources of artifact, particularly when these events are concerning for seizure activity.

Proper analysis of EEG artifacts also relies on the understanding of the expected electrical field of waveforms originating from the cerebral cortex. Analysis of the temporal and spatial distribution of any unexpected or unexplained waveforms may help to determine whether or not those waveforms are cerebral in origin; in addition, many artifacts have a characteristic appearance on EEG that may aid in their identification.

## Physiologic Artifacts

### Cardiac Artifacts

Many naturally occurring electrical dipoles exist within the body, which can lead to a variety of EEG artifacts. The heart is one of the more common sources of artifact; several different types of artifacts can arise as a consequence of electrocardiographic (ECG) activity. The most common is ECG artifact, in which the cardiac QRS complex is detected on scalp EEG. Although the regular QRS complexes of healthy individuals are generally easy to distinguish from cerebral activity, many critically ill patients will have irregular cardiac rhythms including atrial fibrillation, atrial flutter, and premature ventricular contractions (PVCs) or other abnormalities that may make it more challenging to distinguish between ECG artifact and cerebral activity. This issue becomes particularly noticeable in patients with low-voltage EEGs (Fig. 1). Comparison with the ECG lead is crucial in identification of this artifact. Pacemakers can also generate low-voltage, spiky artifacts in the EEG. Comparison with the ECG can aid in the identification of this artifact. In some patients, repositioning the head can aid in elimination of ECG artifact, but in cEEG recording this is usually only a temporary solution to the problem, as patient's movement and routine nursing care will likely lead to repositioning of the patient's head over time.

Pulse artifact is another common EEG finding in the intensive care unit; it occurs when an electrode is placed over a pulsating artery on the head. This creates a rhythmic, rounded artifact in the affected electrode; pulse artifact can easily be mistaken for rhythmic delta activity (Fig. 2). However, it can be distinguished from rhythmic delta activity originating in the cortex by its restriction to one electrode, the presence of more normal activity overlying the artifact, and the time-locked appearance

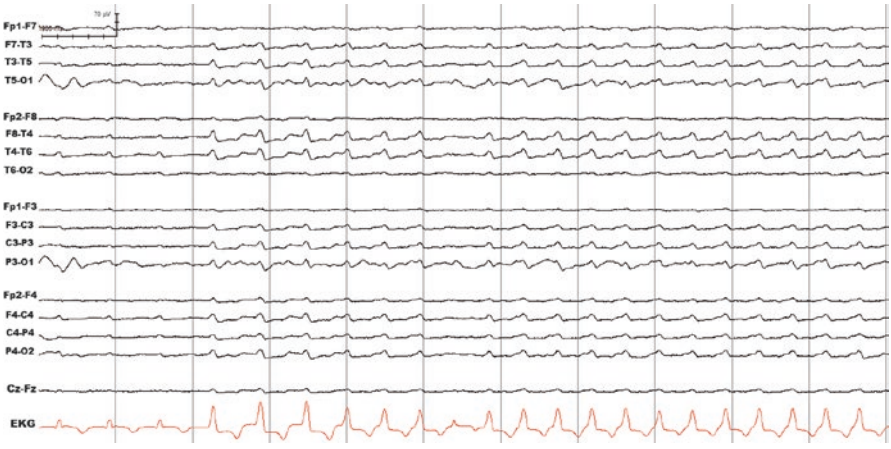


**Fig. 1** ECG artifact. In this low-voltage EEG, the artifact generated by a brief run of ventricular tachycardia can easily be mistaken for generalized periodic discharges

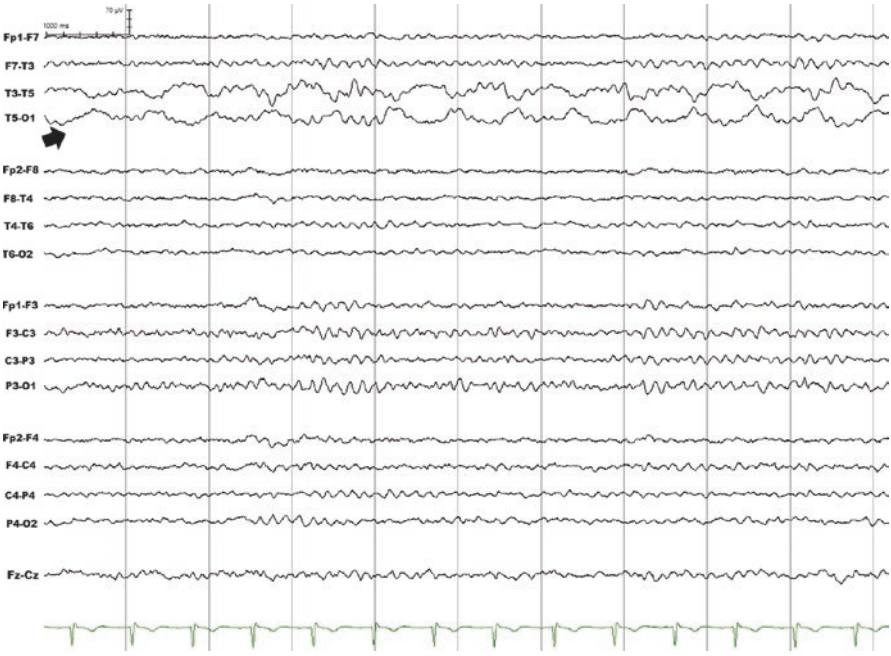


**Fig. 2** Pulse artifact. Here, a typical pulse artifact (*black arrow*) at the T5 electrode resembles 1 Hz rhythmic delta activity

of the artifact in association with the ECG. Pulse artifact can often be reduced or eliminated by moving the electrode off the offending artery.

Another cardiac artifact that can be seen is ballistocardiographic artifact; this artifact results from low-amplitude movements of the patient's head or body in response to the pulsatile movements of the heart. It generally appears as rhythmic delta activity at the same frequency as the patient's heart rate. It may be widespread or confined to a relatively small number of electrodes (Fig. 3). In critically ill patients, who are almost always supine, the artifact tends to be maximal in the posterior electrodes. Repositioning the patient or using a rolled towel beneath the head and neck should minimize the appearance of the artifact but may not eliminate it entirely. In general, ballistocardiographic artifact is more challenging to correct than pulse artifact.

## Eye Movement and Ocular Artifacts

The cornea is positively charged relative to the retina, with a voltage difference between 50 and 100 microvolts. This can result in a detectable electrical field with eye movements, including blinking. The electrical artifacts created by eye movements are generally better seen on anterior electrodes, due to the proximity of those electrodes to the eye. Blinking is associated with a brief upward movement of the

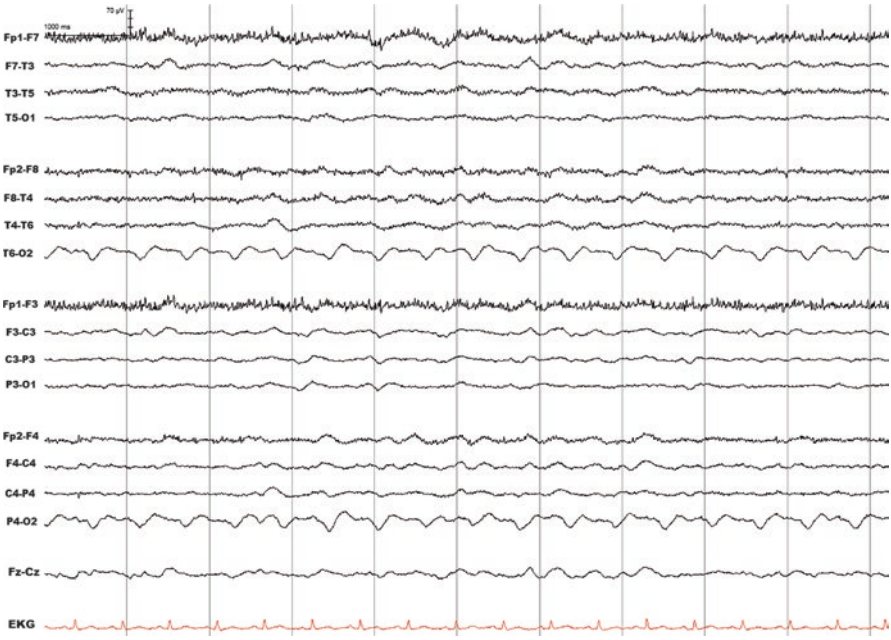


**Fig. 3** Ballistocardiographic artifact. The artifact appears as rhythmic delta activity time locked to the ECG; although it is maximal in the O2 electrode, it can also be seen at times in several other electrodes

cornea (known as Bell's phenomenon.) This movement creates a positive (downward) symmetric deflection on the EEG that is most prominent in the frontal polar electrodes. Rapid blinking (often referred to as "eyelid fluttering") can produce rhythmic activity in the anterior electrodes. The frequency of the artifact depends largely on the frequency of eyelid flutter. Slower 2–3 Hz eyelid flutter can resemble frontally predominant rhythmic delta activity, although it tends to be less uniform in size and appearance than most frontally predominant cerebral rhythmic delta activity (Fig. 4). Faster 6–13 Hz eyelid flutter can produce rhythmic activity that resembles an ictal pattern. If there is a clinical concern for eyelid flutter artifact, the use of electrooculogram recordings from the left and right outer canthus can aid in the identification of this artifact. Additionally, artifacts related to eyelid flutter can be distinguished from electrocerebral activity by close observation of the patient's eyelids. If eyelid flutter or blinking artifacts are extremely disruptive to interpretation of the underlying EEG, the patient's eyelids can be taped closed, but this is rarely necessary.

Both horizontal and vertical eye movements can also give rise to artifacts on the EEG. Lateral eye movements are often preceded by a less than 50 millisecond "lateral rectus spike" related to activation of the lateral rectus muscle with eye abduction. These low-voltage waveforms are typically more prominent in F7 and F8. They are typically followed by a slow potential related to eye movement.

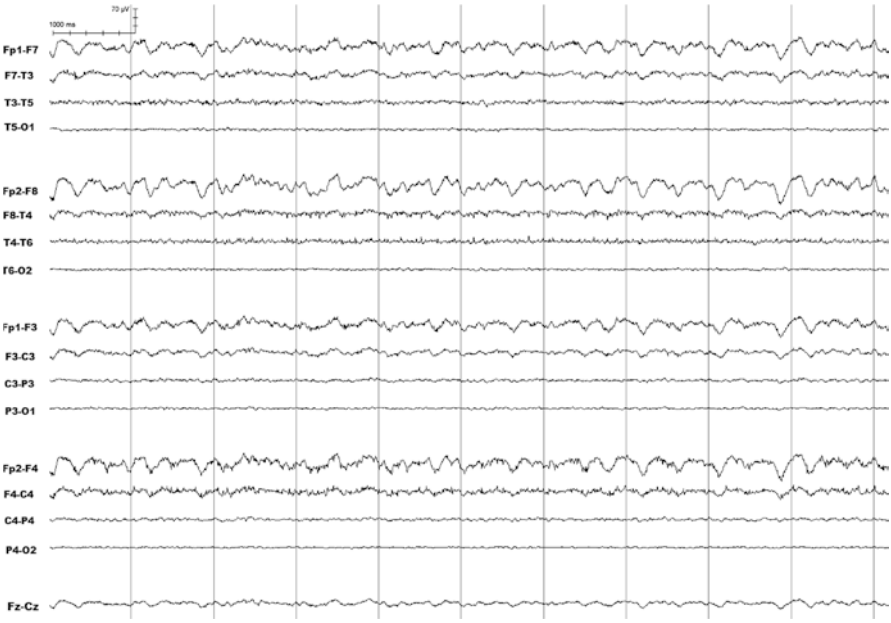


**Fig. 4** Eyelid flutter at a rate of 2–3 Hz can be confused for frontally predominant rhythmic delta activity. Note the irregular frequency and morphology of the waveforms

Dysconjugate gaze, brainstem injury, and cranial nerve palsies, which may be seen in ICU patients with neurologic injuries, can result in either unilateral or asymmetric artifacts from eye movement.

In addition, many ICU patients receive medications or have brainstem or cerebellar injuries that give rise to nystagmus. This artifact often has a "sawtooth" appearance related to the fast and slow components of the nystagmoid eye movements. In patients with horizontal nystagmus, the artifact is typically more prominent on the side of the fast movement, and a phase reversal may be seen at F7 or F8. In patients with vertical nystagmus, the artifact is usually most prominent in the frontal polar electrodes (Fig. 5).

The electroretinogram (ERG) potential is a potential seen at the frontal polar electrodes in response to sudden, flashing light stimulus. In the outpatient setting, this is commonly seen with photic stimulation. However, in the ICU setting, this can occasionally be seen on low-voltage EEGs when a flashlight is used to assess pupil reactivity. In patients who are being evaluated for electrocerebral inactivity (ECI), the presence of an ERG potential should not exclude the diagnosis of ECI.

## Movement-Related Artifacts

Patients in the ICU are prone to a wide variety of abnormal movements including tremors, clonus, myoclonus, rigors, shivering, posturing, and other types of hypermotor activity. Many of these movements have a relatively stereotyped appearance

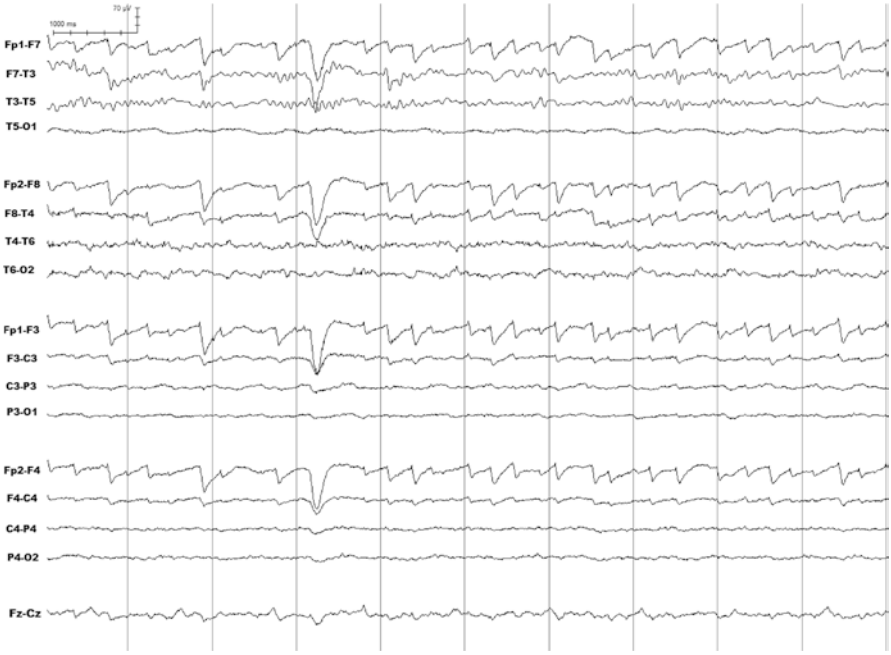


**Fig. 5** Nystagmus artifact. Sharply contoured, sawtooth waveforms are seen at a rate of 2–3 Hz, due to vertical nystagmus in this patient with a pontine infarct

on EEG. Tremors can produce a rhythmic, spiky appearing artifact that corresponds to the frequency of the tremor (commonly between 4 and 12 Hz for conditions such as essential tremor, cerebellar tremor, or Parkinsonian tremor). Artifacts related to tremor typically generate nonphysiologic phase reversals; tremor artifacts are often more prominent in ECG leads than they are in EEG leads (Fig. 6).

Myoclonus also produces an extremely brief, spiky appearing potential. This can be challenging to distinguish from epileptic spikes at a normal paper speed of 30 mm/s. However, by changing the paper speed to 60 or 120 mm/s, it becomes easier to see that these seemingly epileptic spikes demonstrate nonphysiologic phase reversals (Fig. 7). In some instances, myoclonic artifact can be caused by epileptic activity, which can make it particularly challenging to distinguish between electrocerebral activity and artifacts. Under those circumstances, it may be necessary to use neuromuscular blocking agents to better assess the underlying EEG activity.

In addition to patient movements, movements by nursing staff, EEG technologists, and physicians can generate artifacts. Suctioning the patient can create a rhythmic low-voltage artifact in the delta range; the artifact is often frontally predominant (Fig. 8). Rubbing a patient's sternum can create a slightly faster 3–7 Hz, high-voltage artifact with irregular waveforms (Fig. 9). The waveforms can be diffuse or focal, depending on patient positioning.

Cardiopulmonary resuscitation (CPR) may create an artifact that is unfortunately all too common in the ICU. The chest compressions performed during CPR create

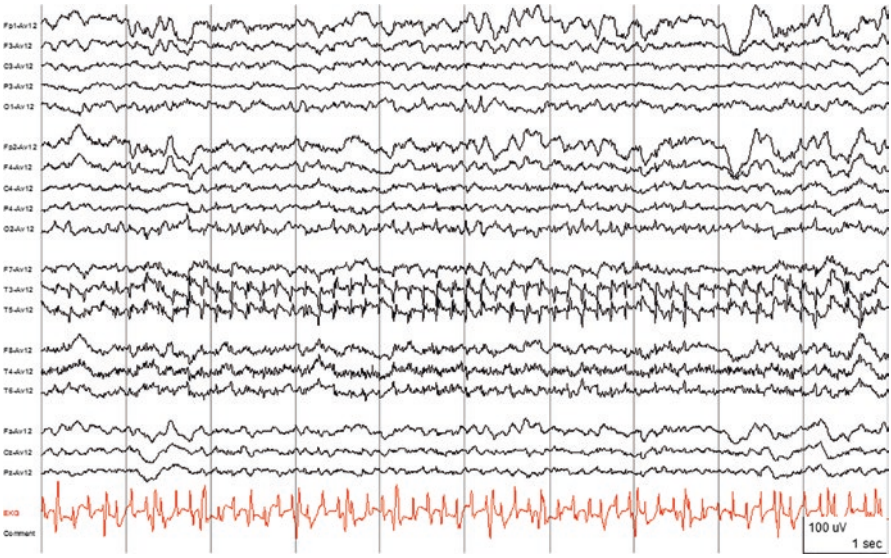


**Fig. 6** A 6 Hz essential tremor produces an asymmetric artifact most prominent at T3 and T5 in this example. The resulting artifact is better seen in the ECG

a pattern of rhythmic delta activity at approximately 2–3 Hz (Fig. 10). The pattern is generally high voltage, although the frequency, voltage, and morphology of the waveforms may wax and wane over the course of resuscitation efforts. Because of these fluctuations, CPR artifact can easily be mistaken for seizure activity. However, careful attention to the electrical field of the activity shows phase reversals consistent with an extracerebral source. Attention to the ECG lead typically shows a rapid, rounded waveform that is time locked with the activity on the EEG.

Many other patient movements and nursing movements can also result in artifacts. Chewing and biting an endotracheal tube can produce a stereotyped high-voltage linear, rhythmic artifact related to muscle activation. Shivering produces a high-frequency, sharply contoured, diffuse pattern of activity. Artifacts commonly result from oral care, clonus, repetitive movements, or agonal breathing. Even ordinary respirations can produce an artifact whose frequency is equivalent to the patient's breathing rate. In neonatal ICUs, artifacts related to sucking on a pacifier or bottle or to patting the baby's back are common. If movements are rhythmic, it is easy for them to be mistaken for seizure activity. Under such circumstances, video recordings should be utilized to better assess whether or not an unusual appearing waveform or series of waveforms is due to artifact.

## Electromyographic Artifact

One of the most commonly encountered and troublesome artifacts seen in the ICU is electromyographic (EMG) artifact. This occurs as a consequence of muscle

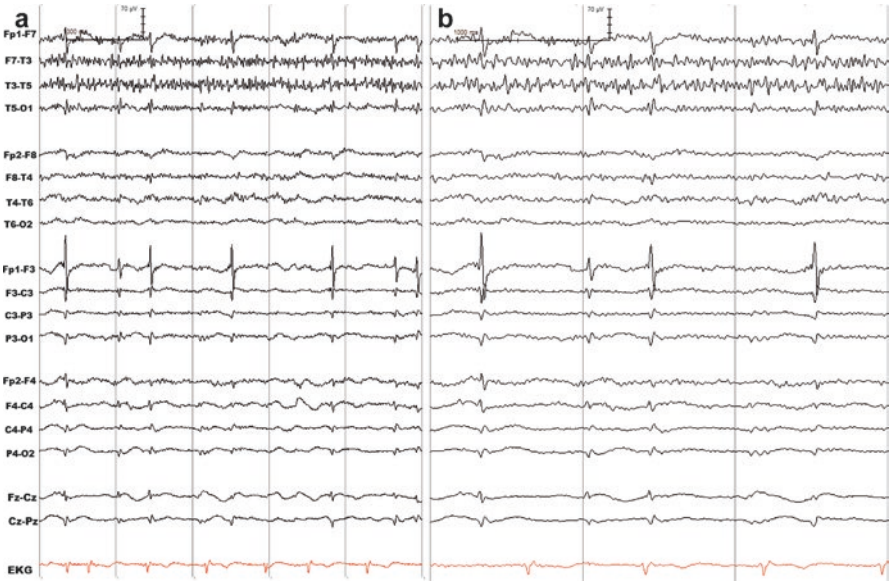


**Fig. 7** Myoclonus artifact. (**a**) At a typical paper speed of 30 mm/s, artifact due to myoclonus appears spiky and is easily mistaken for epileptiform activity. (**b**) At a paper speed of 60 mm/s, the noncerebral morphology of the artifact can be better appreciated

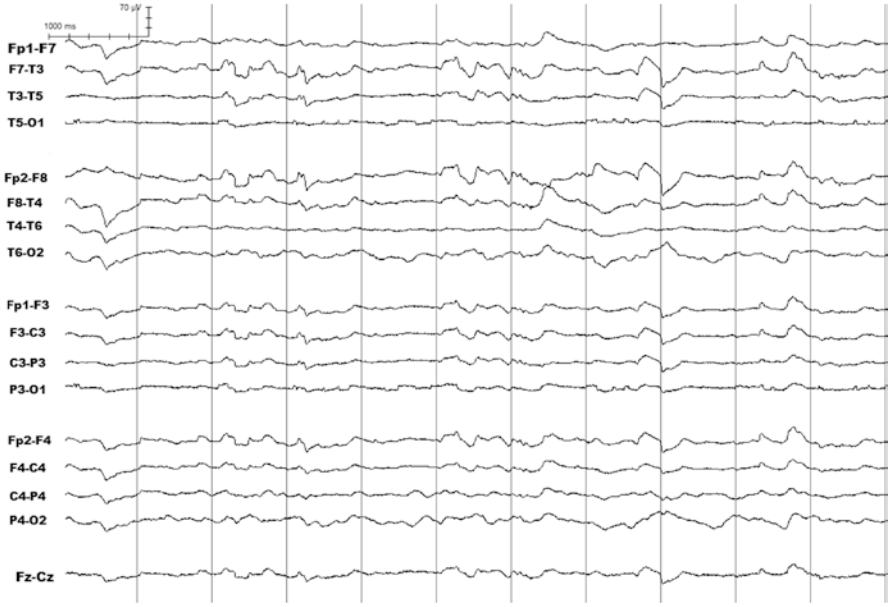


**Fig. 8** Suctioning artifact. Suctioning typically creates diffuse, low-voltage waveforms that resemble either polymorphic or rhythmic delta activity

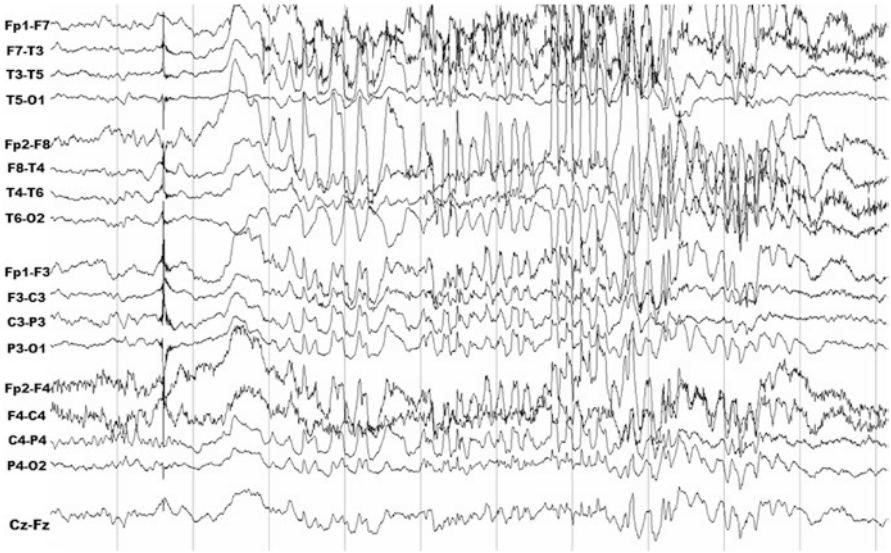


**Fig. 9** Sternal rub artifact. Note the high-voltage, irregular waveforms

activation, especially with activation of muscles in the face, head, and neck. EMG artifact is typically associated with a rapid, spiky artifact that can obscure the underlying EEG. When isolated motor units are activated, they can occasionally appear spiky or epileptiform. Similarly, twitching of the facial muscles can produce a spiky artifact that resembles epileptiform activity. In both cases, however, the field is not consistent with electrocerebral activity.

Because EMG artifact is typically composed of high-frequency activity (greater than 20 Hz), it has a relatively stereotyped appearance on quantitative EEG (QEEG). On a typical color spectrogram, which analyzes the relative power at different EEG frequencies over time, EMG artifact shows increased power at the top of a color spectrogram, whereas a normal EEG has more activity in the middle or lower portion of the color spectrogram (Fig. 11).

## Other Physiologic Artifacts

Less common artifacts can arise from physiologic processes. Glossokinetic artifact is produced by tongue movement. The tip of the tongue has a negative polarity relative to the base of the tongue. Consequently, tongue movements, including the movements that take place with swallowing and phonation, can generate an artifact on EEG. This artifact is most commonly seen as a burst of frontally predominant rhythmic delta activity; it can be unilateral or bilateral, and it may be positive or negative. In alert patients, this artifact can often be reproduced by asking the patient to repeat a word or phrase with frequent tongue movements (e.g., “la la la” or “da

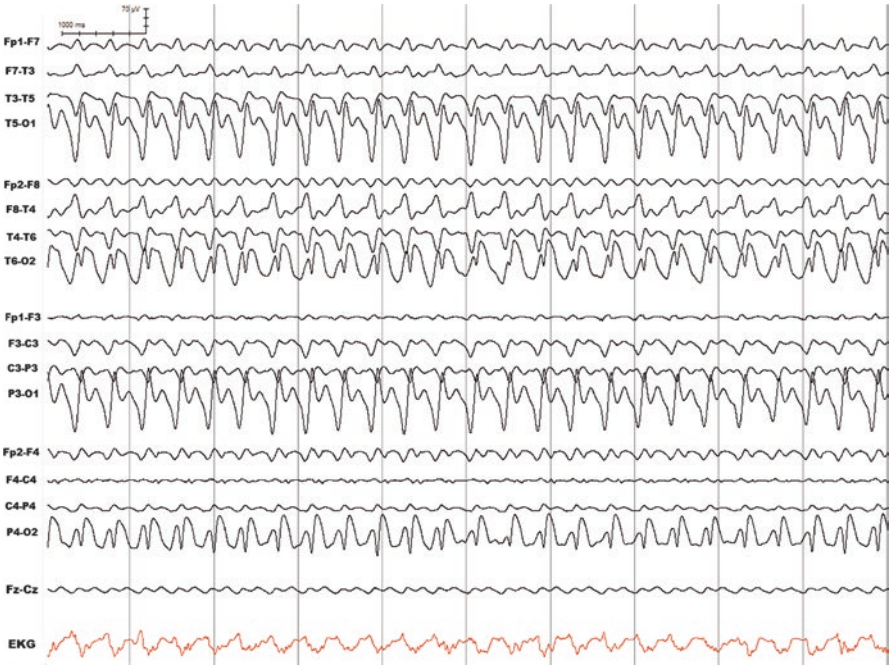


**Fig. 10** Cardiopulmonary resuscitation artifact. This artifact results in a high-amplitude, sometimes sharply contoured pattern of rhythmic 2–3 Hz delta activity. Morphology, amplitude, and frequency of the waveform can vary with time

da da"). In a comatose patient, this artifact can be assessed by placing an electrode over the submental muscle.

Sweat can also create a stereotyped artifact. In the ICU, this artifact is most commonly seen in febrile individuals. It is typically seen in multiple electrodes and is generally associated with very slow (less than 0.5 Hz) delta activity. Although shortening the time constant (increasing the low-frequency filter setting) can reduce this artifact, caution must be used when employing this technique to ensure that important EEG features such as rhythmic or evolving delta activity are not overlooked. When sweat artifact is identified, the EEG technologist should make an effort to dry the scalp prior to applying electrodes. When possible, efforts should also be made to cool the patient (e.g., lowering the room temperature, using a cooling blanket, using a fan).

Skull defects create another common artifact in the ICU. Because the skull is a powerful filter of EEG signals (particularly high-frequency signals), defects in the skull can result in a higher-amplitude, more sharply contoured EEG with more prominent faster frequency activity (Fig. 12). The resultant EEG pattern, known as a breach artifact, can easily be confused with epileptiform or ictal activity. Breach artifacts are commonly more prominent in the central and temporal regions. Caution should be exercised when evaluating possibly epileptiform activity within a breach

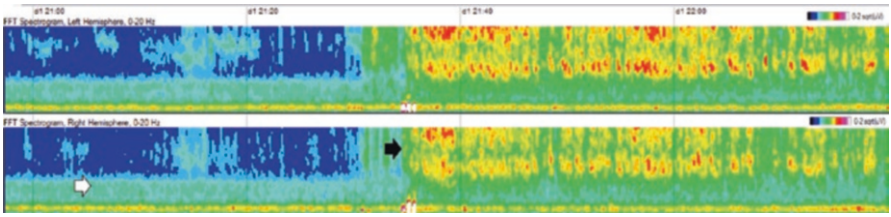

**Fig. 11** Color spectrogram. The left-hand side of the spectrogram shows a typical distribution of EEG power, with the highest powers in the 1–10 Hz range (*white arrow*). The right hand of the spectrogram shows a typical spectrogram when the EEG is heavily contaminated by EMG artifact; under these circumstances, the majority of the power is in the higher (>10 Hz) frequency band (*black arrow*). The lack of any change in power or frequency over time on the spectrogram can help to distinguish the appearance of EMG from seizure activity on QEEG. However, because many seizures are associated with motor activity, these determinations should always be made in conjunction with the raw EEG

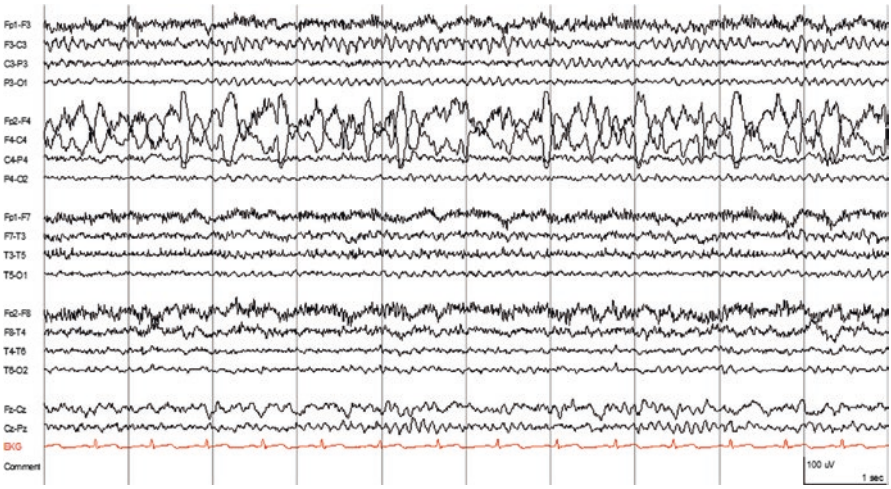


**Fig. 12** Breach artifact. A right frontotemporal breach artifact leads to higher-amplitude, sharply contoured activity maximal at F8. This activity could easily be confused for seizure activity, but is actually just due to a breach artifact

artifact; only waveforms with a convincing electrical field that stands out from background activity should be considered epileptiform.

## Nonphysiologic Artifacts

### Alternating Current Artifact

Alternating current artifact – commonly known as "60 Hz artifact" – is seen when EEG electrodes are placed in close proximity to an electrical device running on an

alternating current (AC). This creates a 60 or 50 Hz (depending on location) sinusoidal artifact on the EEG. This is typically more prominent in high-impedance electrodes. In the ICU, the abundance of electrical devices (including electrically powered beds, continuous venovenous hemofiltration devices (CVVH), electrocardiograms, intravenous (IV) infusion devices, chest percussion devices, and other electrical devices) increases the likelihood of encountering 60 Hz artifact. This artifact can be reduced by reapplying high-impendence electrodes and by moving offending electrical appliances away from the patient's head (or unplugging them, if appropriate). If 60 Hz artifact persists despite these efforts, a 60 Hz notch filter can be employed to selectively reduce EEG signals at 60 Hz (Fig. 13). However, caution should be employed in the use of the 60 Hz notch filter, because its use may diminish the detection of high-impedance electrodes.

## Electrode and Amplifier Artifacts

Electrode artifacts can result from numerous different processes. They can also result from damaged wires, electrode or wire movement, or oxidative changes on metal electrodes. However, the most common source of electrode artifact is high impedance (typically due to an inadequate seal between the electrode and the scalp). A high-impedance electrode may lead to rapid, sharp-appearing activity or slow waves of varying amplitude, morphology, and sharpness. Electrodes in which the impedance suddenly changes frequently have a sharp appearance on EEG (a phenomenon often referred to as "electrode pop"). Recurrent electrode pops can easily

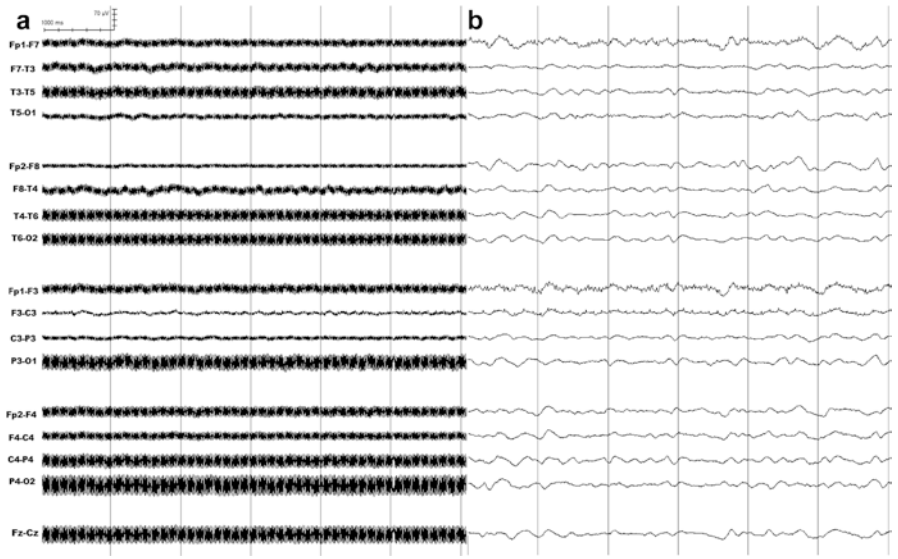


**Fig. 13** (**a**) This recording shows abundant 60 Hz artifact. (**b**) The same tracing after application of a notch filter

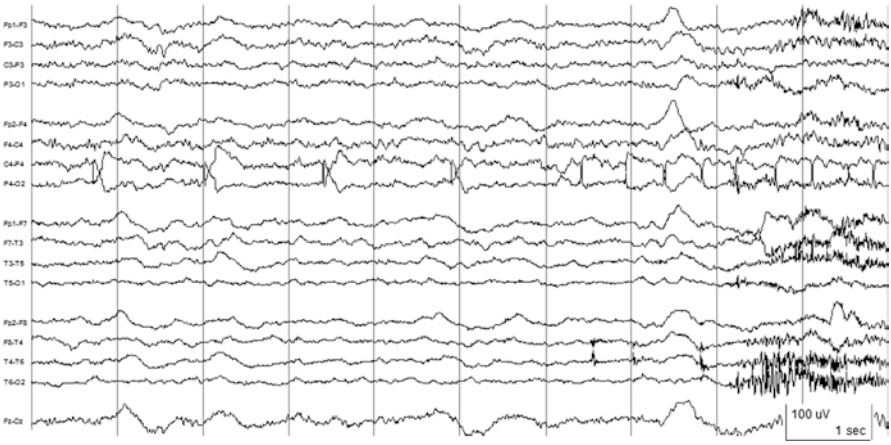


**Fig. 14** Electrode artifact. Here, irregularly squarely shaped waveforms are seen at P4 due to a high-impedance electrode. These waveforms later become increasingly sharply contoured and could easily be mistaken for periodic discharges

be mistaken for periodic discharges or epileptiform activity (Fig. 14). This activity can be identified by the extremely sharp appearance associated with the waveform (which may also be square or irregular in morphology). Oftentimes, observing the electrical activity at the electrode over an extended period of time will clarify the artifactual nature of the waveforms in question. Whenever a concerning waveform is confined exclusively to one electrode, there should be a high index of suspicion that the activity is artifactual. Electrode artifact can be corrected by fixing or replacing the offending electrode.

If a patient is unplugged or disconnected from the EEG amplifier, waveforms may continue to be recorded. It will appear as if the EEG is severely attenuated and may be concerning for very suppressed electrocerebral activity. If the amplifier is moved or jostled, an interference pattern may be created that resembles rhythmic theta or delta activity (Fig. 15). A review of the video, if available, or discussion with the technologist will easily confirm that the EEG amplifier is disconnected.

## Mechanical- and Device-Related Artifacts

The abundance of external electrical devices in most ICU rooms creates frequent artifacts that are device specific. One of the more commonly encountered artifacts results from the use of chest percussion devices. This artifact is related to the physical movement of the patient's head and electrodes with chest percussion. The artifact typically results in widespread, approximately 5 Hz rhythmic theta activity; the activity can be bilateral or unilateral (Fig. 16). Although

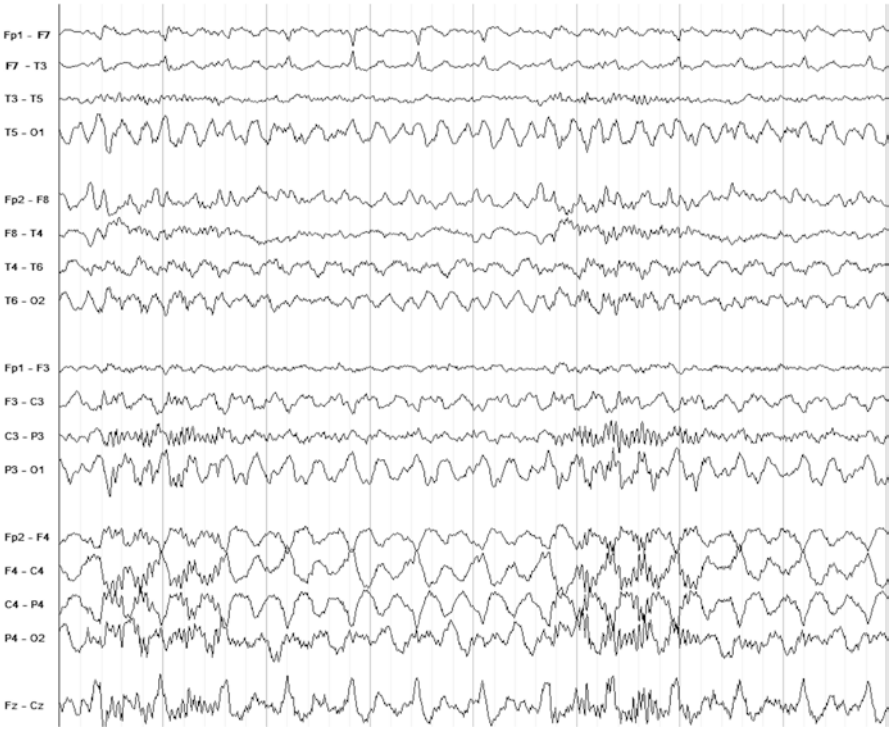


**Fig. 15** After the EEG was disconnected, this interference pattern was recorded from the EEG amplifier

posterior electrodes are more commonly affected, any electrode can potentially be affected by chest percussion. Because the frequency of chest percussion therapy can change over time, chest percussion artifact can easily be confused for evolving seizure activity. The rhythmic, moderate- to high-amplitude activity associated with chest percussion therapy can also create detectable signals on QEEG (Fig. 17). Review of concurrent video, as well as recognition of the characteristic EEG pattern of this artifact on raw EEG, can minimize the risk of misclassification of this finding.

Hemodialysis machines and continuous venovenous hemofiltration devices (CVVH) can also create a rhythmic 5–7 Hz artifact. This artifact is often more sharply contoured than the artifact created by chest percussion; it can be frontally predominant or widely distributed. Mechanical movements associated with ventricular assist devices also create a stereotyped high-amplitude artifact associated with rhythmic, 1–2 Hz widely distributed delta activity (Fig. 18). The frequency of this artifact should be identical to the heart rate. It is otherwise challenging to reduce or eliminate this artifact. Extracorporeal membrane

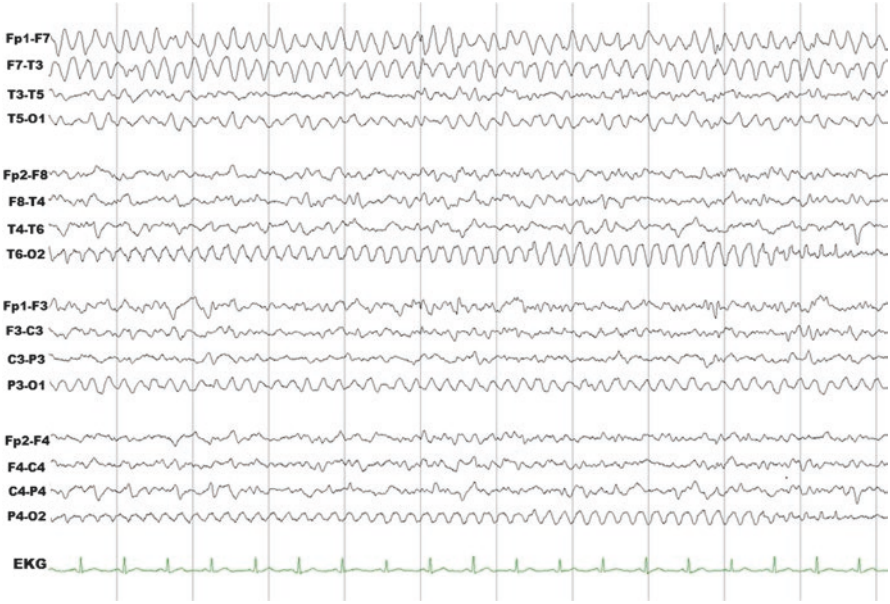


**Fig. 16** Chest percussion artifact. Chest percussion results in widespread ~5 Hz rhythmic theta activity, which typically affects multiple electrodes

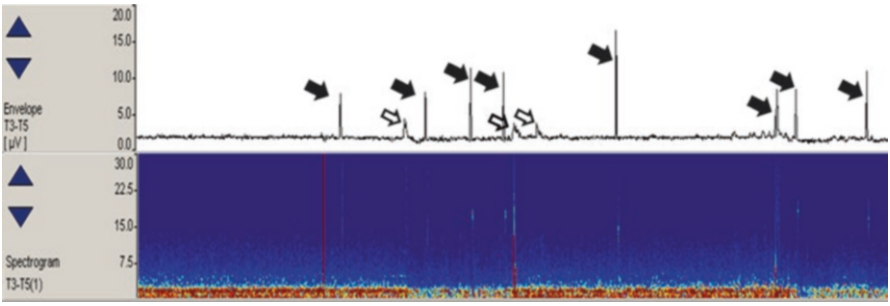


**Fig. 17** Chest percussion on QEEG. Here, the increase in power and rhythmic activity during chest percussion (*open arrows*) can easily be confused with the increase in power seen during seizures (*black arrows*)

oxygenation devices (ECMO) can create an irregular, square-wave artifact when the ECMO device is placed close to the EEG electrodes (Fig. 19). This artifact can often be reduced by moving or repositioning the ECMO device away from the patient's head.

One of the most common device-related artifacts in the ICU results from mechanical ventilation. This artifact occurs every 2–6 s in time with ventilation. The amplitude, morphology, polarity, and localization of the artifact resulting from mechanical

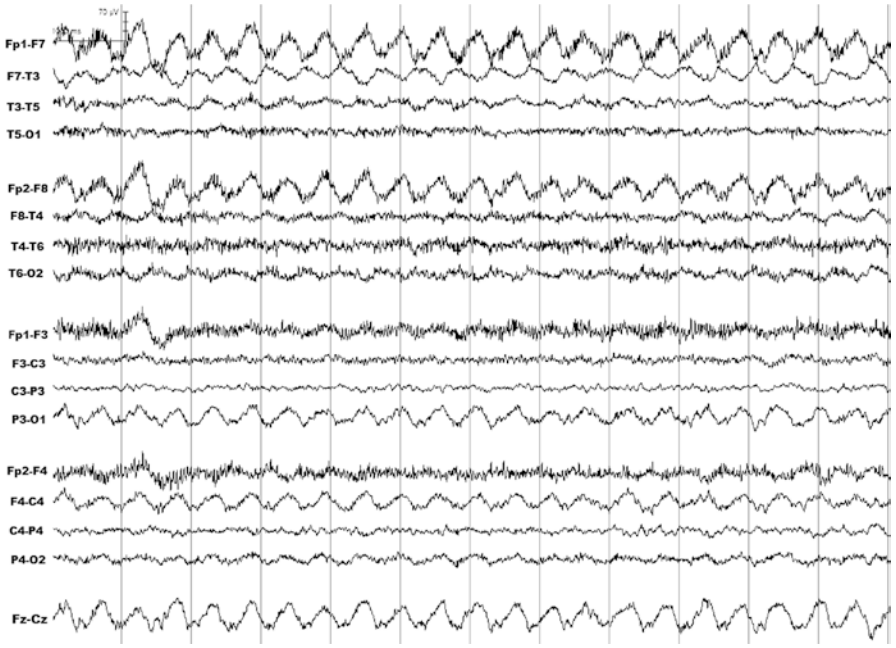


**Fig. 18** Ventricular assist device artifact. Widespread 1–2 Hz rhythmic delta activity is created by a left ventricular assist device in a patient with severe heart failure

ventilation often vary considerably (Fig. 20). If identification of this artifact proves challenging, then monitoring respiration in a separate channel can aid in identification of the artifact. A related artifact often occurs from vibration and oscillation of water within ventilator tubing. This artifact is usually frontally predominant and may produce episodic theta or delta activity with each respiration (Fig. 21). The artifact typically improves with suctioning.

## Other Nonphysiologic Artifacts

Other artifacts can result from the variety of electrical signals present within most ICU rooms. Bending, compressing, or twisting an electrical cable can result in a capacitative artifact with a nonphysiologic field. Discharges of static electricity (from the patient or from staff who come into contact with the patient or the patient's bed) can also produce an irregular high-amplitude electrostatic artifact. Although uncommon, intravenous (IV) infusions in close proximity with the EEG electrodes can occasionally create an artifact related to the movement of electrically charged drops of solution. The artifact is generally spiky and seen diffusely over several electrode channels. Once identified, the artifact can often be eliminated by moving the IV infusion machine away from the patient's head.

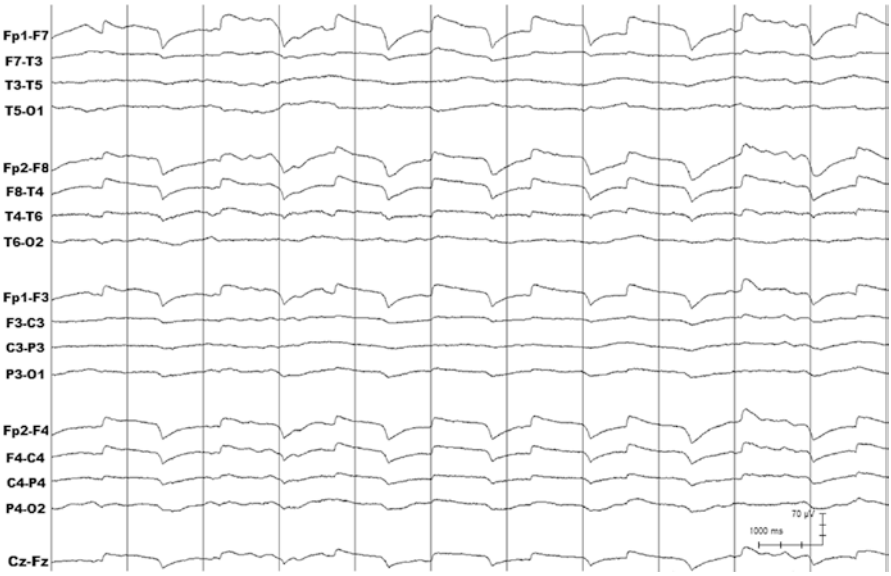


**Fig. 19** Extracorporeal membrane oxygenation device artifact. An irregular, square-wave artifact results from proximity of the ECMO device to the head

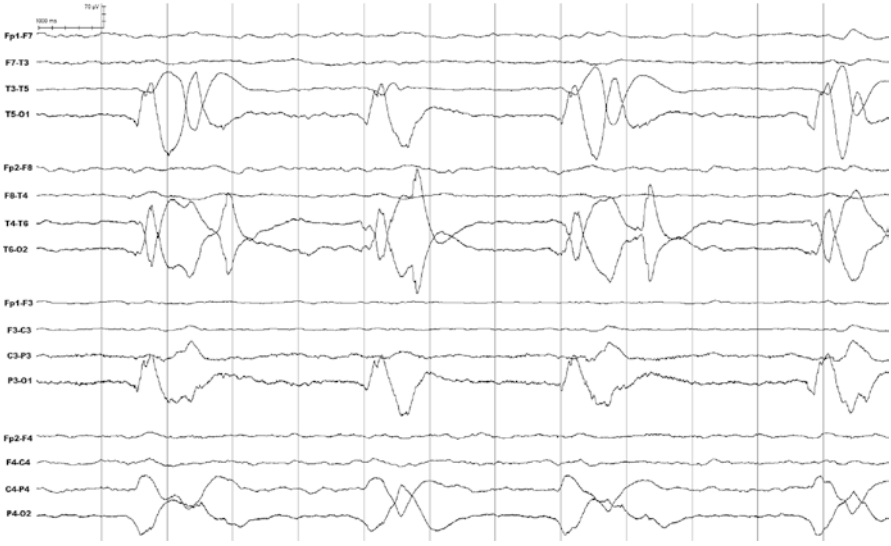


**Fig. 20** Artifact from mechanical ventilation. A high-amplitude, posteriorly predominant artifact occurs every 3–4 s in time with each respiration

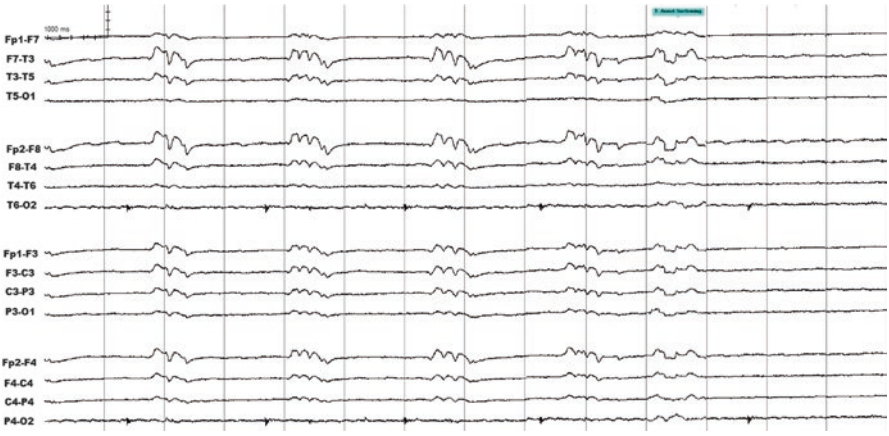


**Fig. 21** Artifact from water in ventilator tubing. Oscillation of water in ventilator tubing creates a characteristic, anteriorly predominant rhythmic theta-range artifact with each respiration. This artifact resolves with suctioning

**Conclusions**

Artifacts remain a significant barrier in the interpretation of ICU EEG. Both EEG technologists and electroencephalographers should maintain a high index of suspicion for identification of artifacts in order to prevent potentially critical EEG misinterpretation.

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3. Tatum WO, Dworetzky BA, Freeman WD, Schomer DL. Artifact: recording EEG in special care units. J Clin Neurophysiol. 2011;28(3):264–77.

# Quantitative EEG Analysis: Basics

# 11

Saurabh R. Sinha

## Contents



## Introduction

Continuous EEG (cEEG) recording in the ICU generates a large volume of data on a daily basis. A 24 h recording, when viewed at 15 s/page, contains 5760 pages of data. Even if reviewed at 5 s/page, it would require approximately 20 min to screen every page. The actual time required is substantially higher when one includes the need to take a closer look at abnormal/changing patterns, artifacts, clinical events, etc. Unlike long-term or epilepsy monitoring, where selective review of a subset of the EEG is reasonable (based on clinical events and screening for abnormal patterns), the entire cEEG record must be reviewed due to the presence of frequent

S.R. Sinha, MD, PhD
Duke University Medical Center, DUMC, Box 102350, Durham, NC 27710, USA
e-mail: Saurabh.sinha@duke.edu



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subclinical or nonconvulsive seizures superimposed on an abnormal background. For a busy cEEG service, review of data can become a daunting task.

Another issue with cEEG analysis is the lack of immediate interpretation. Unlike many other types of monitoring that occur in the ICU setting (e.g., cardiac telemetry or intracranial pressure monitoring), interpretation of cEEG requires a level of subspecialty training in neurophysiology that makes bedside interpretation by ICU staff difficult. Thus, in most settings, the cEEG record is only interpreted/reviewed intermittently even though the data is being recorded, and usually displayed at the bedside, continuously. This can lead to delays of hours in the recognition of seizures and other clinical changes.

Quantitative EEG (qEEG) analysis is one option for reducing the burden of cEEG analysis for the reviewer and potentially allowing for a preliminary, real-time interpretation of cEEG at the bedside by non-neurophysiologists. Quantitative EEG analysis refers to any mathematical processing of the EEG and includes a vast array of tools and techniques. As applied to cEEG, quantitative EEG usually refers to parameters calculated for a brief epoch of EEG data and then plotted versus time. A plot of a calculated parameter versus time is referred to as a qEEG trend.

The application of quantitative EEG analysis to ICU monitoring dates back to its earliest days, initially mainly as a necessity to reduce the amount of data and paper that were generated and as a means of providing continuous monitoring of EEG data [1]. American Academy of Neurology and American Clinical Neurophysiology Society Guidelines from 1997 recommend their use in ICU and OR monitoring to detect physiological changes and seizures [2], although actual use of qEEG was fairly limited at that time, partially due to availability. qEEG is now commonly used as part of cEEG review, with 52% of neurophysiologists reporting its use in a survey of practice [3], although most (75%) still reviewed every page of the raw EEG. Using qEEG trends to guide review of the raw EEG can substantially reduce the time required to review cEEG data [4]. qEEG trends have been demonstrated to be potentially useful for seizure detection at bedside by EEG technologists and ICU nurses [5, 6]. Some larger institutions are using quantitative EEG trends for real-time monitoring of cEEG by EEG technologists and other trained personnel. Quantitative EEG also has the potential to more objectively measure EEG features such as reactivity [7] and to potentially detect seizures automatically [8], although the sensitivity and utility remain to be established.

## Time-Domain qEEG Tools

Time-domain analysis refers to analysis of how the EEG signal amplitude varies over time. This is in contrast to frequency-domain analysis which is based on the contribution made by different frequencies to the EEG signal in a given time window. In practice, most of the qEEG tools used today incorporate features of both and are better thought of as time-frequency analysis.

## Amplitude-Integrated EEG (AEEG)

Amplitude-integrated EEG (AEEG) is one of the earliest qEEG trends and has been in clinical use, especially in neonates [9], for decades. In stand-alone systems, especially in neonates, only 2–4 electrodes are sometimes used (P3-P4 for single-channel systems, C3-P3 and C4-P4 for dual channel systems) for AEEG. However, when used as part of an EEG recording system, any channel or combination of channels can be used for the AEEG to provide additional spatial information. The raw EEG is filtered to a frequency range of interest (e.g., 2–15 Hz), rectified (all points made positive), smoothed (by averaging surrounding time points), and displayed on a compressed time scale. For each epoch (typically 1–2 s), both the maximum and minimum amplitudes (alternatively 75th and 25th percentiles or another range) are plotted, connected by a vertical line (Fig. 1).

AEEG has been extensively used for evaluating cerebral function in critically ill neonates, including commercially available "cerebral function monitors" that provide AEEG for a limited number of channels. AEEG may be a reliable means to detect background EEG patterns and seizures [10], although, used in isolation without raw EEG, a significant proportion of seizures may be missed (sensitivities of

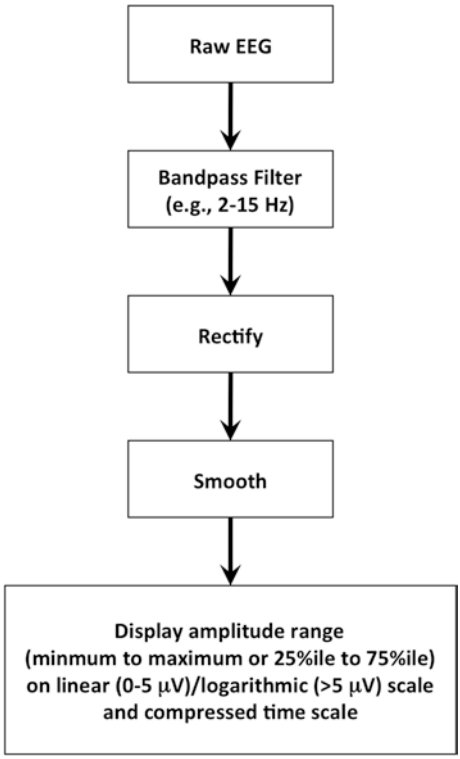



**Fig. 1** Algorithm for calculation of AEEG. The raw EEG is filtered, rectified, smoothed, and the amplitude displayed as a range on a combined linear/logarithmic compressed time scale

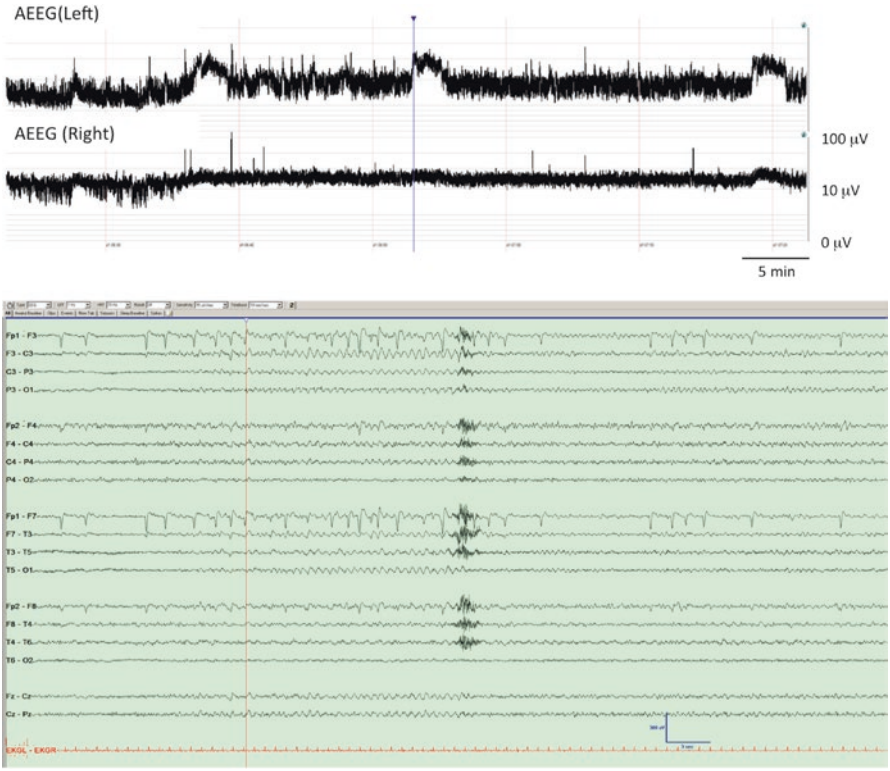



**Fig. 2** Example of focal seizures on AEEG. AEEG for the left hemisphere and right hemisphere electrode derivation is displayed at the *top* (note the combined linear and logarithmic scale for amplitude). Three seizures predominantly involving the left hemisphere are shown in this 1 h sample. The *bottom panel* shows the raw EEG near seizure onset at the time point indicated by the *arrowhead*

38–55 % sensitivity for neonatologist trained in interpretation of cerebral function monitors) [11]. Sensitivity of AEEG for seizure detection in cEEG in adult patients has been reported as >80 % [12] (Fig. 2).

## Envelope Trend Analysis

The envelope trend is similar to the AEEG. The raw EEG is filtered to a specified frequency range (commonly 2–6 Hz), and the median amplitude of the waveforms within the frequency range is plotted for a given epoch (e.g., 10–20 s) (Fig. 3). In neonates, envelope trends have been shown to be fairly sensitive for longer seizures, but performed much more poorly for brief seizures and slowly evolving seizures [13].

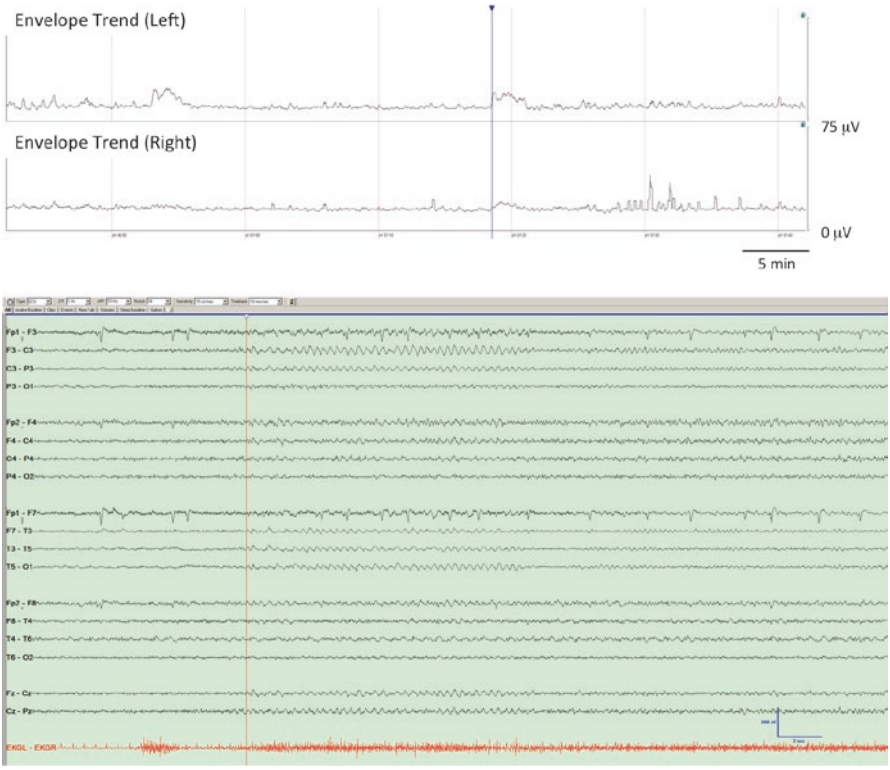



**Fig. 3** Example of focal seizures on envelope trend. Envelope trend for the left and right hemisphere electrode derivations is displayed at the *top*, showing two seizures predominantly involving the left hemisphere. The *bottom panel* shows the raw EEG near seizure onset at the time point indicated by the *arrowhead*

## Burst Suppression Ratio

The burst suppression ratio (BSR) is an algorithm designed to follow the depth of sedation during management of status epilepticus or other condition (like elevated intracranial pressure) with anesthetics, where the goal is to place the EEG in a burst suppression pattern. Traditionally, burst suppression is often described by the duration of the periods of suppression and, sometimes, the duration of the intervening bursts. The BSR is simply the percentage of time in a given epoch that the EEG is suppressed (Fig. 4). Thus, an EEG consisting of on average 3 s periods of suppression with 1 s bursts would have a BSR of 75 %. For the purpose of calculating the BSR, suppression is defined as an EEG amplitude below a certain value (e.g., <5 μV) for a minimum duration (e.g., >0.5 s). As with other qEEG tools/trends, the actual mathematical algorithms used for implementation are more complex [14].

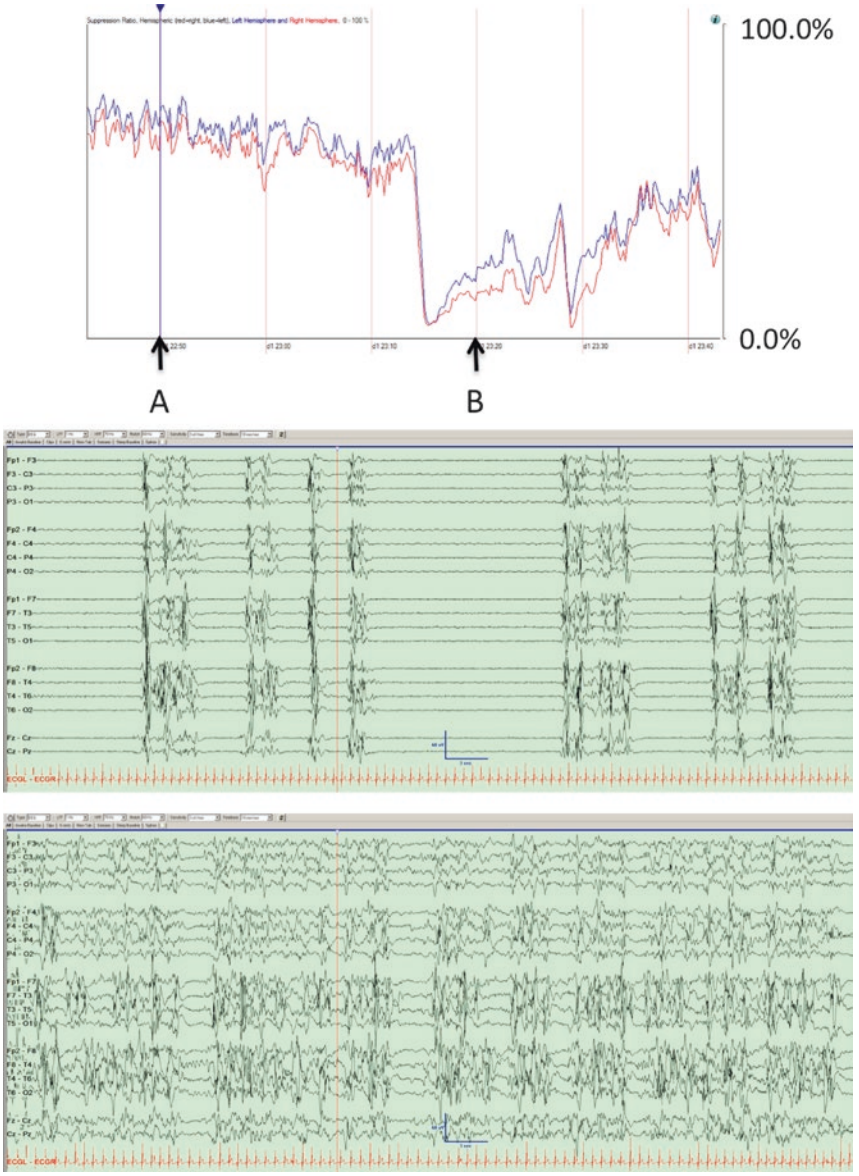



**Fig. 4** Example of burst suppression ratio. A 1 h sample of the calculated BSR for the left and right hemisphere is displayed at the *top*. Raw EEG samples from time points *A* and *B* (*arrows*) are shown at the *bottom*. In (**a**), the BSR is approximately 70 % indicating fairly large fraction of the sample is suppressed. With reduction in sedation, the BSR drops to around 10–15 % at point *B*, and the periods of suppression are much briefer. Raw EEG corresponding to time points *A* and *B* are shown in panels (**a**) and (**b**), respectively

## Frequency-Domain qEEG Tools

Rudimentary frequency-domain qEEG tools have been available for decades, including in analog machines. With the advent of digital EEG recordings and the availability of more powerful computers, they have become much more common.

### Filtering

Although not commonly thought of as a qEEG tool, filtering of the raw EEG using analog or digital filters to reduce/remove certain frequencies is a form of frequency-domain analysis. This allows for the removal of noise (e.g., 60 Hz interference, high-frequency artifact from muscle activity, and low-frequency artifact from sweat). In addition, the EEG can be filtered to highlight the contribution made by certain frequencies, for example, a band-pass filter from 8 to 13 Hz to look at alpha frequencies or from 12 to 16 Hz to look for spindle activity.

### Spectral Analysis

Most frequency-domain analysis relies on Fourier analysis (or spectral analysis). Fourier analysis refers to decomposing a signal (any quantity that varies with time or some other dimension) into simpler pieces – a weighted sum of trigonometric functions, like sine waves, with different frequencies and starting points (phase shifts), referred to as the Fourier series. For periodic signals (those that repeat at some regular interval), this can be done as a series of sine waves that are harmonically related (have frequencies that are integer multiples of the main frequency). For aperiodic signals, the sine waves required to decompose the signal theoretically involve all frequencies. For each frequency, the Fourier series is actually a complex number (having a real and imaginary component, written as $a+ib$). Rather than talking about the real and imaginary components, the Fourier series is usually expressed in terms of an amplitude ($r$, size of the sine wave) and a phase ($\theta$, the point in the cycle of the sine wave at which it starts):

$$r = \sqrt{a^2 + b^2}$$

$$\theta = \tan^{-1} \frac{b}{a}$$

For most signals, calculating the Fourier series is mathematically complicated. The computation of the Fourier series was significantly simplified by an algorithm known as the fast Fourier transform (FFT), which is used to calculate the Fourier series for a discrete (digital) signal. The signal is first broken up into smaller pieces (epochs), and the FFT is calculated by assuming that the epoch repeats itself over and over. Because the signal will not necessarily start and stop at the same voltage,

the repeated epochs would not necessarily create a continuous signal. In order to avoid this discontinuity, the signal is "windowed" – multiplied by a function which minimally impacts most of the epoch but rapidly tapers the edges to a value of 0. This avoids discontinuities. Some examples of commonly used window functions are Hamming and Hann windows. Discussion of specific properties of windows is beyond the scope of this chapter and not relevant for most uses of qEEG; however, it can be relevant when interested in very low frequencies.

Technical aspects of the FFT that can be relevant are the limitations on frequency resolution and maximum frequency. If the digital signal has a temporal resolution of $\Delta t$ (time in seconds between adjacent points in the signal), the maximum frequency in the FFT, $F_{\max}$ (in Hz), is

$$F_{\max} = \frac{1}{2 \times \Delta t}.$$

This is directly related to the Nyquist sampling theorem. If the length of the epoch used to calculate the FFT is $T$ (in seconds), then the frequency resolution, $\Delta f$ (resolution in Hz between adjacent points in the Fourier series), is

$$\Delta f = \frac{1}{T}.$$

Thus, if a digital EEG signal was recorded with a temporal resolution of 200 Hz (i.e., $\Delta t$ is 0.005 s), then $F_{max}$ is 100 Hz. If the FFT is calculated for 2 s epochs (i.e., $T$ is 1 s), then the frequency resolution of the Fourier series is 0.5 Hz. Longer epochs will provide better frequency resolution but at the expense of diluting out rapid or short-lived changes in the frequency content of the signal.

### Power

As mentioned above the Fourier series consists of both an amplitude and a phase for each frequency. For most routine qEEG calculations, the phase is ignored. The amplitude squared ($r^2$) of the Fourier series is referred to as the power (units of $V^2$/Hz). A plot of power versus frequency is the power spectrum (Fig. 5). The power within a given frequency band refers to the area under the power spectrum curve for that frequency range; the relative power is the ratio of the power within a frequency band to the total power. Plots of power with a given EEG frequency band versus time can show the variability of power in that band; more commonly the relative power is used. A decline in relative alpha variability (ratio of alpha frequency power to total power) has been used to detect delayed cerebral ischemia in patients with subarachnoid hemorrhage [15, 16]. Power in a broader frequency band (3.5–20.7 Hz) can also be used to detect changes in cerebral perfusion pressure in patients with strokes [17].

### Compressed Spectral Array

If the EEG was a stationary signal, i.e., one whose frequency content does not vary with time, its power spectrum would be constant. However, the EEG power

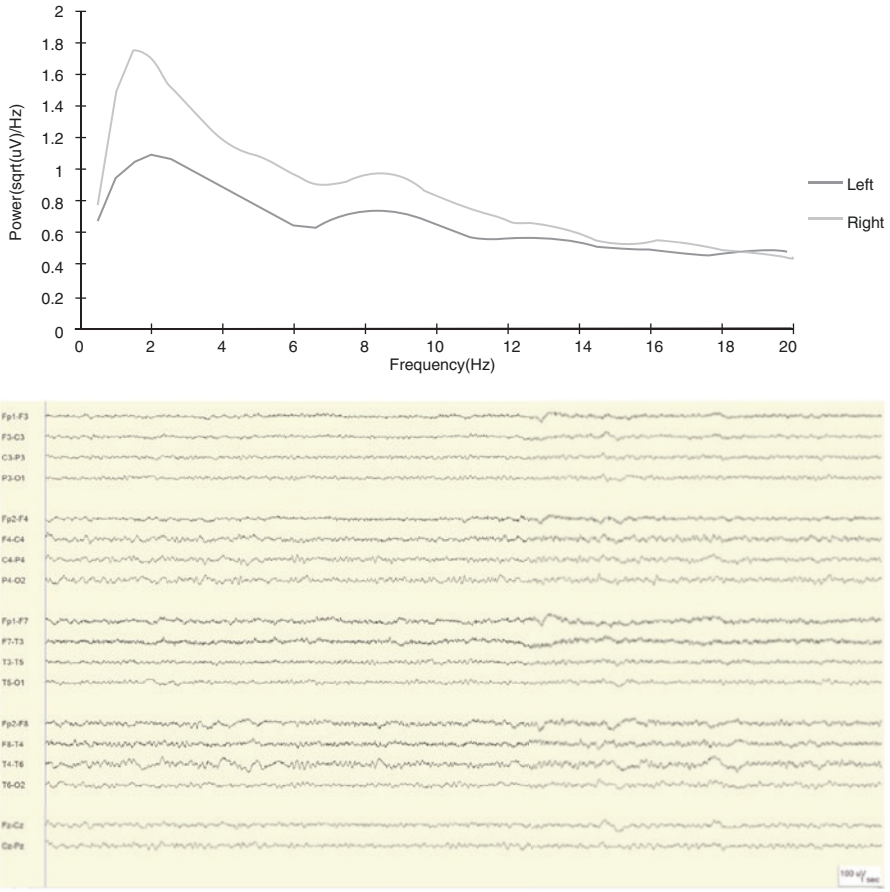



**Fig. 5** Fourier spectrum example. Fourier power spectrum (*top*) and raw EEG (*bottom*) for a patient showing diffuse slowing and focal slowing over the right hemisphere. The most prominent frequency over both hemispheres is ~2 Hz, much more pronounced over the right. There is a secondary peak at about 8.5 Hz

spectrum does vary with time, and this variation may be displayed in one of several ways. Prior to the widespread availability of high-resolution color displays, the power spectra over time were often displayed as a series of line graphs, referred to as a compressed spectral array (CSA). More commonly now, the power spectrum is displayed as a density spectral array (DSA) or color density spectral array (CDSA). Time is plotted on the horizontal axis, frequency on the vertical axis. The power is then coded as an intensity (DSA) or color (CDSA). Variations in the frequency content of the EEG signal over time are easily visualized in such a display (Figs. 6 and 7). Sensitivity for detection of seizures has been reported to be as high as 81.5 % [12]–89.0 % [18]. The latter study also reported 94–100 % sensitivity for detecting background patterns of interest such as epileptiform discharges, rhythmic delta activity, and focal/generalized slowing. Using CDSA as a screening tool to select

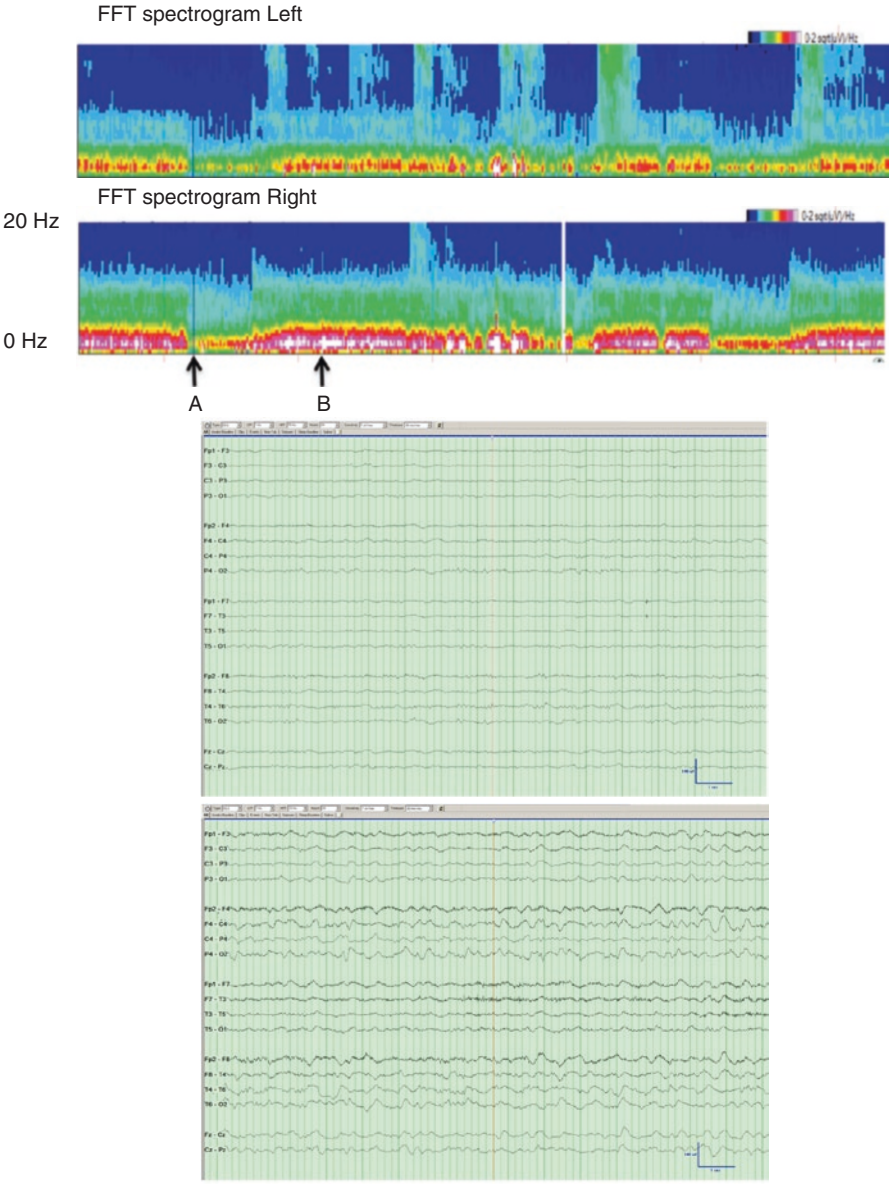



**Fig. 6** Density spectral array example. Spectrograms for the left and right hemisphere electrode derivations are shown at the *top*. At time point, the spectrogram and raw EEG (*middle panel*) show predominantly delta frequencies, slightly higher amplitude over the right. The asymmetry is much more prominent at time point *B* (raw EEG in *bottom panel*)

portions of the raw EEG to review in detail provides a significant reduction in the time required to review a study (from approximately 38 min for 24 h of data down to 8 min) without a significant loss of sensitivity (87.3 % of for seizures and 88.5–100 % for background patterns of interest) [4].

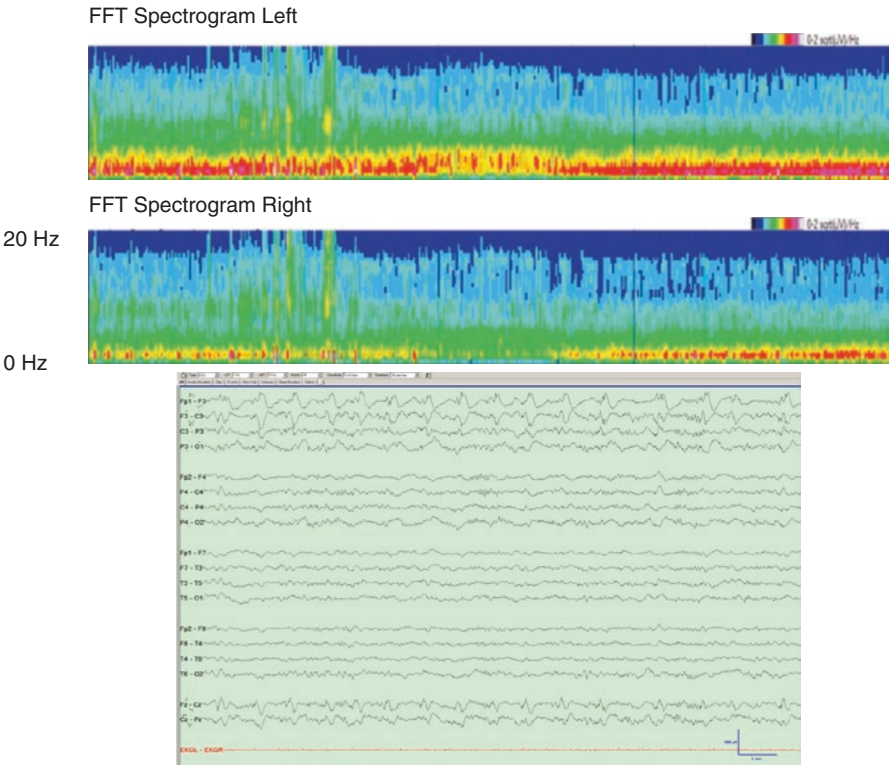
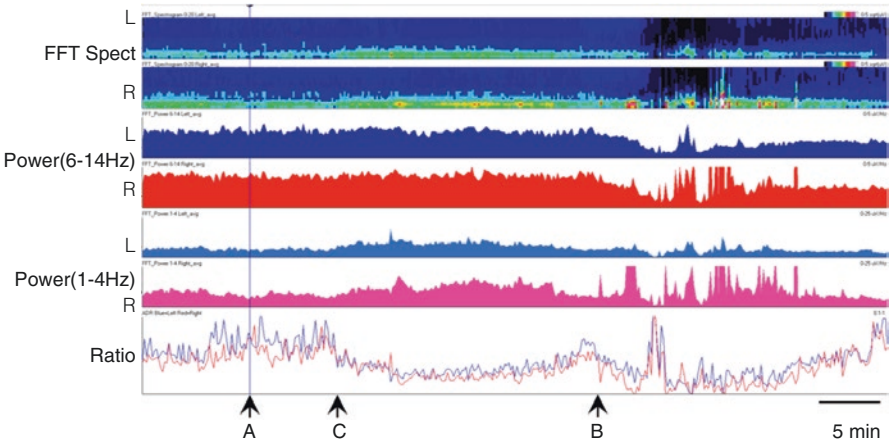



**Fig. 7** Density spectral array example with periodic discharges. The spectrograms for the left and right hemisphere electrode derivations show a diffusely slow background, with more profound slowing over the left hemisphere. However, the spectrogram does not provide adequate detail to discern that the left hemisphere shows periodic discharges over the fronto-central region at approximately 1 Hz

## Power Ratios

More specific information about the power spectrum can be obtained by plotting the power in specific frequency bands such as the alpha (8–13 Hz) or delta (<4 Hz) frequency bands. The power in a frequency band is simply the area under the power spectrum curve in that frequency band.

The ratio of powers in certain frequency bands has physiological/clinical implications. The most commonly used is the alpha/delta ratio, which is the ratio of power in alpha band to that in delta frequency band. This is potentially a good indicator of changes in cerebral perfusion as progressive declines in perfusion are usually associated with a reduction in faster frequencies and an increase in slower frequencies. Thus, the alpha/delta ratio will show a progressive decline during cerebral hypoperfusion and ischemia (Fig. 8). With respect to continuous EEG monitoring, this ratio measure immediately after stimulation of the patient (reactivity) has been demonstrated to be potentially useful for detecting delayed cerebral ischemia after subarachnoid hemorrhage [16].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FFT Spect
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Power(6-14Hz)
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L
Power(1-4Hz)
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Ratio
A
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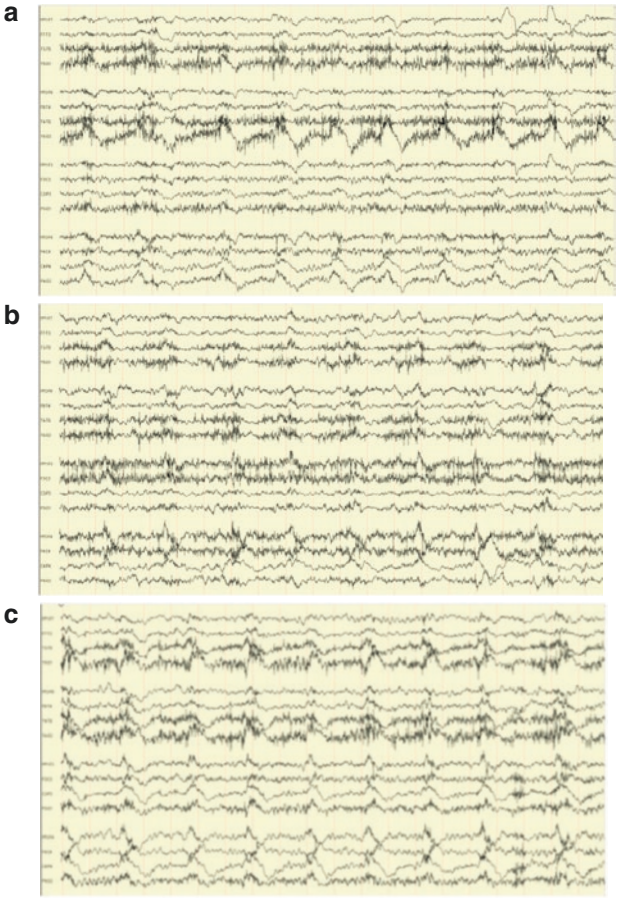
a
b
c

### Asymmetry Index

Measures of asymmetry compare the power in a given frequency band in the right versus left hemisphere. This may be expressed as an absolute number (absolute asymmetry index), where the higher the number, the greater the overall asymmetry in a given frequency band. It may also be expressed as a relative value (relative asymmetry index), where positive and negative values differentiate between higher power on the left and right hemisphere (Fig. 9). A more detailed view can be obtained in a relative spectrogram, where the frequency range is displayed on the vertical axis, the color indicates the side that has more power at a given frequency, and the intensity of the color indicates the level of asymmetry. The asymmetry indices give information about differences in background activity in one hemisphere compared to the other; they are well suited for detection of focal seizures, which are often seen as an increase/change in asymmetry.

## Rhythmic Run Detection and Display

Increased rhythmicity is a hallmark of many electrographic seizures. Rhythmic run detection and display is a proprietary quantitative EEG tool that highlights frequencies with high levels of rhythmicity. Frequency is plotted on the vertical axis and time on the horizontal axis. The intensity at a given frequency indicates the level of rhythmicity. Seizures are often seen as an increase in intensity that moves from one frequency to another (correlating with evolution of discharge frequency on the raw EEG) (Fig. 10).

## Seizure Detection

The qEEG tools and trends described above generally rely on visual inspection by a neurophysiologist or other trained personnel for interpretation. However, there is potential for algorithms employing qEEG tools/trends to automatically detect

**Fig. 8** Cerebral ischemia with alpha/delta ratio. Patient who developed cerebral hypoperfusion while being monitored on EEG. The density spectral array for the left and right hemisphere electrode derivations is shown at the *top*. The power in the 6–14 Hz frequency band and 1–4 Hz frequency bands is shown below, again for the left and right hemispheres. The ratio of power in the 6–14 Hz to 1–4 Hz frequency band is plotted below. *Arrow A* (and associated raw EEG) shows a point before hypoperfusion, and *arrow B* indicates the time point where hypoperfusion was clinically indicated. *Arrow C*, in retrospect, shows a time point when hypoperfusion was apparent on the power ratio. Raw EEG corresponding to time points *A*, *B* and *C* are shown in panels (**a**), (**b**) and (**c**), respectively.

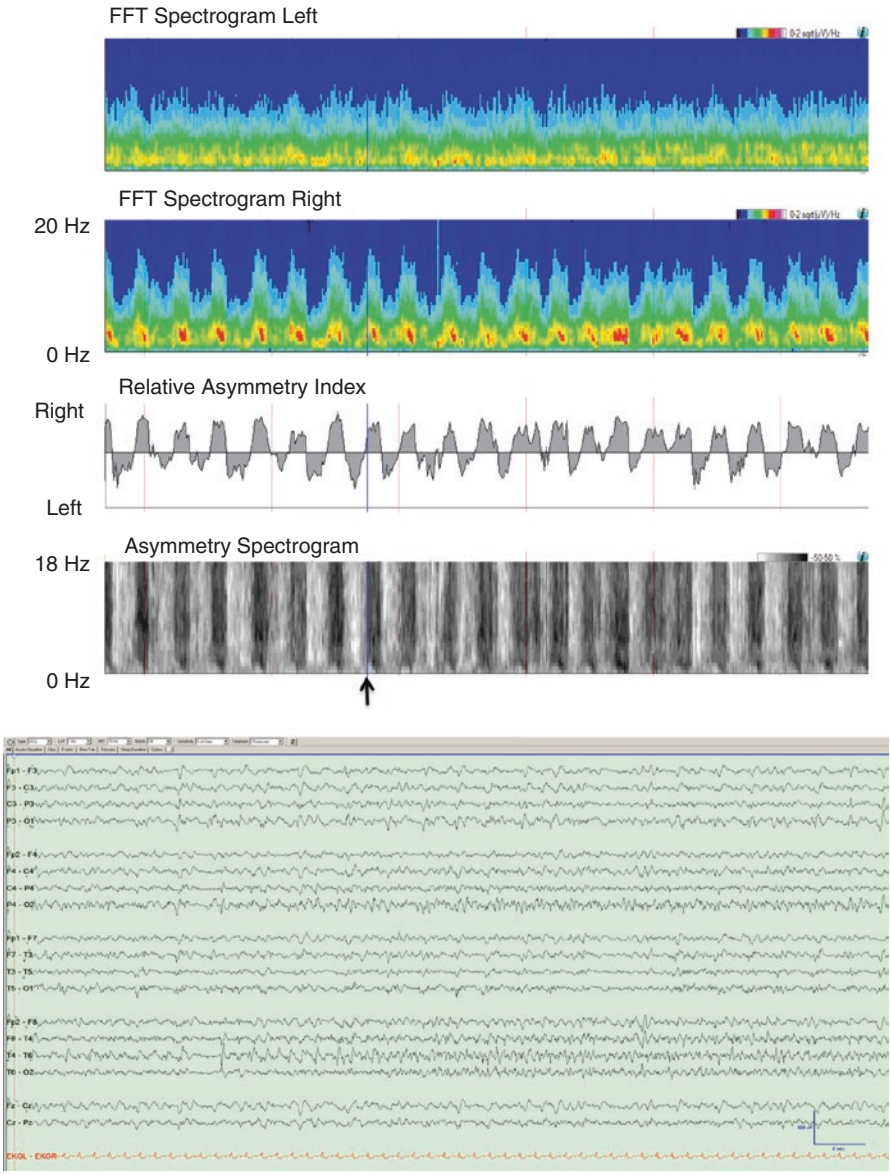


**Fig. 9** Focal seizures on density spectral array and asymmetry index/spectrograms. Data is shown from a patient with frequent focal seizures from the right hemisphere. The density spectral array for the left and right hemisphere electrode derivations is shown at the *top*. The seizures are apparent as increase in power seen at low frequencies on the right. The relative asymmetry index (showing more power on the right as an upward deflection and on the left as a downward deflection). The seizures are apparent as upward deflections; in between seizures, there is relative suppression of activity on the right, leading to a downward deflection. The asymmetry spectrogram shows the asymmetry in power between the left and right hemispheres by frequency (vertical axis; with *darker shades* indicating more power on the right and *lighter shades* indicating more power on the left). A sample of raw EEG is shown at the *bottom* from the time point indicated by the *arrow*

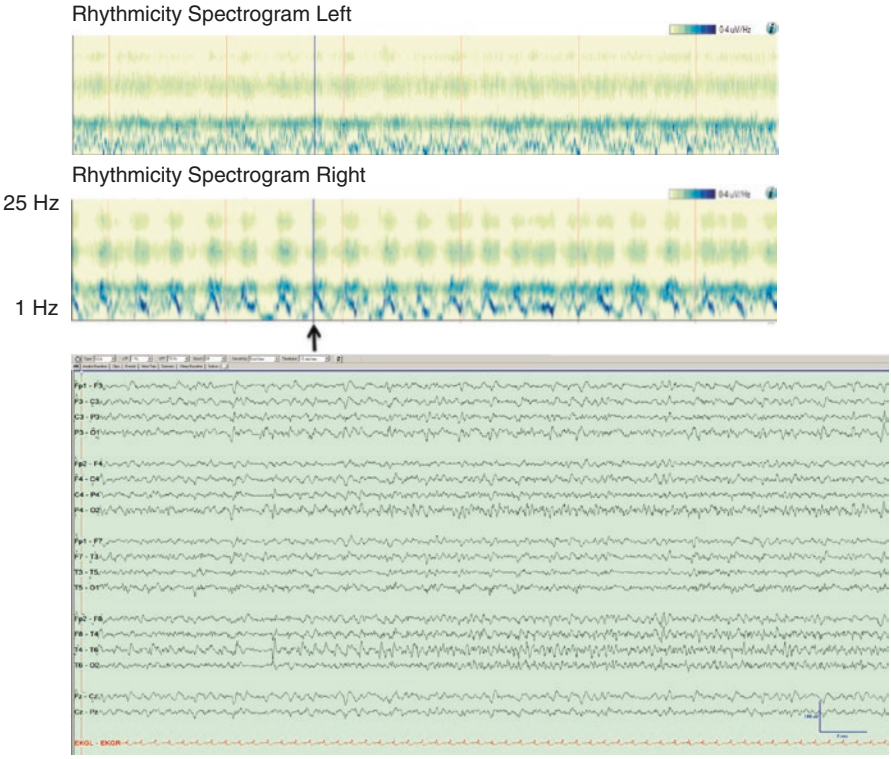


**Fig. 10** Focal seizures on rhythmicity spectrogram. Data is from the same EEG as in Fig. 9 showing recurrent focal seizures from the right hemisphere. The rhythmicity spectrogram from the left and right hemisphere electrode derivations is shown. The seizures consist of increase rhythmicity on the right (*darker shades*). Also, note the change in the frequency with highest rhythmicity during each seizure (showing evolution of frequencies during individual seizures)

seizures. This would allow for nearly instantaneous detection of seizure activity and immediate notification of the clinical team. Most such algorithms are proprietary and full details are not available. However, they generally seem to combine multiple frequency- and time-domain qEEG measures with artifact rejection algorithms to calculate a probability or statistic; when this quantity reaches a certain threshold, a seizure is detected. Little data is available regarding the performance of such tools, especially on cEEG data. In one study [8], a novel algorithm reported a sensitivity of 90.4 % for seizure detection with a false detection rate of 0.066/h. On the same data set, two commercially available algorithms performed poorly (Persyst Reveal with sensitivity of 12.9 % and false detection rate of 1.036/h and Optima IdentEvent with sensitivity of 10.1 % and false detection rate of 0.013/h). Additional data/testing of this novel algorithm has not been reported.

A step beyond automated seizure detection is an automated interpretation of the EEG. Some preliminary attempts at doing so with cEEG have been reported. As with automated seizure detection algorithms, these employ combination of various qEEG tool/trends. In one study, such an algorithm was able to classify >80 % of test

EEGs correctly as isoelectric, low voltage, artifact, burst suppression, generalized periodic discharges, seizures, slowing, or normal [19]. Similar efforts in routine EEG have been disappointing; however, the relatively stationary composition of cEEG in comatose/critically ill patients compared to awake/behaving patients provides some hope that such algorithms may be more successful in this population.

**Conclusion**

Quantitative EEG analysis and trends offer a set of tools that can be used to make review/analysis of cEEG data more efficient and potentially more effective. Efficiency is produced by allowing for faster review by neurophysiologists and preliminary review at the bedside by non-neurophysiologists. Furthermore, qEEG has the potential for making cEEG review more effective by enhancing the ability to recognize events like ischemia. More complex algorithms have the potential for automated seizure detection and other uses in the future. However, the actual implementation of qEEG for review/analysis of cEEG remains quiet variable, both with respect to utilization and the specific tools/trends or combinations of tool/trends that are used. Further research is needed to optimize and standardize qEEG procedure, to determine their true utility, and to encourage broader adoption of these techniques.

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# QEEG in Seizure Detection

# 12

Christa B. Swisher

## Contents



## Introduction

Quantitative EEG (QEEG) refers to a computational method that utilizes mathematical and analytical algorithms to transform and compress raw electroencephalography (EEG) signals into a graphical data representation (Fig. 1). The most common clinical use of QEEG is for seizure detection. However, QEEG applications are widespread and range from applications in psychiatric diseases (such as biomarkers

C.B. Swisher, MD
Department of Neurology, Duke University Medical Center, Box 3824, Durham, NC 27710, USA
e-mail: christa.swisher@gmail.com



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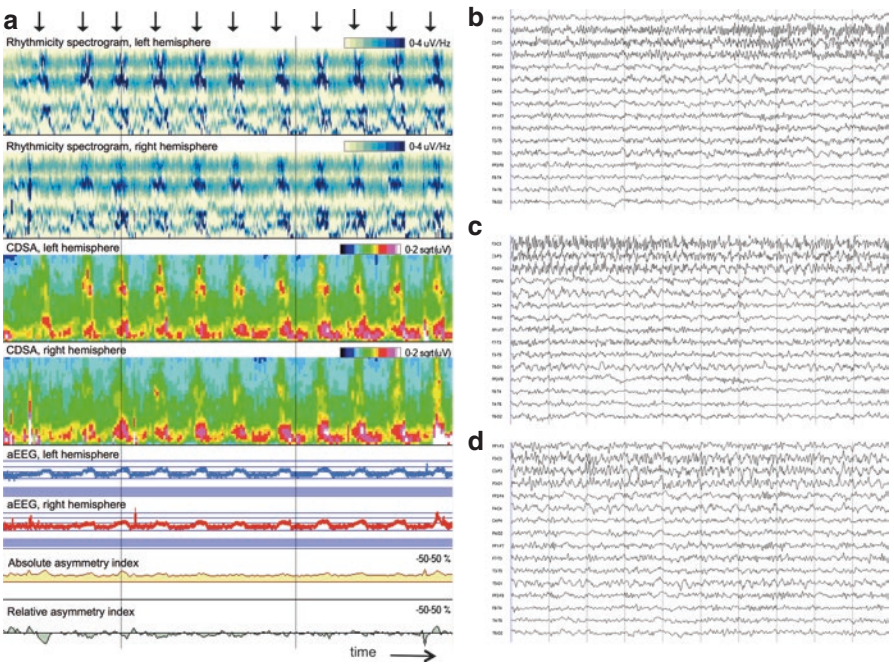


**Fig. 1** Sample 30 min QEEG panel and corresponding raw EEG. (**a**) QEEG panel consisting of the following QEEG tools: rhythmicity spectrogram (displayed for the left and right hemispheres), CDSA (displayed for the left and right hemispheres), aEEG (displayed for the left and right hemispheres), and asymmetry index (displayed as both absolute and relative values). *Vertical black arrows* denote electrographic seizures. (**b**–**d**) Consecutive ictal EEGs (10 s each) corresponding to the first seizure marked on the QEEG panel demonstrating a left central electrographic seizure

and biofeedback) to applications in other neurological diseases (such as dementia and stroke). This chapter will focus on the use of QEEG for seizure identification in critically ill patients. When QEEG is applied in the intensive care unit (ICU) setting, it is sometimes referred to as digital trend analysis (DTA) or digital trending. This chapter will describe the trends used for QEEG seizure identification, summarize the literature, and provide examples of seizures, artifacts, and interictal patterns on QEEG trends.

## Basic Principles

QEEG was initially developed in the 1960s with the development of compressed spectral array (CSA). There are now several types of QEEG trends available for clinical use as part of commercial QEEG software packages. The primary advantage of QEEG is that it allows for a large amount of data to be displayed on a single screen in contrast to only 10–20 s of data with raw EEG. QEEG also simplifies the

information that is displayed, in such a way that it may be amenable for interpretation by non-neurophysiologists. One study found that there was no significant difference in the ability of neurophysiologists, EEG technologists, and neuro ICU nurses to detect seizures on QEEG panels alone [1]. This makes QEEG particularly attractive as a potential bedside patient monitor as a component of ICU multimodality monitoring.

QEEG has several putative advantages over raw EEG review. First, it may reduce the time required for data review. Indeed, raw EEG review is quite labor intensive. One study found that QEEG-guided review of the raw EEG was able to shorten the review process time by 78 % [2]. A survey showed that approximately half of neurophysiologists utilize QEEG as part of their ICU continuous EEG (cEEG) protocol [3]. The usage of QEEG will vary between institutions and readers (various trends used, derivations of trends, frequency of review, and amount of data that is reviewed only by QEEG).

Another potential advantage of QEEG in the ICU setting is that it could allow for real-time data transmission to the treatment team. EEG data obtained by conventional raw EEG review by neurophysiologists is always relayed to the ICU team in a post hoc fashion. Real-time review of the raw EEG is very difficult. In a 2014 survey, the majority of neurophysiologists review each record two or more times a day [3]. Therefore, with conventional EEG-only review, up to 12 h may pass with seizures being undetected. This could lead to delays in treatment of seizures in critically ill patients and potentially adverse outcomes. To date, no clinical studies assessing the role of QEEG on outcomes in the ICU environment are available.

## Trends Used for QEEG Seizure Detection

Although many QEEG trends are available for use, this chapter will discuss the trends that have been studied for seizure detection in critically ill patients. These include envelope trend (ET), color density spectral array (CDSA), rhythmicity spectrogram, asymmetry index, amplitude-integrated EEG (aEEG), and automated seizure detectors. This section will describe these trends and provide examples of seizure appearance for each trend. The QEEG samples in this chapter for CDSA, rhythmicity spectrogram, and aEEG will be displayed for the left and right hemispheres, as this is the preference at the author's institution and was also recently validated in a retrospective trial [1]. It is important to note that other QEEG trends and other derivations may be used. Instead of displaying the left and right hemispheres for each trend, the QEEG trend display may be modified to display individual channels separately or by quadrant. Furthermore, the asymmetry index and aEEG examples in this chapter will be displayed as separate trends, but other institutions may choose to display these as overlapping trends. All QEEG panels displayed in this chapter were created from Persyst (Persyst Development Corporation, Prescott, AZ).

## Automated Seizure Detection

Automated seizure detectors are typically part of QEEG software packages and will vary between manufacturers. The algorithms recognize rhythmic patterns based on waveform morphology, distribution, and evolution over time [4]. Once a certain threshold is reached, the software program assigns a pattern as a seizure. The Persyst 12 automated seizure detector has two types of outputs: a binary output of yes/no based on the detection of discrete electrographic seizure events lasting ≥11 s and a seizure probability curve that displays the probability of each 1 s epoch as being categorized as a seizure (Fig. 2). Of note, most automated seizure detection algorithms (ASDA) are trained on a sample of seizures obtained from various EEGs pooled from the epilepsy monitoring unit (EMU), ICU, and ambulatory EEGs. The complex interictal patterns and sometimes subtle nature of seizures in critically ill patients combined with numerous sources of ICU artifact lead to challenges in successful identification by automated seizure detectors (Fig. 2).

## Frequency-Based Trends

### Color Density Spectral Array

CDSA is known by several other names: Color spectral array (CSA), fast Fourier transform (FFT) spectrogram, and density spectral array (DSA). CDSA displays a three-dimensional, frequency-based graphical display of the EEG data over time. Time is shown on the *x*-axis, and the EEG frequency is shown on the *y*-axis. The various colors represent the power of various frequency bands. The power is the area under the Fourier spectrum curve within a given frequency range (i.e., delta power). In other words, the power is the amplitude (or voltage) of the EEG within a specific frequency range. The power is represented by color. The colors used in the graphical display of the power in the CDSA trend will vary between QEEG software programs. Each program will display a color scale with the CDSA trend. The CDSA trends shown in this chapter were created from Persyst with cooler colors (blue and green) indicating lower power and warmer colors (red, yellow, pink) indicating higher power.

Seizures often consist of an increase in frequency and amplitude and therefore will appear on CDSA trend as a paroxysmal event with increased power. Warmer colors will take the place where cooler colors previously were seen. Additionally, the characteristic seizure evolution in terms of amplitude and frequency can be appreciated on CDSA as an upward arch shape (Fig. 3). Some seizures in critically ill patients consist of little or no increase in amplitude and/or frequency and therefore might be missed on CDSA.

### Rhythmicity Spectrogram

The rhythmicity spectrogram, rhythmic run detection and display, is a proprietary tool developed by Persyst, Inc. An example of a rhythmicity spectrogram is shown in Fig. 4. Like CDSA, the rhythmicity spectrogram is a three-dimensional display. Time is on the *x*-axis and frequency is on the *y*-axis (but on a logarithmic scale to accentuate lower frequencies). Although the power is displayed by color-coding (darker blue

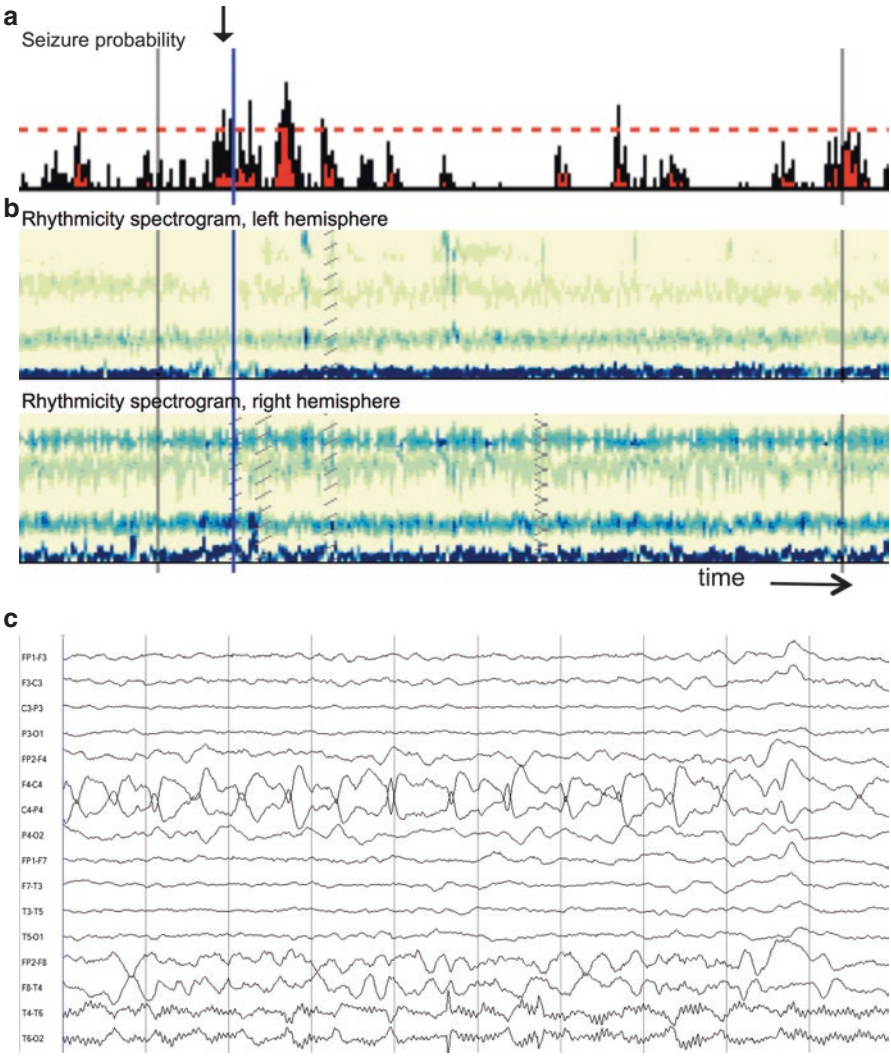


**Fig. 2** Seizure identification on seizure probability trend and corresponding EEG. (**a**) Seizure probability trend containing one electrographic seizure (approximate onset marked by the *vertical black arrow*). The seizure probability trend does identify the seizure, but is not able to discriminate it from numerous non-seizure events. (**b**) Corresponding rhythmicity spectrogram (displayed for the left and right hemispheres). (**c**) Ictal EEG corresponding to the time point on the QEEG trends as marked by the *vertical blue line*. This EEG sample contained abundant artifact (most notably in the T6 electrode), rhythmic delta activity (RDA), and brief rhythmic discharges (BRDs) resulting in poor seizure identification on QEEG

color indicating more power), it differs from CDSA by *only* displaying the power in components that have a high degree of rhythmicity, instead of displaying all the power. Seizures will present as areas that are darker in color. The rhythmicity spectrogram is particularly helpful in displaying the evolution of seizures (Fig. 4).

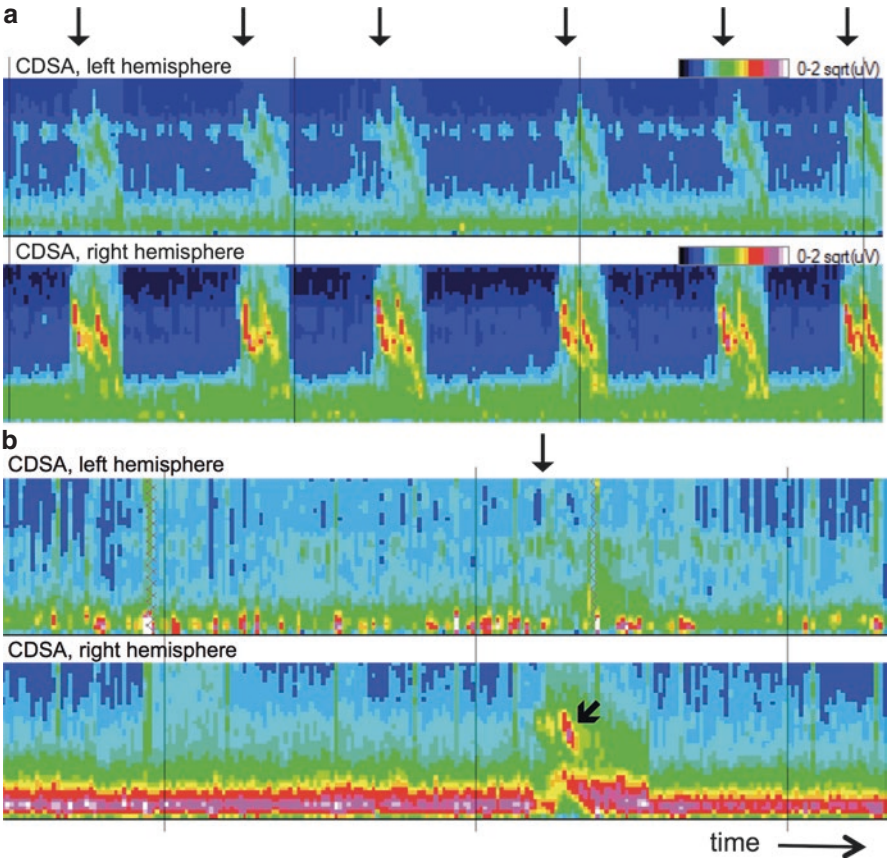


**Fig. 3** Seizure appearance on the CDSA trend, 0–20 Hz (displayed for the left and right hemispheres) for two different patients. *Vertical black arrows* denote the approximate onset of electrographic seizures. The upward arch shape of seizures can be appreciated on both patients. (**a**) Recurrent right hemispheric seizures seen as an increase in power (represented by warmer colors). Note the evolution of power increase (shown by the *red* and *yellow* colors). Soon after the onset of the seizure, there is a gradual decrease in frequency, then increase, and then decrease again before cessation. This is superimposed on a diffuse mild increase in power (shown by *green* and *teal* colors during seizure activity). (**b**) A single right hemispheric seizure on the CDSA trend. Aside from a brief increase in high power (denoted by diagonal *black arrow*) in mid-frequency range, the majority of the seizure consists of highest power (*red*, *pink*, *and white*) in the delta frequency range. This is superimposed on a diffuse mild increase in power (shown by *green* color)

Subtle seizures can often be seen only on the rhythmicity spectrogram while not appearing on other trends. However, the rhythmicity spectrogram is prone to highlighting interictal periods and artifact that are easily mistaken for seizures. Examples of these will be discussed later in the chapter.

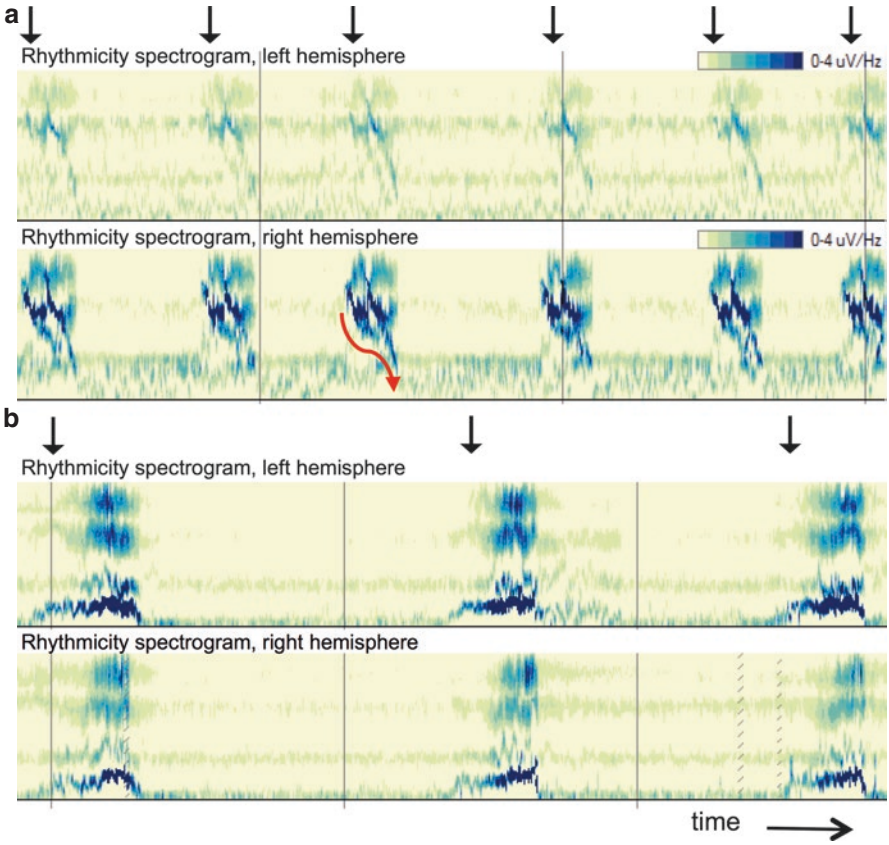


**Fig. 4** Seizure appearance on the rhythmicity spectrogram, 0–25 Hz (displayed for the left and right hemispheres) for two different patients. *Vertical black arrows* denote the approximate onset of electrographic seizures. The evolution of the seizure can be appreciated on both patients. (**a**) Recurrent right hemispheric seizures beginning with an increased power (*darker blue* coloration) in alpha activity. As the seizure progresses (shown by the *red arrow*), there is gradual evolution of increased power into lower frequency ranges before cessation. (**b**) Three generalized seizures (with left hemisphere predominance) beginning with a subtle, increased power in the delta frequency range that gradually increases in power (*light blue* becoming *darker blue*). As the seizure progresses, an increase in power is seen in the alpha and beta frequency ranges as well followed by abrupt cessation

## Asymmetry Index

The asymmetry index compares the difference in power between homologous electrodes (i.e., the difference in power between F3 vs. F4 and O1 vs. O2, etc.). The difference is represented in a graphical display. Typically, there are two graphs that are separate or overlapping: the absolute asymmetry index and the relative asymmetry index (Fig. 5). The absolute asymmetry index (yellow trace) calculates the absolute difference, always displaying a positive score. There is an upward deflection with increasing asymmetry and a downward deflection with decreasing

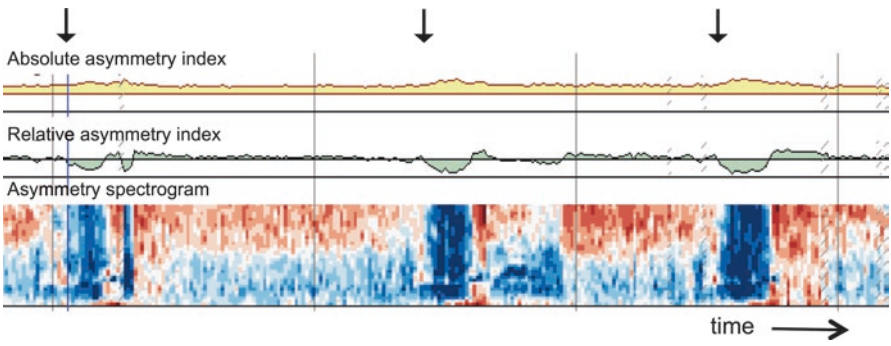


**Fig. 5** Example of three left hemispheric seizures on asymmetry index and asymmetry spectrogram (approximate onset marked by *vertical black arrows*). There is a subtle, upward deflection of the absolute asymmetry index (*yellow trace*) indicating a period of increased asymmetry. There is a corresponding downward deflection of the relative asymmetry index (*green trace*) indicating increased power in the left hemisphere. Interictally, there is equal power in the left and right hemispheres, as seen by equal red and blue coloration on the asymmetry spectrogram. The seizures appear on the asymmetry spectrogram as a period of dark blue indicating higher power in the left hemisphere. There is increased power in the right hemisphere after each seizure due to postictal left hemispheric suppression

asymmetry. The relative asymmetry index (green trace) is able to show lateralization for the asymmetry. An upward deflection represents more power in the right hemisphere, and a downward deflection represents more power in the left hemisphere. This trend is particularly helpful for focal or lateralized seizures. However, a bilateral or generalized seizure with similar power in both hemispheres will likely not show up well on the asymmetry index.

The asymmetry spectrogram (Fig. 5) also displays similar information regarding the power in homologous electrodes. Colors indicate where more power is present (red = more power in the right hemisphere and blue = more power in the left hemisphere). The degree of asymmetry is represented by the darkness of the color. In addition to seizure detection, the asymmetry index and asymmetry spectrogram are also particularly helpful for ischemia detection.

## Amplitude-Based Trends

### Envelope Trend

The envelope trend (ET) is a QEEG trend that is based only on amplitude. The raw EEG is divided into 10–20 s epochs. For each epoch, the median amplitude is calculated and plotted over time, creating the ET display. This trend is often displayed separately for the left and right hemispheres, but can be customized to separately display the ET for a specific set of electrodes. By plotting only the median amplitude, the ET has the advantage of being able to filter out short-duration artifacts. Conversely, it may miss very brief seizures due to the fact that the ET is calculated in 10–20 s epochs. Seizures on ET are visualized as an upward deflection in the trace (Fig. 6).

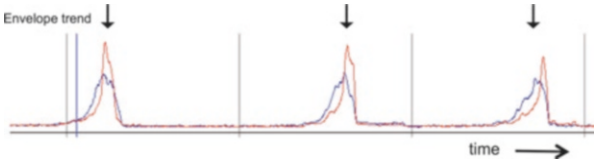


**Fig. 6** Example of three generalized seizures on envelope trend. The *blue* trace corresponds to the left hemisphere and the *red* trace corresponds to the right hemisphere. *Vertical black arrows* mark seizures. For each seizure, there is a clear, upward deflection in both the *red* and *blue* traces. Seizure duration is approximately 5 min

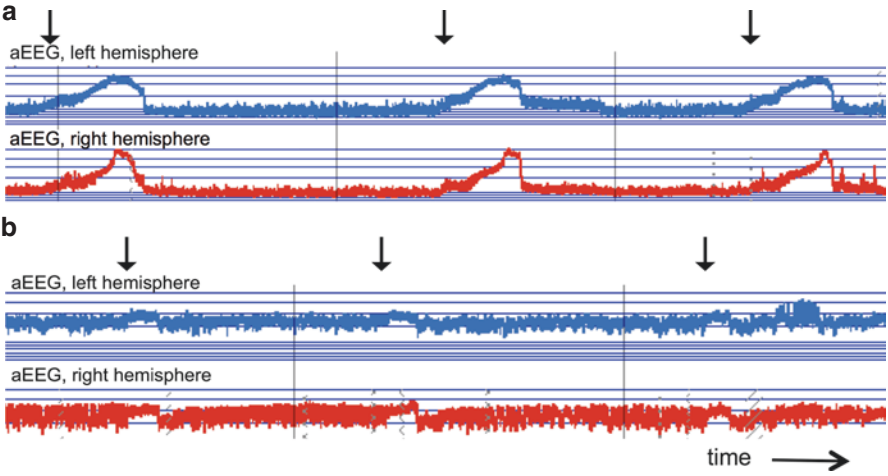


**Fig. 7** Example of seizures on the aEEG trend (displayed for the left and right hemispheres) for two different patients. Approximate seizure onset is marked by *vertical black arrows*. (**a**) Bilateral seizures are represented by a large, upward deflection in the minimum and maximum amplitudes of the baseline of both traces. The gradual increase in amplitude (evolution) can be appreciated well. (**b**) Right hemispheric seizures are represented by an increase in the minimum amplitude of the *red* trace, without a notable change in the maximum amplitude. This subtle seizure appearance on aEEG is more common in critically ill patients than the seizures shown in panel (a)

## Amplitude-Integrated EEG

The amplitude-integrated EEG (aEEG) trend is another trend calculated only by amplitude. For each data point, the raw EEG is filtered and rectified (all values made positive). The amplitude-integrated EEG (aEEG) trend is displays the minimum and maximum amplitude of the raw EEG signal in a predefined time frame (typically 1–2 s) on a semilogarithmic scale. Seizures appear as an increase in the minimum amplitude, creating an upward arch shape (Fig. 7). There is often a corresponding increase in the maximum amplitude. This trend is also known as a cerebral function monitor (CFM) and has been utilized extensively for seizure detection in neonates. The original CFM display represented EEG data from one raw EEG channel placed over the parietal regions (P3 and P4). To have the ability to detect lateralized abnormalities, it is now common for CFM machines to display two channels of data

(C3-P3 and C4-P4). Commercial QEEG software, such as Persyst, has the ability to display aEEG trends by any group of electrodes and is often displayed separately for the left and right hemispheres, incorporating all lateralized electrodes from the standard 10–20 montage.

## Data for Quantitative EEG Utilization in Seizure Detection

### Sensitivity of Quantitative EEG Used in Isolation for Seizure Detection

The majority of studies on QEEG for seizure detection have been in the pediatric and neonatal population, although there are an increasing number of studies evaluating QEEG in critically ill adults. Beyond just patient's age, there is significant heterogeneity in these studies. Some utilize QEEG trends obtained from full-montage cEEGs, while others are obtained from limited channel cEEGs. Furthermore, even when a full cEEG montage is used, the QEEG trend studied may be derived from all channels or from a limited number of channels. Although certain QEEG trends are studied more often than others, the type of QEEG trend studied (commercially available vs. a novel QEEG algorithm) often differs between studies. Some studies may employ only one trend while others use more than one. Another potentially confounding variable in QEEG studies is the variability in expertise of QEEG readers and the extent of QEEG training provided. Studies may use neurophysiologists as readers, but they may not be considered "experienced readers" as many neurophysiologists have not had training/experience with QEEG trends. Conversely, many of the studies in the neonatal population utilize neonatologists as readers since they are more likely to be the ones interpreting the bedside CFM. Neonatologists may not have experience in reading raw EEGs, but they might be considered "experienced readers" since some have had several years experience in interpreting CFMs. Furthermore, the manner in which sensitivity and specificity are calculated (scoring based on capturing individual seizures or scoring based on the presence/absence of seizures in patients or epochs) vary between studies. However, in actual clinical practice, knowing the exact number of seizures present may not be necessary, and simply knowing if seizures are present or not may be sufficient to guide therapy.

There are numerous other variables to consider when comparing QEEG studies: if the readers have access to the raw EEG, the overall QEEG record duration, the display timescale of the QEEG, the QEEG dataset (all patients with seizures vs. some with seizures and some without), and the role of the QEEG reader (mark seizures vs. mark area of concern).

Overall, studies in the adult and pediatric population evaluating individual QEEG trends (ET, aEEG, or CDSA) report sensitivities for seizure detection of 44–83 % when interpreted by neurophysiologists [5–10]. Studies evaluating the ability of non-neurophysiologists (pediatric or neurology residents, general neurologists, intensivists, and neonatologists) to interpret single QEEG trends (ET, aEEG, or

CDSA) for seizure detection report sensitivities of 41–89 % [5, 6, 11–14]. As mentioned previously, there is a significant variability between studies, making direct comparisons very difficult. This heterogeneity contributes to the wide range in reported sensitivities. Therefore, it remains unclear if one QEEG trend is superior to another for seizure detection.

In clinical practice, the bedside QEEG display often shows more than one QEEG trend, which may improve seizure detection. To address this question, there have been two studies evaluating the combination of two QEEG trends [6, 15] and one study evaluating the combination of a panel of QEEG trends [1]. There was an improved sensitivity (66 %) for neurophysiologists when ET and CDSA trends were combined as compared to individually (sensitivity of 50 % for both ET and CDSA). However, non-experienced readers, neurologists, did not reveal an improvement in sensitivity when ET and CDSA were presented as a combination (50 % sensitivity for ET + CDSA and 50 % for individual trends) [6]. Another study reported a very high sensitivity (93 %) for the detection of the presence of seizures by non-neurophysiologists (one fellow, one neurology resident, and two neuro ICU nurses) when readers evaluated a combination of aEEG and CDSA (two channels each). However, this was not compared to their performance on individual trends. Of note, the derivation of the two-channel aEEG and CDSA trends varied between records as the authors preselected the channels that would best display ictal activity [15].

As mentioned previously, it is common for bedside QEEG displays to be customized to show numerous QEEG trends at once. The sensitivity of a panel of QEEG trends (rhythmicity spectrogram (Persyst Development Corporation, Prescott, AZ), CDSA, asymmetry index, and aEEG) was found to be 87 % for five neurophysiologists, 80 % for seven EEG technologists, and 87 % for five neuro ICU nurses for the detection of the presence of seizures on randomized 1 h epochs [1]. However, this was not compared to the reader's performance using individual QEEG trends. There was no significant difference between the three groups with regard to sensitivity. This study utilized QEEG trends derived from all lateralized electrodes in a standard 10–20 montage, while most all other QEEG studies for seizure detection (with the exception of one [14]) employed QEEG trends derived from a limited number of electrodes, even if a full 10–20 montage is performed for the cEEG recording. Seizures in critically ill patients have significant variability in appearance ranging from subtle, low-amplitude, focal seizures to obvious, generalized, high-amplitude seizures. This variability in seizure appearance highlights the importance of a panel of QEEG trends. For example, seizures in one patient may appear best on rhythmicity spectrogram, while another patient's seizures may be best observed on aEEG. Furthermore, a panel of QEEG trends makes it easier to discriminate seizures from artifact.

## False-Positive Rate

One important concern regarding the use of QEEG for seizure detection is the rate of false positives. Previous studies utilizing both single and multiple QEEG trends

for seizure detection by neurophysiologists and non-neurophysiologists have found the false-positive rate to be between 5 and 39 % [1, 7, 8, 11, 12, 15]. One of these studies found that the most common reason for false-positive seizure diagnosis (18 %) by aEEG was movement artifact [7]. However, it is common for various types of artifact to be mistaken for seizures on QEEG in addition to various interictal patterns (to be further discussed later in the chapter). If QEEG trends were used alone without confirmation of events by interpretation of raw EEG by a neurophysiologist, the result would be unnecessary treatment. Therefore, QEEG should not be used in isolation.

## Utility of Combination Raw EEG and QEEG

Although several studies, discussed above, have been performed to evaluate the sensitivity and specificity of isolated review of QEEG trends, many neurophysiologists use QEEG in combination with raw EEG review to assist the review process. A 2014 survey found that 52 % of neurophysiologists utilized QEEG as part of their cEEG protocol [3]. The addition of CDSA linked to raw EEG was found to speed the review process by 78 % with little loss in sensitivity when compared to traditional EEG review without QEEG [2]. In the study group, the reviewer's primary mode of assessment was CDSA interpretation, but reviewers were able to evaluate short periods of the raw EEG. To review 24 h of data, traditional raw EEG review took an average of 38 min compared with an average of 8 min for CDSA-guided review. The sensitivity for CDSA-guided review was 78 % [2].

## Automated Seizure Detection

Automated EEG detection systems were developed 40 years ago. Commercial QEEG software packages often include an automated seizure detection algorithm. Currently, automated seizure detectors are more frequently used to assist with seizure detection in EMUs than in the ICU.

The currently available software for automated seizure detection has either a low sensitivity or a high false-positive rate. Studies have found the sensitivity of these algorithms to range from 33 to 93 % [16], with variability in the algorithms and in the datasets as the likely explanation for the wide range. A recent and very promising study of a novel automated seizure detection algorithm (ICU-ASDA) had a mean sensitivity of 90 % with a false-positive rate of 1.6/24 h when applied to ICU EEG recordings [16]. This was compared against two commercially available automated seizure detection products that resulted in much lower sensitivity (sensitivity of 13 and 10 % with false-positive rates of 1.036/h and 0.013/h).

In a separate study, the Persyst 12 automated seizure detection algorithm (described earlier) was used on ICU EEG samples that contained EEG patterns that typically make identification of seizures problematic (periodic patterns, ictal-appearing artifacts, and normal variants that appear epileptiform). The software

detected 76 % of all seizures with a false-positive rate of 0.9/h [4]. As automated seizure detection algorithms continue to improve the discrimination between seizures and artifacts and interictal events, it is likely that these will begin to enter regular clinical practice in the ICU.

### Seizure Characteristics and QEEG

Several studies have attempted to identify certain EEG characteristics that affect seizure identification on QEEG. These EEG characteristics fall into two categories: intrinsic seizure characteristics and interictal EEG patterns or artifacts. All studies that have evaluated the relationship between seizure duration and identification on QEEG have found that shorter seizures (typically less than 1–2 min) are more likely to be missed by experienced and non-experienced QEEG readers alike [1, 2, 8, 10, 12, 15]. Additionally, there appears to be a consistent finding that low-amplitude seizures (typically less than 75 μV) are more likely to be missed by QEEG readers [10, 12, 15]. The relationship between other seizure characteristics and seizure identification on QEEG has been inconsistent. Focal or bilateral independent seizures may be missed more often by QEEG readers [1, 12, 15], although others have not found a relationship between seizure spatial extent and seizure identification [8].

It is not entirely clear how the interictal EEG pattern affects seizure identification on QEEG. Two studies have correlated lower QEEG interpretation performance with EEGs that either contain abundant interictal discharges [10] or periodic patterns [4]. However, another report found that neurophysiologists were more likely to correctly identify seizures in the presence of a periodic EEG background [1].

## Recognizing Seizures on QEEG

The most challenging aspect of QEEG in critically ill patients is discriminating artifact and interictal patterns from seizures and being able to recognize subtle seizures. The most common reason for false-positive seizure diagnosis by aEEG was movement artifact [7]. As discussed previously, short- and low-amplitude seizures tend to be missed by QEEG readers [1, 2, 8, 10, 12, 15]. Furthermore, various interictal patterns may hinder correct seizure identification. This section will give several examples of QEEGs highlighting these issues.

### Artifact Recognition

Many sources of artifact are present in the ICU and are unavoidable. Some sources of artifact (such as bed percussion) are easily differentiated from seizures due to the long duration and invariable appearance of bed percussion artifact on QEEG. Conversely, other artifacts may easily be mistaken for seizures due to a shorter time course and appearing to show evolution (sternal rub and

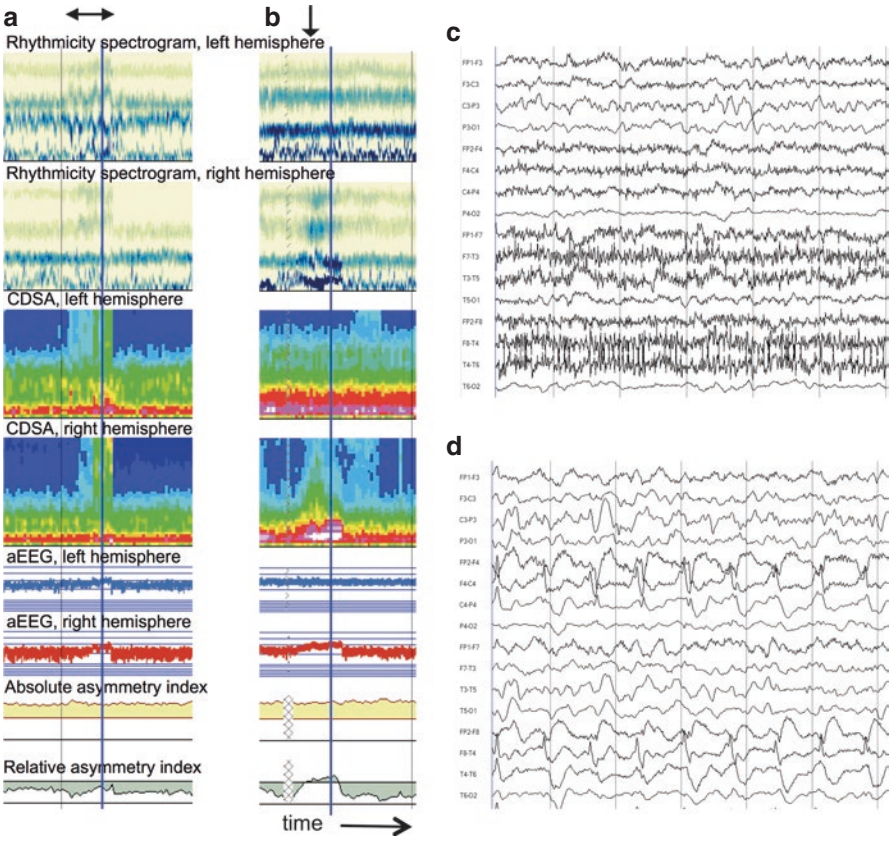


**Fig. 8** Appearance of EMG artifact compared with seizures on QEEG. (**a**) QEEG panel (rhythmicity spectrogram, CDSA, aEEG, and asymmetry index) displaying a period of EMG artifact (marked by *horizontal black arrow*). (**b**) QEEG panel containing one seizure (approximate onset marked by *vertical black arrow*) occurring later in the recording for the same patient. Note the difference in appearance of artifact and seizure on the rhythmicity spectrogram and CDSA. The appearance on aEEG is strikingly similar. If aEEG were used in isolation, there would be a high likelihood of a false positive. (**c**) Raw EEG consisting of EMG artifact corresponding to the time point on panel **a** marked by the *vertical blue line*. (**d**) Ictal EEG corresponding to the time point on panel (b) marked by the *vertical blue line*

electromyographic (EMG) artifact) (Figs. 8 and 9). Other common sources of QEEG artifact in the ICU include chewing (Fig. 10), alternating current (AC) artifact from various ICU devices, patient disconnection (Fig. 11), and electrode artifact from high-impedance electrodes. These artifacts result in paroxysmal changes on raw EEG and QEEG, and it can be extremely difficult to distinguish seizures from artifact on QEEG. Review of the raw EEG is critical to avoid false-positive results.

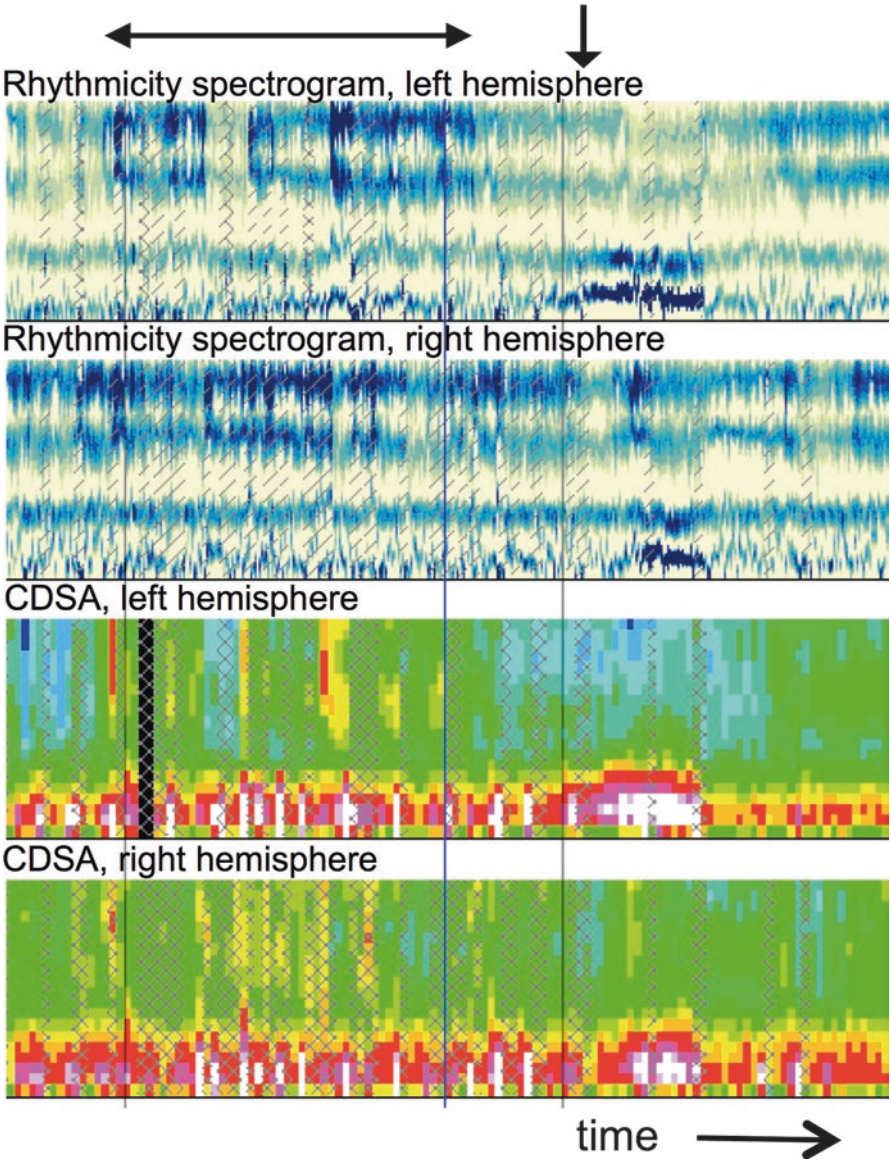


**Fig. 9** Appearance of EMG artifact compared with seizures on a QEEG panel (rhythmicity spectrogram and CDSA, displayed for the left and right hemispheres). The rhythmicity spectrogram and CDSA trends display a period of EMG artifact (marked by *horizontal black arrow*) and an electrographic seizure (approximate onset marked by *vertical black arrow*). The appearance of EMG artifact in the alpha and beta frequency ranges on the rhythmicity spectrogram is very common

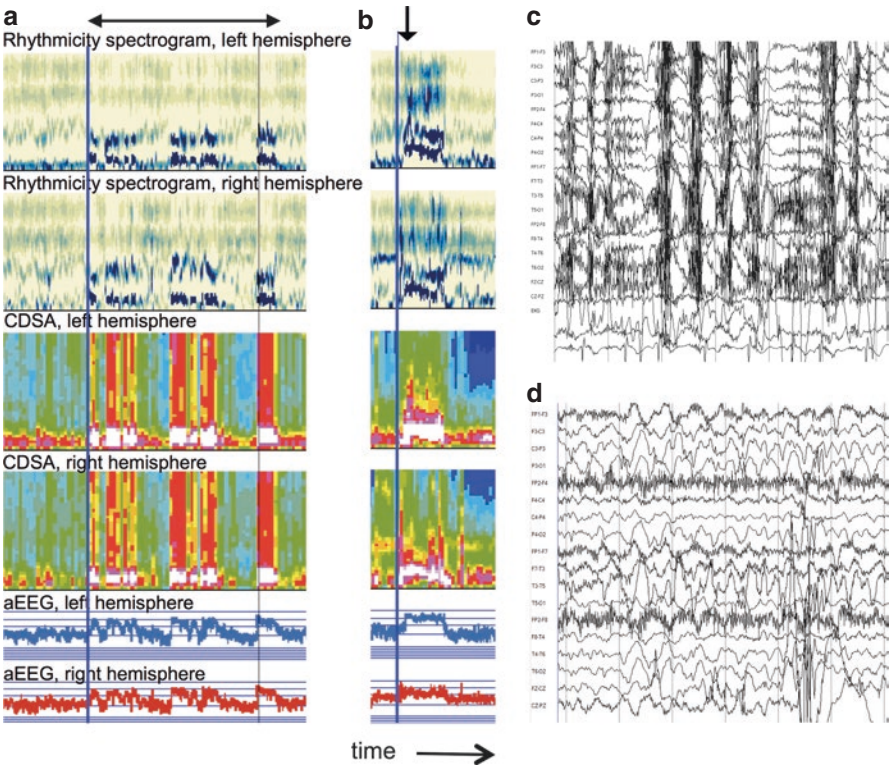


**Fig. 10** Appearance of chewing artifact compared with seizures on QEEG. (**a**) QEEG panel (rhythmicity spectrogram, CDSA, and aEEG for the left and right hemispheres) displaying recurrent periods of chewing artifact (marked by *horizontal black arrow*). (**b**) QEEG panel containing one seizure (approximate onset marked by *vertical black arrow*) occurring later in the recording for the same patient. (**c**) Raw EEG consisting of chewing artifact corresponding to the time point on panel (a) marked by the *vertical blue line*. (**d**) Ictal EEG corresponding to the time point on panel (b) marked by the *vertical blue line*

Figures 8, 9, and 10 show examples of QEEG panels that contain both discrete seizures and periods of artifact. Although it may initially be difficult to distinguish artifact from seizures on QEEG, the skill of pattern recognition will improve with continued experience. As with raw EEG, seizure evolution can often be appreciated, especially on rhythmicity spectrogram (Fig. 4). In contrast, artifact often has a sudden onset and offset without displaying evolution. Artifacts in the ICU (especially EMG artifact) tend to appear in the higher-frequency ranges, while it is common for seizures in critically ill patients to be limited to the delta and theta range (Fig. 9). Furthermore, seizure morphology on QEEG tends to be stereotyped, making subsequent seizure identification easier over time. Due to inter-patient seizure variability, it is common for seizures not to be well defined on all QEEG trends. Seizure characteristics will determine varying appearance on different QEEG trends. The author's institution utilizes a panel of QEEG trends for this reason.

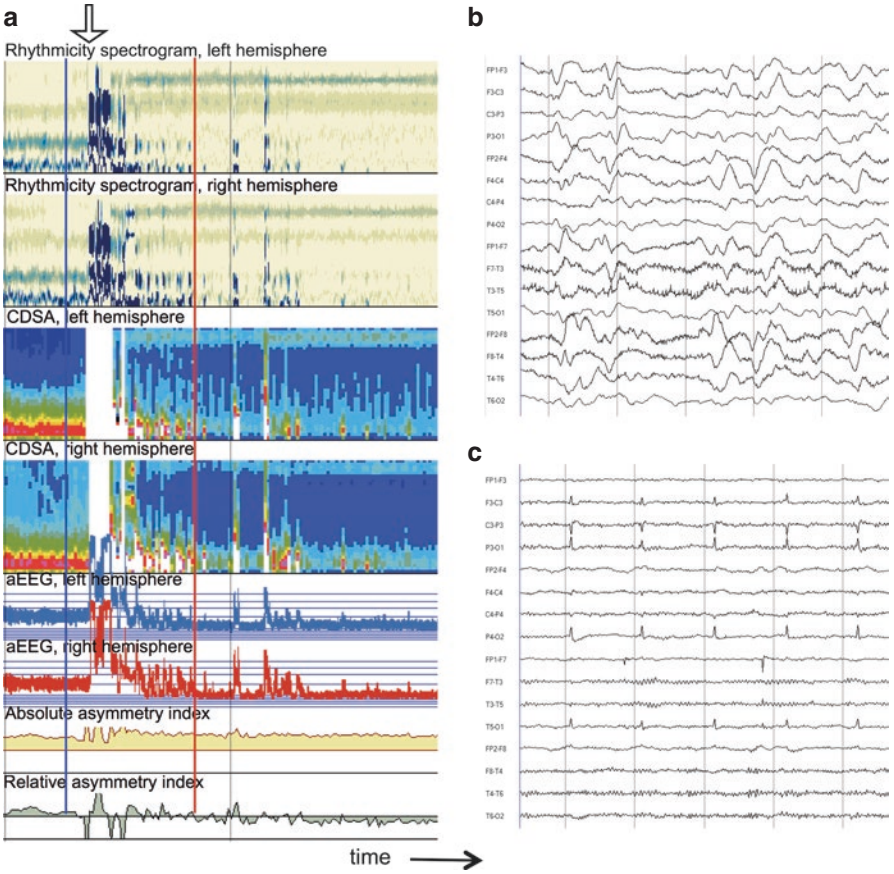


**Fig. 11** Appearance of EEG disconnection on QEEG. (**a**) QEEG panel (rhythmicity spectrogram, CDSA, aEEG, and asymmetry index). Disconnection is marked by the *vertical white arrow*. (**b**) Raw EEG corresponding to the time point on panel (a) marked by the *vertical blue line* showing the patient's background EEG pattern. (**c**) Raw EEG corresponding to the time point on panel (a) marked by the *vertical red line* after the patient was disconnected from EEG. After disconnection, the QEEG is picking up a large amount of artifact from the environment and from movement as seen by the large deflections on all QEEG trends. After the artifact subsides, the EEG appearance looks similar to electrocerebral inactivity (ECI)

## Interictal Patterns

There are numerous rhythmic and periodic EEG patterns encountered in critically ill patients that pose difficulties when interpreting QEEG.

### Periodic Patterns

Periodic EEG patterns, such as burst suppression, burst attenuation, lateralized periodic discharges (LPDs), and generalized periodic discharges (GPDs), can appear as paroxysmal events on QEEG under certain circumstances. Short-duration,

low-frequency, monotonous periodic patterns will likely not change the QEEG background appearance. However, if the duration of bursts in burst suppression/attenuation patterns is of sufficient duration, a paroxysmal change on QEEG may appear. Similarly, a change in the frequency of LPDs and GPDs to higher-frequency runs of LPDs and GPDs can appear as a paroxysmal event on QEEG especially if this change is rather abrupt. Figure 12 displays an example of a discrete (but subtle) seizure on QEEG contrasted with interictal activity of consisting of LPDs.

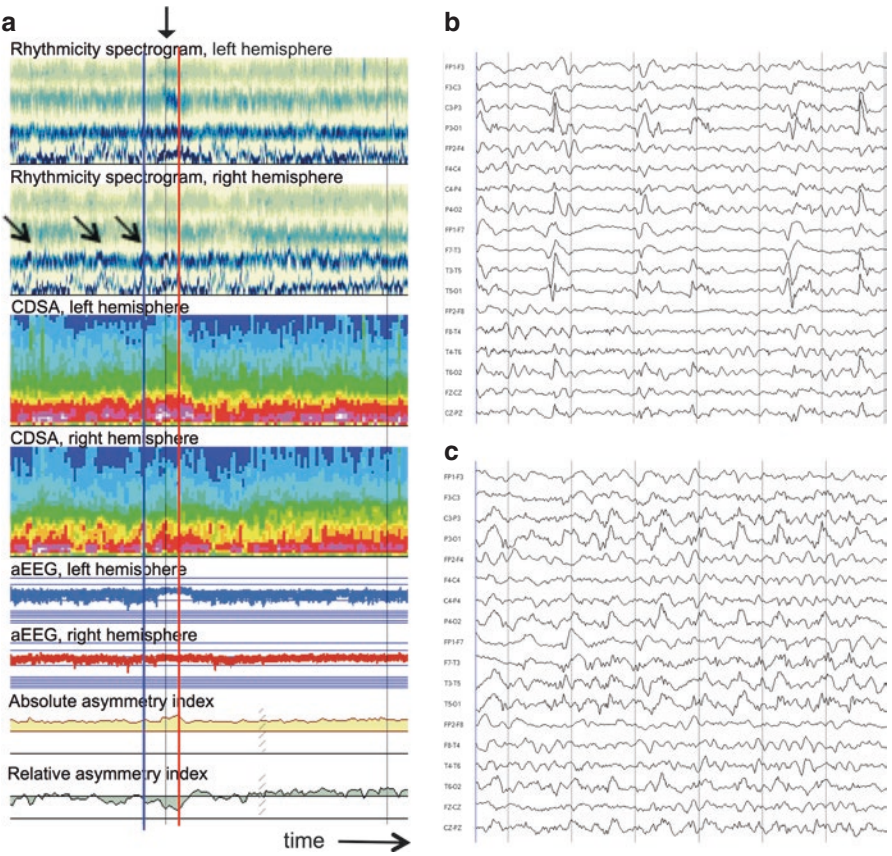


**Fig. 12** Appearance of lateralized periodic discharges (LPDs) compared with seizures on QEEG. (**a**) QEEG panel (rhythmicity spectrogram, CDSA, aEEG, and asymmetry index). (**b**) Interictal raw EEG demonstrating continuous left hemispheric LPDs corresponding to the time point on panel (a) marked by the *vertical blue line*. Although the LPDs occur continuously throughout the patient's record, there are some periods when the LPDs become more prominent and spread to the right posterior quadrant and result in a very subtle change in the rhythmicity spectrogram (marked by *diagonal black arrows*). (**c**) Ictal EEG corresponding to the time point on panel (a) marked by the *vertical red line*. Although this seizure is subtle, its appearance on QEEG (panel **a**) can be visualized on the left hemisphere rhythmicity spectrogram as darker blue coloration in the alpha frequency range and by a thinned, arch-like shape on left hemisphere aEEG

### Nonperiodic Interictal Patterns

There are certain nonperiodic, episodic, interictal EEG patterns that may make QEEG interpretation difficult. These include brief rhythmic discharges (BRDs), lateralized or generalized rhythmic delta activity (LRDA or GRDA), stimulus-induced rhythmic periodic or ictal discharges (SIRPIDs), and state changes. BRDs, LRDA, GRDA, and SIRPIDs may appear as discrete events on QEEG, depending on characteristics such as duration, amplitude, frequency, and deviation from baseline. Figures 13, 14, and 15 show examples of the appearance of BRDs, RDA, and state changes on QEEG, respectively.

## Subtle Seizures

Similar to raw EEG interpretation, subtle seizures can be difficult to identify on QEEG. These include seizures that are short duration, low amplitude, low frequency, slowly evolving, and of limited spatial extent. These seizures are especially difficult to identify on QEEG when the appearance of artifact is more prominent

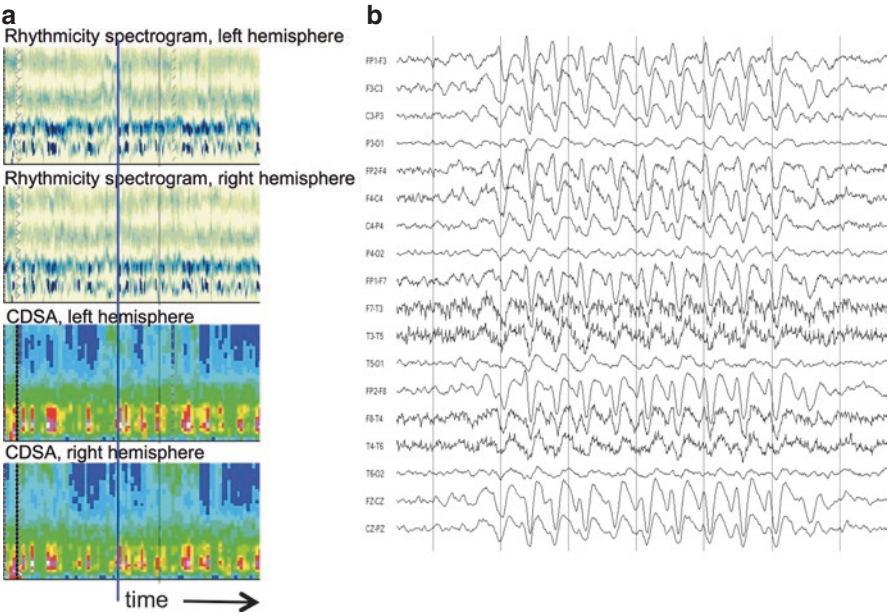


**Fig. 13** Appearance of a brief rhythmic discharge (BRD) on QEEG. (**a**) QEEG panel (rhythmicity spectrogram and CDSA, for the left and right hemispheres). Asymmetry index and aEEG are not shown as there was no change in these trends during the BRDs for this patient. During each BRD, there is an increase in power in the lower frequency ranges that appears on rhythmicity spectrogram as intermittent darker blue coloration and on CDSA as intermittent episodes of white/red/yellow coloration. (**b**) Raw EEG displaying a 5 s long BRD consisting of rhythmic 3 Hz spike and wave discharges corresponding to the time point on panel (a) marked by the *vertical blue line*

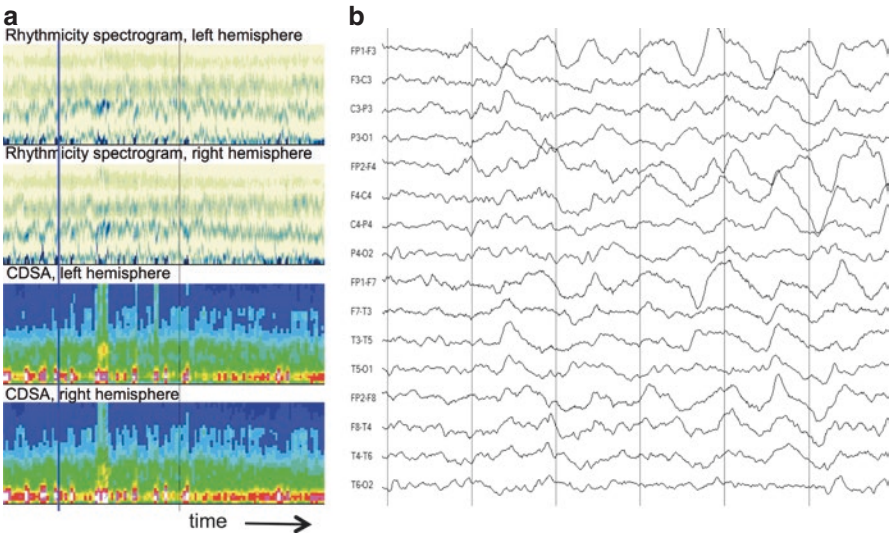


**Fig. 14** Appearance of frontally predominant generalized rhythmic delta activity (GRDA) on QEEG. (**a**) QEEG panel (rhythmicity spectrogram and CDSA, for the left and right hemispheres). During each episode of RDA, there is a subtle increase in power in the delta (and to a lesser extent theta) frequency range that appears on rhythmicity spectrogram as intermittent darker blue coloration and on CDSA as intermittent occurrences of white/red/yellow coloration. The periods of RDA are more prominent in the first half of the QEEG panel. (**b**) Raw EEG demonstrating an example episode of frontally predominant GRDA corresponding to the time point on panel **a** marked by the *vertical blue line*

than the seizures themselves (Fig. 16). Furthermore, even though an individual patient's seizures initially appear easy to detect, treatment with antiepileptic drugs may cause them to become subtle in appearance on QEEG by reducing the spatial extent, duration, frequency, and/or amplitude (Fig. 17).

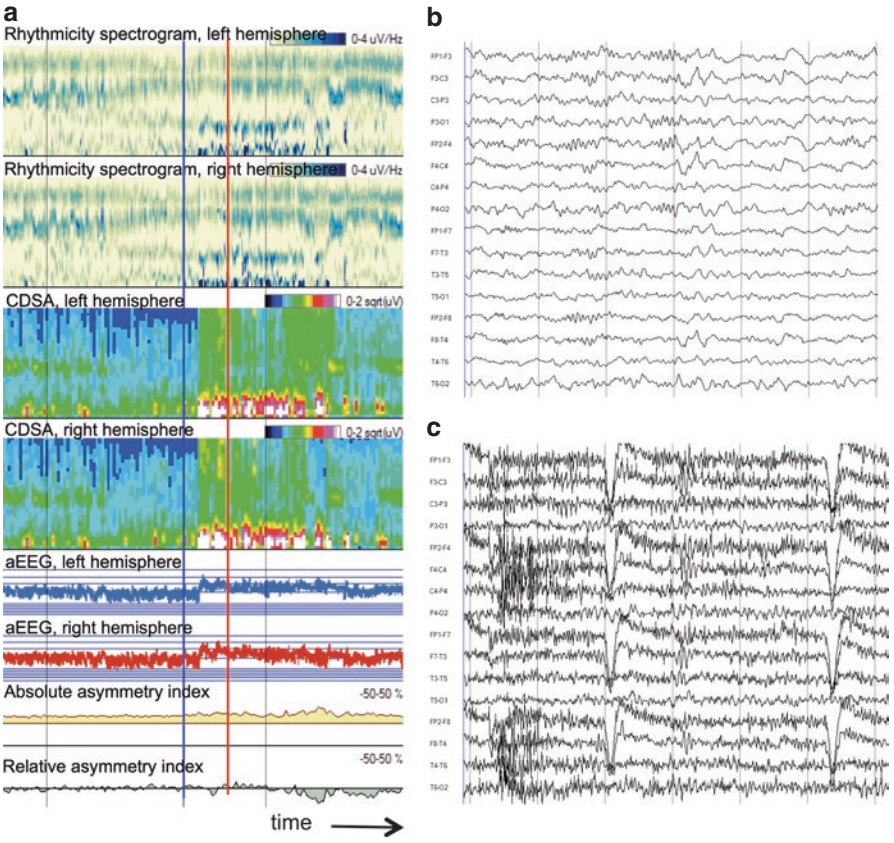


**Fig. 15** Appearance of patient's state change and EMG artifact on QEEG. (**a**) QEEG panel (rhythmicity spectrogram, CDSA, aEEG, and asymmetry index). (**b**) Raw EEG corresponding to the time point on panel **a** marked by the *vertical blue line* while the patient is sleeping. (**c**) Raw EEG corresponding to the time point on panel **a** marked by the *vertical red line* after the patient awakens and is moving. During this period, there is a diffuse change in power bilaterally that is seen on rhythmicity spectrogram and CDSA. On aEEG, there is an increase in the maximum and minimum amplitude. Little difference is seen on asymmetry index

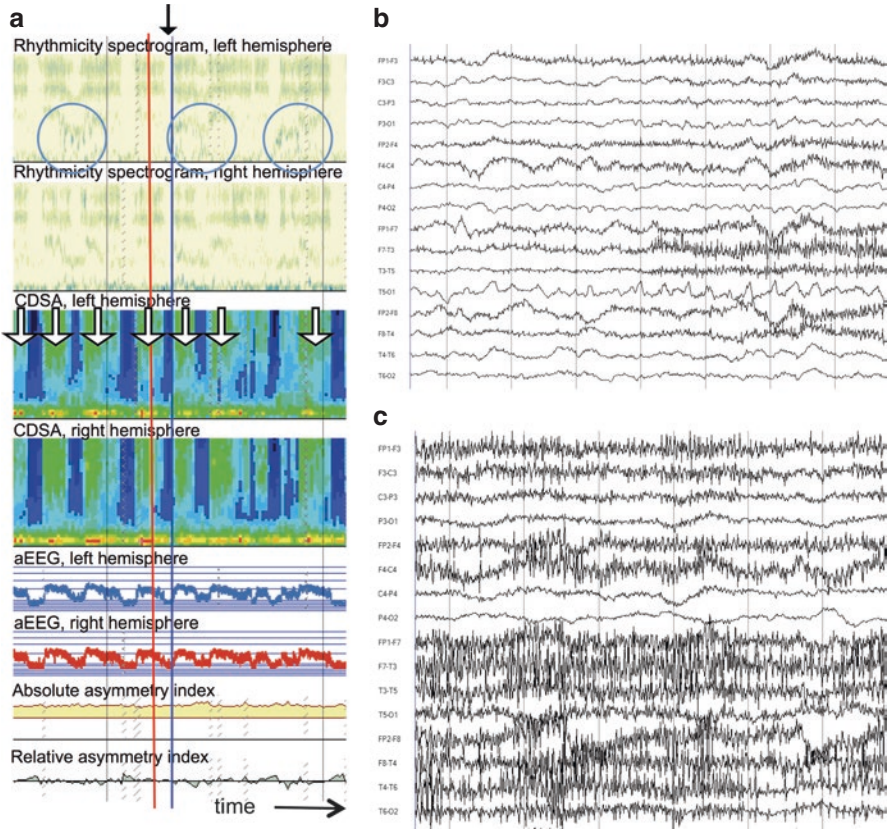


**Fig. 16** Appearance of episodic EMG artifact compared with very subtle seizures on QEEG. (**a**) QEEG panel (rhythmicity spectrogram, CDSA, aEEG, and asymmetry index) displaying intermittent periods of EMG artifact (marked *vertical white arrows*) and three extremely subtle seizures (marked by *blue circles*). Due to the periodic, prominent EMG artifact and very subtle nature of seizures, it would be easy to overlook the seizures and mistake the artifact for seizures. (**b**) Ictal EEG demonstrating the seizure corresponding to the time point on panel (a) marked by the *vertical blue line*. This seizure is only seen slightly on left hemisphere rhythmicity spectrogram. The seizures do not appear on the other QEEG trends. (**c**) Raw EEG consisting of EMG artifact corresponding to the time point on panel (a) marked by the *vertical red line*. This artifact appears prominent on CDSA and aEEG

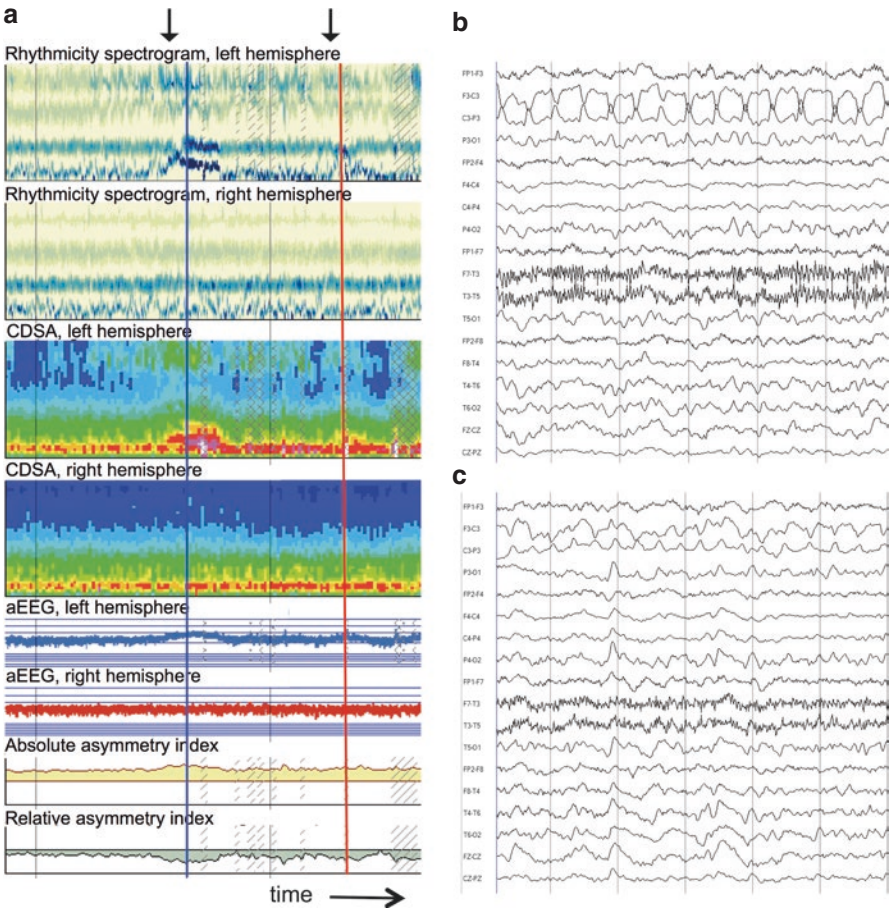


**Fig. 17** Appearance of obvious vs. subtle seizures on QEEG. (**a**) QEEG panel (rhythmicity spectrogram, CDSA, aEEG, and asymmetry index) displaying two seizures in the same patient, separated by approximately 15 min. (**b**) Ictal EEG demonstrating a focal left central seizure corresponding to the time point on panel (a) marked by the *vertical blue line*. This seizure is seen predominantly on left hemisphere rhythmicity spectrogram and left hemisphere CDSA. It is difficult to visualize this seizure on aEEG and asymmetry index. (**c**) Ictal EEG demonstrating a focal left central seizure corresponding to the time point on panel (a) marked by the *vertical red line*. This seizure, in the same patient, consists of rhythmic sharp waves in the same distribution and frequency, but of lower amplitude. Due to the reduced amplitude, this seizure is less noticeable on left hemisphere rhythmicity spectrogram than the seizure in panel (b) and even less noticeable on the other QEEG trends

## Conclusion

There has been an increased clinical utilization of QEEG for detection of seizures in critically ill adult and pediatric patients. The goals of QEEG for seizure detection are to assist in interpretation of large volumes of cEEG data and possibly expedite seizure identification and treatment. Ongoing research efforts are

attempting to answer various questions such as which QEEG trends should be used; which personnel can serve as QEEG readers, if automated seizure detectors can be used; and which is the best electrode derivations for QEEG trends.

Although QEEG trends can be used to assist cEEG data interpretation, it cannot be used in isolation. Patient treatment decisions must be made on the basis of raw EEG interpretation by neurophysiologists. As QEEG software continues to improve, it is likely that QEEG will continue to have a growing presence in the ICU for seizure detection.

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# Quantitative EEG in Neonatal Seizures

# 13

Juliet K. Knowles and Courtney J. Wusthoff

## Contents



## Introduction

While continuous EEG (cEEG) remains the ideal method of monitoring for seizures in neonates, quantitative EEG (qEEG) trends are often used. In particular, amplitude-integrated EEG (aEEG) is increasingly popular and can be a helpful complementary tool to cEEG monitoring. In situations in which cEEG is not practical, aEEG may be used as a stand-alone method of neuromonitoring. Alternately, aEEG may be used in conjunction with cEEG to allow bedside caregivers in the neonatal unit to monitor EEG trends in real time or to facilitate rapid review of neonatal cEEG by a

J.K. Knowles
Division of Child Neurology, Stanford University, Stanford, CA, USA

C.J. Wusthoff, MD (✉)
Stanford Division of Child Neurology, Lucile Packard Children's Hospital Stanford, Palo Alto, CA, USA
e-mail: wusthoff@stanford.edu



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neurophysiologist. Understanding the fundamentals of how aEEG is recorded and displayed helps clinicians accurately interpret background patterns and identify seizures. Specific factors can impact accuracy of aEEG for seizure detection; modification of these factors can improve sensitivity and specificity. Awareness of limitations of aEEG facilitates appropriate clinical use.

The use of aEEG for seizure detection has advantages as well as pitfalls; cEEG remains the gold standard, but aEEG can be a very useful extension of cEEG monitoring. This chapter will focus on features of aEEG relevant to neonates and, in particular, the use of aEEG in detection of neonatal seizures. Other forms of quantitative EEG are much less often used in infants, though they have potential for seizure detection. Likewise, while aEEG has additional applications, such as background assessment for prognostication, this chapter focuses on its use for neonatal seizure detection.

## Background

For the last half century, advances in intensive care, with an emphasis on neuroprotection, have led to the need for increased monitoring of brain function. Yet several features of cEEG monitoring were, and continue to be, an obstacle to universal use. These include cost, bulky equipment, and the need for technologist and neurophysiologist expertise. Such obstacles prompted the need for a simplified method. In the 1960s, Douglas Maynard and Pamela Prior described the use of a continuous "cerebral function monitor" (CFM) using just two electrodes placed in the parietal region to monitor brain activity in critically ill patients [9]. This CFM, the precursor of today's aEEG, processed the raw, single-channel EEG recording into a simplified, compressed display. The goals of this monitoring strategy were to create a simple, less costly, noninvasive, reliable measure of brain function at the bedside. Initially, the CFM was used mainly in the settings of adult anesthesia, cardiac surgery, cardiac arrest, and status epilepticus (SE) [3]. CFMs were first applied in neonatal intensive care units (ICUs) in the 1980s in the Netherlands, and they were found to be particularly useful in prognostication for neonates with hypoxic ischemic encephalopathy [3]. With advances in digital technology, the use of aEEG increased dramatically. There is now an extensive literature describing the interpretation of aEEG and normative values for term and preterm infants. Indeed, recent surveys suggest that at least 55% of neonatologists use aEEG, with a higher number in academic centers [14]. aEEG is by far the most commonly used type of quantitative EEG used in the neonatal ICU.

The rise of aEEG has been largely driven by the neonatology community. In contrast to conventional EEG, aEEG is typically applied by neonatal ICU staff and interpreted by neonatologists, without extensive neurophysiologic training. The advent of therapeutic hypothermia for hypoxic ischemic encephalopathy (HIE) and the discovery that aEEG was useful for prognostication in HIE have also fueled interest in the use of aEEG by neonatologists [2, 3].

Given the increasing impact aEEG has on clinical decision-making, neurologists should be knowledgeable regarding indications for, interpretation of, and pitfalls inherent to aEEG. There is a large evidence base consistently showing that aEEG

background patterns are prognostically accurate for term neonates with HIE [6, 8]; this is one major indication for the use of aEEG in the neonatal ICU. Even more popular is the use of aEEG as a screening tool for neonatal seizure detection. While clinical neurophysiologists caution that aEEG is not a suitable replacement for conventional EEG monitoring [16], neonatal ICUs increasingly turn to aEEG for seizure detection. About one half of neonatologists in the United States, the United Kingdom, Europe, and Canada indicate they are equally likely to use aEEG as conventional EEG to diagnose seizures, while neurologists more often rely on EEG [5]. These two technologies are not mutually exclusive; the proper combination of aEEG and EEG can be powerful in seizure diagnosis and management.

## Clinical Indications

Neonates with critical illness are at high risk for seizures; this particularly includes infants with HIE, stroke, hemorrhage, inborn errors of metabolism, congenital heart disease, and those infants on extracorporeal membrane oxygenation (ECMO) [1]. Yet seizure detection can be quite difficult in neonates, because the vast majority of seizures (80–90 %) are electrographic only [1]. When seizures are clinically evident, their semiology is different from older patients and can be quite subtle. Clonic movements, gaze deviation, and apnea are the most common signs when outward manifestations are present. When clinically evident seizures are correctly recognized, treatment with medication can lead to electroclinical dissociation in as many as 58 % of cases, meaning previously evident seizures become electrographic only [16]. Thus, when suspected clinical seizures are observed, EEG monitoring may be employed to assess ongoing seizure burden, especially after medication is administered.

At the same time, there is not only the risk of missed diagnosis but also a risk of overdiagnosis of neonatal seizures. Some events which are clinically suspicious for seizures are actually not seizures; EEG monitoring can be useful in ruling out seizures in these cases and for the differential diagnosis of funny spells. In one study using cEEG to monitor neonates at risk for seizures, 73 % of the clinically documented suspected seizures actually had no corresponding EEG evidence of seizure [10]. Heightened vigilance for clinical seizures in ill neonates may lead to erroneous diagnosis of seizure in the absence of EEG corroboration.

Given these challenges in diagnosis, the American Clinical Neurophysiology Society (ACNS) recommends conventional cEEG monitoring whenever neonatal seizures are suspected, whether because of clinical signs or because a patient's condition confers a high risk of subclinical seizures [16]. While cEEG remains the gold standard for diagnosis of neonatal seizures, aEEG is used in a variety of situations.

Few neonatal ICUs have around-the-clock cEEG access; stand-alone aEEG can be a useful temporary measure when cEEG is limited. When cEEG availability is delayed (such as nights or when there is not enough equipment available), aEEG may be used until cEEG becomes possible. In these cases, aEEG electrodes can be applied by nursing staff, neonatologists, or respiratory therapists. A beside aEEG machine can be started within minutes, allowing early monitoring to begin while cEEG is awaited. Similarly, some centers may have no access to cEEG monitoring

and may use aEEG as a screening tool for neonates with suspected seizures while awaiting transfer to a referral neonatal ICU for cEEG. In these situations, the neurologist at the receiving hospital may need to review initial aEEG tracings obtained prior to transfer as part of their evaluation. Even when cEEG is available, aEEG may be used in place of cEEG in those occasional cases when there are logistic barriers to cEEG, such as physical space limitations at the bedside or a need for the patient to frequently have electrodes removed (as in some neurosurgical cases). While stand-alone aEEG does not have the accuracy of cEEG (as below), it can be a useful stopgap when cEEG is not immediately possible.

Increasingly, aEEG is also being used in conjunction with cEEG to facilitate more rapid identification of seizures. Many commercially available cEEG systems have the ability to record conventional cEEG for neurophysiologist to review remotely and also display the same recording at the bedside as aEEG, for real-time review by the neonatal ICU team (Fig. 1). This combination of methods has numerous strengths. First, display of aEEG at the bedside empowers neonatal ICU caregivers to participate in the neuromonitoring of their patients even without formal training in neurophysiology. With relatively straightforward training, neonatal ICU nurses and providers can learn to identify features on aEEG that might suggest seizures. Because aEEG is displayed in real time for constant review, the bedside team becomes a set of eyes for early identification of subclinical seizures. This is particularly helpful in settings where cEEG is recorded continuously, but only reviewed by neurophysiologists intermittently. Ideally, the neonatal ICU continuously monitors the aEEG display, and if an event concerning for seizure is identified, a neurophysiologist can be contacted to review the corresponding cEEG for confirmation as to whether or not that event was a seizure.

Similar to the use of qEEG in older patients, aEEG display may also be used by neurophysiologists to screen large quantities of cEEG recording to quickly identify presence or absence of seizures before a more detailed review is undertaken. This allows for more targeted review of long periods of cEEG recording and expedited intervention in many cases. Typical aEEG settings allow display of 3–6 h of EEG on a single screen; an overview of a day of recording can be viewed in minutes.

For all of these reasons, even if neurophysiologists typically rely on cEEG for neonatal seizure detection, aEEG is often indicated either to supplement or in conjunction with cEEG for seizure detection.

## Recording and Display

As mentioned previously, cEEG is widely considered to be the gold standard method for seizure detection. Full array cEEG uses 9 to 16 electrodes placed according to the international 10–20 system, modified for the smaller neonatal head (Fig. 2). Up to 16 channels result. This is generally thought to capture all but exceptionally rare spatially restricted seizures [3]. cEEG provides detailed information about background activity as well as the location, form, evolution, and migration of ictal patterns. The addition of video allows rapid identification of artifacts and correlation of

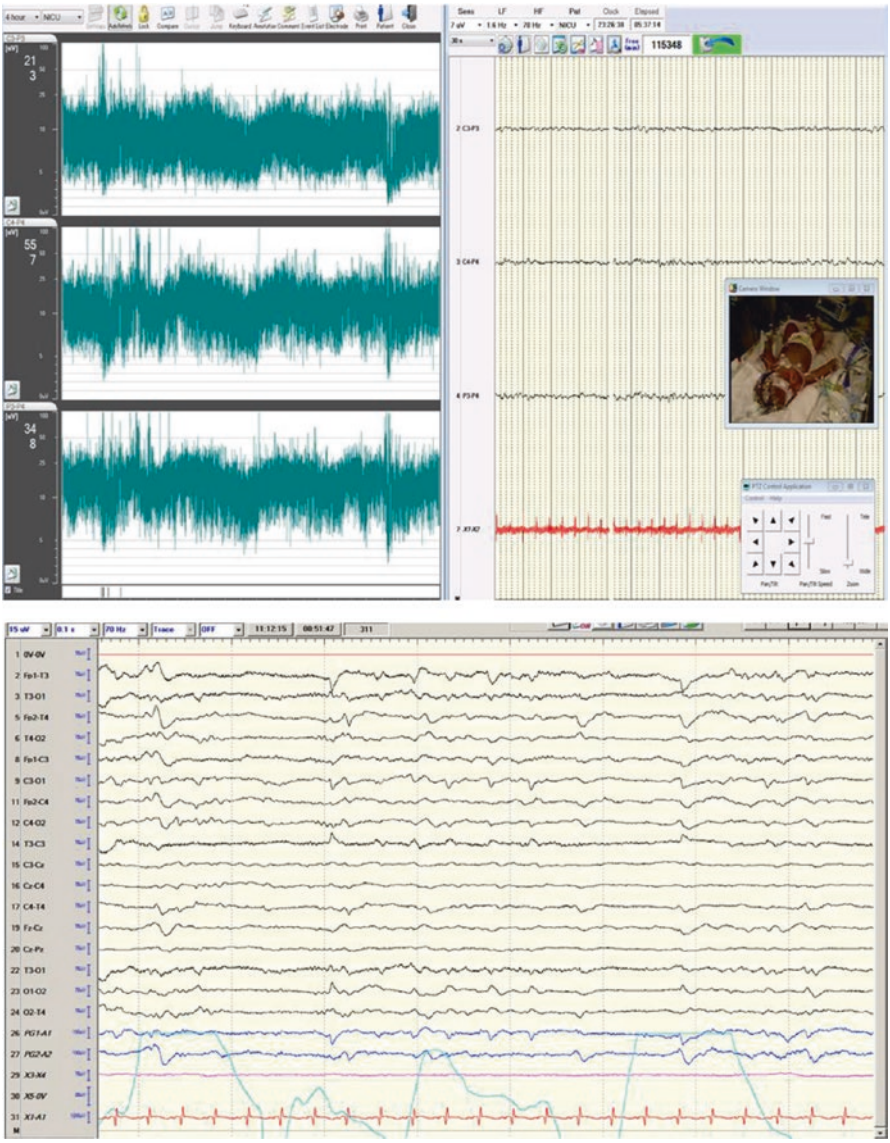

**Fig. 1** Example of simultaneous aEEG and cEEG recorded from a single patient. The aEEG with select source channels (*top*) is displayed at the bedside for the neonatal team to review in real time, while the full cEEG (*bottom*) is available for remote review by a neurophysiologist

electrographic seizures with clinically apparent phenomena. In contrast, aEEG records less information, typically from just two to four electrodes, which is then simplified and compressed, allowing for more rapid but more limited assessment of cerebral function, including by those without formal neurophysiology training.

A key feature is that aEEG uses a reduced array, with a minimum of three electrodes – two placed in the biparietal location (P3-P4) and one to serve as a ground to record "single-channel" EEG. Various types of electrodes are available. Subdermal needle electrodes have the advantage of being easily secured for long-term monitoring and having reduced impedance. However, concerns for needle-sticks may make disk or sticker electrodes preferred by some users [7]. Hydrogel electrodes can be used in extremely preterm infants, though scalp preparation with abrasive cream is still typically required to achieve acceptable impedances [3, 7].

The reduced array of electrodes records limited channels of EEG, just as in conventional EEG. Originally, aEEG systems recorded only at P3–P4 to generate "single-channel" EEG. Increasingly, aEEG systems use four electrodes (placed at C3, P3, C4, and P4) with a ground [15] (Fig. 2). This "dual-channel" configuration provides information about laterality (using C3–P3 and C4–P4 as hemispheric channels) in addition to a cross cerebral channel (P3–P4). The use of dual-channel aEEG increases sensitivity for seizure detection as compared to single-channel aEEG, as discussed further below [13]. More electrodes can be used, though not all commercial systems have this ability. Some aEEG systems allow a machine to start recording limited array EEG for aEEG from a reduced number of channels (such as when a recording is started by a nurse in the middle of the night) and then "flex up" to a full array of EEG channels later in the recording (such as when a technologist becomes available).

Electrodes should be placed in the centroparietal region to maximize sensitivity for seizure diagnosis. This vascular "watershed" area is particularly susceptible to injury; most neonatal seizures arise from this region [7]. This area is also less

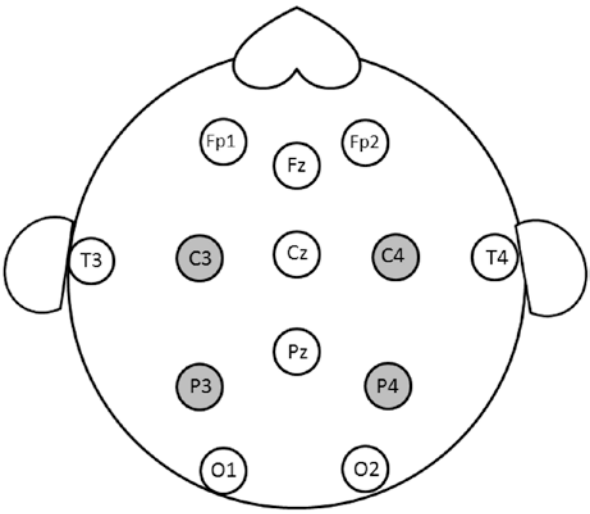


**Fig. 2** Illustration of electrode placement in cEEG vs aEEG. *Open circles* represent typical electrode placement for neonatal EEG. *Shaded circles* (C3, C4, P3, P4) represent typical electrode placement for dual-channel aEEG

affected by eye movements or scalp muscle artifact, which can be problematic with frontal or temporal electrode placement [7]. Furthermore, while electrode placement in the frontal area may be more convenient (given no hair interferes with the application), frontal electrodes show more artifact and have reduced sensitivity for seizures. Over half of seizures are missed with single-channel EEG using frontal electrodes [20].

This reduced array of electrodes records channels of EEG, just as in conventional recordings. Voltage differences between electrical potentials at two different scalp areas are recorded. The aEEG machine or software then processes the raw EEG tracing to facilitate its interpretation. The raw recording is filtered, removing signal with frequencies below 2 Hz and above 60 Hz. The filter parameters are designed to eliminate artifact, but the high pass 2 Hz filter can also eliminate normal and pathologic features, including low-frequency seizures. Recorded electrical potentials are rectified, with negative voltages converted to positive values [3, 7]. Amplitudes are then plotted on a time-compressed display, with the *x*-axis representing time and the *y*-axis a semilogarithmic representation of amplitude (linear from 0 to 10 μV and logarithmic above 10 μV) (Fig. 3). Amplitude data is plotted in consecutive, thin, vertical lines, with each line representing 15 s of recording. For each line, the top point on the *y*-axis represents the maximum amplitude recorded during the interval, while the bottom point on the *y*-axis represents the minimum amplitude during that interval. In neonates with impaired brain function, the majority of amplitudes will be between 0 and 20 μV, and the display emphasizes a finer degree of detail within this range. As the display progresses, the side-by-side vertical lines form the activity band [15], which serves as a graphical representation of amplitude of brain activity on a compressed time scale. While many systems allow adjustment of the time scale, typical aEEG displays 1 h of recording over 6 cm or 1 min of recording per millimeter. Of note, aEEG displays only the amplitude of the EEG signal over time. There is no information regarding frequency, power, or other features that may be included in other qEEG techniques.

Newer machines can display the raw EEG tracing corresponding to a particular area of the processed data, which is critical for identification of artifacts or subtle

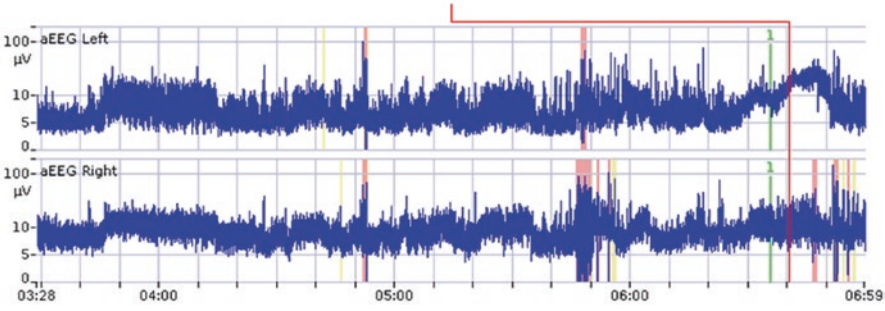


**Fig. 3** Example of dual-channel aEEG tracing, with time displayed on the *x*-axis and amplitude in uV semi-logarithmically displayed on the *y*-axis

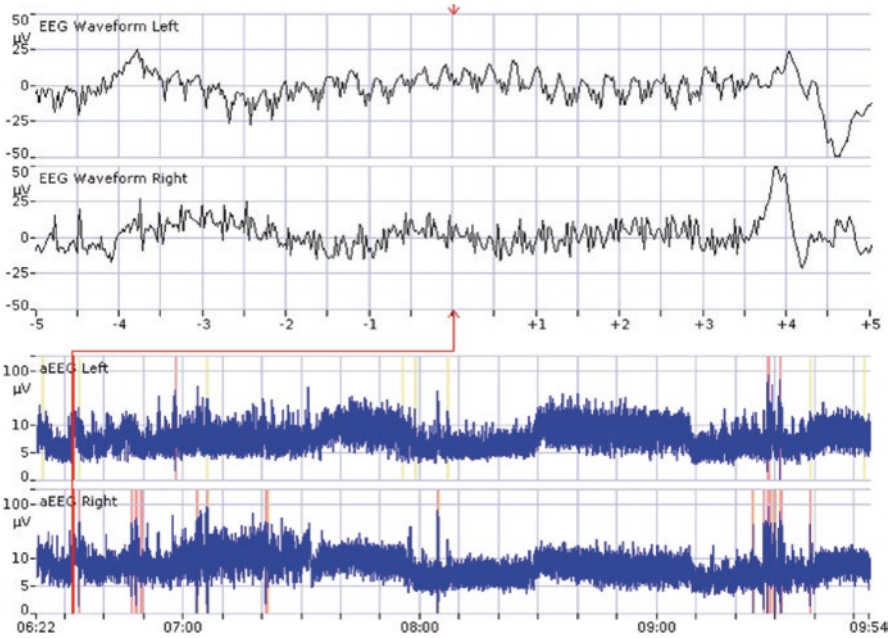


**Fig. 4** aEEG (*bottom* two panels) displayed along with source EEG (*upper* two panels). Line at left of aEEG panels indicates area of interest selected for review, with arrow pointing up to corresponding segment of source EEG, in this case, confirming presence of seizure

seizures (Fig. 4). Some machines can also display other metrics, such as impedance, with alarms for excessively high impedance during recording. There is commercially available software for automated seizure detection based on aEEG, though this has not been approved for use in all countries. As above, some cEEG acquisition systems allow display of aEEG at the bedside during cEEG recording, with cEEG displayed for a neurophysiologist at a review station [3].

## Interpretation

### Background

Accurate detection of neonatal seizures on aEEG recordings requires a basic understanding of overall aEEG interpretation. As with conventional EEG, critical elements of neonatal aEEG interpretation include background assessment, detection of seizures, and identification of artifacts. In general, there is good consistency between aEEG background patterns and their correlates on cEEG [6]. There is not one universally accepted method for describing or classifying aEEG patterns; the approach described here has been adapted in various forms.

One approach to aEEG background interpretation focuses on quantitative assessment of the aEEG activity band, with some pattern recognition (Table 1) (reviewed

**Table 1** Assessment of aEEG background

| Background category | Upper margin of activity band (μV) | Lower margin of activity band (μV) | Variability: upper margin | Variability: lower margin |
|---|---|---|---|---|
| Continuous | 10–50 | >5 | Present | Present |
| Discontinuous | >10 | <5 | Present | Present |
| Low voltage | <10 | <5 | Present | Present |
| Burst suppression | Bursts >25 | 0–2 | Widely variable (bursts) | Absent |
| Inactive | <5 | 0–2 | Absent | Absent |

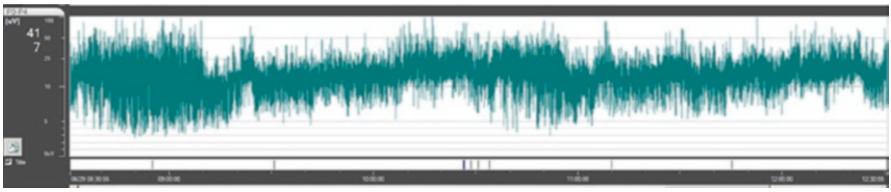

**Fig. 5** Example of continuous aEEG. The lower margin of the activity band is above 5 uV, while the upper margin is above 10 uV

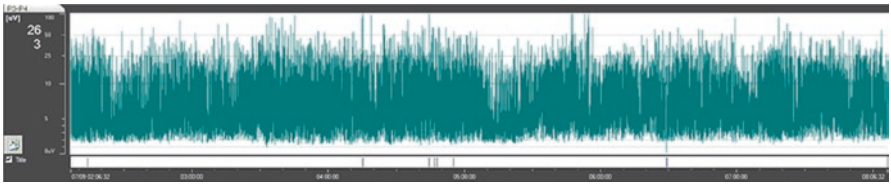

**Fig. 6** Example of discontinuous aEEG. The lower margin of the activity band is below 5 uV, while the upper margin is above 10 uV

in detail elsewhere [8]). This system classifies aEEG into five categories: continuous, discontinuous, low voltage, burst suppression, or inactive. In a term neonate, only a continuous background is normal. In preterms, depending on gestational age, a discontinuous background pattern may also be normal. Low-voltage, burst-suppression, and inactive patterns are always abnormal. In normal aEEG recording from a term newborn, the lower margin of the activity band is greater than 5 μV, and the upper margin is greater than 10 μV and often greater than 25 μV (Fig. 5). This reflects a raw EEG pattern with consistently normal amplitudes. In contrast, a discontinuous EEG pattern will have some periods of higher amplitude alternating with very low amplitude; this wider range of amplitudes is reflected in a wider activity band, with the lower margin sometimes below 5 μV (Fig. 6). In these patterns, normal variability in amplitudes is reflected in variability in the margins of the activity band. This is in contrast with abnormal patterns such as burst suppression. In burst suppression, the lower margin is also below 5 μV and the upper margin greater than 25 μV, but the lower margin has no variability – it is a near flat line,

reflecting the true suppression of the background between bursts on the corresponding EEG. This suppression alternating with short, high-amplitude bursts results in a "comb-like" pattern. A severely abnormal aEEG background pattern may be described as low voltage when the upper margin is below 10 μV or inactive when the upper margin is below 5 μV and the lower margin below 2 μV and invariant (Fig. 7).

Additionally, aEEG background is often assessed for the presence of sleep-wake cycling, which has been found to carry prognostic importance in HIE. Sleep-wake cycling is expected in term neonates and may begin to emerge in preterm neonates as early as 32 weeks. Quiet sleep is reflected on aEEG by a widening of the activity band, reflecting the wider range of amplitudes present in quiet sleep. This contrasts with the narrower band of active sleep and while awake, during which amplitudes are more consistent. Overall, the alternation between quiet sleep, active sleep, and awake results in a widening and narrowing of the activity band in a sinusoidal pattern (Fig. 8).

As with conventional EEG, gestational age and medication can affect the background aEEG pattern. In preterm infants, normative values for aEEG have been published describing expected amplitudes for different degrees of prematurity [8]. Medications such as morphine, phenobarbital, and midazolam can affect the aEEG background (typically, by decreasing amplitude) [8]. In some reports, surfactant administration has been associated with decreased amplitudes and increased bursting [18].

## Seizure Identification

On conventional EEG, neonatal seizures are defined as a sudden, repetitive, evolving EEG patterns, with a clear beginning, middle, and end. Waveforms may include spikes, sharp waves, spike wave complexes, or rhythmic slow waves

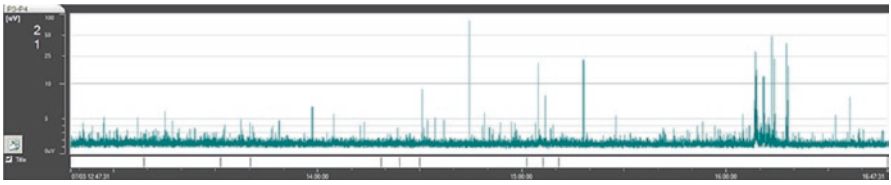

**Fig. 7** Example of severely abnormal aEEG. The trace is predominantly inactive with absent lower margin variability and upper margin typically <5 uV

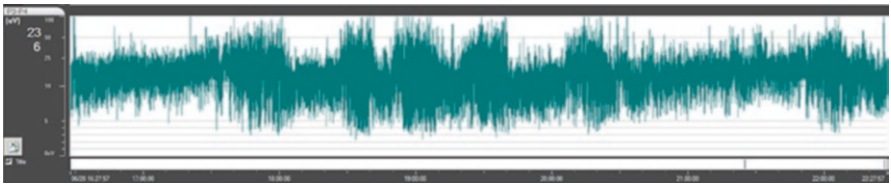

**Fig. 8** Sleep-wake cycling. The sinusoidal pattern of the activity band, which widens and narrows, reflects cycling through sleep and awake states

[7]. Many neurophysiologists define a neonatal seizure as lasting at least 10 s [19]. Seizures that are characterized by an increase in amplitude are most evident on aEEG. When occurring amidst a continuous, normal voltage background, seizures often appear as an abrupt "jump" in the activity band, with a sudden rise in the minimum and maximum voltage reflecting the higher amplitude of the seizure (Fig. 9). This sudden abrupt elevation in amplitude may be seen more easily in the lower border than the top border, particularly if there is wide variability in the upper margin of the background. Some seizures are followed by a period of postictal suppression, during which the activity band is lowered transiently.

Not all neonatal seizures are apparent on aEEG. Some neonatal seizures are recognizable on EEG as distinct, repetitive patterns, but have amplitudes similar to background activity. These are very difficult to identify on aEEG. Similarly, most neonatal seizures are brief, lasting less than 2 min. On aEEG at typical display speeds, this corresponds to just 2 mm of the display, making individual, brief seizures difficult to identify [7]. Indeed, direct comparison of aEEG and continuous, conventional EEG demonstrated that aEEG missed seizures up to 30 s long [12]. Prolonged seizures and repetitive seizures may be more easily seen. Frequent seizures or SE may be evident as a "sawtooth" pattern on aEEG.

## Artifacts and Seizure Mimics

There are numerous sources of potential artifact in aEEG recordings, particularly in the neonatal ICU. These are often related to the quality of electrodes and proper electrode placement, interference due to other devices, and various patient movements. Excessively high electrode impedance can be due to poor contact with the skin or sweating. This may result in falsely elevated amplitudes. Alternatively, there may be intermittent periods where electrode loses contact with the skin, resulting in intermittently elevated impedance and falsely elevated amplitudes. Typically, these findings will be unilateral, on the side of the affected electrode. However, electrode impedance can be easily checked either as directly displayed by the monitor or by inspection of the raw EEG signal, which reveals a nonphysiologic pattern. If not recognized, the falsely elevated activity band will mask any underlying seizure activity. In contrast, when there is significant scalp edema present, amplitudes may be diminished, resulting in a falsely lowered activity band and again obscuring lower-amplitude seizures.

The most common artifacts mistaken for seizures on aEEG are movement or patting artifacts. Patting typically results in a rhythmic artifact in the EEG that has a

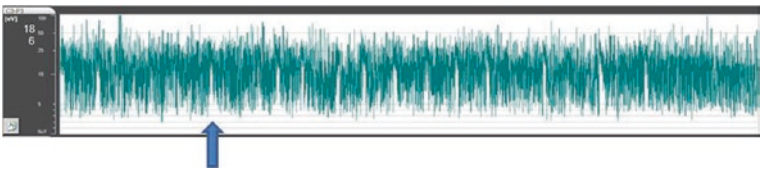

**Fig. 9** Example of seizures on aEEG. *Arrow* indicates one of several seizures in this aEEG. Each is characterized by an abrupt elevation of the lower margin of the activity band

frequency of 1–4/sec, evolves in intensity, and slowly stops over a period of seconds to minutes. Spontaneous movements, including movement of the limbs, respiration, or even sucking, can cause an artificial increase in the background amplitudes, mimicking seizures. Infants undergoing therapeutic hypothermia may shiver, with resulting artifact on aEEG. Similarly, movements due to manipulation of the patient by caregiver can be mistaken for seizures. In each case, artifact is also present and may be more easily recognized on the corresponding raw EEG. Whenever possible, concurrent video monitoring is extremely helpful for identifying these artifacts. Unfortunately, video recording is typically not available if aEEG is from an aEEG machine rather than in conjunction with cEEG [6, 15]. When video is not available, meticulous annotation of events such as movement and patting by bedside caregivers is essential for proper distinction between artifact and seizure.

Continuous electrocardiographic (ECG) recording can contaminate the aEEG record, particularly in patients with low-voltage backgrounds or burst suppression. This can cause the upper margin of the activity band to appear higher than it actually is, masking a low-voltage background (Fig. 10). This is also true of artifact from mechanical ventilation, particularly high-frequency oscillation ventilation causing rapid, repetitive movements. When such artifact comes and goes or the raw EEG trace is examined in isolation, these artifacts may be misinterpreted as frequent seizures or SE. As with other forms of artifact, consideration of both the aEEG in

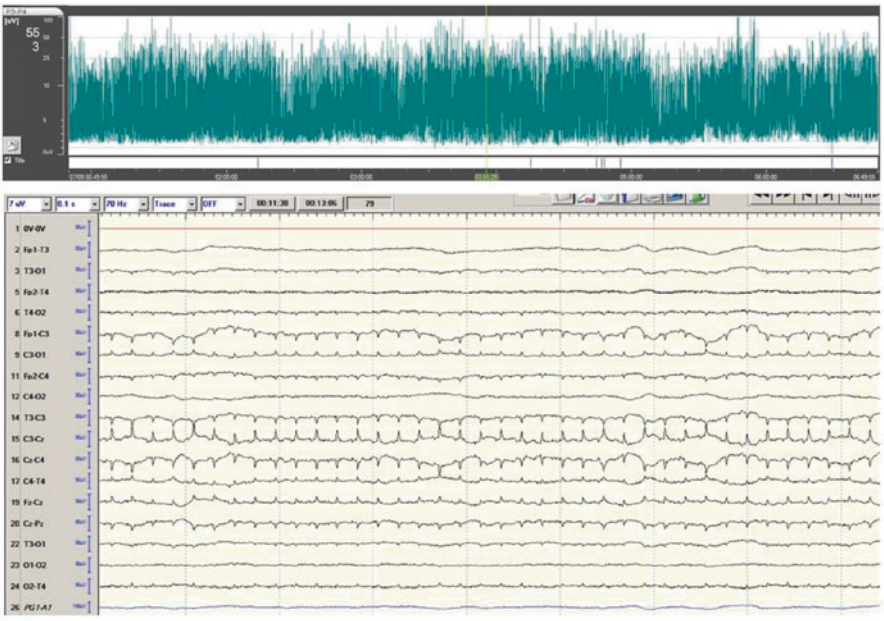

**Fig. 10** Example of aEEG with falsely elevated activity band due to ECG artifact. In this patient, the aEEG appears to show a background that is only discontinuous (*upper panel*). However, review of the corresponding cEEG reveals diffuse ECG artifact as the only source of increased amplitude beyond a very suppressed background (*lower panel*)

conjunction with EEG, annotation of the circumstances of recording, and user experience are needed to avoid misinterpretation.

## Accuracy and Limitations

A number of studies have now examined the utility of aEEG for seizure detection (Table 2). Taken together, various investigators evaluating the sensitivity of single- or dual-channel aEEG for individual seizures in neonates have determined that anywhere between 25 and 84 % of seizures are correctly identified with aEEG [6]. Some studies have made a distinction between detection of individual seizures and detection of *any* seizure in a record containing seizures; this is to simulate the clinical scenario in which quantification of seizure burden is not sought, but rather when aEEG is used to identify whether a neonate is having any seizures (and thus would need treatment or initiation of cEEG). The sensitivity of aEEG to identify whether there are any seizures within a record is somewhat better, 40–85 %. There is less data regarding the specificity of aEEG for seizure detection, though this appears to also be imperfect [6].

Much of the variability in reported accuracy of aEEG relates to the methodology used in individual studies. One study provided aEEG from near-term infants (38–50 weeks) to neonatologists with at least a year of experience with aEEG and asked them to identify seizures using just aEEG, without the raw EEG available [17]. With this approach, sensitivity for identifying individual seizures was only 25.5 ± 10.6 %.

**Table 2** Sensitivity of aEEG for seizure detection

| First author | Subjects, conceptional ages (CA) | aEEG | aEEG readers | Sensitivity for individual seizures | Sensitivity for a seizure-positive record |
|---|---|---|---|---|---|
| Shellhaas | Mixed group of near-term neonates, 38–50 weeks | Single channel | 6 neonatologists, all with ≥1 year experience | 25.5 % | 40.3 % |
| Rennie | At-risk neonates, 24–42 weeks | Single channel | 4 neonatologists, newly trained with no prior experience | 38 % | 4/19 correctly identified by all 4 neonatologists |
| Frankel | At-risk neonates, 24–43 weeks | Single channel and dual channel | Neonatologist, neonatology fellow, and medical student | 71–84 % | 68–84 % |
| Shah | Neonates with seizures, term | Single channel, dual channel, and dual channel with source cEEG | 2 neonatologists, each with >3 years experience | 76 % with dual channel + raw EEG<br>27–56 % with single- or dual-channel EEG without raw EEG | 85 % |

Sensitivity for identifying at least one seizure in a record containing seizures (i.e.. sensitivity for a seizure-positive record) was 40.3 ± 16.8 %. This contrasts with the method used by another study [13] to address a similar question. In that study, two neonatologists with 3 years of experience interpreting aEEG reviewed various forms of aEEG. Using single-channel aEEG without the raw EEG, they correctly identified 41–56 % of seizures. Allowing access to dual-channel aEEG without raw EEG did not improve sensitivity, but when the neonatologists were allowed to review dual-channel aEEG plus raw EEG, sensitivity increased to 76 % with improved inter-rater variability. The specificity using this method was 78 %.

As expected, nonexperts are less successful in identifying seizures on aEEG. One study assessed sensitivity of aEEG when used by nonexperts [11]. The authors examined the accuracy of aEEG for seizure detection in a broader population of newborns, ranging from very preterm to term (24–42 weeks), including those with HIE, meningitis, clinically suspected seizures, or intraventricular hemorrhage. Four neonatologists with no prior aEEG experience were newly trained for aEEG interpretation. When they examined aEEG records derived from cEEG traces in this population, the sensitivity for individual seizures was found to be 38 %. Inter-rater agreement was poor, with only 4 out of 19 records being correctly identified as containing seizures by all four neonatologists. Similarly, in another study comparing aEEG to routine EEG, the specificity was significantly higher when aEEG was read by a fellow or neonatologist (86–97 %) as compared to when it was read by a student (39–66 %) [4]. Of note, these studies used aEEG recorded primarily from term born neonates; there have not yet been studies demonstrating the accuracy of aEEG for seizure detection specifically in preterm infants. The presence of specific graphoelements in preterm EEG, such as delta brushes, may make interpretation of aEEG more challenging in this population; further research is needed in this area.

Translating these findings to clinical practice, new users may struggle with aEEG, and even experienced users cannot identify all seizures using aEEG. When aEEG is used alone, over half of seizures may be missed. However, if aEEG is interpreted by experienced users, including dual-channel aEEG and raw EEG for confirmation, sensitivity is much improved [4, 17]. aEEG can most reliably detect longer seizures and identify patients who have multiple seizures [12, 17]. The location of seizures may also affect sensitivity: because of electrode location, seizures are more often missed if originating in the occipital or frontal lobes [4, 13]. Frontal or forehead electrode placement should be avoided, as this tends to introduce more artifacts (e.g., myogenic), and few seizures originate in or propagate to the frontal lobes of neonates [6, 15]. Use of frontal electrodes can decrease sensitivity of seizure detection in single-channel EEG from 73 to 46 % as compared to centrally placed electrodes [20].

## Conclusions

While cEEG remains the preferred method of monitoring for seizures in neonates, aEEG is increasingly popular and can be a helpful complementary tool. Understanding the fundamentals of how aEEG is recorded and displayed helps the clinician accurately interpret patterns and distinguish normal features from artifact. The benefits of aEEG are maximized when it is used in combination with cEEG to allow easy, bedside monitoring as well as rapid review of neonatal cEEG trends.

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# Quantitative EEG for Non-seizure Indications

# 14

Sahar Zafar and M. Brandon Westover

## Contents



## Introduction

Detection of pathological changes in the brain's "background" activity plays a key role in optimal management of several common conditions in the neurological intensive care unit (neuro ICU). Important applications include monitoring for delayed

S. Zafar, MD
Department of Neurology, Massachusetts General Hospital, Harvard Medical School, Boston, MA, USA
e-mail: sfzafar@partners.org

M.B. Westover, MD, PhD (✉)
Massachusetts General Hospital,
Neurology WACC 735 55 Fruit St, Boston, MA 02114, USA
e-mail: mwestover@partners.org



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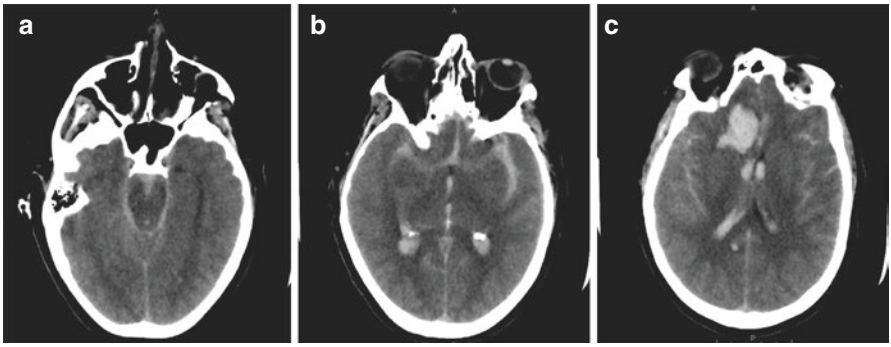


**Fig. 1** Diffuse subarachnoid hemorrhage in the interpeduncular cistern and ambient cistern (**a**), extending to the suprasellar cistern and Sylvian fissures (**b**), with associated intraventricular hemorrhage and left frontal intraparenchymal clot (**c**)

ischemia in patients with subarachnoid hemorrhage (SAH), monitoring for recovery following anoxic brain injury, monitoring for signs of secondary injury following traumatic brain injury (TBI), monitoring the depth of pharmacologically induced coma in patients undergoing treatment for refractory status epilepticus (SE), and evaluating cerebral metabolism with deep hypothermia during surgery. Quantitative EEG (qEEG) plays a key role in each of these applications, as a technology that enables more effective visualization of the relevant EEG features than is possible with conventional visual analysis used in isolation. In this chapter, each of these applications will be reviewed.

## Aneurysmal Subarachnoid Hemorrhage

### Background

Aneurysmal SAH is a neurological emergency with an incidence of 2–22 per 100,000 per year [1]. Aneurysmal SAH may present in many different ways, with the "classical" presenting symptom being sudden onset of severe headache [2]. Other clinical manifestations include transient loss of consciousness, seizures, and vomiting prior to headache [2]. The neurological exam may be normal, or more commonly patients may have a decrease in the level of consciousness. Patients may also present with focal neurological deficits. Diagnosis is usually made using non-contrast computed tomography (CT) scans (Fig. 1), CT angiography (Fig. 2), conventional catheter angiography, and in some cases lumbar puncture. Multiple SAH grading scales that use clinical and radiographic data are utilized in clinical practice (Tables 1, 2, and 3) [3–5] to help stratify the severity of the SAH and to assist with prognostication.

Delayed cerebral ischemia (DCI) is one of the most significant complications that occurs after aneurysmal SAH and can be seen in up to 50 % of patients [6, 7]. DCI is

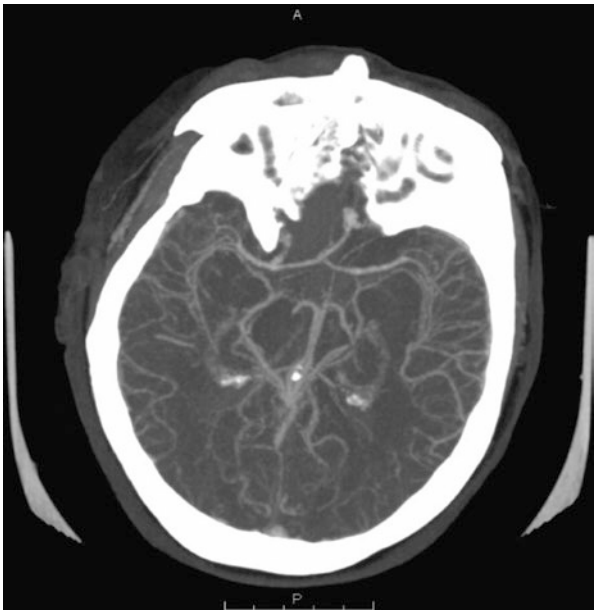


**Fig. 2** CT angiography demonstrating an ACA aneurysm

**Table 1** Hunt and Hess Scale [3]

| Grade | Clinical exam |
|---|---|
| 1 | Asymptomatic, mild headache, slight nuchal rigidity |
| 2 | Moderate to severe headache, nuchal rigidity, no neurologic deficit other than cranial nerve palsy |
| 3 | Drowsiness, confusion, mild focal neurologic deficit |
| 4 | Stupor, moderate-severe hemiparesis |
| 5 | Coma, decerebrate posturing |

**Table 2** Fisher Scale [4]

| Grade | CT imaging findings |
|---|---|
| 1 | No detectable subarachnoid blood |
| 2 | Subarachnoid hemorrhage less than 1 mm thick |
| 3 | Subarachnoid hemorrhage more than 1 mm thick |
| 4 | Subarachnoid hemorrhage of any thickness with intraventricular hemorrhage (IVH) or parenchymal extension |

often associated with radiographic vasospasm (Fig. 3) and has traditionally been considered the most probable cause of DCI. However, DCI can occur in the absence of vasospasm; hence, the two need to be distinguished [8]. The various pathophysiological mechanisms that have been proposed for delayed ischemia include vasospasm, cortical spreading depression, and loss of cerebral autoregulation [6].

**Table 3** World Federation of Neurological Surgeons Grading system [5]

| Grade | Glasgow coma scale score | Motor deficit |
|---|---|---|
| 1 | 15 | Absent |
| 2 | 13–14 | Absent |
| 3 | 13–14 | Present |
| 4 | 7–12 | Present or absent |
| 5 | 3–6 | Present or absent |

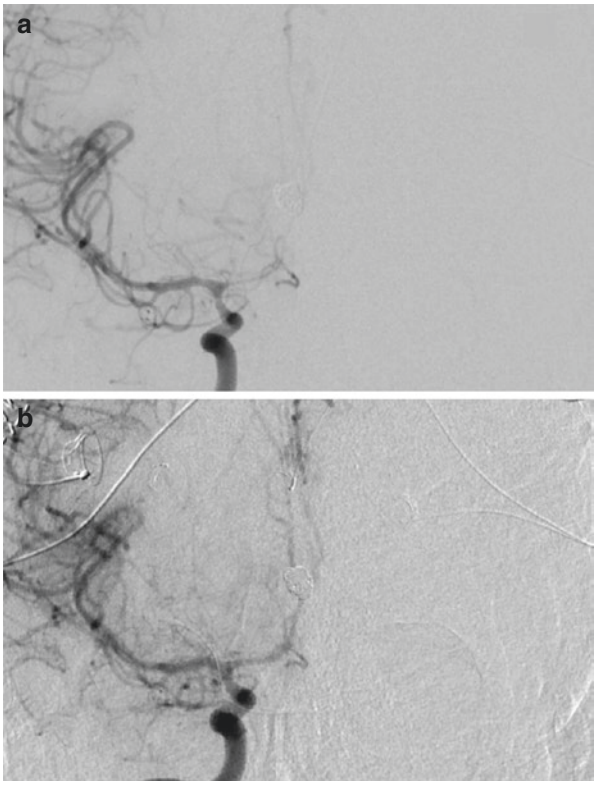


**Fig. 3** Right A1 vasospasm before (**a**) and after (**b**) treatment with intra-arterial nicardipine

Operationally, the diagnosis of delayed neurological decline due to ischemia usually distinguishes between imaging-confirmed cerebral infarction, and deficits attributable to ischemia in the absence of imaging confirmation, usually called "delayed ischemic neurologic decline" (DIND). More detailed definitions adapted from consensus definitions [9] are provided in Table 4.

DCI/DIND is typically seen 4–12 days after the initial hemorrhage and is a major cause of morbidity and death [7, 10]. Risk factors for DCI/DIND include high clot burden in the basal cistern and thick ventricular clots, along with poor grade SAH [6]. Treatment is centered on ensuring adequate perfusion to the brain. This is accomplished by achieving euvolemia with fluid resuscitation. If symptoms of delayed ischemia persist despite euvolemia, the next step is inducing a

**Table 4** Consensus definitions of DCI and DIND

| **Delayed ischemic neurologic decline (DIND)** |
|---|
| *One of these:* |
| A. New focal neurological impairment (i.e., hemiparesis, aphasia, apraxia, hemianopia) |
| B. Decrease of at least 2 points on the Glasgow Coma Scale |
| *And all of these:* |
| Must last at least 1 h |
| Must not be apparent immediately after aneurysm occlusion |
| Not attributable to other causes based on CT, MRI, or other laboratory studies |
| **Delayed cerebral infarction (DCI)** |
| *One of these:* |
| Cerebral infarction on CT or MR scan of the brain within 6 weeks after SAH |
| Cerebral infarction on the latest CT or MR scan made before death within 6 weeks |
| Cerebral infarction proven at autopsy |
| *All of these must be true:* |
| Not present on the CT/MRI within 48 h after early aneurysm occlusion |
| Not attributable to other causes such as surgical clipping or endovascular treatment. |
| Hypodensities on CT attributable to ventricular catheter placement or intraparenchymal hematoma should not be counted as DCI |

Adapted from Vergouwen et al. [9]

state of hypertension using intravenous pressors and mineralocorticoids. The final step in managing DCI involves angiography, with intra-arterial injection of vasodilators, typically calcium channel blockers such as nicardipine, and angioplasty [11].

Given the morbidity and mortality associated with DCI, several screening modalities are used in neuro ICU to identify early signs of DCI. Transcranial Doppler (TCD) ultrasonography is one of the most commonly used screening modalities. TCD is used to measure blood flow velocity in the major cerebral arteries. For the anterior circulation, a mean blood flow velocity less than 120 cm/s is consistent with the absence of vasospasm, and a mean blood flow velocity greater than 200 cm/s is suggestive of cerebral vasospasm. Studies have shown TCD to have a sensitivity of 38–91 %, and a specificity of 83–100 % for detecting vasospasm [12–14]. However, TCD is operator dependent, and typically is only done once a day. Other diagnostic techniques used to screen for DCI and vasospasm include CT angiography, CT perfusion, xenon CT, and magnetic resonance imaging (MRI). CT angiography has been shown to have a sensitivity of 80 % and specificity of 93 % for the detection of vasospasm [15].

## Continuous EEG Monitoring

Continuous EEG (cEEG) monitoring can be utilized for ischemia detection and is particularly attractive for detecting DCI. EEG has the advantage of providing continuous data, as opposed to TCD or radiographic data, and can serve as an important tool to detect ischemia prior to development of irreversible injury.

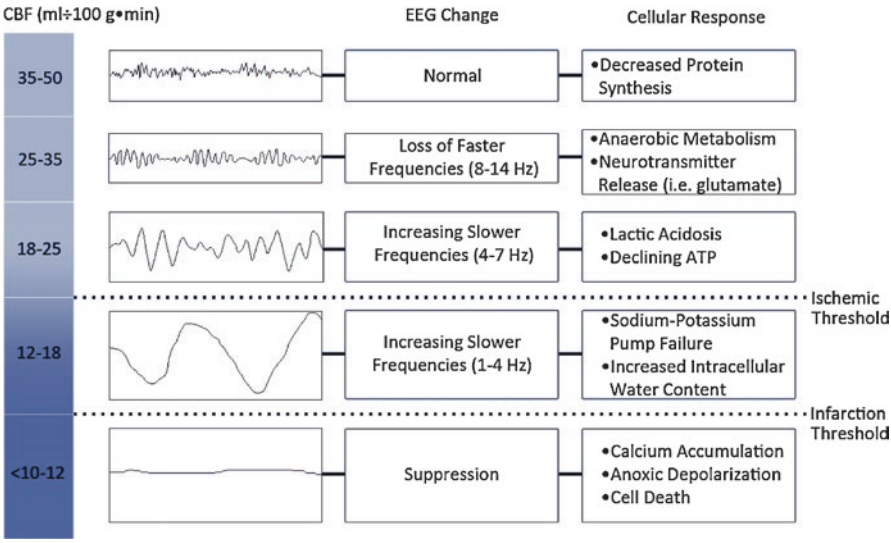


**Fig. 4** Changes in EEG with decreasing cerebral blood flow [16] (Reprinted from [16] and BioMed Central is the publisher. RightsLink/Springer license no: 3562491446946)

The impact of cerebral blood flow (CBF) on the EEG is shown in Fig. 4 [16]. CBF of 12–18 ml/100 g/min is effectively an ischemic threshold, and as CBF approaches this threshold, predominantly slower frequencies are seen on the EEG. As the CBF approaches the ischemic threshold, there is reversible cellular injury caused by decreasing adenosine triphosphate (ATP) and loss of the transmembrane potential [16]. As CBF decreases to less than 10–12 ml/100 mg/min, there is irreversible cellular damage and cell death, and the EEG reveals a suppressed pattern. Early detection of decreasing CBF creates an opportunity to treat ischemia prior to the development of irreversible injury or infarction, and hence makes cEEG a useful tool for early detection of DCI in SAH patients.

SAH can produce several systematic changes in the EEG background, including slowing, periodic discharges, seizures, and impaired reactivity to external stimulation [16, 17]. cEEG patterns that have demonstrated predictive value for DCI include focal delta slowing corresponding with the area of injury, bursts of frontal biphasic delta waves, continuous rhythmic delta activity, and continuous polymorphic or unreactive delta [18]. In a retrospective study of high grade SAH patients, EEG changes suggestive of early ischemia were present before 78 % of DCI events [19].

## Quantitative EEG Monitoring

The primary challenge in using cEEG to identify ischemia in real time is the time-consuming and subjective nature of raw EEG interpretation. qEEG monitoring

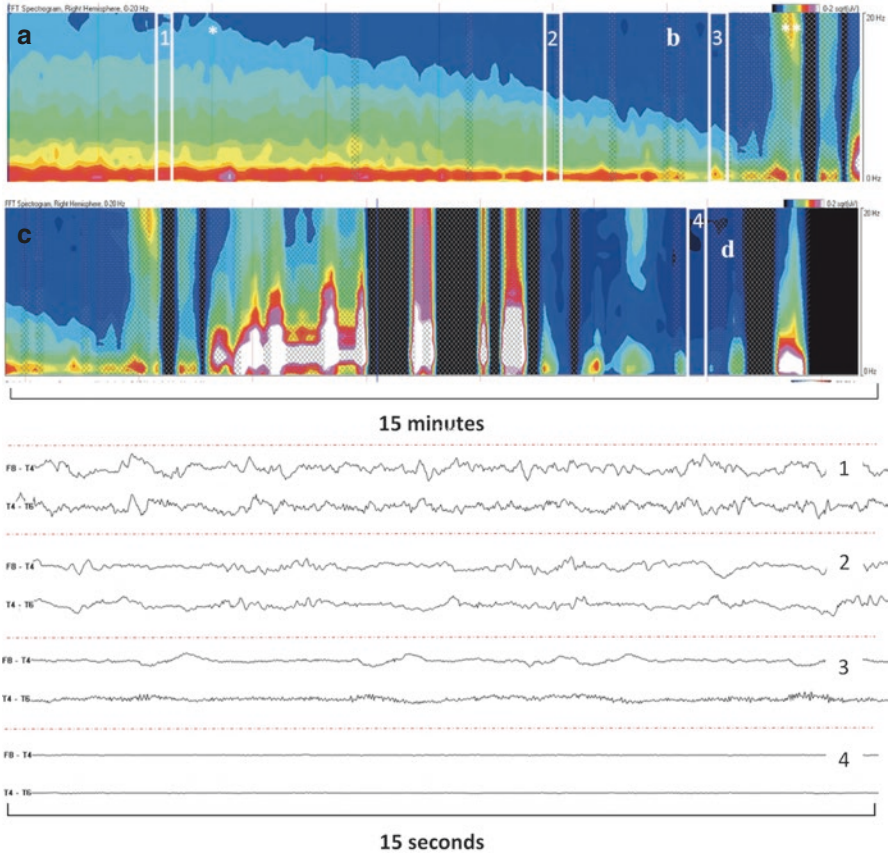


**Fig. 5** Spectrogram changes in a patient with cardiac arrest. There is an initial loss of alpha frequencies (**a**), followed by loss of slower frequencies (**b**, **c**), and eventual suppression of the EEG (**d**)

provides an essential complementary set of tools to facilitate effective, sensitive, and timely detection of ischemia.

The key qEEG changes that signal the onset of ischemia are well illustrated in a spectrogram from an elderly medical ICU patient with sepsis who unexpectedly suffered a cardiac arrest while undergoing cEEG monitoring (Fig. 5). As evidenced in the figure, as cerebral ischemia ensues, there is early drop out of alpha frequencies followed by loss of delta frequencies and eventual suppression. The same changes are characteristic of ischemia in SAH patients with impending DCI, albeit with a progression that is typically much more gradual.

Most clinical practice of qEEG for the early detection of ischemia is based on the observation that ischemia produces trends of decreased fast and increased slow oscillations in the EEG. Both studies are based on ratios of power within specific bands within the EEG spectrogram [15, 16].

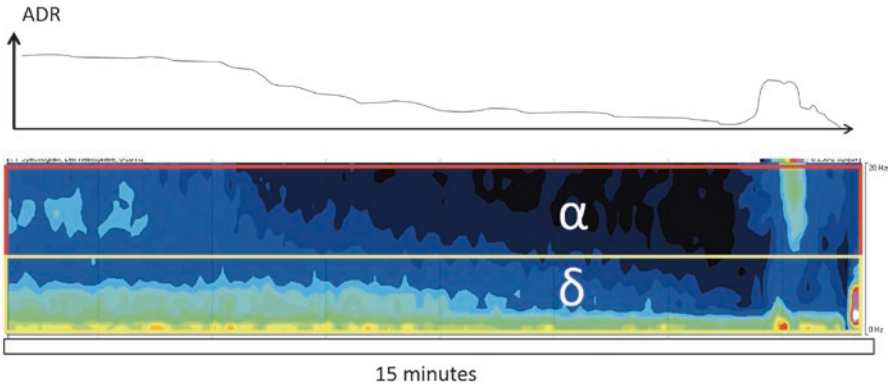


**Fig. 6** Alpha-to-delta ratio (*ADR*). The ADR is defined as the ratio of the sum of the power within two bands, the "alpha" band (8–13 Hz) and delta band (1–4 Hz)

### Alpha-to-Delta Ratio

One method of detecting DCI with qEEG is based on the alpha-to-delta ratio (ADR) [16, 19]. The ADR is defined as the ratio of the sum of the power within two bands, an alpha band (8–13 Hz) and delta band (1–4 Hz), illustrated in Fig. 6. The ADR is often displayed either as a smooth curve, derived by applying a moving average to repeated sequential ADR measurements, or as a histogram showing sequential measurements from non-overlapping windows (Fig. 7). Significant or sustained decreases in ADR are considered "alarms" signaling impending DCI. In a study of qEEG in 34 high grade (Hunt and Hess (HH) 4 and 5) SAH patients, the ADR had the strongest association with DCI [16, 19]. Nine of 34 patients developed DCI and had a median decrease of ADR of 24 %. Among several possible rules for triggering an "alarm," the study suggested two as having particular clinical utility. First, six consecutive recordings with a 10 % decrease in ADR from baseline had a sensitivity of 100 % and specificity of 76 % for subsequent DCI. Second, any single measurement with a 50 % ADR decrease had a sensitivity of 89 % and specificity of 84 % for subsequent DCI. Figure 7 shows an example of how the ADR ratio varies in relation to changes in GCS, neurological exam, imaging findings, and treatment [16, 19].

### Relative Alpha Variability

Another common method used to assess DCI is relative alpha variability (RAV) as an early predictor of ischemia, operationally defined as vasospasm evidenced by TCD mean velocities of greater than 120 m/s in the middle cerebral artery (MCA) distribution and a Lindegaard ratio (MCA/internal carotid artery (ICA) velocity) of greater than 3, or evidence of vasospasm on conventional angiogram. This method was investigated in 32 SAH patients with HH1-HH3 grade hemorrhages [20]. This method assigns a score to histograms derived from 8- to 12-h segments of EEG. Bars in the histogram represent sequential measurements, derived from 2-min epochs, of the "alpha" to "total" power ratio, defined as the power within the 6–14-Hz ("alpha") band expressed as a percentage of power within the 1–20-Hz band [16]. Periods with high variability are assigned a score of 4 ("excellent" RAV), whereas periods

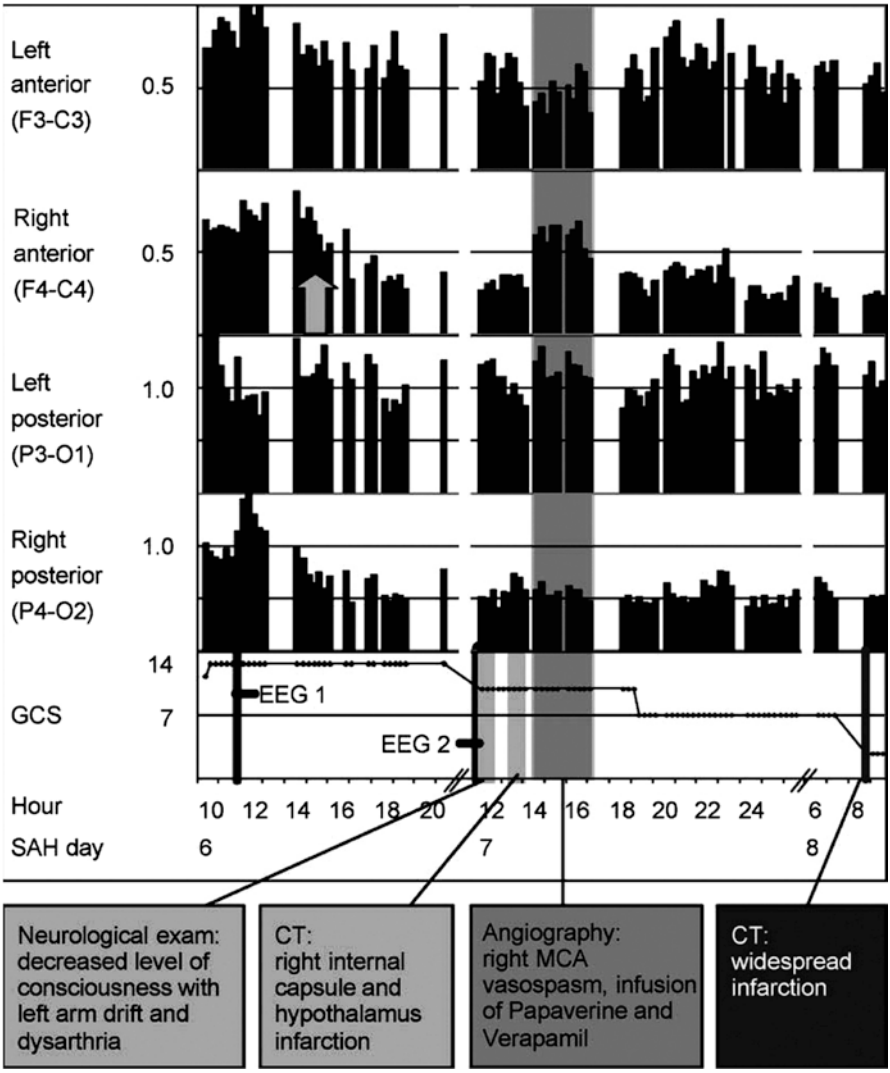


**Fig. 7** Alpha-to-delta ratio calculated every 15 min and GCS score [19] (Reprinted from [19] with permission from Elsevier, License no: 3940350912437)

with nearly absent variability are assigned a score of 1 ("poor" RAV). Periods with intermediate degrees of variability are assigned a value of 2 ("fair" RAV) or 3 ("good" RAV) (Fig. 8). A deterioration of RAV by 1 visual grade in one or more monitored channels was considered to be an "alarm" signaling impending DCI. Inter-rater agreement using this visual scale was reported to be high, with 100 % agreement for cases with "excellent" and "poor" RAV, and 90 % agreement for cases with "good" and "fair" RAV [16].

Of 19 patients with angiographic vasospasm, the RAV decreased by a mean of 2 grades, and improved as vasospasm improved. In ten of these patients, the RAV

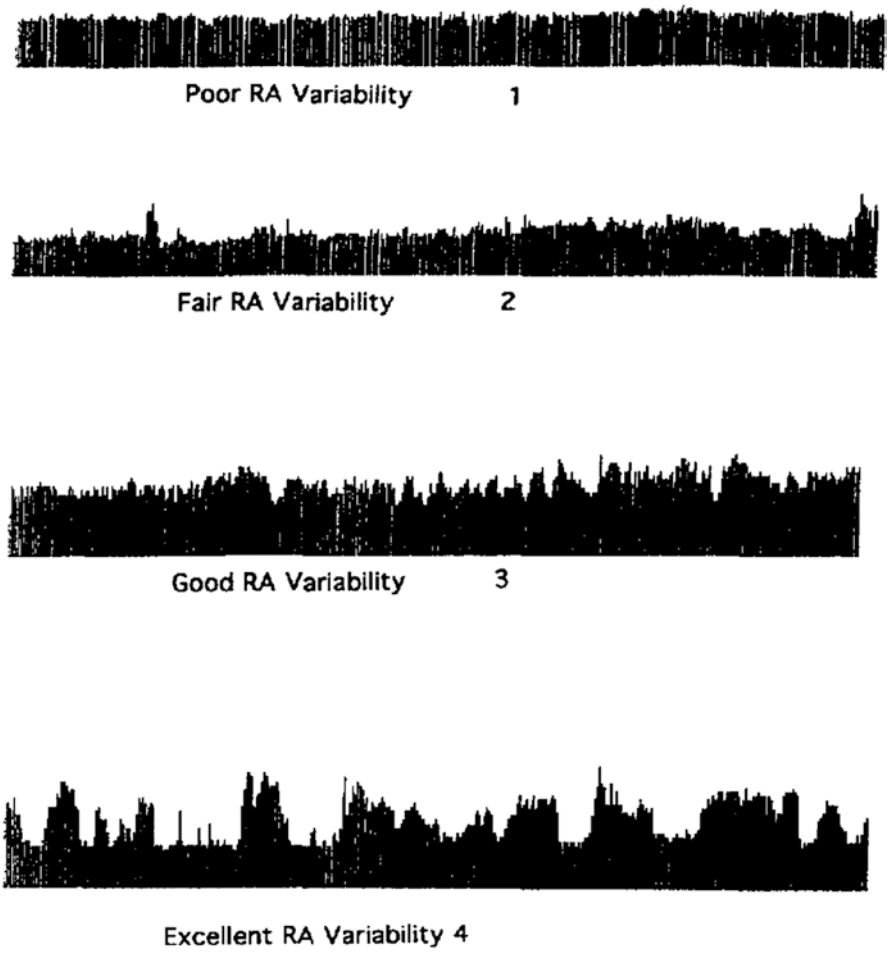


**Fig. 8** Visual grading scale for relative alpha variability (RAV) [20]. Each histogram is a time series of serially computed alpha-to-total power ratios (power in the 8–14-Hz band expressed as a percentage in the 8–20-Hz band). The time window shown is 8 h (Reprinted from [20] with permission from Elsevier, License no: 3940290199754 )

reduction was observed prior to the detection of angiographic vasospasm by a mean of 2.9 days (SD 1.73). Reduction in RAV had a positive predictive value of 76 % and negative predictive value of 100 % for vasospasm.

## Limitations

A major historical limitation of qEEG is the effect of artifacts on its parameters. In current practice frequent manual inspection is required when using the ADR and RAV indices to avoid being misled. However, commercially available qEEG

**Table 5** Protocol for continuous EEG monitoring in patients with SAH

| |
|---|
| *Inclusion criteria for patients:*<br>Nontraumatic aneurysmal SAH<br>Poor mental status (HH Grade IV,V) or IVH or thick cisternal blood (Fisher 3) |
| *Purpose of EEG monitoring:*<br>Ischemia detection<br>Seizure detection |
| *Timing of monitoring:*<br>Start within 2 days of admission, or STAT if indicated, and stop after 10 days of monitoring |
| *EEG monitoring and reporting:*<br>Continuous EEG monitoring; bedside raw EEG and quantitative EEG displayed<br>EEG service evaluates for changes q8h and generate twice daily reports<br>Reports contain the raw EEG (+ spectrogram) finding, RAV, ADR<br>Patient nurse scores PAV/ADR trends q4h and documents them in the flow sheet and reports significant changes to the ICU team<br>ICU team response: evaluate patient and EEG, decide on further clinical testing or potential interventions if indicated, and follow up response and reevaluate EEG |

software has made steady improvements in automated artifact removal. Future studies should investigate whether these improvements allow more accurate and/or more efficient use of qEEG data for ischemia detection. Development of automated statistical trend detection algorithms currently under development are expected to further improve upon the present state of the art.

## Practical Protocol

A practical protocol for using EEG/qEEG to monitor patients with SAH for early signs of ischemia is shown in Table 5. Clinical reporting of EEG for ischemia detection is generally more labor intensive than monitoring solely to detect seizures, as the findings of interest (new slowing, alpha attenuation, and asymmetry) are often subtle and develop gradually. Consequently, the authors recommend a disciplined, 4-step approach to reading and reporting cEEG in SAH, using the data layout shown in Figs. 9, 10, and 11: first, evaluate the raw EEG and accompanying spectrogram; second, inspect the ADR for any systematic downward trends; third, assign a visual RAV score to each vascular territory; and last, formulate an overall impression of the data, stating whether or not the findings suggest the development of ischemia.

The recommended approach is illustrated using data from the case shown in Figs. 9, 10, and 11. On day two following SAH, the raw EEG data showed diffuse irregular delta/theta slowing without any significant asymmetry. The asymmetry spectrogram (difference between the average spectrogram over the left and right hemispheres) confirmed that a pattern was stable over longer epochs, as evidenced by the largely pastel red and blue colors, indicating that EEG spectral power differences between corresponding sites on the right and left head regions were largely near zero. The red (right) and blue (left) ADR lines fluctuated with state changes but consistently stayed nearly superimposed and did not show any progressive separation or

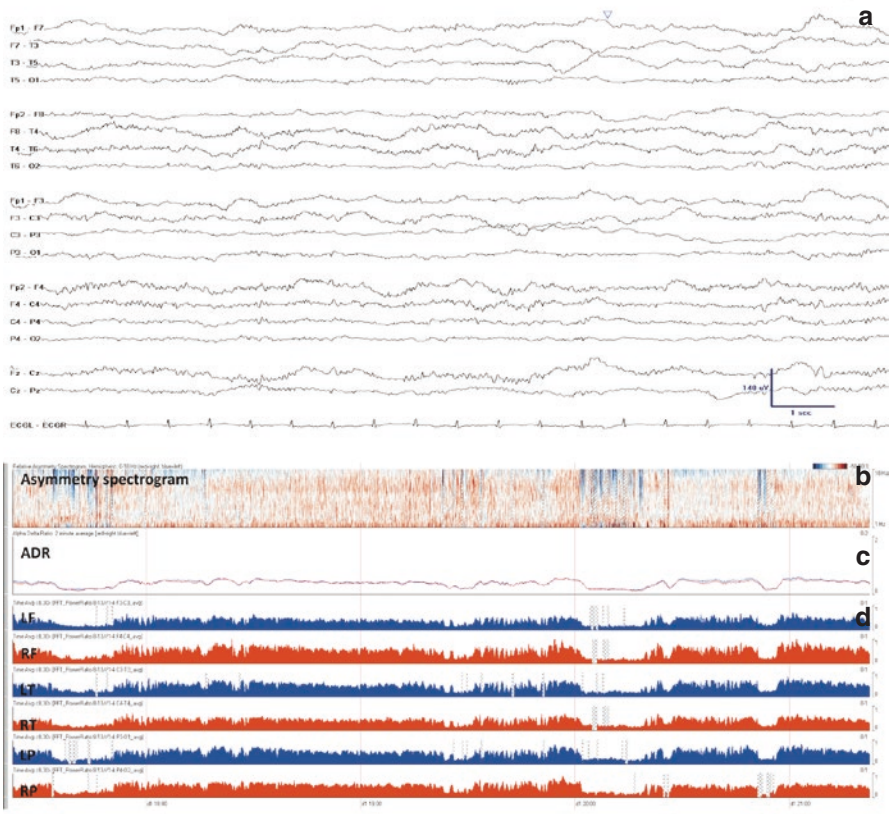


**Fig. 9** EEG data from a patient at day 2 after SAH. (**a**) Standard 15-s view of primary EEG data, shown in bipolar montage. (**b–d**) Show qEEG measures used to aid ischemia detection, within a 4-h time window. (**b**) Difference between the average spectrogram over the left and right hemisphere. Shades of *red colors* indicate higher relative power over the right hemisphere. Shades of blue indicate higher relative power over the left hemisphere. Pastel colors (center of the *color scale*) indicate mild asymmetry. Darker shades of *red* or *blue* indicate more pronounced asymmetry. (**c**) Alpha-to-delta ratio (*ADR*) trends for the left (*blue line*) and right (*red line*) hemisphere. (**d**) Relative alpha variability (RAV) trends. *Abbreviations*: note: *LF/RF* left/right frontal, *LT/RT* left/right temporal, *LP/RP* left/right posterior

downward trends. RAV scores for the left and right frontal, temporal, and occipital regions were symmetric, and all were assigned a score of 3, indicating "good" variability. A concise sample report of these findings is given in Fig. 12a.

On day four following SAH, the EEG demonstrated mild intermittent irregular delta slowing, best appreciated on the asymmetry spectrogram. The right hemisphere (red) ADR trace showed slight but persistent downward separation relative to the left (blue) curve. The regional RAV panels still showed some periods of "good" variability, but overall showed less variability in the right frontal and temporal regions compared with the preceding two days, and were thus given a score of 2, indicating "fair" variability. Overall, these changes are concordant in suggesting the

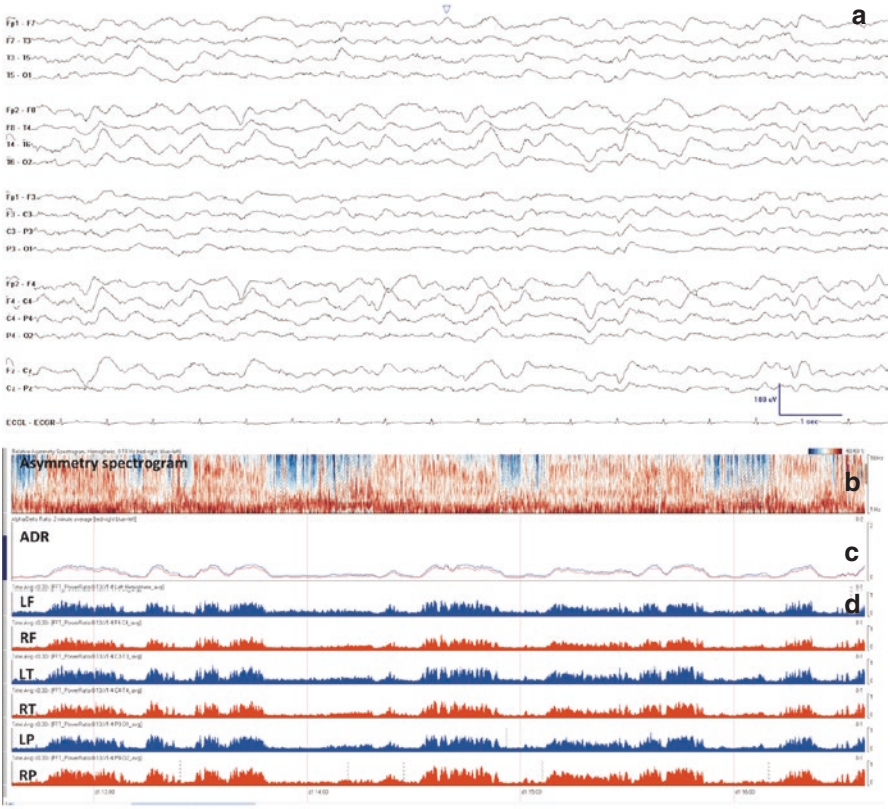


**Fig. 10** Fifteen-second view of raw EEG (**a**) and 4-h panel of qEEG measures (**b**–**d**) from ischemia monitoring on post-bleed day 4. The format of the data is the same as in the previous figure

development of ischemia. A report of these findings and impression is given in Fig. 12b. At this stage, the clinical team had not detected any focal deficits. However, on day 6 following SAH, the patient developed clinically apparent focal weakness in the left leg. Figure 13 shows side-by-side head CT scans from days 3 and 6, demonstrating a new right greater than left anterior cerebral artery (ACA) territory infarct.

## Anoxic Brain Injury

### Background

CEEG monitoring can assist with prognostication after cardiac arrest and therapeutic hypothermia. Patterns associated with higher probability of poor outcome include burst suppression, generalized periodic discharges, generalized epileptiform discharges, and generalized background suppression [21]. These findings have

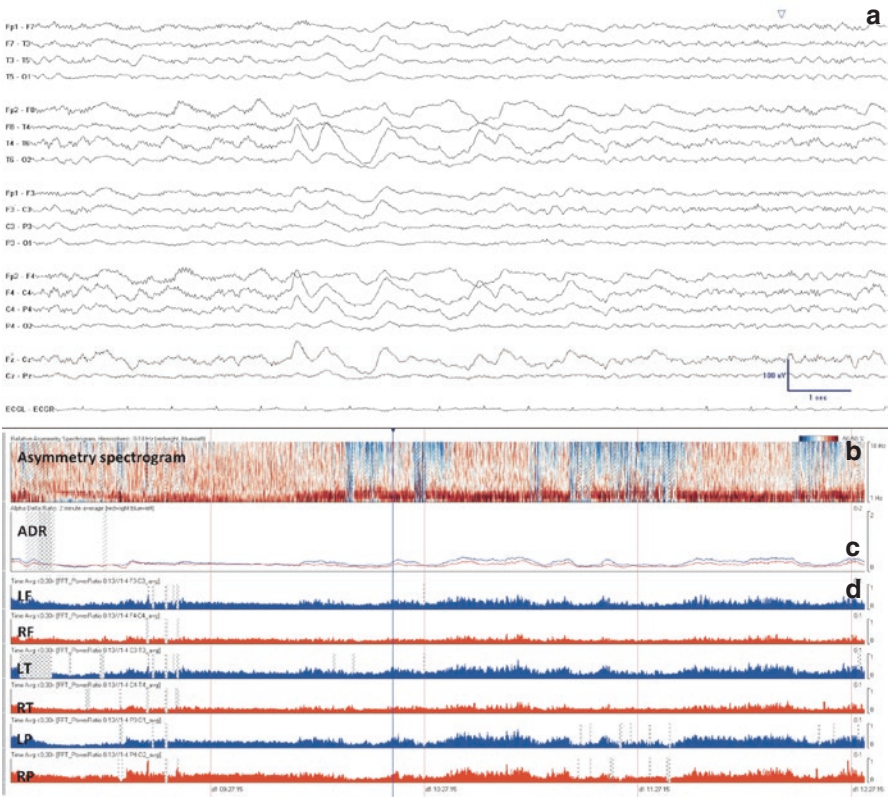


**Fig. 11** Fifteen-second view of raw EEG (**a**) and 4-h panel of qEEG measures (**b**–**d**) from ischemia monitoring on post-bleed day 6. The format of the data is the same as in the previous two figures

been shown to be associated with poor outcome regardless of treatment with therapeutic hypothermia (TH). The false-positive rate for predicting poor outcome is higher in patients with TH, and no single finding is 100 % predictive of a poor outcome [21]. More recently, the absence of background reactivity both during and after therapeutic hypothermia has been shown to be a predictor of poor prognosis [21, 22]. Understanding of features predictive of favorable neurological outcomes is much more limited.

Temporal changes in the EEG patterns have been studied on a small scale and may serve as additional useful prognostic indicators. EEG changes with time include transitions, fluctuations, and responses to external stimuli [23]. Transient fluctuations are spontaneous transient changes in the EEG pattern that can be seen during 30-min recordings. Examples include intermittent suppressions, episodic transients, blocking of generalized periodic discharges (GPD), and trains of polyspikes in GPDs [23].

**a. Report for EEG Monitoring on post-bleed day #: 2**
EEG: Diffuse irregular delta/theta slowing, without focality.
QEEG trends:
-ADR: Stable, no concerning trends. Fluctuated between 0.25-0.5
-RAV: F/T/O: R: 3/3/3, L 3/3/3
IMPRESSION: No changes concerning for ischemia.

**b. Report for EEG Monitoring on post-bleed day #: 4**
EEG: Frequent intermittent right frontal delta slowing
QEEG trends:
-ADR: concerning trend, decreased on R frequently (anteriorly)
-RAV: F/T/O: R: 2/2/3, L 3/3/3
IMPRESSION: New persistent focal slowing of the background in the setting of SAH. In the absence of an alternative explanation, these findings suggest ischemia.

**Fig. 12** Reports describing (**a**) the EEG and qEEG data in Fig. 9 from day 2, and (**b**) the EEG and qEEG data in Fig. 10 from day 4, at the time when evidence for ischemia/impending DCI was first detected

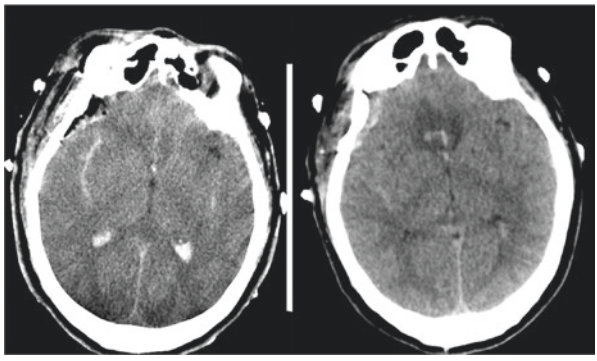


**Fig. 13** CT scans of the head for the patient whose EEG data was shown and reported in Figs. 9, 10, 11, and 12. The scan done on day 6 was done following the development of new left leg weakness. It shows a new hypodensity, consistent with an ACA territory infarction, diagnostic of radiographic DCI

Another form of fluctuation in the EEG pattern with time is the response to external stimuli. These changes are usually reproducible, and as mentioned previously, the presence of EEG reactivity is probably an indicator of better prognosis. An exception is the presence of stimulus-induced rhythmic, periodic, or ictal discharges (SIRPIDS), which are equivalent to the absence of reactivity from a prognostic standpoint [24].

Transitions are more long-lasting changes in the EEG pattern. Examples include transition to GPDs from alpha or theta coma, and an evolving pattern from slow activity to GPDs into low-voltage EEG [23]. Studies in rodents have demonstrated a characteristic sequence of transitions after return of spontaneous circulation following anoxia, beginning with generalized suppression, then the emergence of intermittent

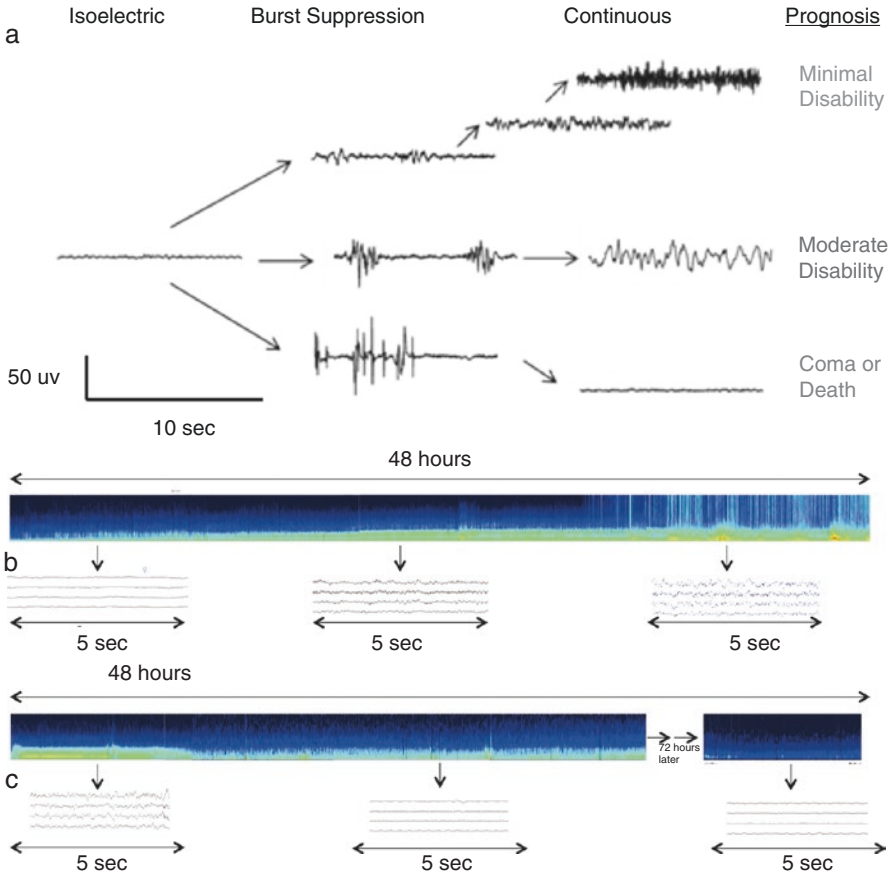


**Fig. 14** (**a**) Schematic illustration of the typical sequence of transitions following anoxic brain injury. (**b**) Spectrogram showing evolution of the EEG over 48 h following rewarming from therapeutic hypothermia in a patient who ultimately had a full recovery neurologic following postanoxic coma. The background initially shows diffuse suppression. A burst-suppression pattern then emerges (not well seen in this spectrogram). This is followed by a return of continuous background activity, beginning with low amplitude slow oscillations, then gradual normalization of background amplitude and the filling in of higher frequency activity. This patient remained comatose without clinically evident improvement during the first 36 h of this EEG recording. (**c**) Spectrogram showing evolution of the EEG in a comatose post-cardiac arrest patient who ultimately had a poor neurologic outcome. The EEG initially shows diffuse continuous irregular delta slowing, but there is a progressive loss of background voltage amplitude, culminating in an isoelectric EEG

bursts of activity (burst-suppression pattern), and finally the return of cEEG activity [25]. In rodents, the duration of each stage (i.e., generalized suppression, burst suppression) predicts eventual functional neurologic outcome. A similar progression of transitions is often seen in humans following anoxia, as illustrated in Fig. 14. The prognostic value of these dynamic changes in the human EEG over time has only recently come under careful investigation.

## Quantitative EEG

As with ischemia detection in patients with SAH, qEEG analysis in patients with anoxic brain injury has the potential advantages of being more objective and less time-consuming to interpret, enabling evaluation of EEG trends and transitions over time.

qEEG parameters that have been studied in anoxic brain injury include the burst-suppression ratio, response entropy, state entropy, and wavelet subband entropy [26]. In one study, these measures were investigated at 24 h and at 24–48 h after cardiac arrest in patients who were treated with TH [26]. Spectral entropy is calculated from a range of 0.8–32 Hz and is designed to reflect cortical activity, while response entropy is calculated from a range of 0.8–47 Hz and is designed to reflect "responsiveness," including electromyographic responses [26]. Wavelet subband entropy can be used to detect some forms of epileptiform activity in the setting of postanoxic coma, with decreasing values indicative of epileptiform activity on the EEG. The investigators found that the burst-suppression ratio was significantly lower during the first 24 h and at 24–48 h after cardiac arrest in patients who had better outcomes. The response entropy and state entropy were higher among patients with good outcomes only in the first 24 h after cardiac arrest. The wavelet subband entropy was higher in patients with good outcome only at 24–48 h after cardiac arrest and not during the first 24 h. They also found that at 24 h, a response entropy of less than or equal to 12.53 and a subband entropy of less than or equal to 11.84 had a 78 % sensitivity and an 81 % specificity for predicting poor outcome [26].

More recently, the cerebral recovery index (CRI) [27] using combined qEEG parameters has been studied as a prognostic index for patients with anoxic brain injury [27]; see Fig. 15. The index combines five parameters, including the power, Shannon entropy, alpha-to-delta ratio, "regularity," and coherence in the delta band. The power of the EEG is calculated from the standard deviation of the EEG within the sliding window. The entropy quantifies the degree of irregularity or unpredictability of a signal. Regularity is an index designed to distinguish between burst suppression and cEEG. The authors started by selecting 5-min-long EEG epochs every hour for the first 48 h after arrest, and every 2 h thereafter. These 5 min epochs were selected after application of an artifact detection algorithm. The power, Shannon entropy, alpha-to-delta ratio, and coherence in the delta band amplitude were calculated per EEG channel and per 10-s segments and then were averaged over all channels and over time. The "regularity" was calculated per channel for the entire 5 min at a time and then averaged. Each parameter value was normalized to lie within a range from 0 (pathological) to 1 (normal/physiological), and then all values were combined to create the CRI.

Patients with higher CRI scores had better outcomes. In particular, a CRI score of less than 0.29 24 h after cardiac arrest was always associated with poor neurologic outcome and had a sensitivity of 55 %. Twenty-four hours after a cardiac arrest, a CRI score of greater than 0.69 was associated with better neurological outcome and had a sensitivity of 0.25.

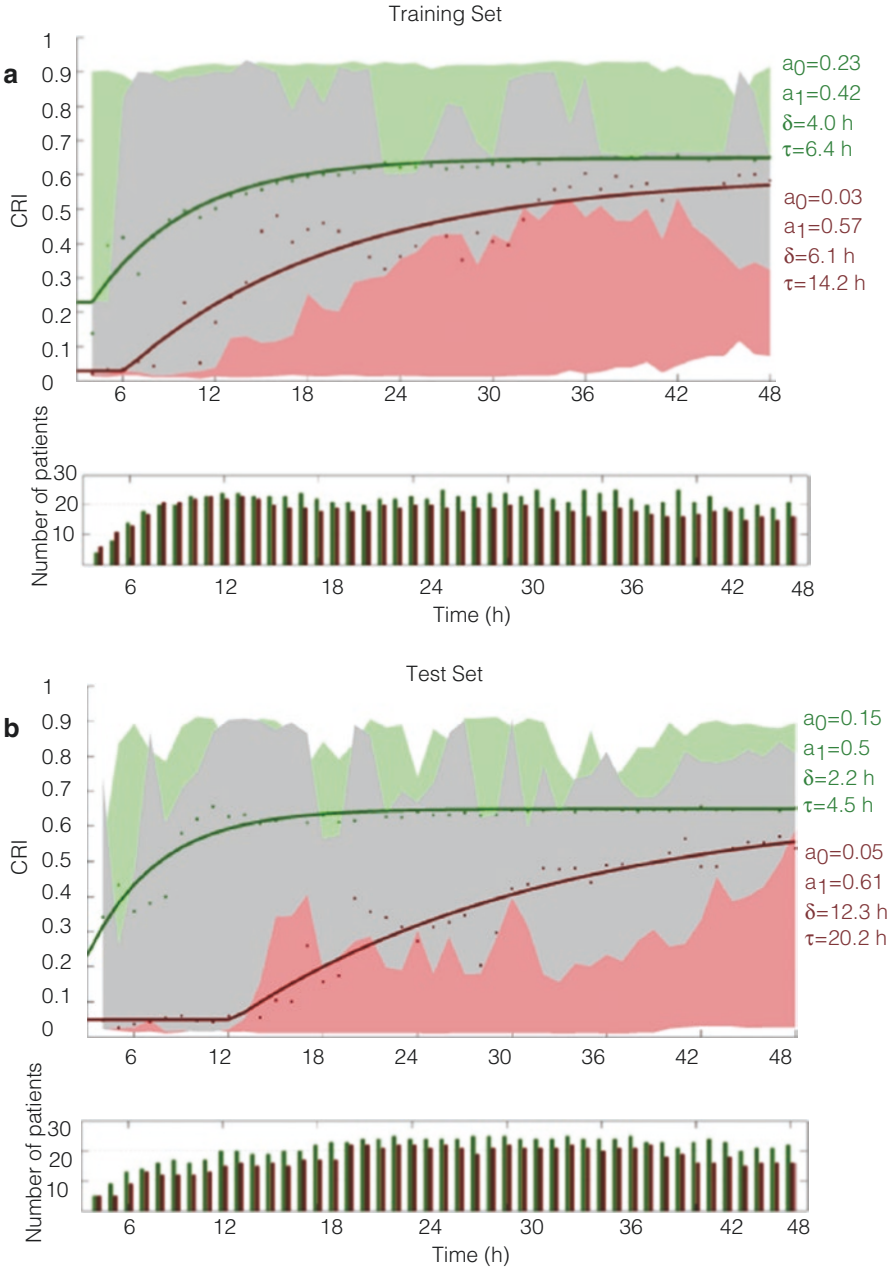


**Fig. 15** Cerebral recovery index (CRI) [27]. Values of the cerebral recovery index (CRI) for training (**a**) and testing (**b**) data sets. *Green* and *red dots*: median values for patients achieving good and poor neurologic outcome at each time point. Areas shaded in *green* and *red* represent the ranges. The *gray area* shows where the regions overlap. The *solid curves* show the fits of a "recovery model." The CRI are maximally separated between 12 and 24 following cardiac arrest (Reproduced from [27] an open access article, published by BioMed Central, and distributed under the terms of the Creative Commons Attribution License (http://creativecommons.org/licenses/by/2.0))

Recently, there has also been data to show that an addition of a mismatch negativity-based auditory discrimination paradigm to the EEG increases its prognostic value in patients with anoxic brain injury and coma [28]. In one study, this was investigated by using a mismatch negativity paradigm with a series of standard sounds that were mixed with deviant sounds of varying duration and pitch. EEG was recorded immediately after the clinical exam, for the auditory discrimination paradigm both during therapeutic hypothermia and after rewarming. The auditory discrimination paradigm was found to have a 100 % positive predictive value (95 % confidence interval of 0.69–1.0) for awakening in comatose patients with anoxic brain injury. Patients that had a reactive hypothermic EEG with concomitant improvement in the auditory discrimination paradigm were more likely to survive and have better outcomes. The studies combining mismatch negativity paradigm and EEG findings have been small in size, and larger scale studies are needed to improve the clinical applicability of these findings.

## Traumatic Brain Injury

RAV can be used as a prognostic indicator in patients with TBI [29]. RAV was described above in the setting of qEEG monitoring for ischemia detection in patients with SAH. In the TBI literature, RAV is usually referred to as percent alpha variability (PAV). An average PAV value of less than 0.1 has been shown to be associated with poorer outcomes and higher mortality rate in TBI patients. The PAV during the first three days post TBI has an 86 % positive predictive value and 63 % specificity for predicting poor outcomes. A PAV score of 0.2 or higher has been shown to be associated with favorable outcomes. PAV can therefore be combined with clinical parameters, such as GCS score, pupillary reaction, and neuroimaging to predict outcomes after TBI [29].

## Burst Suppression

Pharmacologically induced burst suppression can be used to treat elevated intracranial pressure, refractory SE, and for cerebral protection during cardiac surgery. Burst suppression offers cerebral protection by decreasing cerebral metabolic rate and decreasing cerebral blood volume [30].

The decreased cerebral metabolic rate results in decreased ATP production in cortical neurons. One model of burst suppression proposes that the end of each burst occurs when ATP consumption drives the metabolic rate below a critical point, while suppressions periods end when regeneration of ATP raises the metabolic rate above a threshold critical for initiation of background neuronal activity [31].

The degree of burst suppression is often quantified using the burst-suppression ratio (BSR), which is the percentage of time within an arbitrarily chosen epoch of EEG spent in the suppressed state [32]. This ratio can help guide the intensity of pharmacologically induced burst suppression. However, manually evaluating cEEG data for assessment of the BSR can be cumbersome and is time-consuming.

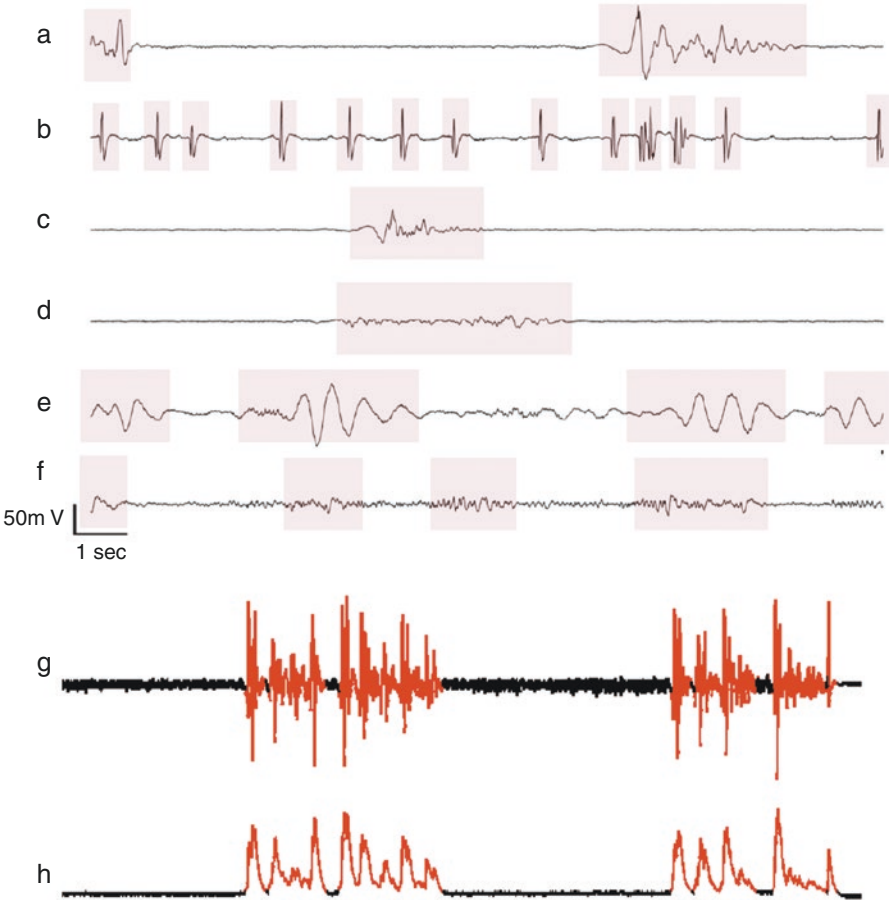


**Fig. 16** Automated detection of bursts and suppressions. Tracings (**a**) through (**f**) show six single-channel EEG examples of bursts suppression from different patients with pharmacologically induced burst suppression. Pink rectangles show automatically detected bursts; the unmarked portions are detected as suppression periods. In all cases the automated real-time segmentation results are comparable to segmentations performed by human experts. Tracings (**g**) and (**h**) illustrate how the automated segmentation procedure works. A local mean is first computed and subtracted from the EEG, yielding a baseline-corrected signal (**g**). A running estimate of the local amplitude of the signal is then calculated (**h**). This amplitude signal is then subjected to a threshold. Segments with amplitude above threshold are counted as bursts. The remaining portions are counted as suppressions

An automated real-time method for monitoring the depth of burst suppression in critically ill patients using automated segmentation of the EEG has recently been described and validated [32]. This method involves two components. The first is an algorithm for detecting periods of background suppression (Fig. 16). The authors validated their results against manual segmentations of the EEG into burst and suppression periods performed by two human experts. Automated segmentation was

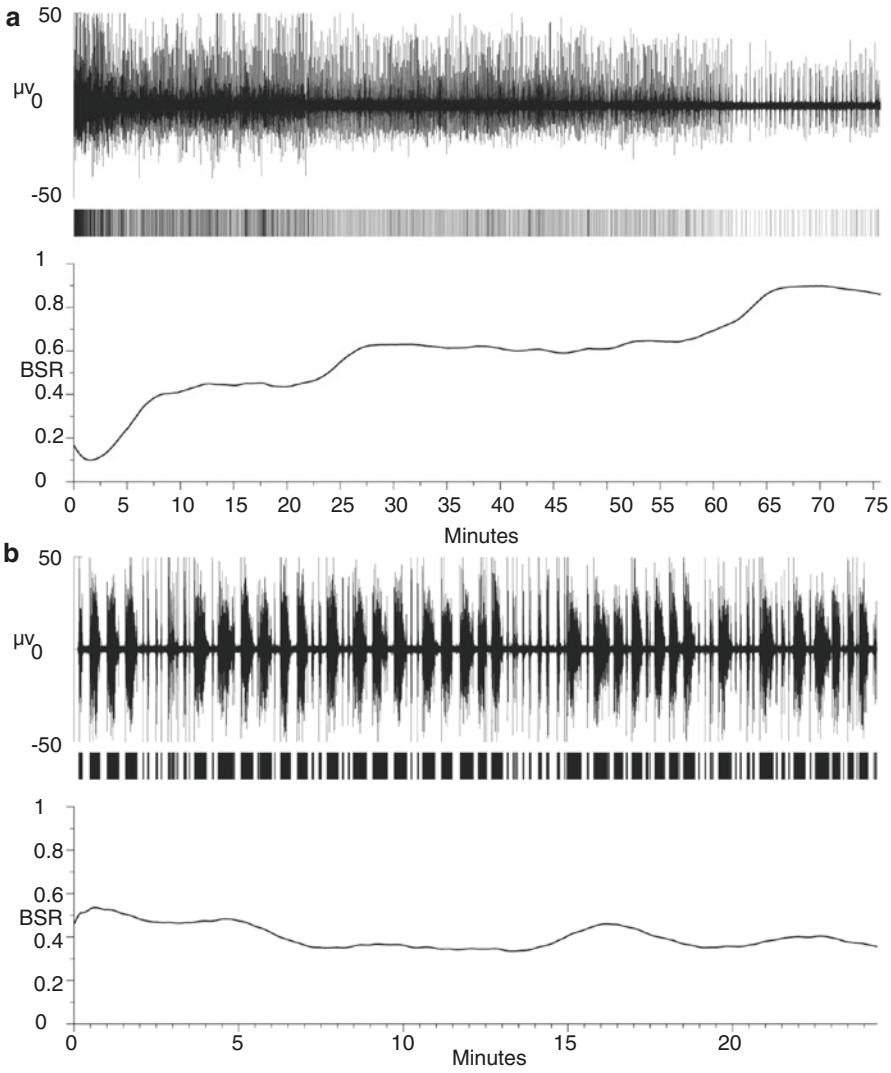


**Fig. 17** Monitoring the burst-suppression probability (BSP) in two patients (**a**, **b**) receiving continuous infusions of propofol as treatment for refractory SE. The top trace in each example shows a single channel of EEG; the middle panel with a bar-code-like signal shows automatic detections of bursts (*black*) and suppression (*white*); the *bottom panel* shows the BSP. The EEG in (**a**) begins with a low level of burst suppression around BSP = 0.2, which gradually increases to around BSP = 0.9 as the rate of propofol infusion is increased. The EEG in (**b**) shows a relatively stable pattern of burst suppression with BSP near 0.5

demonstrated to be comparable to manual segmentation. The second component is a real-time statistical estimation algorithm for tracking the instantaneous probability of suppression, the "burst-suppression probability" (BSP), illustrated in Fig. 17 [32, 33].

## Deep Hypothermia

Hypothermia-induced burst suppression is routinely used for neuroprotection during surgical procedures that require complete circulatory arrest (Figs. 18 and 19). The rate of cooling and rewarming and the optimum temperature for circulatory arrest continue to be subjects of investigation. Typically, the temperature targeted during deep hypothermia range from 14 to 20° centigrade, and deep hypothermia may be combined with inhalational anesthetics to achieve burst suppression [34].

The effect of temperature on burst suppression and the pattern of burst suppression during cooling, deep hypothermia and rewarming was investigated recently [34]. The investigators found that the BSP systematically increases with decreasing temperature. They also found that bursts shorten and decrease in amplitude, and the periods of suppression increase in length with decreasing temperature. With a temperature decrease from 30 to 20 °C, the suppressions nearly doubled in duration and bursts decreased by half. At lower temperatures (17–22 °C), the median burst amplitude was 12.6 microvolts, and at higher temperatures (27–32 °C), the medial burst amplitude was 76.9 microvolts. Finally, the spectral morphology of bursts was essentially preserved after normalizing for total spectral power. This suggests that there is relative preservation of the underlying neuronal dynamics, albeit with recruitment of a smaller fraction of the cortical activity that underlies bursts at normal temperatures.

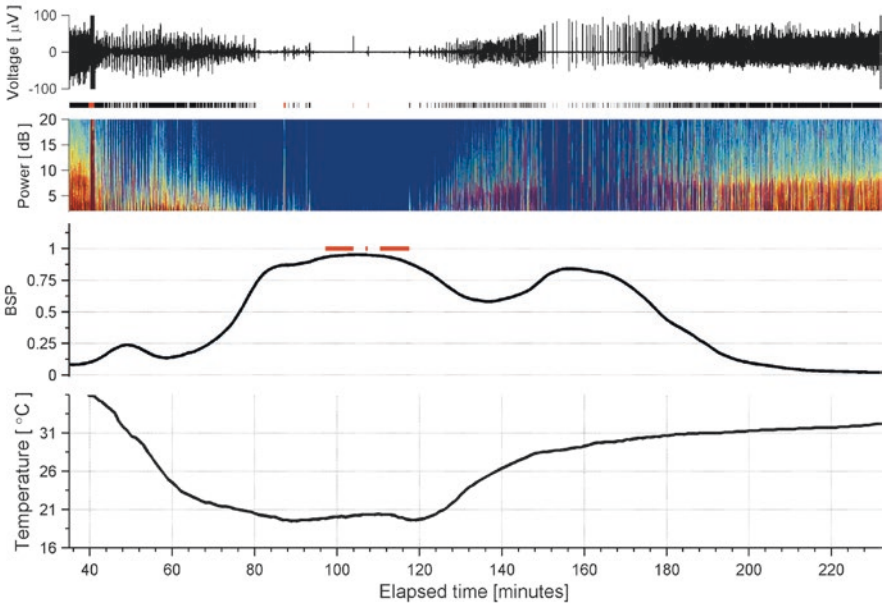


**Fig. 18** Example of qEEG changes during deep hypothermia. From *top* to *bottom*: single lead of EEG (Fp1); segmentation of the EEG into periods of suppression (*white*), non-suppression ("burst" state) in black, and periods of artifact (*red*); spectrogram; burst-suppression probability (*BSP*), with overbars in *red* indicating periods of isoelectricity (two or more minutes with EEG voltage continuously less than 2 microvolts); temperature

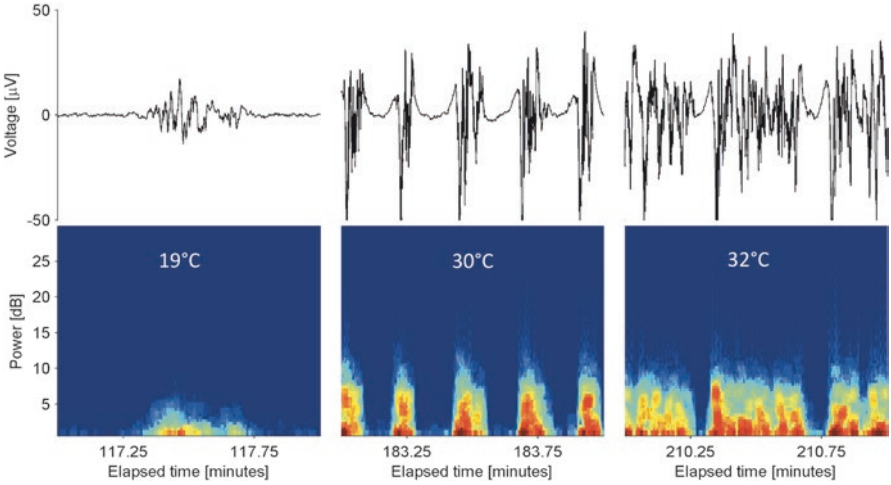


**Fig. 19** Representative examples of bursts and their corresponding spectrograms at three different temperatures. Burst amplitudes and durations tend to decrease with temperatures

These findings, reported in patients who emerged neurologically intact from deep hypothermia, suggest a possible new role for qEEG for monitoring during complete circulatory arrest for cardiac surgery. Monitoring the spectral morphology of bursts as hypothermia deepens may be useful for tracking integrity of the underlying neuronal circuitry. So long as there is no neuronal damage, the bursts are expected to have preserved spectral morphology. A change in the spectral morphology within bursts would suggest ischemic or anoxic injury and could be used to guide intervention [34].

**Conclusions**

QEEG monitoring can serve as a vital tool in detection of ischemia and prognostication in the neuro ICU. Numerous small studies have been done on its use in non-seizure indications. In order to improve the application of QEEG, a better developed method for artifact detection is needed, and improved training of physicians and nurses is indicated.

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# QEEG Training Module

15

Christa B. Swisher

## Contents



## Introduction

The goal of this chapter is to provide a training module for residents, neurophysiology fellows, neurocritical care fellows, nurses, EEG technologists, and any other non-neurophysiologists interested in evaluating bedside quantitative EEG (QEEG). Due to the increasing utilization of continuous EEG (cEEG) monitoring in intensive care units (ICUs), large volumes of EEG data are being generated. To assist with evaluation of large amounts of cEEG data, QEEG software programs are frequently employed. While raw EEG interpretation is performed by neurophysiologists,

C.B. Swisher, MD
Department of Neurology, Duke University Medical Center, Box 3824, Durham, NC 27710, USA
e-mail: christa.swisher@gmail.com



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QEEG software provides a compressed and simplified view of the raw EEG signals, potentially allowing for evaluation by non-neurophysiologists. QEEG software can be seen running at the bedside in many ICUs. This chapter will be limited to the basics of QEEG trends for seizure recognition and artifact recognition. While there is ongoing research evaluating the performance of QEEG for other purposes (ischemia detection, evaluation of depth of burst suppression, prognosis in hypoxic-ischemic encephalopathy, etc.), the majority of current clinical QEEG utilization is for seizure detection.

## Why Non-neurophysiologists Should Be Trained in Evaluating Quantitative EEG

Neurophysiologists often use QEEG in conjunction with raw cEEG review. In a 2014 survey of neurointensivists and neurophysiologists responsible for ICU EEG monitoring, 52 % of respondents utilized QEEG as part of their cEEG protocol [1]. Neurophysiologists typically perform cEEG and QEEG review intermittently throughout the day and/or night at predefined intervals and at additional times when alerted to an event of concern by the ICU staff. Because cEEGs are read intermittently throughout the day, data is relayed to the primary team in a post hoc fashion. Non-neurophysiologists (such as neurology and neurosurgery residents, neurocritical care fellows, nurses, and EEG technologists) are often physically present at the patient's bedside and have the advantage of being able to incorporate current clinical information with the data that is being shown on the bedside QEEG display. Therefore, non-neurophysiologists are in a unique position to evaluate QEEG trends in real time.

To determine if QEEG should be part of routine practice, studies have evaluated the performance of non-neurophysiologists for seizure detection on QEEG. Neuro ICU nurses and EEG technologists were able to detect seizures on QEEG panels (containing 4 QEEG trends) with a similar sensitivity than neurophysiologists. Neuro ICU nurses had a sensitivity of 87 %, EEG technologists 80 %, and neurophysiologists 87 % for the presence or absence of seizures on QEEG without having access to the raw EEG [2]. Although all groups displayed a poorer performance when asked to identify the number of seizures, the clinical relevance of the precise number of seizures is uncertain. In practice, it may only be necessary to know if seizures are present or absent to determine the patient's response to therapy.

Other studies evaluating only 1 or 2 QEEG trends found that the sensitivity for non-experienced readers (neurology residents, general neurologists, neonatologists, or intensivists) to be lower at 41–60 % [3–7]. One study showed a very high sensitivity for inexperienced users (93 %); however, the study authors preselected QEEG trend displays created from electrode pairs that would best reflect ictal activity for each individual patient [8]. To simulate a real-life scenario, one study evaluated the ability of inexperienced QEEG users to identify periods of concern, rather than discrete seizures. Although the false-positive rate was high (14 segments marked for every seizure identified), the sensitivity was also high at 89 % [9].

## Goals of Non-neurophysiologist QEEG Interpretation

A non-neurophysiologist should not interpret the QEEG data in isolation without a neurophysiologist who is able to review the raw cEEG data. A study reported a false-positive rate of 31 % from all readers (neurophysiologists, neuro ICU nurses, and EEG technologists) when QEEG is used in isolation on retrospective review [2]. Actual, real-time QEEG interpretation may have a lower false-positive rate due to better artifact recognition. If QEEG readers are present in the patient's room, it might be clear when certain forms of artifact are being generated (i.e., sternal rub, bed percussion, etc.). Nevertheless, if QEEG trends were used without raw EEG review by a neurophysiologist, unnecessary treatment would occur. The goal of non-neurophysiologist interpretation of QEEG should be to identify periods of concern during live recording. This should then be followed by a discussion with the interpreting neurophysiologist who is able to correlate the QEEG findings with the raw cEEG. It is particularly important for the neurophysiologist to review the raw cEEG and determine if events seen on QEEG are true seizures or not.

## Understanding the Basics of Quantitative EEG

QEEG is the application of mathematical and analytical techniques to process raw EEG signals, resulting in graphical displays of the data that are referred to as "trends." There are numerous types of QEEG trends that have been created, and they all have the advantage of displaying data on a compressed time scale. This allows for the user to visualize extended periods of data on one screen. One screen of raw EEG contains 10–20 s of data. One page of QEEG typically displays 1 h of data, but this can be modified to be shorter or longer. In addition, the user can select a single trend to be displayed or a customized panel of various trends can be displayed (Fig. 1). This chapter will often display a panel of QEEG trends, as this is the preference at the author's institution.

Often, the QEEG trends are broken down into separate graphical displays of the left and right hemispheres; however, this can be modified to have greater spatial resolution of various areas of the brain. Many QEEG trends display a color-coded graphical representation of various EEG parameters (with the colors varying between software programs). Some QEEG trends report numerical information in a bar-graph format over time, such as the alpha-delta ratio or burst-suppression ratio. This highlights another advantage of QEEG; unlike raw EEG, QEEG is able to provide a method of converting the subjective data of raw EEG signals into objective QEEG data.

QEEG software is sold separately from EEG software. Persyst (Persyst Development Corporation, Prescott, AZ) is a commonly used QEEG software and is compatible with clinical EEG software. The QEEG trends in this chapter were created from Persyst. This software can often be seen running at the bedside in neuro ICUs on a split screen shared with the continuously running conventional EEG.

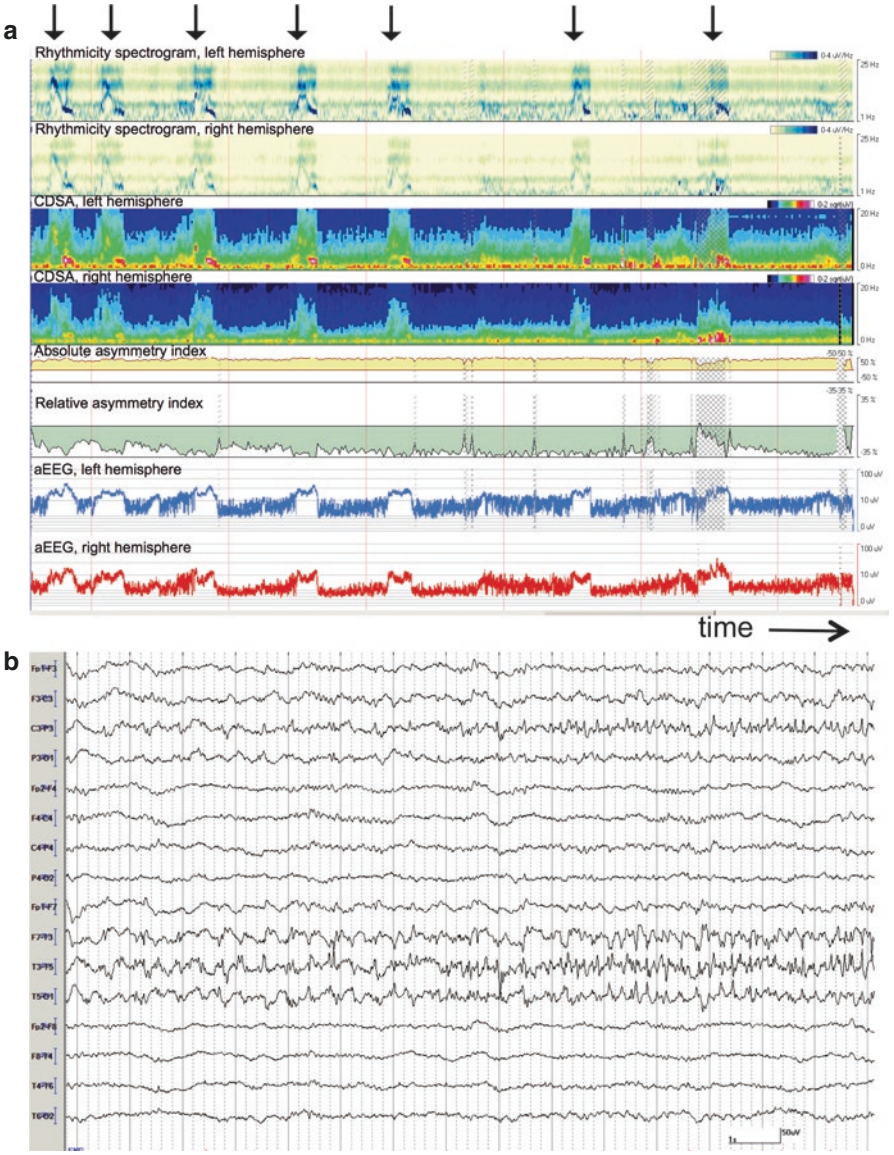


**Fig. 1** One-hour QEEG panel and corresponding raw EEG. (**a**) Example of a QEEG panel consisting of the following QEEG tools: rhythmicity spectrogram (displayed for the left and right hemispheres), CDSA (displayed for the left and right hemispheres), asymmetry index (displayed as both absolute and relative values), and aEEG (displayed for the left and right hemispheres). *Black arrows* denote electrographic seizures. (**b**) The corresponding raw EEG (16 s) for one of the seizures is shown displaying a left hemispheric seizure

## Quantitative EEG Trends

There are numerous QEEG trends available. Typically, neurophysiologists at an individual institution will select the trends that are displayed on the real-time QEEG display that is running at the bedside. Therefore, the QEEG display may vary in appearance from institution to institution. The basics of some of the most commonly used trends for seizure detection will be discussed, since this chapter is directed at non-neurophysiologists, but more detail and information about other QEEG trends can be found elsewhere in this text.

## Frequency-Based Trends

Before individual frequency-based QEEG trends are explained, it is first important to understand the concept of Fourier domain analysis, as this is the basis for many of the frequency-based QEEG trends. Fourier domain analysis refers to the contribution of different frequencies to the EEG signal. The EEG signal is represented as a weighted sum of sine waves of different frequencies. For each frequency, there is an amplitude. A Fourier spectrum displays a plot of amplitude vs. frequency. From this, a specific parameter called power can be calculated (Fig. 2). The power is the area under the Fourier spectrum curve within a given frequency range (i.e., delta power). In other words, the power is the amplitude (or voltage) of the EEG within a specific frequency range. This may be expressed as an absolute power (delta power,

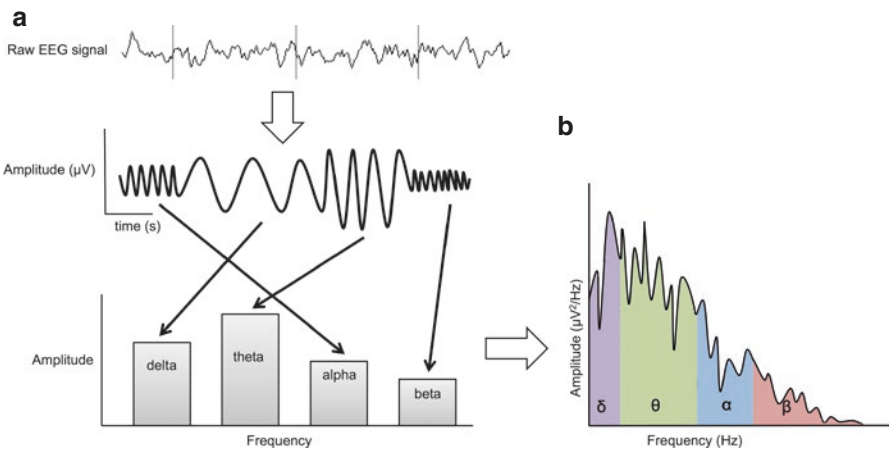


**Fig. 2** A diagrammatic representation of the creation of a Fourier spectrum plot. (**a**) The raw EEG signal is represented as a weighted sum of sine waves of different frequencies. For each frequency band (delta, theta, alpha, and beta), the amplitude is calculated. The amplitude is then plotted against frequency. (**b**) A sample Fourier spectrum curve is shown. The power of each frequency band (color-coded) is calculated as the area under the curve at specific frequency intervals

theta power, alpha power, and beta power) or as a relative power compared with the total power of all the frequency ranges (i.e., alpha-delta ratio). The Fourier spectrum changes over time as the EEG signals change due to medication effect, state changes, seizures, ischemia, etc. Frequency-based QEEG trends are able to show these changes in a graphical display over time.

### Color Density Spectral Array

An example color density spectral array (CDSA) trend is shown in Fig. 3. Often, the CDSA trend is displayed separately for the left and right hemispheres. Time is shown on the *x*-axis and the EEG frequency is shown on the *y*-axis. The various colors represent the power (described above) of various frequency bands. Cooler colors (blue and green) indicate lower power and warmer colors (red and yellow) indicate higher power. Seizures appear on the CDSA trend as increased power, and can be visualized as an episode of an increased amount of warmer colors (Fig. 3). Seizures tend to appear as an arch-like shape on the CDSA trend.

### Rhythmicity Spectrogram

The rhythmicity spectrogram, rhythmic run detection and display, is a proprietary tool developed by Persyst, Inc. An example rhythmicity spectrogram is shown in Fig. 4. This trend is often displayed separately for the left and right hemispheres, but may be modified to display individual channels (Fig. 5) or groups of channels. It is very similar to the CDSA trend, because time is on the *x*-axis and frequency is on the *y*-axis (but on a logarithmic scale to accentuate lower frequencies). Although the power is displayed by color-coding (darker blue color indicating more power), it differs from CDSA by *only* displaying the power in components that have a high degree of rhythmicity, instead of displaying all the power. Seizures will appear as areas that are darker in color (i.e., more power). Since seizures often consist of a

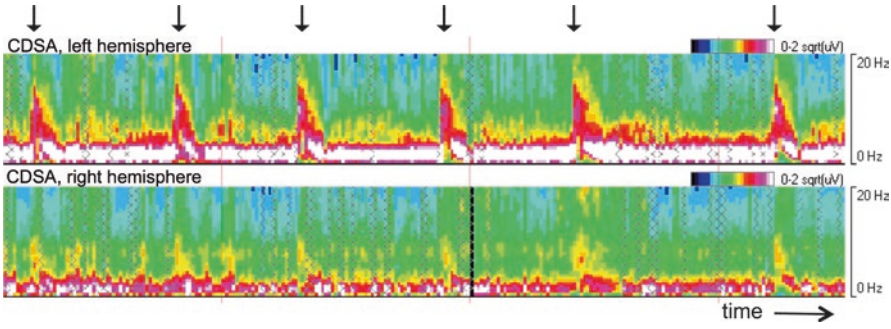


**Fig. 3** Recurrent left hemispheric seizures displayed on the CDSA trend (displayed for the left and right hemispheres). *Black arrows* denote electrographic seizures. An increase in power is seen during seizure activity resulting in warmer colors (*pink* and *red*) replacing areas previously occupied by areas of lower power (represented by cooler colors, *blue*, *teal,* and *green*). With each seizure, there is an initial abrupt increase in power in the alpha and theta frequency ranges. This quickly decreases, and the seizure evolves into having more power in the lower-frequency ranges before cessation

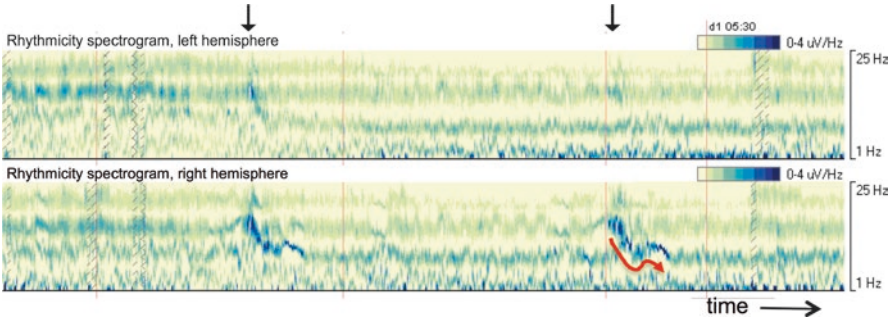


**Fig. 4** Example of two right hemispheric seizures on the rhythmicity spectrogram trend (displayed for the left and right hemispheres). *Black arrows* denote electrographic seizures. The seizure begins with an increased power (darker blue coloration) in alpha activity. As the seizure progresses (shown by the *red arrow*), there is gradual evolution of increased power into lower-frequency ranges (theta and delta)

gradual increase (evolution) in frequency, amplitude, and/or rhythmicity, the progression of the seizure can often be appreciated on the rhythmicity spectrogram more so than other trends (Fig. 4). Seizures on rhythmicity spectrogram will show a gradual incline when the frequency is increasing or decline when the frequency is decreasing.

The stereotyped nature of seizures can be appreciated on the rhythmicity spectrogram. The appearance of seizures on the rhythmicity spectrogram can differ greatly between patients, especially in the ICU setting. However, an individual patient tends to have a stereotyped appearance of recurrent seizures on QEEG trends, facilitating easier recognition over time (Fig. 6).

### Asymmetry Index

In this trend there are two graphs that are separate or overlapping: the absolute asymmetry index and the relative asymmetry index (Fig. 7). Both trends compare the difference in power between homologous electrodes (i.e., the difference in power between F3 vs. F4, O1 vs. O2, etc.). The absolute asymmetry index (yellow trace) calculates the absolute difference, displaying a positive score always. There is an upward deflection with increasing asymmetry and a downward deflection with decreasing asymmetry. The relative asymmetry index (green trace) is able to show lateralization for the asymmetry. An upward deflection represents more power in the right hemisphere and a downward deflection represents more power in the left hemisphere. A seizure would be seen as an upward deflection in the yellow trace and a corresponding upward or downward deflection in the green trace if the seizure was in the right hemisphere or left hemisphere, respectively.

The asymmetry index is most helpful for detecting unilateral seizures. If a bilateral or generalized seizure resulted in similar power in each hemisphere, the difference in power between homologous electrodes would be small or none. Therefore, generalized or bilateral seizures will likely not result in deflections of the asymmetry indices. Furthermore, if there was a large amount of diffuse muscle artifact

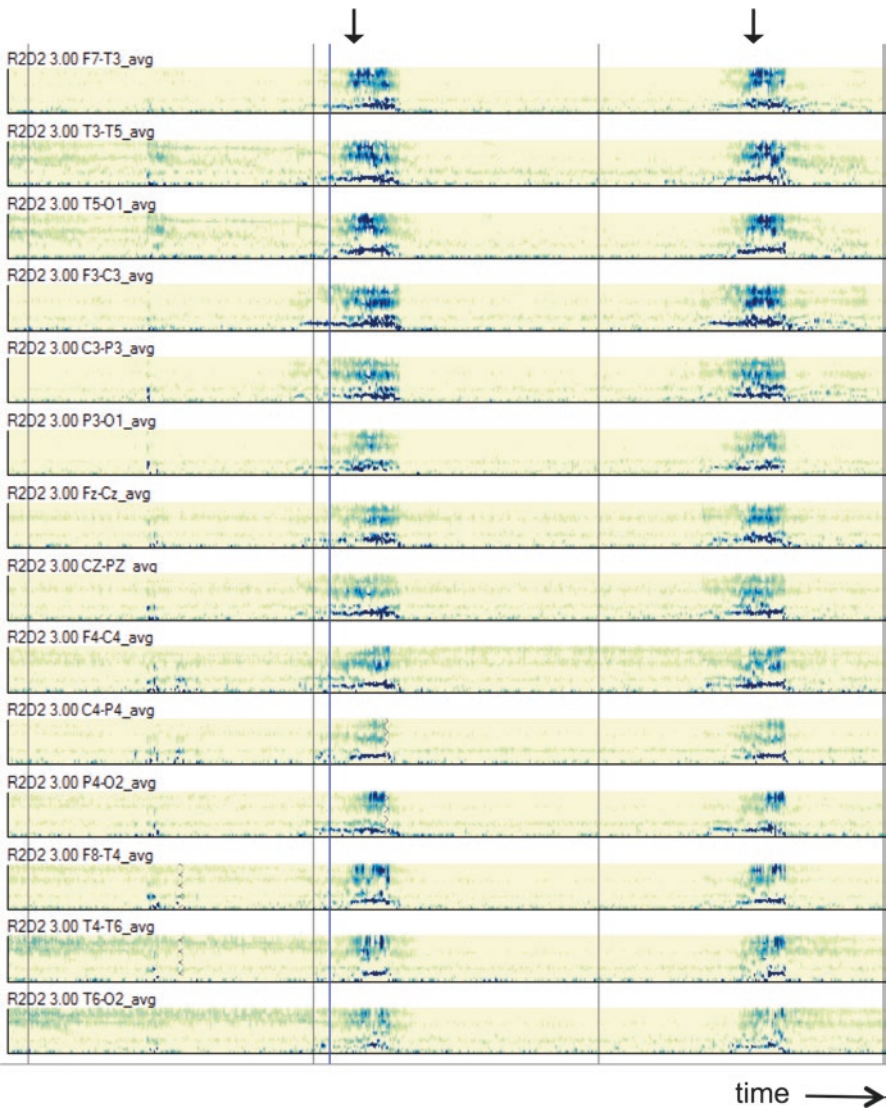


**Fig. 5** A QEEG panel consisting of rhythmicity spectrograms derived from individual electrode pairs. Seizures are marked by *vertical black arrows*

occurring during a seizure, it is unlikely that the asymmetry index will show the seizure well given that the total power would likely be similar in homologous electrodes.

The CDSA and rhythmicity spectrogram trends perform better in this scenario, since the power is calculated separately for the various frequency bands as opposed to displaying the total power. In other words, the muscle artifact (typically in the

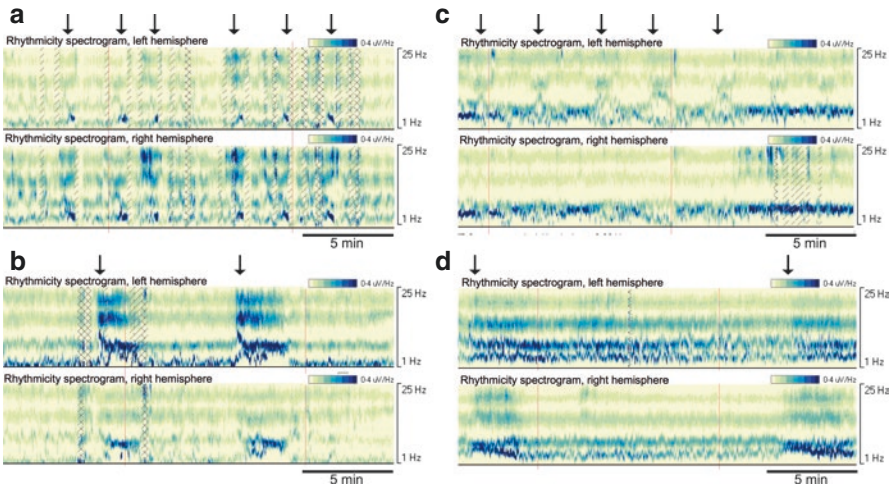


**Fig. 6** Example of seizure appearance variability on the rhythmicity spectrogram trend from four different critically ill patients. Despite the varying appearance between patients, the seizures tend to be stereotyped for each patient. (**a**) Brief right hemispheric seizures with increased power at various frequency bands and some spread to the left hemisphere. (**b**) Left hemispheric seizures with some spread to the right hemisphere. These are much longer in duration when compared to seizures in panel **a**. There is increased power at all frequency bands. (**c**) Left hemispheric seizures without spread to the right hemisphere. The increase in power is limited primarily to the theta and delta frequency ranges. (**d**) Right hemispheric seizures without spread to the left hemisphere. The increase in power is seen primarily in the delta frequency band

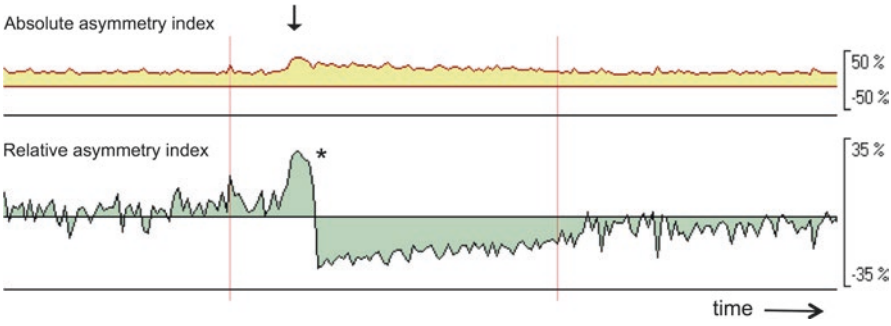


**Fig. 7** Example of a right hemispheric seizure on the asymmetry index trend. There is a subtle, upward deflection of the absolute asymmetry index (yellow trace) indicating a period of increased asymmetry. There is a corresponding upward deflection of the relative asymmetry index (green trace) indicating increased power in the right hemisphere. After seizure cessation (marked by the *), there is a downward deflection of the relative asymmetry index (green trace) that corresponds to postictal right-sided suppression (i.e., more power in the left hemisphere)

beta frequency range) on CDSA and rhythmicity spectrogram trends would be represented in the higher-frequency ranges while not affecting the lower-frequency ranges (where seizures tend to occur). This allows the power increase of lower-frequency seizures to be visually separated from the power increase of higher-frequency muscle artifact on CDSA and rhythmicity spectrogram trends. The asymmetry index would not be able to discriminate between the two types of increased power.

## Amplitude-Integrated EEG

Amplitude-integrated EEG (aEEG) is a type of QEEG trend that is not frequency based, rather it is based on amplitude of the EEG. An example aEEG trend is shown in Fig. 8. This trend has also been referred to as a cerebral function monitor (CFM) and has been utilized extensively for seizure detection in neonates. For each data point, the raw EEG is filtered and rectified (all values made positive) and then the aEEG trend displays the minimum and maximum amplitude of the raw EEG signal in a predefined time frame (typically 1–2 s). Despite the fact that most seizures display a progressive increase in amplitude, the hallmark of seizures on the aEEG trend is not an increase in the maximum amplitude, but rather an increase in the minimum amplitude. The increase in the minimum amplitude during a seizure is seen on aEEG, because the mixed-frequency, low-amplitude background EEG activity is no longer present during a seizure. This loss of low-amplitude activity is often greater than the overall increase in amplitude of the seizure.

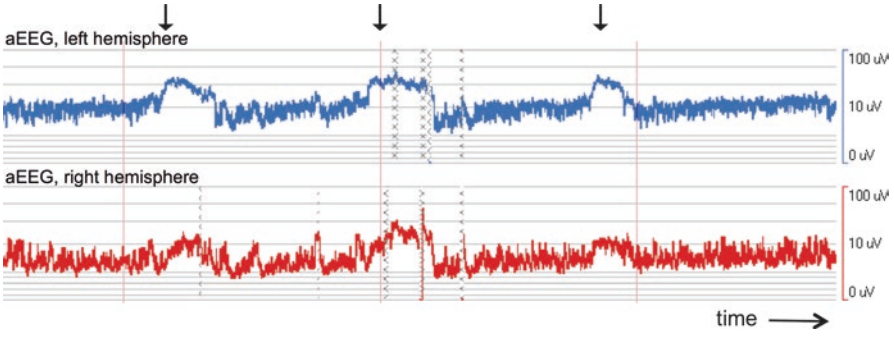


**Fig. 8** Example of three recurrent left hemispheric seizures on the aEEG trend (displayed for the left and right hemispheres). Seizures are represented by an upward deflection in the minimum and maximum amplitudes of the baseline of the blue trace. During the seizure, the increase in the minimum amplitude is greater than the increase in the maximum amplitude compared with the baseline activity. There is spread to the right hemisphere as can be seen by a similar, but less robust, upward deflection in the red trace

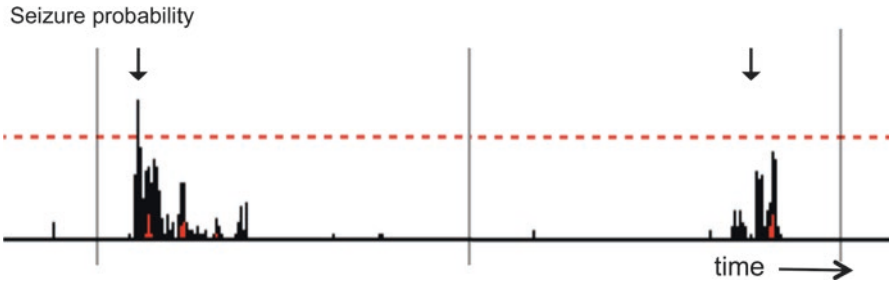


**Fig. 9** Seizure identification on the seizure probability trend. This figure shows an example of a seizure probability trend containing two electrographic seizures (marked by *vertical black arrows*). The seizure probability trend is able to identify both seizures

### Automated Seizure Detectors

QEEG software typically contains a seizure probability trend that is an automated seizure detection algorithm. The output is a binary value (yes/no) or a seizure probability curve (Fig. 9). Given the various and sometimes subtle seizure morphologies seen in the ICU, the performance of automated seizure detection algorithms has been disappointing. There are various rhythmic artifacts seen in the ICU (such as sternal rub and chewing) that can be mistaken for seizures, which is another reason why automated seizure detectors have not been implemented into regular clinical practice.

## Artifact

There are numerous sources of artifact present in the ICU, which result in a paroxysmal change seen on QEEG trends. These artifacts may appear to even show evolution (such as a sternal rub that is gradually getting faster). Other common sources of QEEG artifact in the ICU include chewing, bed percussion (Fig. 10), muscle artifact, alternating current (AC) (60 Hz) artifact from various ICU devices, and electrode artifact from high-impedance electrodes. It can be extremely difficult to distinguish seizures from artifact on QEEG. The Persyst software program can help identify periods of artifact by highlighting areas where a significant amount of artifact is detected by the software algorithms. These are highlighted on the QEEG trends by areas that have overlying cross-hatching (Fig. 11). These periods of artifact should not be completely disregarded, since seizures can still occur during these periods, but extra caution should be made when this is seen (Fig. 12). The newest version of Persyst (P12) contains an artifact reduction function that automatically removes artifact from the QEEG as well as the raw EEG. However, the gold standard remains the neurophysiologist review of the raw EEG corresponding to a period of concern on QEEG. The goal of this section is to help non-neurophysiologists recognize artifact on QEEG trends and differentiate those from seizures.

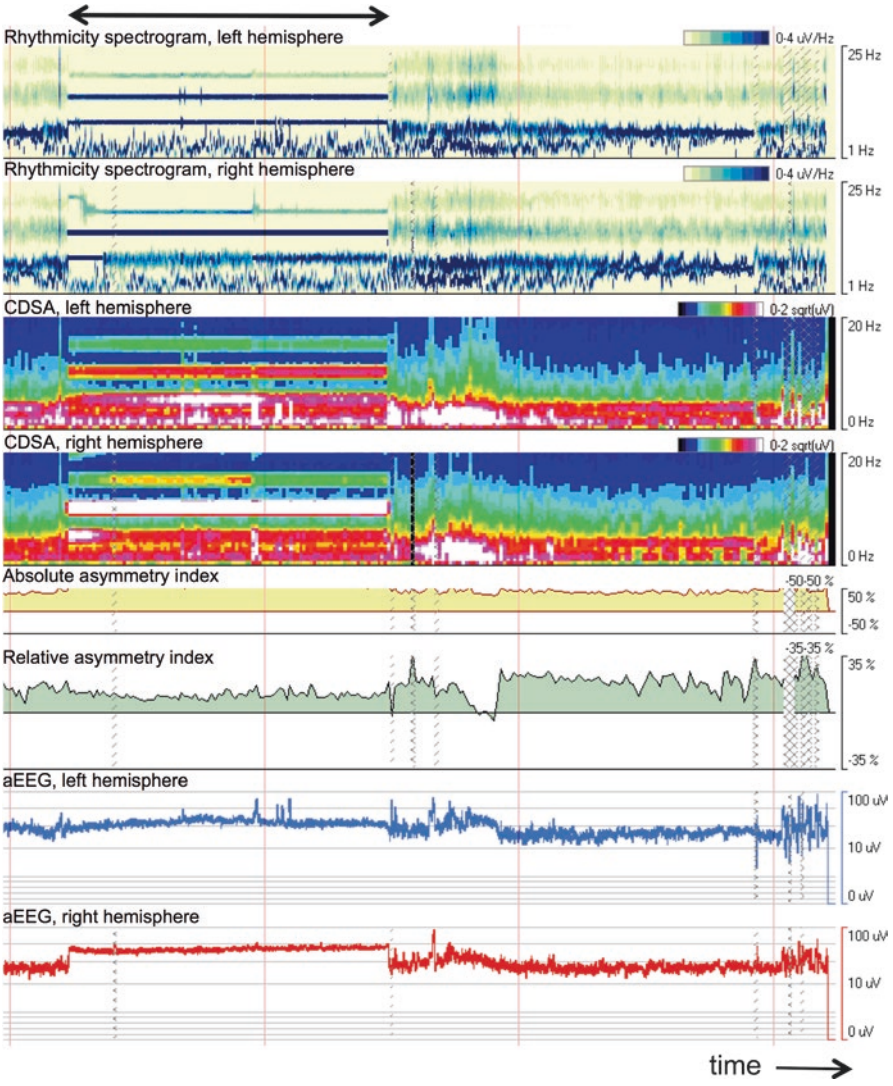


**Fig. 10** Appearance of bed percussion artifact on a QEEG panel (rhythmicity spectrogram (left and right hemispheres), CDSA (left and right hemispheres), asymmetry index (absolute and relative), and aEEG (left and right hemispheres)). The bed percussion (marked by *double-headed horizontal arrow*) results in a long-duration, constant, monotonous artifact that is visualized on all trends except the asymmetry index

## Differentiating Seizures from Artifact on Quantitative EEG

Figures 13, 14, and 15 show examples of QEEG panels that contain both discrete seizures and periods of artifact. A main component of interpretation of QEEG is pattern recognition, and the user's skill will improve with continued practice.

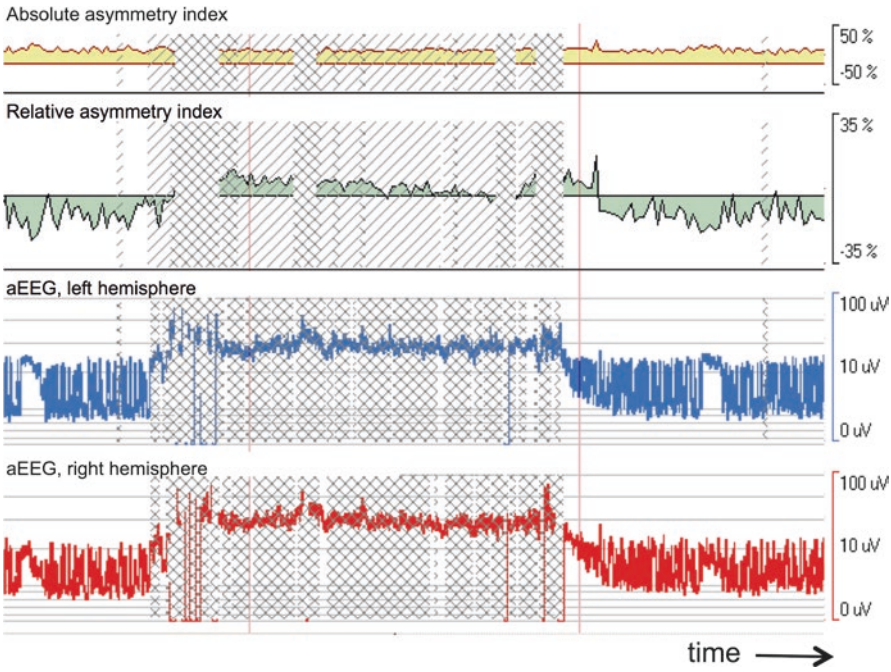


**Fig. 11** Periods of excessive artifact as detected by the QEEG software program, Persyst (Persyst Development Corporation, Prescott, AZ). The software represents artifact by overlying cross-hatching

However, there are a few generalizations that can help one begin to differentiate seizures from artifact on QEEG. As stated previously, the evolution of the seizure frequency can be visualized well on the rhythmicity spectrogram and can also be appreciated on CDSA. In contrast, artifact often has a sudden onset and offset without displaying evolution. Seizures in critically ill patients tend to appear in the lower-frequency ranges, while periods of artifact tend to appear in the higher-frequency ranges.

Once a period of concern is identified on QEEG, other QEEG trends in the panel should be closely examined. Often there is a corresponding change in the other trends, and this pattern will likely be repeated with subsequent seizures. However, some seizures are not represented well on all QEEG trends, highlighting the importance of utilizing a panel of trends. For example, the seizures in Fig. 14 are visualized well on the rhythmicity spectrogram and aEEG trends, but not visualized well on the CDSA and asymmetry index trends. Conversely, the seizures in Fig. 15 are seen easily on all QEEG trends in the panel. Lastly, although it is possible for an individual patient to have two independent sources for seizures creating two concurrent seizure morphologies/locations, the vast majority of critically ill patients have only one single seizure type. The result is a stereotyped appearance of recurrent seizures. If a paroxysmal change is seen on QEEG that is quite different in

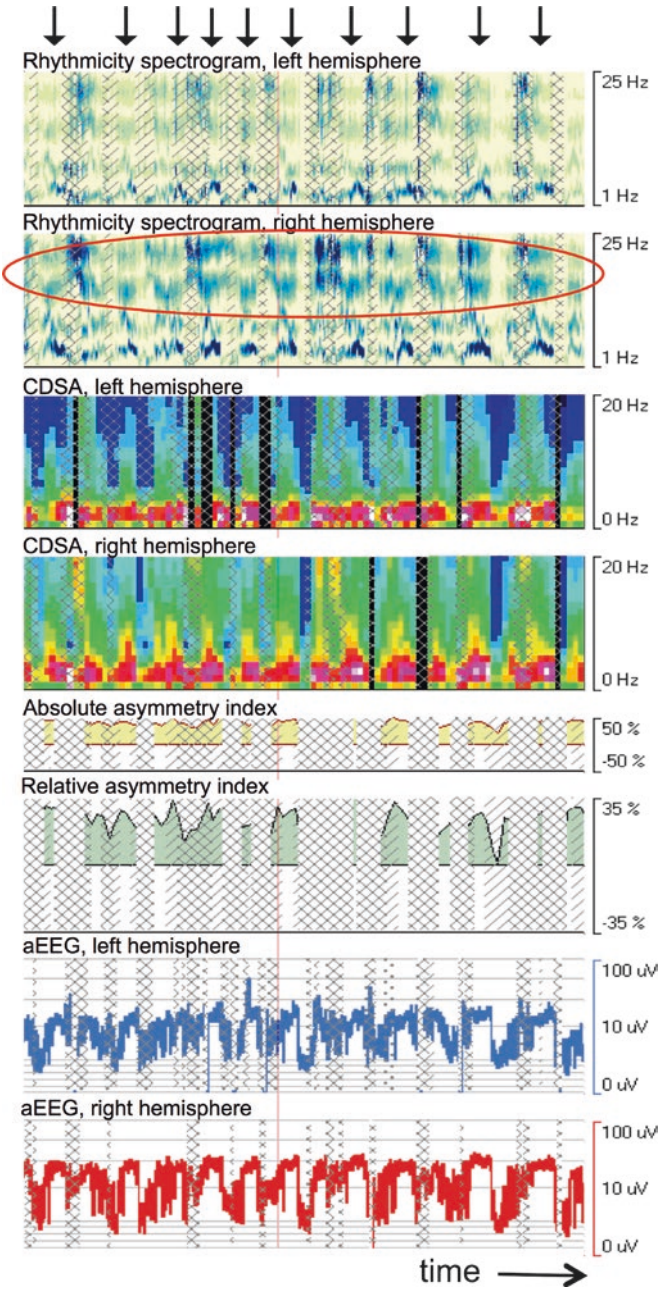


**Fig. 12** Example of concurrent seizures and artifact on a QEEG panel (rhythmicity spectrogram (left and right hemispheres), CDSA (left and right hemispheres), asymmetry index (absolute and relative), and aEEG (left and right hemispheres)). Despite the significant amount of artifact detected by the QEEG software program (indicated by cross-hatching throughout the record), frequent seizures are seen on the rhythmicity spectrogram, and CDSA and aEEG trends. The seizures in this sample are not detected by the asymmetry index. *Vertical black arrows* mark the seizures. Episodic artifact can be seen best on the right hemisphere rhythmicity spectrogram (*red circle*). Note that the seizures occur in the delta frequency band, while the artifact occurs in the alpha and beta frequency bands

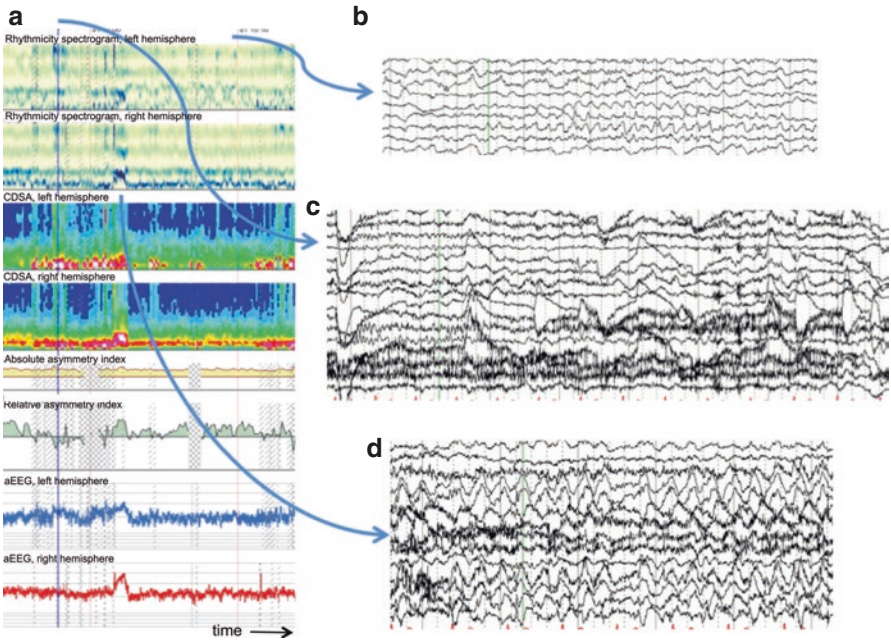


**Fig. 13** Appearance of a seizure vs. artifact vs. brief rhythmic discharges (BRDs) on a QEEG panel. (**a**) QEEG panel consisting of the following QEEG trends: rhythmicity spectrogram (left and right hemispheres), CDSA (left and right hemispheres), asymmetry index (absolute and relative), and aEEG (left and right hemispheres). (**b**) The interictal activity in this sample contains left hemispheric BRDs, lasting 5–6 s with each occurrence. There is a corresponding, but very subtle, change in the left hemispheric rhythmicity spectrogram in the lower-frequency ranges. This activity is not visualized on the CDSA, asymmetry index, or aEEG trends. (**c**) Period of muscle artifact resulting in changes in the rhythmicity spectrogram and CDSA trends. Note that the change in the rhythmicity spectrogram occurs in the higher-frequency ranges. (**d**) Right hemispheric seizure activity corresponding to changes in all QEEG trends displayed

appearance from previously identified seizures, these are likely to be related to artifact, but still should be investigated by raw EEG inspection if suspicious.

## Interictal Patterns

Periodic EEG patterns, such as burst suppression or burst attenuation, can appear as paroxysmal events on QEEG if the burst duration is of sufficient length. In these situations, it can be difficult to discriminate seizures from interictal activity on QEEG alone. Figure 16 displays an example of a discrete seizure on QEEG contrasted with interictal activity consisting of burst attenuation. Lateralized periodic discharges (LPDs) and generalized periodic discharges (GPDs) may potentially show up on QEEG as discrete events, particularly if runs of LPDs or GPDs occur suddenly at a faster frequency (but less than 3 Hz and without evolution, therefore not qualifying as a seizure). Stimulus-induced rhythmic periodic or ictal discharges (SIRPID) can certainly show up as a discrete event on QEEG. Brief

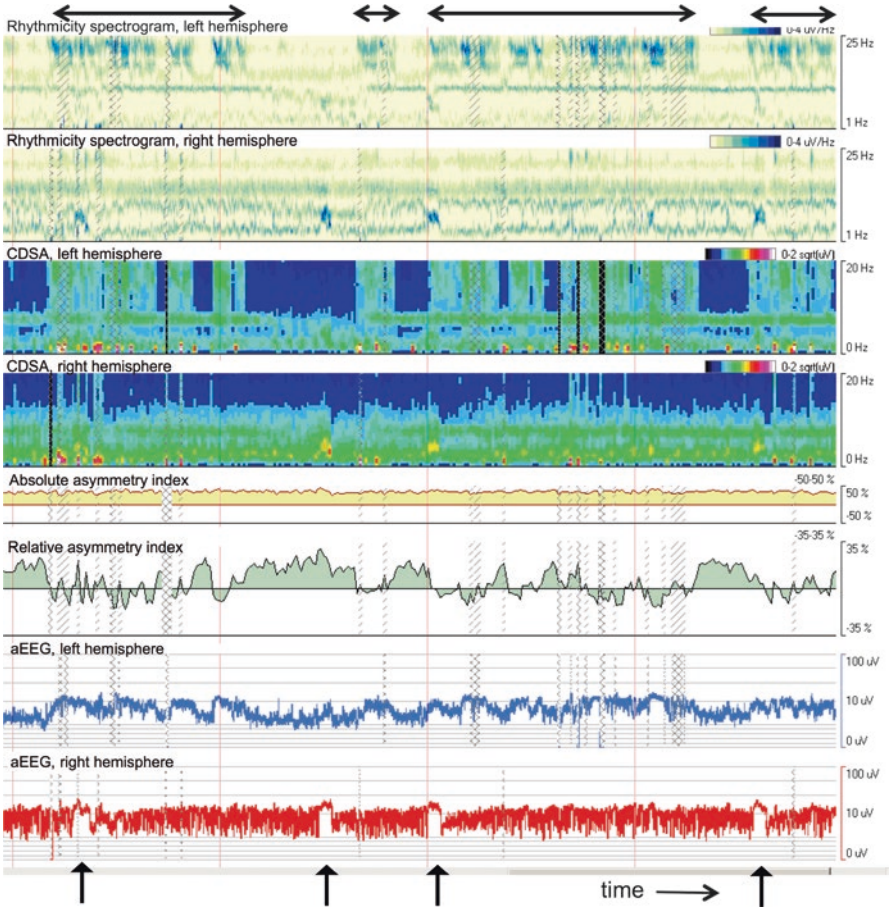


**Fig. 14** Appearance of episodic muscle artifact compared with seizures on a QEEG panel (rhythmicity spectrogram (left and right hemispheres), CDSA (left and right hemispheres), asymmetry index (absolute and relative), and aEEG (left and right hemispheres)). *Vertical black arrows* denote seizures. Right hemispheric seizures are visualized clearly on the right hemisphere rhythmicity spectrogram (in the lower-frequency range) trend and the right hemisphere aEEG trend. There is a very subtle change in the right hemisphere CDSA trend during the seizures. No clear change is seen in the asymmetry index trend during the seizures. Periods of left hemisphere artifact are marked by *horizontal double-headed arrows*. Note that the periods of artifact are appreciated on the rhythmicity spectrogram and the CDSA trends only. As opposed to the seizures seen in this sample (that occur in the lower-frequency ranges), the artifact results in an apparent increased power in the beta frequency range, which is a common finding for muscle artifact

rhythmic discharges (BRDs) may also appear as discrete events on QEEG. BRDs are events that appear to have characteristics consistent with seizures, but are not of sufficient duration (less than 10 s) to qualify as a seizure. Figure 13 shows an example of the appearance of a BRD on QEEG, contrasting it to the appearance of a seizure.

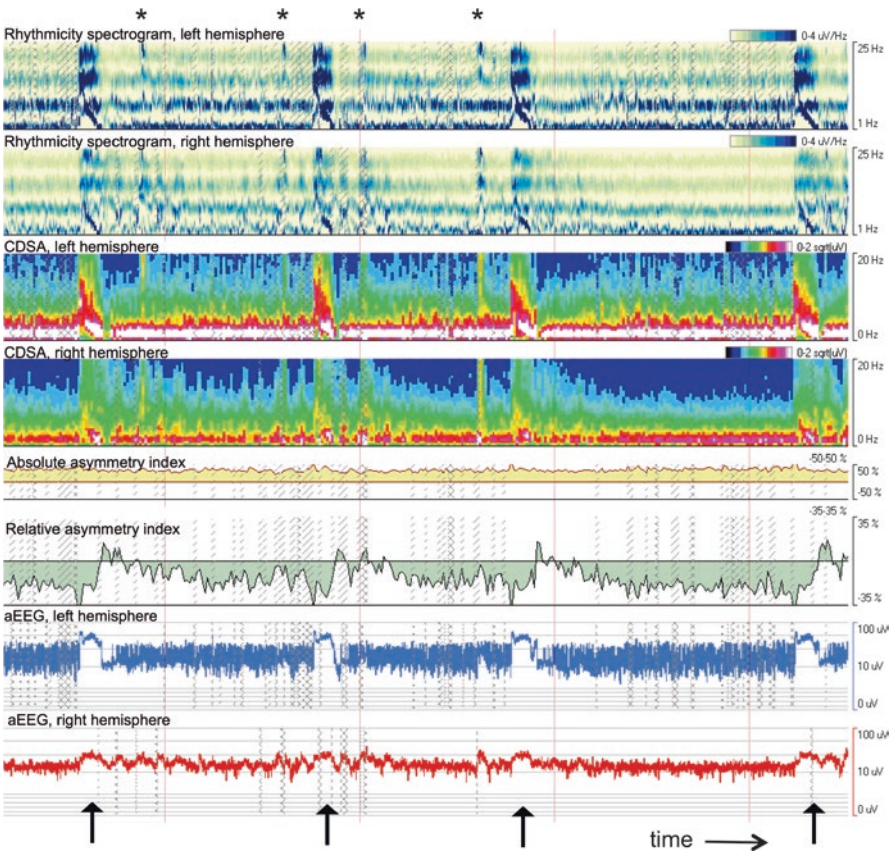


**Fig. 15** Appearance of episodic artifact compared with seizures on a QEEG panel (rhythmicity spectrogram (left and right hemispheres), CDSA (left and right hemispheres), asymmetry index (absolute and relative), and aEEG (left and right hemispheres)). *Black single-headed arrows* denote seizures. Left hemispheric seizures (with some spread to the right hemisphere) are visualized clearly on all QEEG trends shown. Periods of short-duration artifact are denoted by an *asterisk* (*). The periods of artifact are appreciated primarily on the rhythmicity spectrogram and the CDSA trends and occur primarily in the higher-frequency ranges without resulting in a change in the lower-frequency ranges. The difference in seizure and artifact appearance can be seen particularly well in the delta frequency range in the rhythmicity spectrogram

## Subtle Events

Seizures that are easy to identify on QEEG tend to have longer duration, high amplitude, and generalized spatial extent. However, there are many seizure morphologies seen in critically ill patients. Seizures that are limited in spatial extent, of low amplitude, and of short duration are not visualized as well on QEEG. Figure 17 shows an example of subtle seizures on QEEG. In comparison to the seizures in Fig. 1, the seizures in Fig. 17 are much more difficult to detect. Furthermore, even though an individual patient's seizures initially appear fairly easy to detect, treatment with

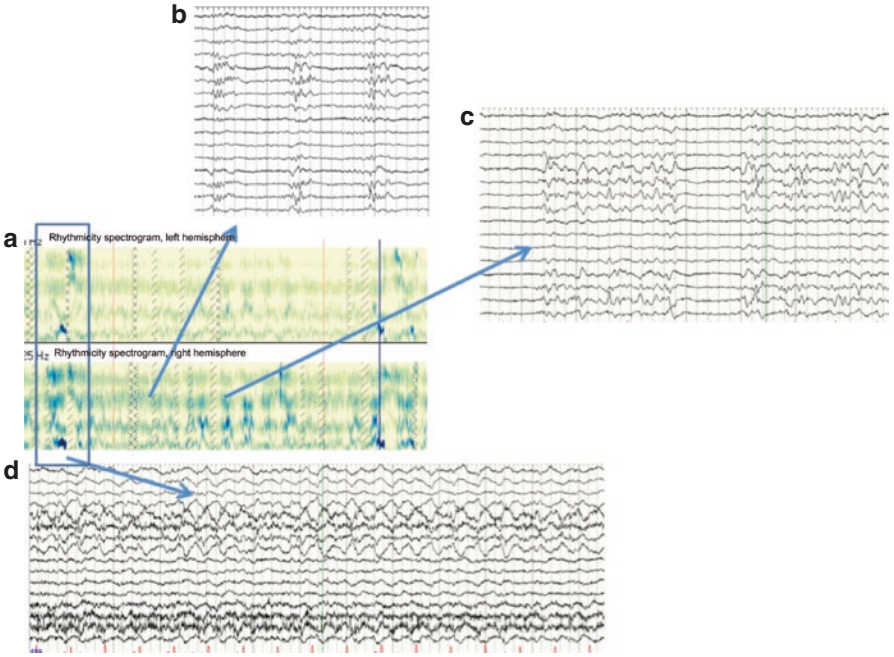


**Fig. 16** Appearance of burst attenuation compared with a seizure. (**a**) Rhythmicity spectrogram (displayed for the left and right hemispheres). (**b**) The interictal activity in this sample contains a burst attenuation pattern, with the bursts being more prominent in the right hemisphere (burst duration 0.5 s). This activity does not correspond to any particular changes in the rhythmicity spectrogram trend. (**c**) The interictal activity in this sample also contains periods of longer bursts. Given the sufficient duration of these bursts, there is a corresponding change in the right hemisphere rhythmicity spectrogram trend. (**d**) Right hemisphere electrographic seizure activity. The seizure is differentiated from the interictal activity on the rhythmicity spectrogram most notably by the increased power seen in the delta range in the right hemisphere during the seizure. This feature is absent from the rhythmicity spectrogram trend when the longer bursts occur. However, without raw EEG analysis, it would be difficult to differentiate interictal activity from ictal activity in this sample

antiepileptic drugs may cause them to become subtle in appearance on QEEG by reducing the spatial extent, duration, and/or amplitude (Fig. 18).

## Conclusions

Initially, the complicated appearance of QEEG trends may be intimidating to the untrained reader. However, with training and continued practice, it is feasible for non-neurophysiologists to be comfortable with interpreting bedside QEEG. Providers that are at the bedside in the ICU have a distinct advantage of being able to incorporate the real-time QEEG data with ongoing clinical information. However, sole QEEG interpretation by neurophysiologists or non-neurophysiologists should not be performed in isolation without raw cEEG review by neurophysiologists. An analogy can be made with bedside telemetry. It is important for nurses, residents, and

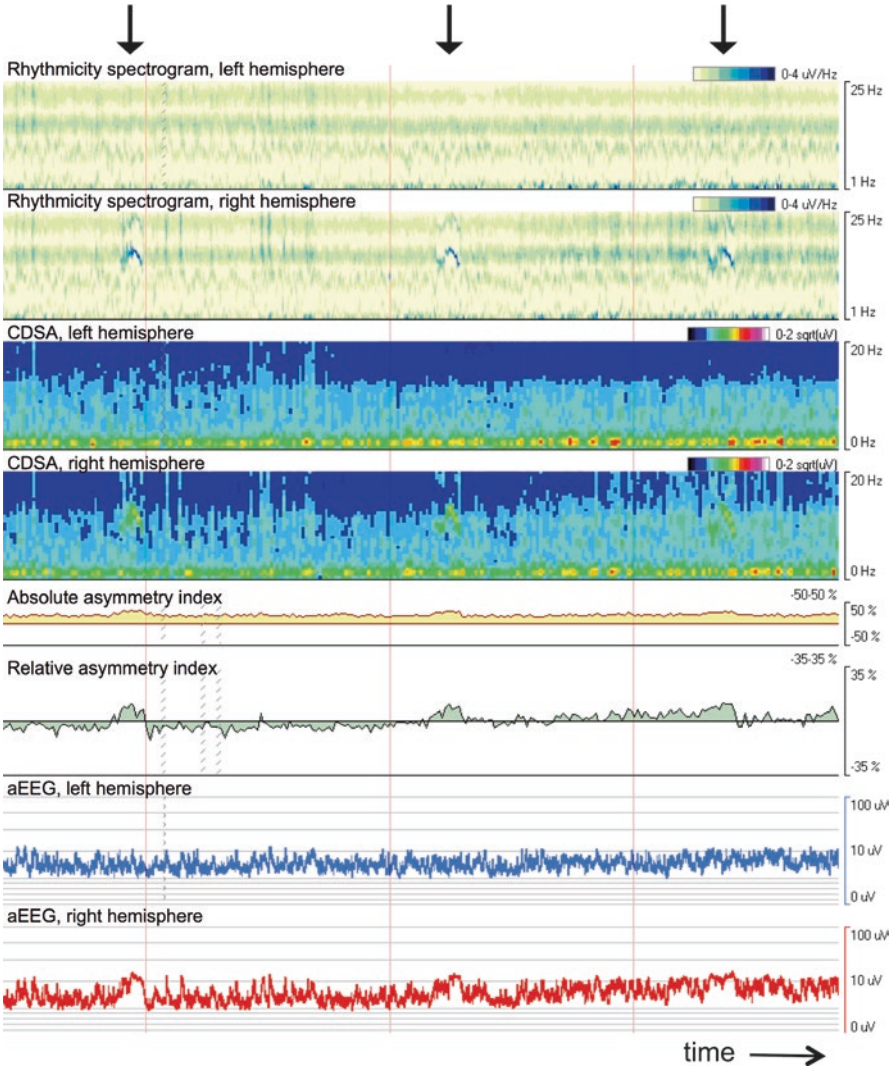


**Fig. 17** An example of subtle seizures on a QEEG panel (rhythmicity spectrogram (left and right hemispheres), CDSA (left and right hemispheres), asymmetry index (absolute and relative), and aEEG (left and right hemispheres)). Three right hemispheric electrographic seizures are marked by *vertical black arrows*. These are visualized on all the QEEG trends displayed on the panel; however, these seizures may be difficult to detect given their subtle appearance

fellows to continuously evaluate a patient's bedside telemetry. However, when there is concern for an abnormality, a 12-lead electrocardiogram (ECG) is obtained and evaluated by an attending intensivist or cardiologist. Yet it is critical to have ongoing evaluation of the telemetry by nurses, residents, and fellows, since they are a critical first line to identify periods of concern.

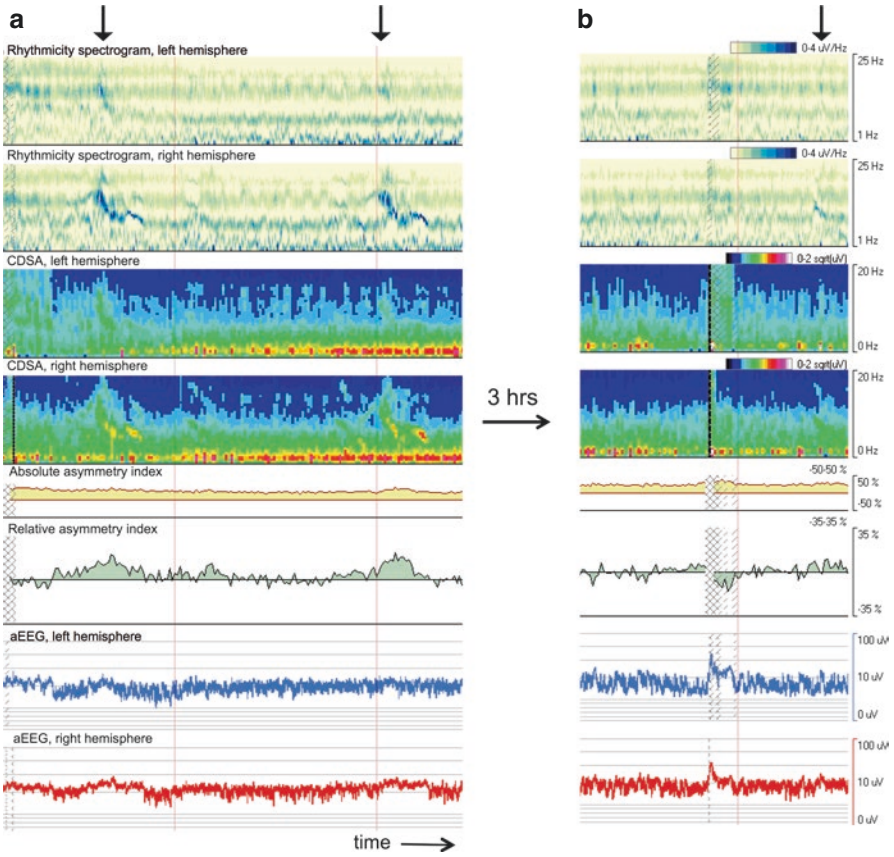


**Fig. 18** Example of seizure appearance change over time. (**a**) A QEEG panel consisting of the following QEEG trends: rhythmicity spectrogram (left and right hemispheres), CDSA (left and right hemispheres), asymmetry index (absolute and relative), and aEEG (left and right hemispheres). There are two right hemispheric electrographic seizures (marked by the *vertical black arrows*) visualized well on the rhythmicity spectrogram, CDSA, and asymmetry index trends. There is a subtle corresponding change in the aEEG trend during the seizures. (**b**) A second QEEG panel (consisting of the same trends) three hours later after antiepileptic drug treatment was initiated. One right hemispheric seizure is marked by the *vertical black arrow*. Although the morphology on the rhythmicity spectrogram trend appears similar to the initial seizures in panel **a**, the overall appearance of the seizure is much more subtle on the rhythmicity spectrogram and CDSA trends, and no longer is seen on the asymmetry index and aEEG trends

It is likely that QEEG will continue to have a growing presence in the ICU as additional applications beyond seizure detection become established. Thorough QEEG training for non-neurophysiologists is necessary to reduce the number of false-positive and false-negative alarms.

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# Neuroimaging in Status Epilepticus

16

Ana M. Cartagena and G. Bryan Young

## Contents



## Introduction

Radiographic descriptions of findings related to status epilepticus (SE) have been described for over 50 years. The initial description of changes on radiographic imaging was using pneumoencephalograms on children with seizures [1]. Eventually, neuroanatomic correlations to seizure foci were published as seen on computed tomography (CT) scan [2]. Now with the advent of magnetic resonance imaging (MRI), our ability to detect pathology related to the causes and sequelae of SE has dramatically increased.

The primary role of neuroimaging in SE is to identify the etiology and to help establish the safety in doing a lumbar puncture in de novo cases of seizures and then to detect early changes resulting from the SE, which can be of assistance in management and prognosis.

A.M. Cartagena, MD, FRCPC (✉) • G.B. Young, MD, FRCPC
Department of Clinical Neurological Sciences, Western University, Victoria Hospital, 800 Commissioners Rd. E., London, ON N6A 5W9, Canada
e-mail: ana.cartagena@lhsc.on.ca



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## Neuroimaging and the Etiology of Status Epilepticus

When patients present with SE as their initial seizure, neuroimaging is indicated after initial stabilization of the patient. CT is usually the most expedient imaging modality and can help exclude intracranial hemorrhage, venous sinus or cortical vein thrombosis, ischemic stroke, advanced encephalitis, tumors, traumatic lesions, brain abscess, and major malformations. CT to exclude threatening mass effect and screening for coagulopathy are essential steps before a lumbar puncture is performed. Many clinicians will initiate acyclovir therapy if there is any suspicion of herpes simplex encephalitis and MRI is going to be delayed. Other subtle lesions must await more elective MRI.

In investigating the etiology of SE, MRI is usually needed. Overall, the most common etiology of convulsive SE is lesional, with stroke being the leading cause of SE in adults (Fig. 1). Other lesional causes of SE include infection and tumor [3] (Fig. 2). In nonconvulsive SE (NCSE), the most common cause is unknown (cryptogenic) [4]; however, "remote symptomatic" (remote lesional) is also almost as likely. Focal NCSE and epilepsia partialis continua (EPC) are usually due to structural cerebral abnormalities (acute or remote symptomatic); however, EPC can also be due to diffuse inflammatory and/or metabolic causes (i.e., mitochondrial disease, prion disease, multiple sclerosis, etc.).

Anoxic ischemic encephalopathy (AIE) is an uncommon cause of SE. Most cases of myoclonic seizures in AIE have a brainstem reticular formation origin and usually, but not invariably, a poor prognosis. AIE can also present with NCSE. A trial of antiepileptic drugs (AEDs) is usually warranted. Abnormal MRI findings in AIE include areas of restricted diffusion in the periventricular white matter, corpus callosum, internal capsule, and subcortically. These findings occur early after AIE [5]. Initial evidence suggested that cerebral gray matter is more vulnerable to global anoxia and ischemia due to its unique metabolic rate [6, 7]; however, white matter involvement has been found to occur early after the insult [5, 8]. The term "acute

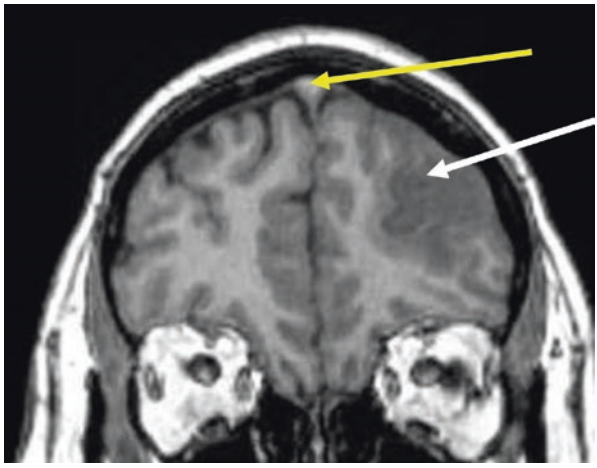

**Fig. 1** Coronal T1-weighted magnetic resonance imaging (MRI) with gadolinium revealing a clot in the superior sagittal sinus (*yellow arrow*) and infarct in the left frontoparietal region (*white arrow*). This 50-year-old woman presented in focal status epilepticus

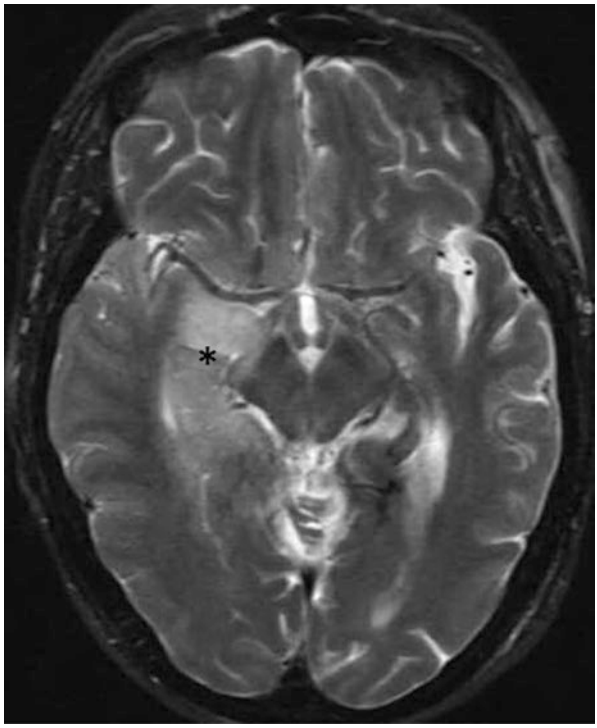

**Fig. 2** Axial T2-weighted MR image of a 42-year-old woman with ongoing complex partial seizures, etiology was herpes simplex encephalitis. There are increased T2 signal and swelling of the right mesial temporal lobe (star)

myelinopathy" caused by cerebral anoxia has been used and can be manifested as restricted diffusion with low ADC values on MRI. The usefulness of MRI in AIE with has been mainly for prognostic purposes. When diffusion-weighted imaging (DWI) or fluid attenuation inversion recovery (FLAIR) imaging reveals extensive cortical and subcortical damage, the prognosis for recovery is very poor.

## Complications of SE and Subsequent MRI Changes

Often seizure-induced MRI abnormalities are left as a diagnosis of exclusion, and repeat imaging is necessary in order to exclude inflammatory or infectious etiologies as the cause of the MRI abnormalities. Examples of MRI abnormalities resulting from SE include areas of increased signal intensity on FLAIR, T2, or diffusion-weighted images, patchy cerebral contrast enhancement, leptomeningeal enhancement, and even cerebral swelling. Changes can be reversible or irreversible [9, 10]; even if the initial MRI findings disappear, often they will leave sequelae of mesial temporal sclerosis, focal and/or global atrophy [9, 11].

The most well-described changes are those that occur in the hippocampi [12, 13]. Other less well-described changes include involvement of the extratemporal cortex, subcortical structures, thalamus, and cerebellum and more widespread hemispheric atrophy [9, 10].

## Hippocampal Changes

The magnetic resonance (MR) signal changes that can occur during SE most often involve the hippocampus, the most vulnerable region for SE-induced damage [14]. Histologically, the CA1, CA3, and hilus are the most affected regions. Hippocampal changes can often be pronounced. T2-weighted sequences will often demonstrate

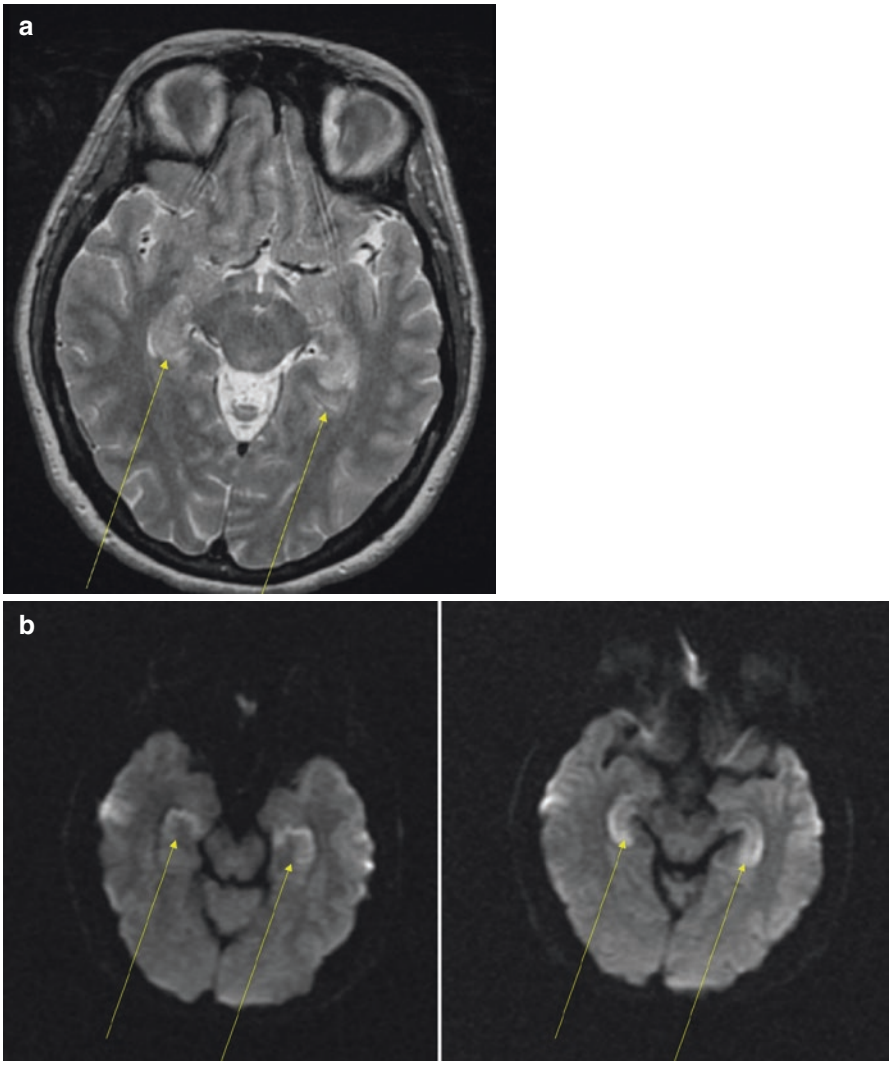


**Fig. 3** A 40-year-old woman with a history of untreated complex partial seizures who presented in convulsive in status epilepticus. (**a**) Axial weighted T2 sequence reveals marked increased T2-weighted signal bilaterally in the hippocampal heads and bodies (*yellow arrows*). The hippocampi appear mildly swollen. (**b**) There is some mild associated restricted diffusion of the hippocampus on axial diffusion-weighted imaging (DWI) (*yellow arrows*)

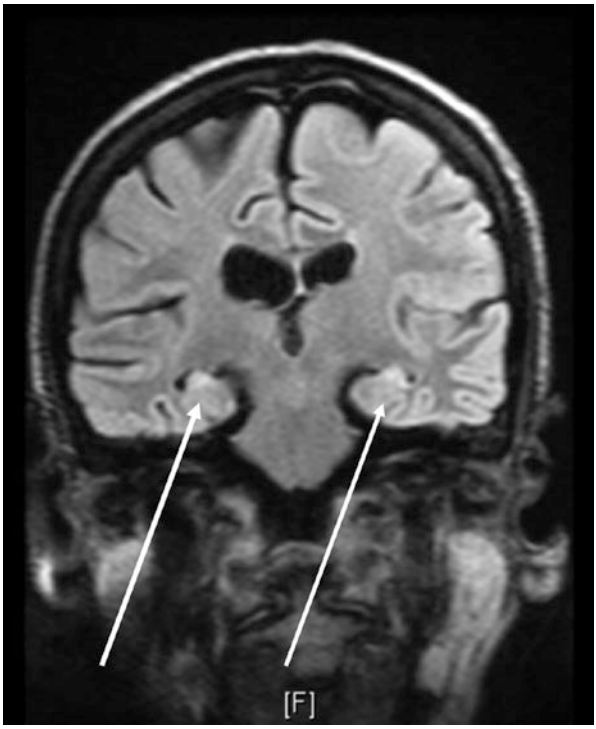


**Fig. 4** Follow-up of same patient (Fig. 3) several months after initial presentation. The hippocampi are hyperintense on coronal fluid attenuation inversion recovery (FLAIR) imaging and are now smaller than seen previously (*white arrows*)

abnormally increased signal in the hippocampus, which can be followed by swelling and gliosis [12] (Figs. 3 and 4).

### Extratemporal Changes

Reversible and irreversible abnormalities have been described in the extratemporal cortex, basal ganglia, insula [9], and thalamic pulvinar [15]. Hemispheric atrophy is sometimes a consequence of prolonged focal status epilepticus (Fig. 5). Cerebellar changes as a consequence of a supratentorial epileptic focus have also been reported and are explained by crossed cerebellar diaschisis (Fig. 6a, b) [16]. The frequency with which various regions of the brain are involved during SE is shown in Table 1.

## Pathophysiology

The pathological explanation for MRI changes following SE is due to neuronal injury or necrosis [17]. Attributed mechanisms include: adenosine triphosphate (ATP) deficiency due to failure of the Na/K ATPase pump, lactic acidosis, release of excitatory neurotransmitters and inflammatory mediators, increased membrane permeability, and possible activation of caspase pathways leading to apoptosis [18].

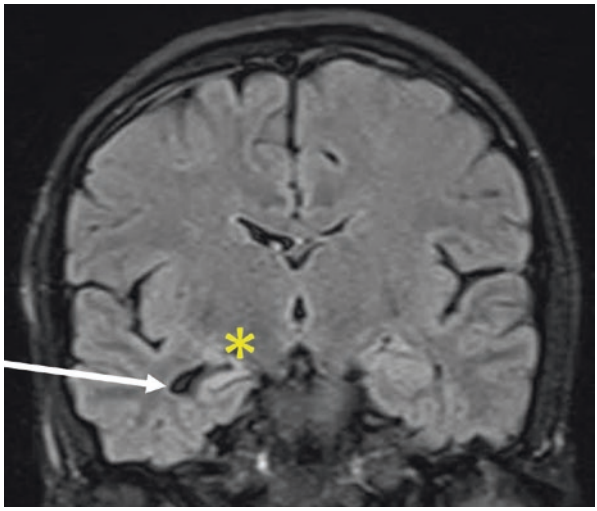

**Fig. 5** A 28-year-old male with temporal lobe seizures and remote status epilepticus. The patient continues to have temporal lobe seizures. On coronal fluid attenuation inversion recovery (FLAIR) imaging, there is atrophy of the right hippocampus, as demonstrated with an enlarged temporal horn (*white arrow*). There are also increased signal within the right hippocampus (*yellow star*) and global right hemispheric volume loss compared to the left

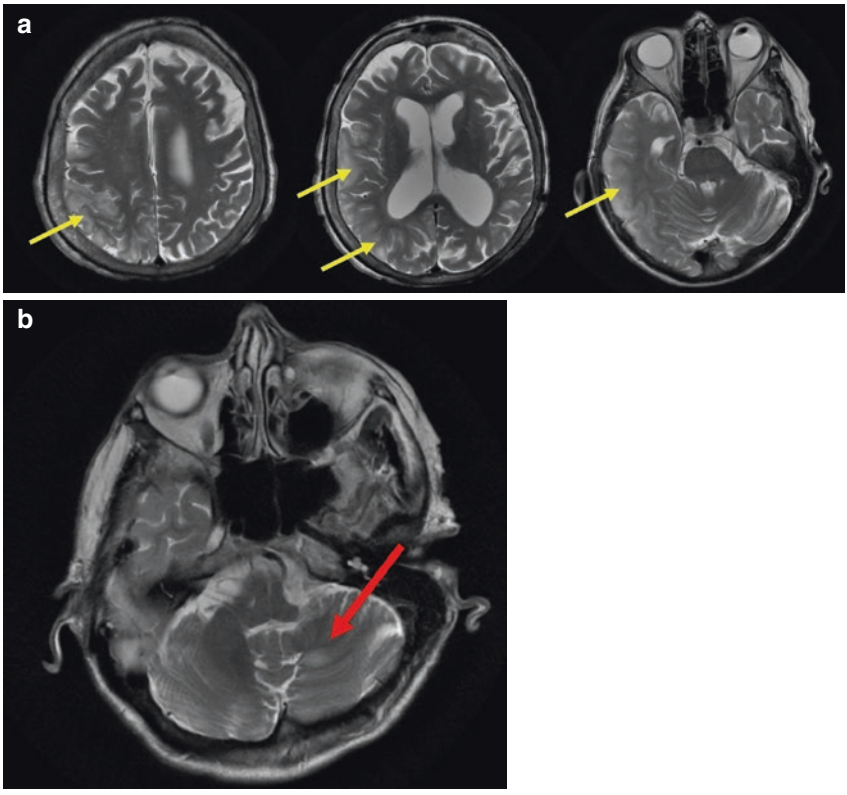


**Fig. 6** A 59-year-old woman with a history of steroid-responsive encephalopathy and seizures was admitted to the intensive care with nonconvulsive status epilepticus (NCSE) manifested by an acute confusional state. (**a**) MRI revealed increased T2-weighted hyperintensity over the right parietal, posterior frontal, and posterior temporal lobes in a gyriform distribution (*yellow arrows*). (**b**) A small focus of increased T2 signal is seen in the left cerebellum (*red arrow*). These changes were resolved after treatment with corticosteroids and antiepileptic drugs

**Table 1** Structures involved in SE and their relative frequency

| | |
|---|---|
| Hippocampus | 0.60 |
| Subcortical (white matter) | 0.57 |
| Cortical (gray) | 0.45 |
| Leptomeningeal (enhancement) | 0.28 |
| Thalamus | 0.23 |
| Basal ganglia | 0.16 |
| Corpus callosum | 0.14 |
| Cerebellum | 0.08 |

These factors can ultimately lead to tissue injury, swelling, and irreversible neuronal death.

## Imaging in the Critically Ill Patient

In the intensive care unit (ICU), serial MR imaging can be a challenge due to the critically ill patient requiring life support. Initial imaging with cranial CT may be the only option due to time and mobility constraints. If cranial CT is the only appropriate modality, contrast enhancement should be considered in order to assess the integrity of the blood-brain barrier. Once the patient has been stabilized, serial MR imaging is recommended.

### Conclusions

The initial role of neuroimaging in cases of SE is to establish the etiology and then to look for the effects of SE on the brain.

Transient cerebral abnormalities in patients with SE can easily be misdiagnosed as inflammatory or infectious conditions, demyelinating diseases, or tumors and as a consequence result in unnecessary and invasive investigations. Knowledge regarding well-described MRI brain changes is key in appropriately managing the critically ill patient.

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# Part II

# Special Situations

# Acute Anoxic Injury and Therapeutic Hypothermia in Adults

17

Amy Z. Crepeau

## Contents



## Introduction

Acute anoxic injury is common in the adult population, occurring most commonly due to sudden cardiac arrest. In patients that remain comatose after resuscitation, there is a period of uncertainty, accompanied by high morbidity and mortality. Therapeutic hypothermia (TH) has been used for neuroprotection during this time period, though its true benefit remains uncertain. As a result, the focus shifts to determining prognosis, with EEG being one of the most widely used, well-studied

A.Z. Crepeau, MD
Department of Neurology, Mayo Clinic,
5777 East Mayo Boulevard, Phoenix, AZ 85054, USA
e-mail: Crepeau.amy@mayo.edu



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resources available. From the time EEG became available, specific findings after acute anoxic injury have been detailed and correlated with outcomes. Multiple grading scales have been proposed to simplify clinical decision-making. As clinical protocols have evolved, and TH has become the standard of care, specific EEG patterns, including nonreactivity, low-voltage output pattern, and nonconvulsive seizures (NCS) and nonconvulsive status epilepticus (NCSE) remain worrisome. When combined with complementary clinical data, EEG remains a powerful tool for predicting prognosis after acute anoxic injury. In this chapter, the pathophysiology of anoxic brain injury and value of TH will be presented. Various EEG features that are associated with anoxia and TH and their prognostic value will also be discussed.

## Background

Acute anoxic injury results in cerebral damage, and the extent of damage is not always immediately evident. Causes for acute anoxic injury include respiratory failure, drowning, strangulation, and medication overdose. The most common cause is sudden cardiac arrest, with an incidence between 0.04 and 0.13 % of the population in industrialized countries [1]. Mortality, as estimated by EMS response, is approximately 94 % [2], and despite advances in acute hospital care, in-hospital mortality remains high at 60 % [3]. Overall, acute anoxic injury is associated with an extremely high morbidity and mortality. For this reason, there has long been a focus on determining how to mitigate the damage once the injury occurs and accurately prognosticate as to who is likely to do well, and who will have a poor outcome.

From the time electroencephalography became clinically available in the 1930s, practitioners have been interested in describing findings after anoxic injury and determining how these patterns relate to prognosis. As much as clinical algorithms, diagnostic ability, and technology have evolved since that time, EEG remains an important part of clinical care after anoxic injury. As an example, in Fig. 1 is an EEG of a patient obtained 12 hours after cardiac arrest who was undergoing TH during the time of EEG.

## Anoxia and Neuronal Injury

Cerebral anoxia results in disruption of adenosine triphosphate (ATP) production, which then leads to glutamate release and activation of *N*-methyl-D-aspartate (NMDA) receptors. This increase in excitotoxicity results in cell death. Neurons in the cerebral cortex, cerebellar Purkinje cells, and the CA-1 region in the hippocampus are most vulnerable to neuronal death from anoxic injury due to their increased metabolic demands. The severity of injury depends upon the duration of anoxia and ability to restore cerebral blood flow [4]. Attempts have been made to identify neuroprotective agents that may ameliorate neuronal injury after anoxic injury. Barbiturates, glucocorticoids [5], sodium channel blockers [6], magnesium [7], and benzodiazepines [8] have all been proposed, but compelling clinical data are lacking.

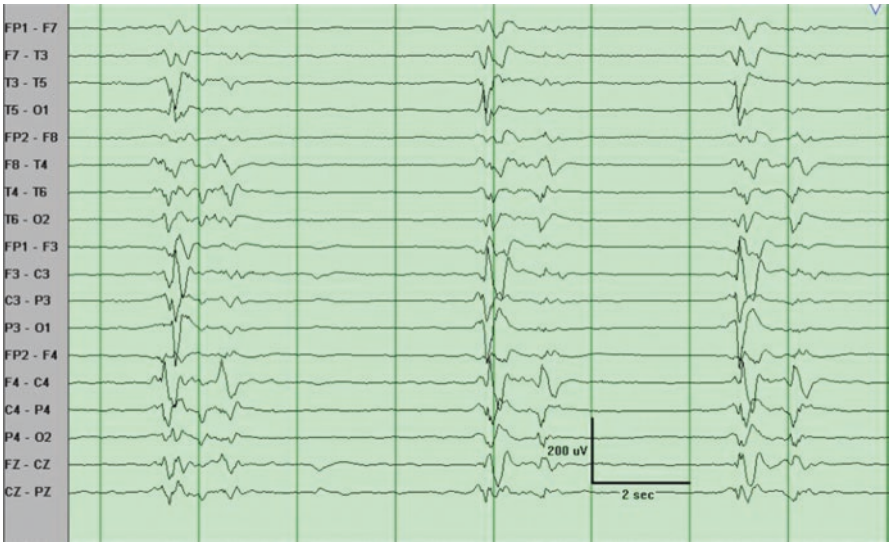


**Fig. 1** Burst suppression pattern seen 12 h after cardiac arrest. The patient is on TH protocol, with a core temperature of 33 °C

## Therapeutic Hypothermia

Approaches to neuroprotection after anoxic injury from cardiac arrest changed in 2002, with the publication of two pivotal trials. Both trials demonstrated a positive outcome when using mild TH for neuroprotection after cardiac arrest. In both trials, patients were cooled to between 32 and 34 °C for 12–24 h after cardiac arrest. Those patients that were cooled showed improved neurologic outcomes [9, 10]. As a result of these two trials, TH after cardiac arrest became standard of care. The protocols for TH often include sedation and paralytics, which confound the physical exam in this critical period.

Despite these initial large trials demonstrating improved neurologic outcomes after cardiac arrest, additional trials have shown that there may not be a significant benefit to TH. A 2013 randomized trial of 939 patients compared TH of 33 °C versus targeted temperature control at 36 °C and found no significant difference in regard to mortality or neurologic outcomes at 180 days [11]. A second randomized trial, published in 2014, compared prehospital cooling versus no prehospital cooling in 1539 patients, and found no difference in mortality or neurologic outcome at hospital discharge [12]. These data suggest that it may actually be the controlled avoidance of fever, rather than mild TH, which confers benefit in regard to neurologic outcomes after cardiac arrest.

The use of TH must be taken into account when considering the significance of EEG patterns, and data in the literature. As practice parameters change in regard to TH, published data regarding EEG findings may not be applicable across all clinical situations.

## Early Descriptions of EEG After Circulatory Arrest and During Hypothermia

Experimental animal studies looking at the relationship between anoxia and EEG changes emerged in the 1930s, though human data were not published until the 1950s. Pampiglione made observations based upon intraoperative cardioplegia and restoration of cerebral blood flow with carotid massage. He described progressive diffuse slowing, followed by attenuation of cerebral activity, and return of cerebral activity after carotid massage [13]. Pampiglione expanded on his observations outside of the operating room (OR), correlating EEG findings after anoxic injury with outcomes. His descriptions of early EEG findings after cardiopulmonary arrest and clinical outcomes foreshadowed what would be repeatedly confirmed later [14].

Many of the early reports regarding EEG findings with anoxia did occur in the OR, where hypothermia was used in conjunction with circulatory arrest. These observations allowed for the determination that hypothermia had an effect on cerebral activity and EEG. In 1966, Harden published a series of OR cases, concluding that mild hypothermia alone had little effect on EEG, but that temperature affected EEG activity with circulatory arrest. EEG persisted longer after circulatory arrest with a temperature between 18.5 and 24.5 °C, versus between 28 and 32 °C. The postulation was cerebral function in moderate hypothermia had lower metabolic demands and was neuroprotective [15]. These early series provided a basis for expansion of data regarding EEG findings and prognosis after anoxic injury.

## EEG After Acute Anoxic Injury

In patients who suffer an acute anoxic injury, the time period after successful resuscitation is fraught with uncertainty and waiting. EEG has been shown to provide important prognostic information in this critical situation.

### Variability and Reactivity

The EEG background, in regard to variability and reactivity, can be a strong correlate of outcome. A well-modulated background contains a mix of frequencies and amplitudes, and varies in response in internal and external stimulation. In general, spontaneous variability is a positive sign, while an invariant background portends a poor prognosis. Nonreactivity as an indicator of poor prognosis has validity after TH as well (Fig. 2). After induced mild TH (33 °C), the false-positive rate of a nonreactive background and a poor outcome is 0.07 [16]. Caution needs to be taken to ensure that appropriately noxious stimulation, including deep painful stimulation, is deployed.

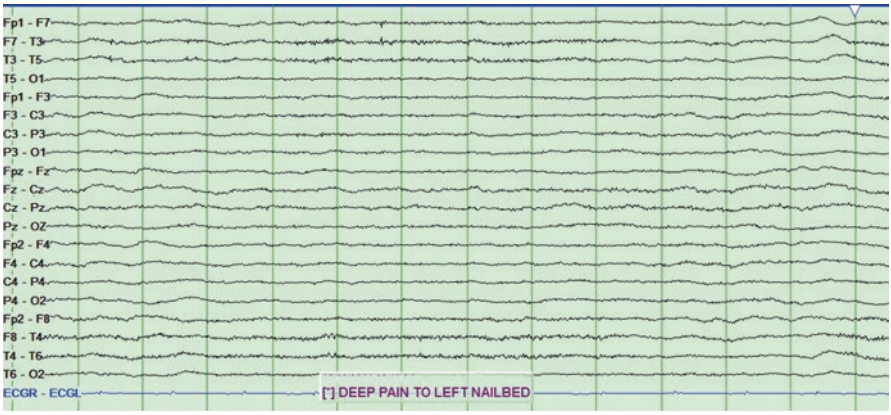


**Fig. 2** No reactivity is seen in response to deep painful stimulation

## Alpha and Theta Coma

Alpha and theta coma are specific nonreactive patterns that traditionally were correlated with poor outcome after anoxic injury. The alpha coma pattern was first described in 1975 [17]. The pattern was described as being similar to an awake pattern, with 8–13 Hz alpha activity, which was broadly distributed with slight spontaneous variability and was nonreactive (Fig. 3). All of the patients with anoxic injury in the initial study died [17]. Theta coma has been considered a variant of alpha coma. This pattern is characterized by broadly distributed 5–6 Hz theta activity with minimal spontaneous variability and reactivity. The initial patient in whom this was described after anoxic injury did not survive [18].

Though alpha and theta coma were initially described as being associated with poor prognosis, further studies have shown that this is not the case, and outcomes can be more variable [19, 20]. In some instances, better outcomes may be predictable based upon features of the EEG. There are gradations of alpha or theta coma, some of which may not be as highly correlated with poor outcomes after anoxic injury. Features consistent with "incomplete" alpha or theta coma, and less likely to be associated with poor outcomes, include a pattern which is not entirely monotonous and hyporeactive (compared to nonreactive) and has a posterior, rather than anterior, distribution [21]. It is inadvisable to make determinations regarding prognosis when alpha or theta coma is seen at a single time point after acute anoxic injury. These coma patterns may evolve over time, and serial EEGs or continuous EEG (cEEG) monitoring are required to determine the true significance in an individual.

## Burst Suppression

Burst suppression is defined as alternating bursts of cerebral activity with periods of background attenuation that comprises at least 50 % of the record [22]. Burst

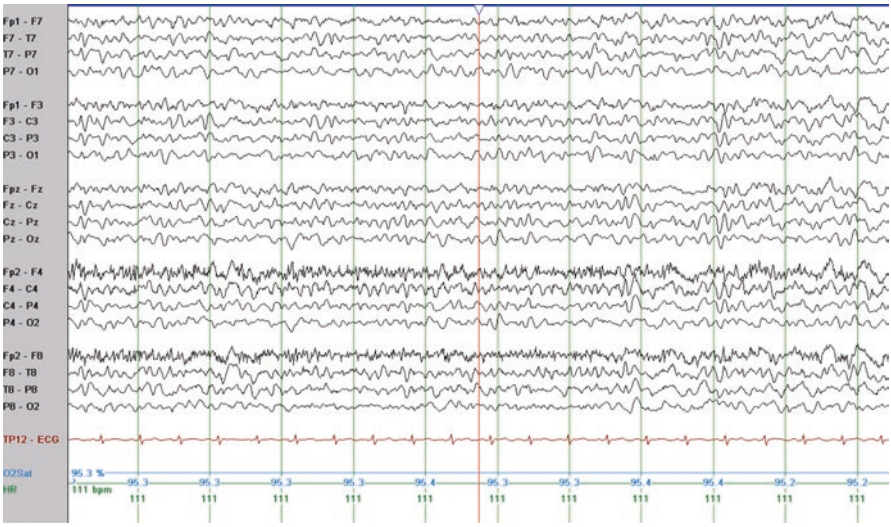


**Fig. 3** Alpha coma. This pattern, consisting invariant diffuse alpha activity in a comatose patient, may be associated with poor outcomes if no reactivity is seen. Serial or cEEG is required to determine if the pattern resolves over time

suppression can occur as a physiologic pattern, in response to certain medications, such as anesthetic agents, or moderate to severe hypothermia. It can also be pathologic, occurring after acute anoxic injury and is associated with the degree of injury. Bursts may occur in response to stimulation, variably include epileptiform activity, and may be time locked with myoclonus. Grading scales regarding EEG patterns and clinical outcomes have consistently regarded burst suppression as a malignant pattern [23–25], and electrographic seizures may arise out of this background [26]. When confounding variables, including medications and hypothermia, are absent, bursts suppression after cardiac arrest is correlated with a poor prognosis. A reactive burst suppression pattern does not portend a better outcome [27].

The specifics of the composition of the bursts may provide more refined prognostic data. The concept of "identical bursts" has been advocated as being more specific for poor outcomes [28]. On visual analysis, bursts are considered identical if the initial 500 ms of each burst are consistent in morphology. Quantitative analysis provides objective evidence of identical bursts. This specific pattern was not seen in burst suppression due to etiologies other than anoxia, including with anesthesia.

## Episodic Low-Amplitude Events

Episodic low-amplitude events are characterized by brief periods of diffuse background attenuation. Compared to burst suppression, this is a relative minor feature of the record, occurring intermittently (Fig. 4). Initial descriptions of this pattern after anoxic injury associated the finding with poor outcomes [29, 30]. However,

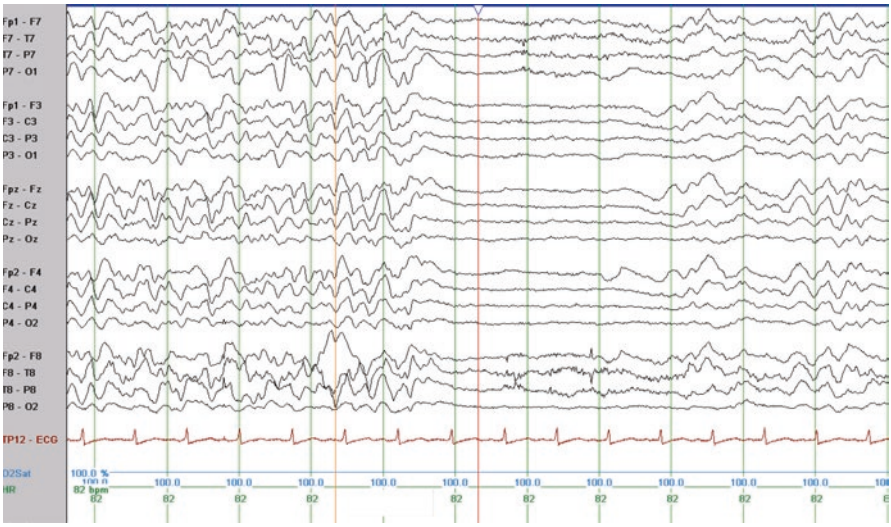


**Fig. 4** Episodic low-amplitude events. These are periods of background attenuation, which occur intermittently and compromise a minority of the record. They may occur with or without TH and in some instances may be related to medication, hypothermia, or alerting

later studies have found that this pattern is common after anoxic injury and has no association with poor outcomes. In the setting of TH, this pattern may be an alerting pattern or related with hypothermia or medications commonly used as part of clinical protocols [31].

## Generalized Periodic Discharges

Generalized periodic discharges (GPD), previously referred to as generalized periodic epileptiform discharges (GPED), may occur as part of a burst suppression pattern or over a continuous background (Fig. 5). Most commonly in acute anoxic injury, GPDs are superimposed on an isoelectric background and are a feature of a burst suppression pattern. In this instance, GPDs are associated with poor outcomes. GPDs can also occur with myoclonic seizures, which is consistent with a poor outcome. It is not well understood if GPDs superimposed on a continuous background with spontaneous variability correlates with a better prognosis.

## Seizures and Status Epilepticus

Postanoxic seizures and status epilepticus (SE) are common after cardiac arrest and have significance in regard to outcomes. The majority of seizures in this population are subclinical, requiring cEEG monitoring to detect them [26, 32, 33]. NCS occur in 9–30 % of patients treated with TH. NCSE occurs in 10–12 % of these patients

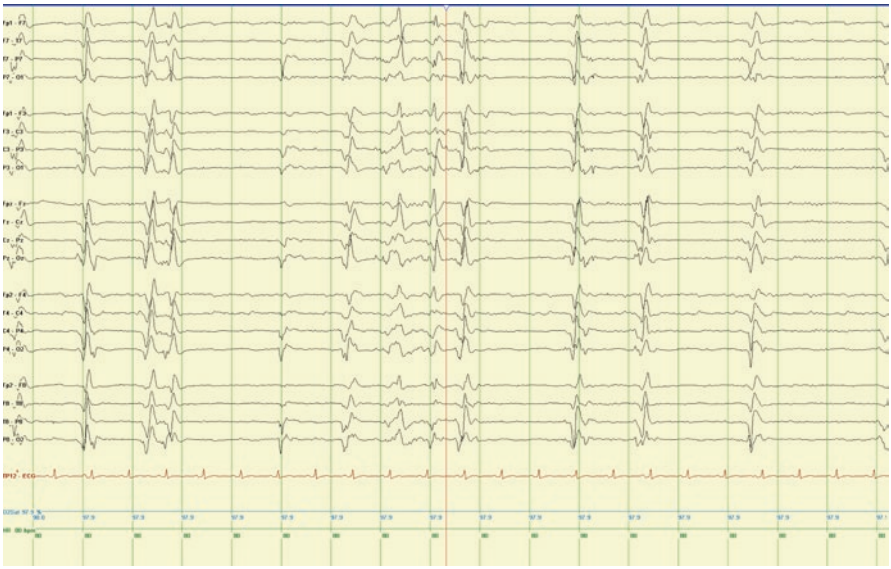

**Fig. 5** GPEDs superimposed on an otherwise isoelectric background

[31, 34–36]. After cardiac arrest, the mean time for onset of NCS and NCSE is 15 h, occurring during TH [26]. Those patients at risk for NCS can often be identified by EEG, as NCS are likely to be preceded by interictal epileptiform discharges [35] (Fig. 6).

NCS and NCSE are nearly universally associated with poor outcomes, even with attempts at treatment. In multiple studies using cEEG monitoring, the presence of NCS or NCSE were associated with mortality rates from 80 to 100 %. When poor neurologic outcomes and mortality are combined, the mortality rate approaches 100 % [16, 26, 31, 34, 36, 37]. There have been reports of exceptional recovery after anoxic injury and SE. In these cases, however, other encouraging findings were present, including a reactive EEG, preserved brainstem reflexes, and preserved cortical responses to somatosensory-evoked potentials [38]. There has been some suggestion that focal seizures after anoxic injury may be more readily controlled with antiepileptic drugs (AED) and portend a slightly better outcome, but this has not been borne out well in subsequent literature [39].

Myoclonic status epilepticus (MSE) is often grouped with NCS and NCSE, and many studies do not make definite separations between the three. MSE occurs in the first 24 h after acute anoxic injury while the patient remains comatose. Myoclonus can often be triggered by stimulation, and correlates with GPDs or the bursts in a burst suppression pattern. Occasionally, myoclonus can be seen without EEG correlate in a comatose patient. In these instances, it is thought that the myoclonus arises from the brainstem. In either case, MSE is strongly associated with a poor outcome after anoxic injury, even with attempts at treatment [40].

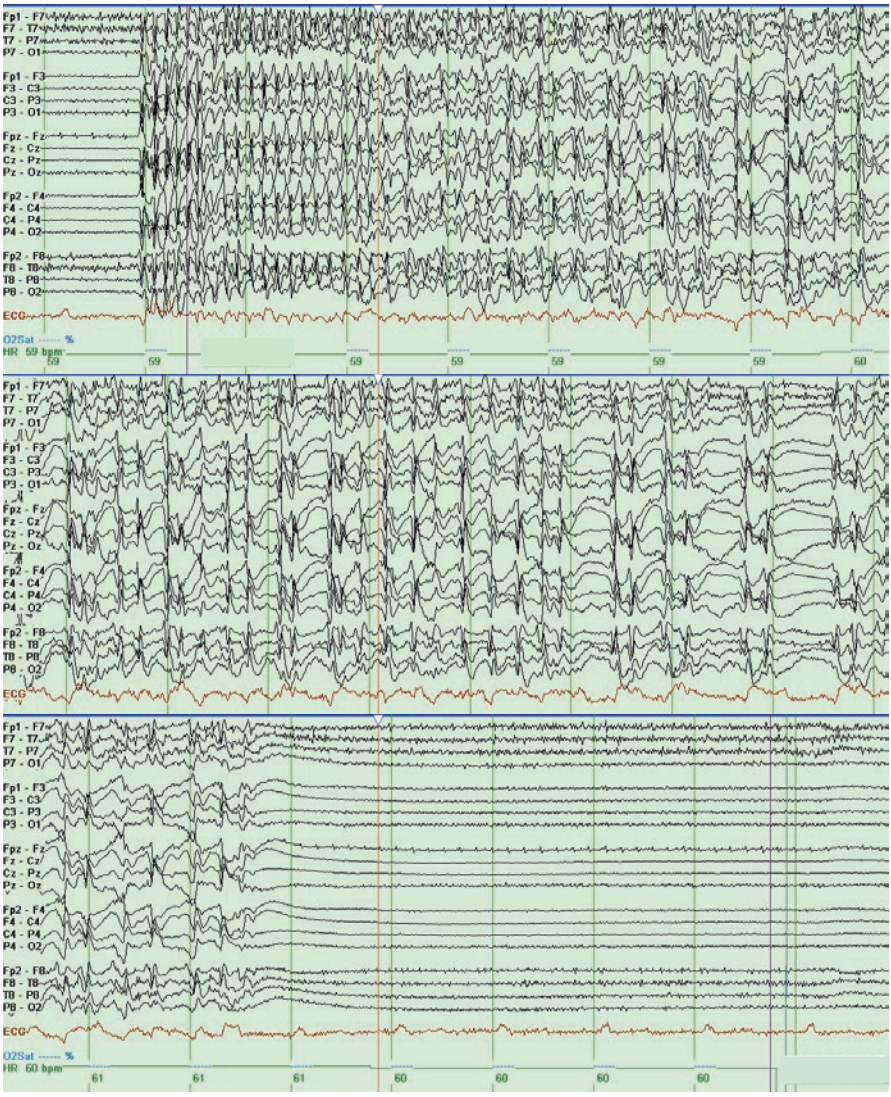


**Fig. 6** Evolving electrographic seizure arising from an otherwise isoelectric background

## Low-Voltage Output Record

A low-voltage output record after acute anoxic injury may also be referred to a low-voltage pattern. This pattern consists of background activity less than 10 μV and is not due to sedation or hypothermia. There is no reactivity to stimulation (Fig. 7). In the absence of confounding factors, this pattern correlates with poor outcomes with reported specificities as high as 100 % [41].

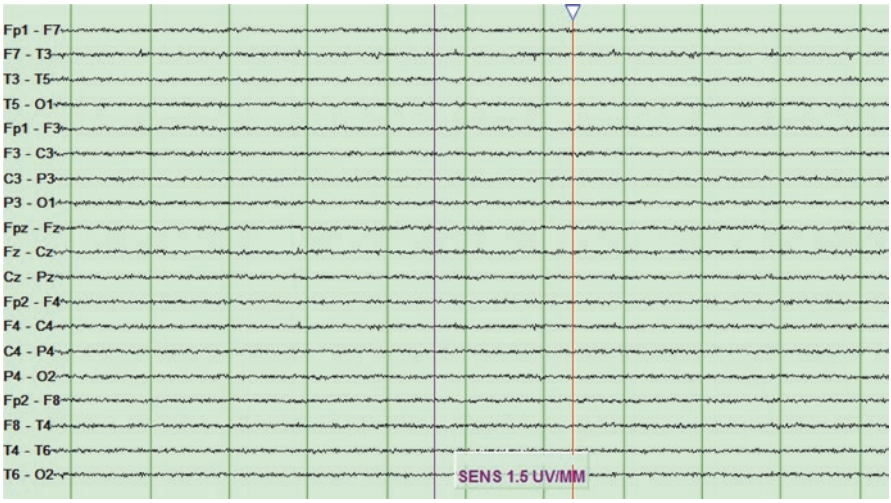


**Fig. 7** Low-voltage output pattern. Note the flat and featureless background, even sensitivity at 1.5 uV/mm

**Table 1** EEG patterns and associated outcomes

| Good outcomes | Poor outcomes |
|---|---|
| Continuous background | Nonreactive background |
| Spontaneous variability | Burst suppression |
| Reactivity | GPEDs |
| | Low-voltage output pattern |
| | Seizures/status epilepticus |

## Classification Systems

Multiple classifications have been proposed to correlate EEG findings with clinical outcomes. These scales vary in regard to the timing and duration of EEG, patient diagnosis included, and number of grades in each scale but remain remarkably consistent regarding the identified "malignant" patterns and outcomes (Table 1).

The earliest scale proposed in 1965 classified background alpha activity or occasional theta activity as normal [23]. Burst suppression and low-amplitude output records were associated with poor outcomes.

In 1973, criteria based upon 52 EEGs in 31 patients were published [42]. The classification consisted of two categories with a total of six subcategories. Category 2 was comprised of diffuse theta and delta slowing, low voltage with occasional low-amplitude fast activity, burst suppression, and low-voltage background with epileptiform activity. All patients (ten) in this category died.

In 1990, a five-grade system based upon EEGs performed 24–36 h after anoxic injury was described [24]. Malignant patterns were low-amplitude slowing with brief periods of attenuation, burst suppression, an isoelectric background, and alpha/theta coma patterns. All patients with malignant patterns died [24].

Finally, a 2005 classification described five categories and six subcategories. Burst suppression, alpha and theta coma, and isoelectric backgrounds were considered malignant patterns. These patterns correlated with poor outcomes with 89 % sensitivity and 84 % specificity [25].

These classification systems were developed prior to the routine use of TH, and EEGs were performed at variable times after cardiac arrest. A classification system proposed in 2013 was based upon EEGs performed during TH, through rewarming and normothermia. Similar to earlier schemes, burst suppression patterns, GPDs, nonreactive backgrounds, and low-voltage output patterns all correlated with poor outcomes [31]. Application of these classification systems requires attention to the timing of the EEG and factors which may affect EEG background, including TH and sedative medications. Even taking these factors into account, there remain commonalities across the classification systems. Despite significant changes in clinical care and protocols in obtaining EEGs, patterns which were identified as malignant early on still raise concerns for poor prognosis.

## Conclusions

After acute anoxic injury, EEG provides valuable data regarding prognosis. Though the standards of care have evolved in regard to critical care and implementation of TH, specific EEG patterns continue to be associated with poor outcomes despite these changes. However, caution must be taken in assigning prognosis based upon EEG. Patterns can evolve over 48–72 h, and the effects of TH and sedatives must not be ignored. In addition, it is essential to consider additional clinical testing to determine concurrent data before any statement regarding prognosis is concluded (Table 2). Physical exam findings, somatosensory-evoked potentials, serum neuron-specific enolase, and neuroimaging all provide important information regarding extent of neuronal injury.

In a patient who remains comatose after acute anoxic injury, there is uncertainty regarding prognosis. EEG, along with additional clinical data, can provide well-established guidance as to the likely outcome.

**Table 2** Additional testing for prognosis [43]

| Test | Timing | Results associated with poor outcomes |
|---|---|---|
| Physical examination | Day 1–3[a] | Lack of brainstem reflexes<br>Pupil<br>Cornea<br>Oculocephalic<br>Cough<br>Extensor or absent motor response<br>Myoclonus |
| Somatosensory-evoked potentials | Day 1–3[a] | Absent N20 response |
| Neuron-specific enolase | Day 1–3[a] | Serum level >33 μg/L |
| Neuroimaging | Day 1–3 | Indeterminate |

[a]In the absence of hypothermia, paralytics and sedatives

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# Autoimmune, Infectious, and Metabolic NCSE/NCS

# 18

Abeer J. Hani and William B. Gallentine

## Contents



A.J. Hani, MD (✉)
Division of Pediatric Neurology, Department of Neurology, Gilbert and Rose-Marie Chagoury School of Medicine, Lebanese American University, Beirut, Lebanon
e-mail: abeer.hani@gmail.com

W.B. Gallentine, DO (✉)
Division of Pediatric Neurology, Department of Pediatrics, Duke Children's and Health Center, 2301 Erwin Road, Durham, NC 27710, USA
e-mail: William.gallentine@duke.edu



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## Introduction

The role of autoimmune etiologies in the genesis of epilepsy and encephalitis has been recently discovered. Historically, infectious and to a lesser degree metabolic etiologies have also been implicated in convulsive and nonconvulsive seizures (NCS) and status epilepticus (SE). With the recent advances in and recommendations for continuous EEG (cEEG) monitoring, NCS and nonconvulsive SE (NCSE) are being increasingly detected in these conditions. It is imperative to diagnose abnormal movements that are associated with such disease states and to differentiate between epileptic and nonepileptic events. Hence, cEEG monitoring serves a vital role in spell characterization and identification of seizures and SE.

A recent study of the incidence of electrographic seizures in the pediatric intensive care unit (ICU) found that 30 % of children monitored with cEEG had seizures, of which 36 % were subclinical or nonconvulsive [1]. Electrographic seizures were found in 33 % of patients with diagnosis of central nervous system (CNS) inflammation or autoimmune disorder, in 29 % of patients with a CNS infection, and in 29 % of patients with a metabolic disorder. Similar findings have also been documented in the adult ICUs.

In the following sections, the presentation of patients with autoimmune, infectious, and metabolic encephalopathies will be discussed. The occurrence of clinical and subclinical seizures and/or SE in these patients will be reviewed. Finally, treatment recommendations will be suggested.

## Autoimmune Encephalitis

The range of autoimmune disorders presenting to the ICU with seizures or SE includes the autoimmune encephalitides, CNS vasculitis, demyelinating diseases, and neurologic involvement of systemic autoimmune disorders (i.e., systemic lupus erythematosus and Hashimoto encephalopathy). Rarely, other diseases with suspected autoimmune etiology may also be seen including Rasmussen's encephalitis and febrile-infection-related epilepsy syndrome (FIRES) [2]. In the following sections, the focus will be on antibody-mediated autoimmune encephalitides, namely, limbic encephalitis where the limbic system is almost invariably involved and seizures and SE are a common presentation.

### Presentation

The recent discovery of intracellular and cell surface antigens that could be targets of antibody-mediated limbic encephalitis has led to better identification of the ensuing disorder and allowed for more targeted therapy. Many of these antibodies have been found to be associated with paraneoplastic diseases, requiring a detailed search for an underlying oncologic etiology. A list of the common antibodies often associated with limbic encephalitis is presented in Table 1 [3].

**Table 1** Antibodies causing limbic encephalitis

| Antibody | Seizure predominance | Prevalence in the epilepsy population | Associated tumors |
|---|---|---|---|
| VGKC (includes LGI1 and CASPR2) | Major feature (80–90 % of cases) | 6.5–11.5 % | Ovarian teratoma, thymoma |
| NMDA receptor (may have more diffuse involvement of the CNS) | Major feature (70–80 % of cases) | 2.5–7 % | Ovarian teratoma |
| AMPA | Minor feature (up to 40 %) | | Small cell lung cancer, breast cancer, thymoma |
| GABA-B | Major feature (80–100 %) | | Small cell lung cancer |
| mGluR5 | Minor feature | | Hodgkin lymphoma |
| GAD65 | Major feature | 1.6–8.7 % | Small cell lung cancer |
| ANNA-1 (Hu) | Minor feature | | Small cell lung cancer |
| Ma 1/2 | Minor feature | | Ma1: lung, renal, skin, gastrointestinal<br>Ma2: germ cell (males) |

Modified from Correll [3], Springer publication
*Abbreviations*: *ANNA-1* anti-neuronal nuclear antibodies-1 (ANNA-1), *GAD* glutamic acid decarboxylase (GAD65), *VGKC* voltage-gated potassium channel, *NMDA N*-methyl-D-aspartate, *AMPA* alpha-amino-3-hydroxy-5-methyl-4-isoxazole-proprionic acid, *GABA* gamma-aminobutyric acid, *mGluR5* metabotropic glutamate receptor 5, *LGI1* leucine-rich glioma-inactivated 1 protein, *CASPR2* contactin-associated protein 2

Often patients with limbic encephalitis present with a combination of seizures, psychiatric disturbances, abnormal movements, and autonomic disturbances. The presentation may vary by age with more movement and speech disorders seen in children and more memory disturbances and autonomic disturbances seen in older patients. The specific clinical presentations for the specific antibody-mediated encephalitis are presented in Table 2.

## Evaluation

The workup of patients with suspected autoimmune etiology should include a magnetic resonance imaging (MRI) scan of the brain, EEG, and lumbar puncture. In patients with anti-*N*-methyl-D-aspartate (NMDA) receptor encephalitis, MRI abnormalities consisting of nonspecific lesion are seen in 30 % of cases, EEG is abnormal in 90 %, of cases and CSF may show elevated oligoclonal bands. Blood and cerebrospinal fluid (CSF) samples to screen for paraneoplastic and autoimmune antibodies should be obtained. Several companies offer panels of tests for these antibodies. Markers of inflammation like erythrocyte sedimentation rate (ESR), C-reactive protein, and von Willebrand factor antigen may help determine the burden of the inflammatory process. At times, further testing is needed to exclude other etiologies that may be considered in the differential diagnosis of limbic encephalitis

**Table 2** Common presentations of the specific antibody-mediated limbic encephalitis

| Antibody | Clinical presentation | Seizure types[a] |
|---|---|---|
| VGKC | Impaired episodic memory, confusion and disorientation, behavioral changes such as aggression and agitation, psychotic symptoms such as hallucinations, seizures, and low sodium secondary to SIADH | Complex partial and generalized tonic–clonic, mesial temporal or hippocampal foci more common than extratemporal – faciobrachial dystonic seizures in 90 % of LGI1 cases |
| NMDAR | Stage 1: psychiatric symptoms including hallucinations, psychosis, depression, and anxiety; confusion; memory deficits and amnesia; aphasia; and seizures<br>Stage 2: reduced consciousness, oro-lingual-facial dyskinesias and choreoathetoid movements, dysautonomia including tachycardia/brachycardia and labile blood pressure, and central hypoventilation | Simple partial, complex partial, and generalized tonic–clonic, which can be localized temporally, extratemporally, or multifocally |
| AMPA | Short-term memory loss, confusion, behavioral changes, agitation/aggression, and hypersomnolence or decreased consciousness | Temporal seizures |
| GABA-B | Memory deficits, behavioral changes, sleep disturbances, psychosis, and aphasia | Temporal seizures |
| mGlu5R | Confusion, short-term memory loss, emotional lability, hallucinations, and delusions | Temporal seizures<br>Myoclonic jerks |
| GAD-65 | Short-term memory loss, behavioral changes such as anxiety, and seizures | Temporal lobe seizures |
| ANNA-1 | New onset seizures, memory loss, and psychiatric disturbance | Temporal and extratemporal seizures<br>Epilepsia partialis continua |
| Ma1/2 | Memory loss, psychiatric disturbances and seizures | Temporal seizures |

From Correll [3]

[a]All of these antibody-mediated encephalitides may be present with NCS/NCSE

including herpes simplex virus (HSV) and human herpesvirus (HHV)-6 encephalitis, systemic lupus erythematosus, Hashimoto thyroiditis, Sjogren syndrome, antiphospholipid syndrome, and primary angiitis of the CNS [4]. In addition, evaluation for an associated neoplastic entity may require doing a computed tomography (CT) of the chest, abdomen, and pelvis or a positron emission tomography (PET) scan and pelvic or scrotal ultrasound.

## EEG

The EEG in cases of limbic encephalitis is almost invariably abnormal, as noted above. There is often diffuse slowing in the theta to delta range. There may be evidence of epileptiform discharges over one or both temporal lobes. Seizures may be clinical or

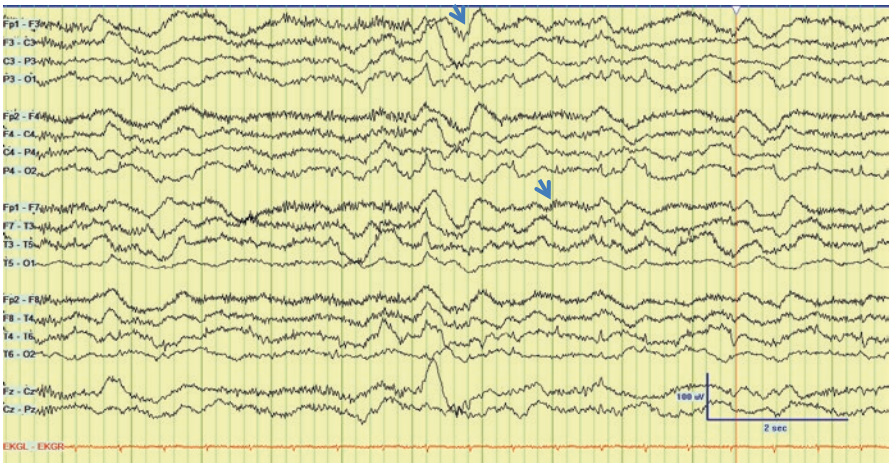


**Fig. 1** Interictal EEG in a patient with anti-NMDA receptor encephalitis with evidence of diffuse background delta slowing and extreme delta brush with superimposed beta activity riding on the delta wave seen at the *arrows*

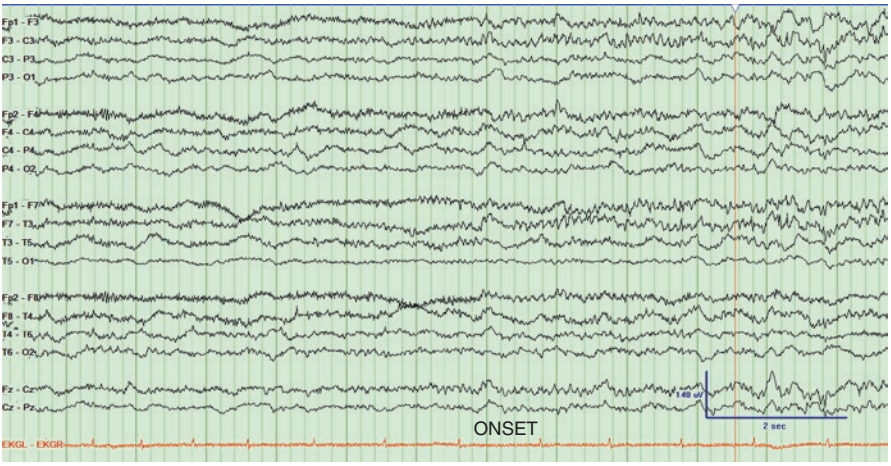


**Fig. 2** EEG showing onset of a left anterior quadrant nonconvulsive seizure in a 16-year-old patient with anti-NMDA receptor encephalitis

subclinical, and in some cases NCSE or epilepsia partialis continua (EPC) may be seen [5]. An extreme delta-brush pattern may be seen in some cases of anti-NMDA receptor encephalitis, illustrated in Fig. 1 [6]. The use of cEEG may at times be helpful to identify recurrent NCS. Samples of EEG changes seen in cases of limbic encephalitis, namely, in anti-NMDA receptor and anti-voltage-gated potassium channel (VGKC) complex encephalitides may be found in Figs. 2 and 3. In cases of anti-NMDA receptor encephalitis, abnormal orofacial dyskinesias may mimic seizures, and cEEG shows no associated epileptiform correlates with these events.

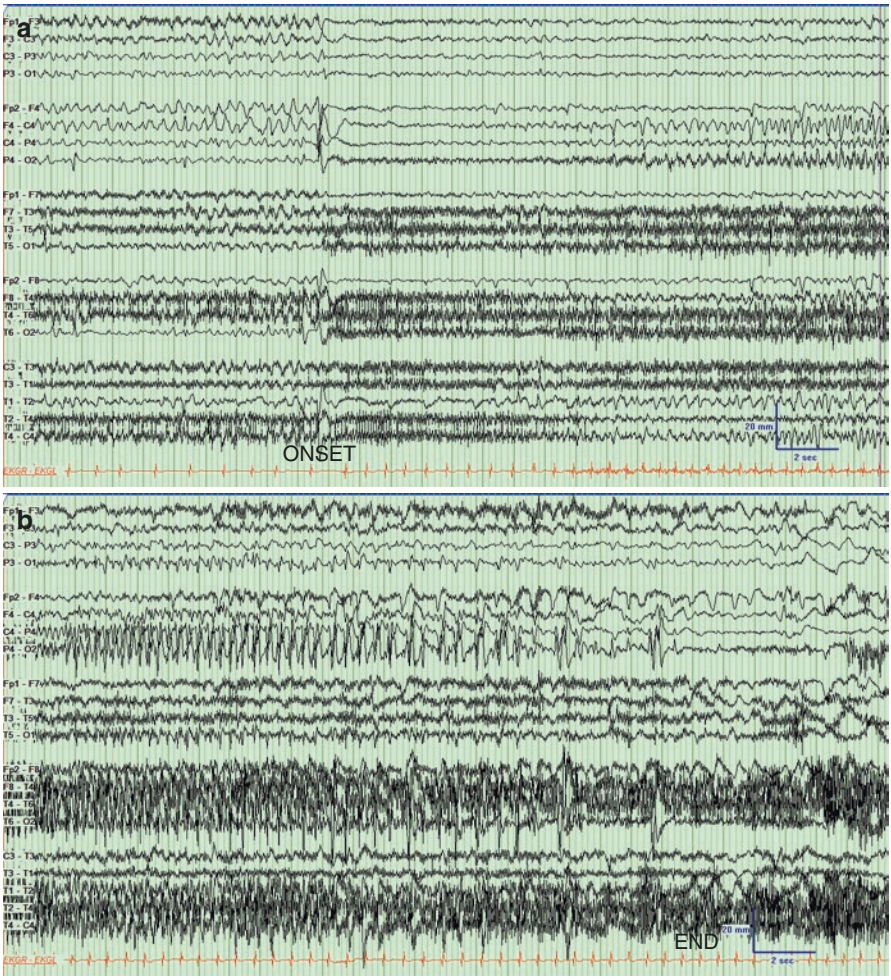


**Fig. 3** EEG showing a convulsive seizure in a patient with anti-VGKC complex encephalitis. The EEG record in **a** marks the onset of the seizure and the one in **b** shows the ictal pattern 2 min into the seizure

## Treatment

In patients with autoimmune limbic encephalitis, it is important to establish whether there is a tumor associated with the encephalitis. If a tumor is found, removal of the tumor allows for neurologic improvement. In many cases a tumor may not be present and immunotherapy is needed. Often, a course of steroids or intravenous immunoglobulin (IVIG) is tried with or without plasma exchange. Many patients also require additional immunotherapy with rituximab, cyclophosphamide, or other immunomodulatory agents. It is well known that autoimmune encephalitides related to cell surface antigens respond to immunotherapy. These patients often recover over few months, and some may require continued use of immunotherapy.

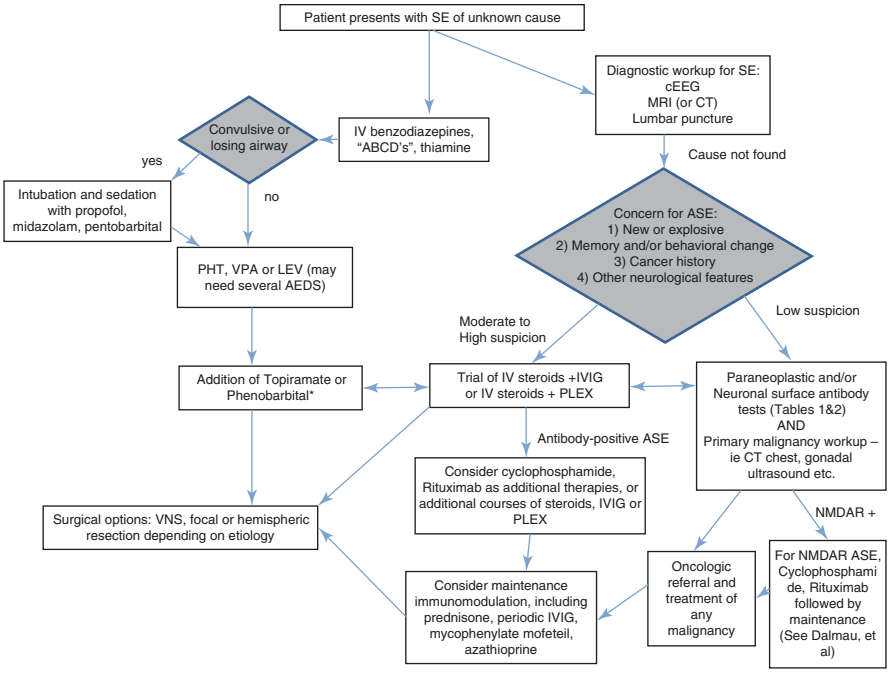


**Fig. 4** Diagnosing autoimmune status epilepticus is done in parallel to initiating treatment for status epilepticus (Adapted from LoPinto-Khoury and Sperling [7], Springer publication). *Abbreviations*: *PHT* phenytoin, *VPA* valproic acid, *LEV* levetiracetam, *VNS* vagal nerve stimulation, *PLEX* plasma exchange

As for the treatment of convulsive seizures, NCS and NCSE often seen in these disorders, antiepileptic drugs (AEDs) are used in addition to immunotherapy. In cases of refractory seizures or SE, alternative strategies may be considered such as the use of vagal nerve stimulation (VNS) or epilepsy surgery if an epileptic focus can be identified. A suggested algorithm for identification and treatment of an autoimmune SE is presented in Fig. 4 [7].

## Infectious Encephalitis

Patients in the ICU may present with CNS infections in the form of meningitis, encephalitis, ventriculitis, and abscesses. Often, mental status changes, elevated intracranial pressure (ICP), and clinical or subclinical seizures and SE may complicate the patient's ICU course. The most common CNS infections are usually due to viral and bacterial agents, and fungal and parasitic agents are less commonly seen. Iatrogenic CNS infections may be seen following neurosurgical procedures often caused by staphylococci and gram-negative bacilli.

After the neonatal period, the most common severe form of infectious encephalitis is that caused by HSV-1. Other infectious agents include varicella zoster virus (VZV), Epstein–Barr virus (EBV), cytomegalovirus (CMV), HHV 6 and 7, enteroviruses,

adenovirus, influenza viruses A and B, and *Mycoplasma pneumoniae* [8]. Arthropod-borne viruses (e.g., Japanese encephalitis) are a major cause of morbidity and mortality worldwide.

Bacterial meningitis and encephalitis are usually caused by *Streptococcus pneumoniae* or *Neisseria meningitidis* in adults and children (less commonly by *Haemophilus influenzae* due to widespread vaccination) and by beta-hemolytic *Streptococcus* group B and *Escherichia coli* in neonates [9]. Rarely tuberculous meningitis may also be seen.

In contrast to the acute infectious encephalitides, subacute sclerosing panencephalitis (SSPE) caused by an altered measles virus in nonimmunized children often has an insidious onset. In addition, the main human disease caused by prions affects the CNS causing Creutzfeldt–Jakob disease (CJD).

## Presentation

The common presentation of infectious encephalitis includes fever (seen in 90 % of adults with proven HSV encephalitis) and mental status changes including confusion, stupor, or coma. In addition, headaches with or without nuchal rigidity and nausea and vomiting may be seen. Mood changes with irritability, poor judgment, and hallucinations have been described. Commonly, focal neurologic deficits and seizures and SE may be seen. Extrapyramidal signs may be seen in patients with Japanese encephalitis due to involvement of the basal ganglia. Brainstem signs may occur due to tonsillar herniation from cerebral edema or due to organisms with predilection for the brainstem (*Listeria monocytogenes*, *Brucella*, *Mycobacterium tuberculosis*, and HSV-2). Flavivirus encephalitides (caused by West Nile virus and Japanese encephalitis virus) may cause a poliomyelitis-like syndrome and present with peripheral neurological signs. Radiculitis may be seen in EBV encephalitis. Rashes may be seen in encephalitis caused by rickettsia or enteroviruses. In SSPE, initially psychiatric manifestations occur along with mental status changes followed by myoclonic seizures and a final stage of akinetic mutism. In CJD, the disease onset is marked by rapidly progressive dementia and myoclonus that may be spontaneous and stimulus sensitive.

## Evaluation

In a patient with suspected infectious encephalitis, appropriate isolation precautions must be put in place. Diagnostic evaluation often involves brain imaging (MRI preferred over CT), lumbar puncture, and EEG to look for evidence of NCS and NCSE. The CSF analysis with cells, glucose, protein, and cell culture often helps determine the likely etiologic agent. Testing for serum and CSF-specific antibodies and agent-specific polymerase chain reactions (PCR) or viral titers can also help identify the exact cause of the encephalitis.

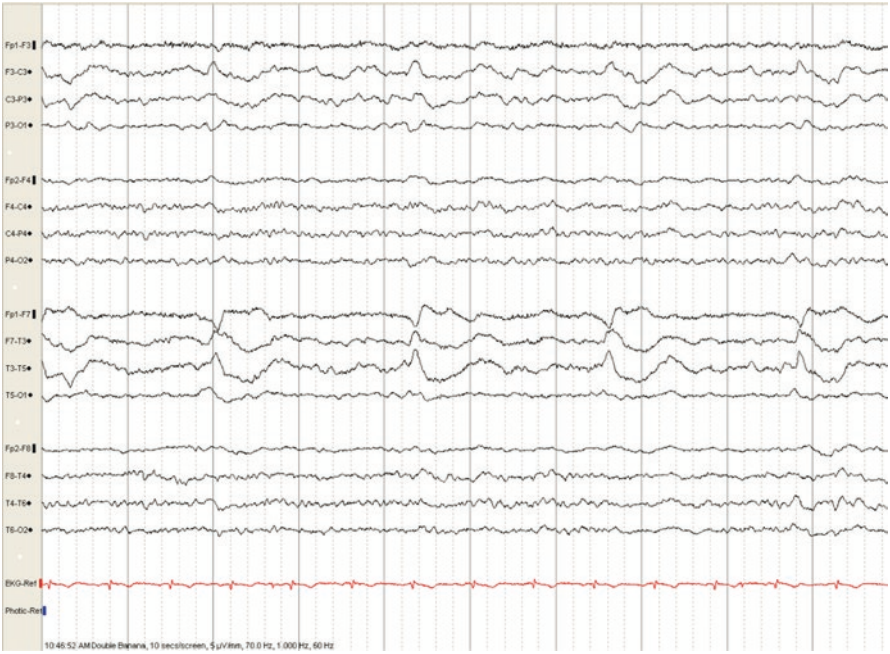


**Fig. 5** Interictal EEG showing the characteristic pattern of lateralized periodic discharges seen in the left temporal lobe in this patient with HSV encephalitis (Courtesy of Dr. Aatif Husain)

## EEG

The EEG patterns that can be seen in CNS infections are varied and include mild to severe generalized background slowing, focal slowing, focal epileptiform discharges, lateralized periodic discharges (LPDs), generalized periodic discharges (GPDs), bilateral independent periodic discharges (BIPDs), and frontal intermittent rhythmic delta (FIRDA).

Often HSV encephalitis may present with characteristic LPDs, which are seen in about 65 % of cases (Fig. 5). SSPE often has a characteristic finding of periodic complexes with bilaterally symmetric, synchronous high-voltage bursts of polyphasic delta waves occurring every 3–10 s and having a close relationship with myoclonic jerks (Fig. 6) [10]. The sporadic form of CJD also has a characteristic pattern of periodic wave complexes occurring at 0.5–2 Hz (often seen in the mid and late stages of the disease) (Fig. 7).

## Management

The key to initial management of an infectious encephalitis is to suspect an infectious etiology of the encephalitis. Broad-spectrum antibiotics and antiviral agents are recommended with subsequent targeted therapy once the offending agent has

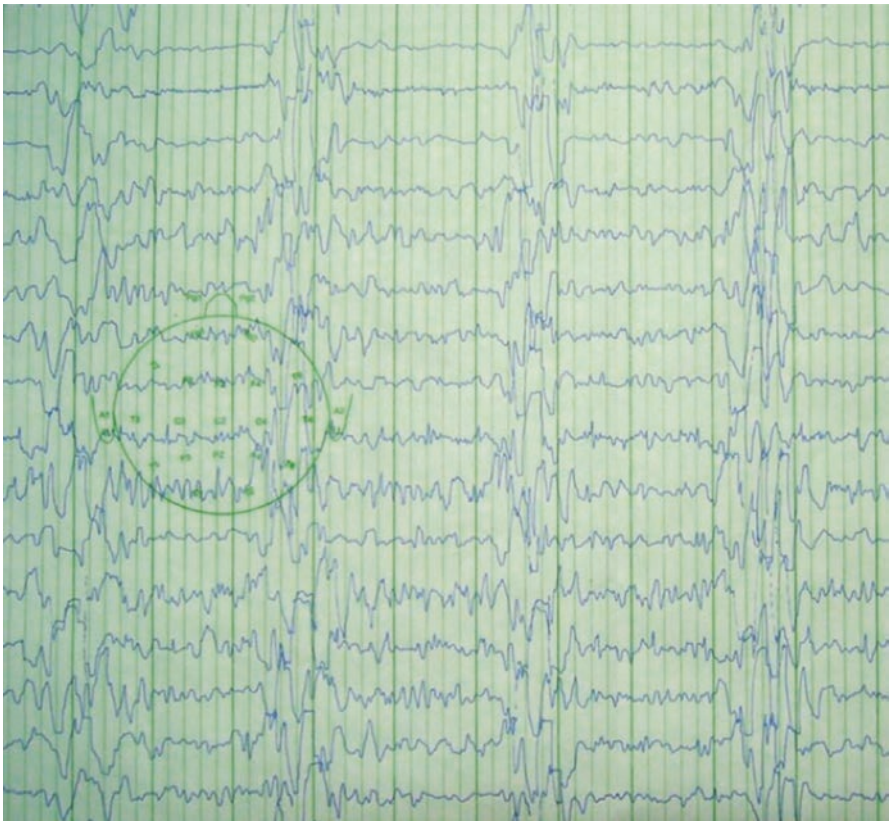

**Fig. 6** EEG in a patient with subacute sclerosing panencephalitis. An awake EEG showing slowing along with high-voltage, generalized, stereotyped periodic complexes occurring synchronously throughout the recording (Record settings: paper speed = 30 mm/s; sensitivity, 7 mm = 50 μV; high filter = 70 Hz; low filter = 1 Hz)

been identified. The use of steroids, mannitol, and even decompressive hemicraniectomy may be needed when ICP is elevated. Management of seizures or SE, whether clinical or nonconvulsive, is similar to that of other encephalitides.

The mortality with HSV encephalitis has been markedly reduced due to the use of antiviral agents such as acyclovir, but morbidity remains in the form of memory impairment, personality changes, dysphagia, and epilepsy (seen in about 24 % of cases). The course is often fatal with SSPE and CJD.

## Metabolic Encephalopathy

Metabolic encephalopathies due to inborn errors of metabolism can present with refractory seizures or SE in neonates, infants, and children and should be considered

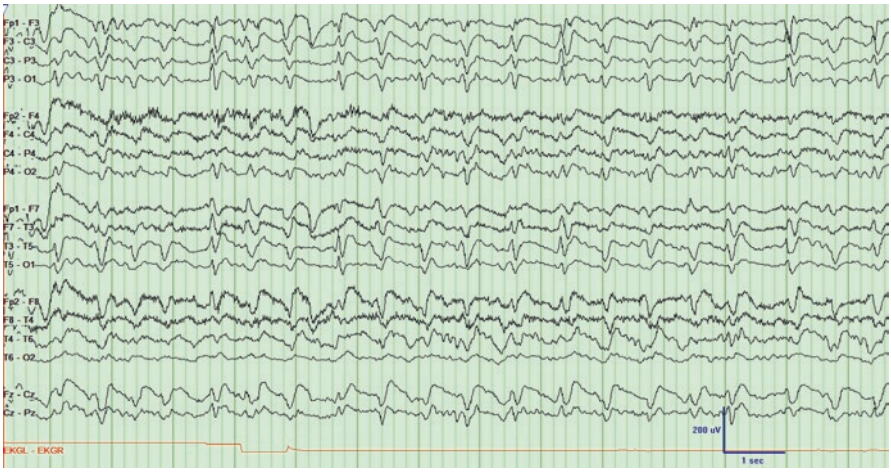


**Fig. 7** EEG in Creutzfeldt–Jakob disease (CJD) showing periodic generalized sharp waves. This tracing is from a 73-year-old woman with a rapidly progressive dementia. The EEG demonstrates continuous, high-amplitude, periodic sharp waves at 0.5–1 Hz that are bilateral

in the differential diagnosis of ongoing seizures in this age group. The most widely known example is that of pyridoxine-dependent epilepsy that is due to a mutation in the antiquitin gene interrupting the pyridoxine pathway. Other examples include deficiencies in serine synthesis and biotinidase deficiencies that may present with severe refractory seizures. Mitochondrial disease due to polymerase gamma (POLG)-related disease may also present with SE in children. In adults, inborn errors of metabolism due to energy metabolism disorders, lipid metabolism disorders, lysosomal storage disorders, and acute intermittent porphyrias may also present with seizures or SE.

## Presentation

In patients presenting with refractory or ongoing clinical or subclinical seizures, the features listed below may suggest a metabolic etiology [11]. Often the type of epilepsy does not match any classic epilepsy syndrome or there is a combination of generalized and partial seizures (e.g., combination of myoclonus and partial seizures). Cases with progressive myoclonic epilepsy warrant investigation of a metabolic cause. The association of seizure onset with other neurological impairments (cerebellar, pyramidal, etc.), decline in cognitive skills or unexplained intellectual disability, and other organ system involvement also raises concern for metabolic cause for the seizures. Any case with unexplained SE with lack of response or worsening with classic AEDs warrants an evaluation for a metabolic etiology, especially when other more common etiologies have been ruled out.

## Evaluation

When a metabolic cause for the seizures is suspected, a more detailed workup should be undertaken to identify the etiology. Testing may include checking plasma amino acids, urine organic acids, ammonia, lactate, plasma acylcarnitine profile, CSF amino acids, CSF glucose to serum ratio, and (in case of pyridoxine-dependent epilepsy) serum pipecolic acid and alpha aminoadipic acid semialdehyde. Genetic testing targeting specific mutations may also help identify the specific metabolic disorder. MRI of the brain as well as magnetic resonance spectroscopy may be used, and cEEG is often needed in case of concern for NCS and NCSE. This workup is best done in coordination with a metabolic diseases specialist.

## EEG

There are no pathognomonic EEG features of most metabolic diseases that present with refractory seizures and SE. Patients with pyridoxine-dependent epilepsy, however, may present in NCSE, and vitamin B6 (pyridoxine) administration helps stop the SE within a few minutes to hours (Fig. 8). Patients with POLG-related disorder may also present with NCSE that often is refractory to multiple AEDs (Fig. 9).

## Management

The management of the metabolic diseases discussed above starts with the identification of the specific disorder and providing the deficient or needed substrates in order to bypass the interruption present in the neurometabolic pathway. This can be done in case of pyridoxine-dependent epilepsy, pyridoxal phosphate-dependent epilepsy, folic acid-dependent epilepsy, and serine deficiencies. In other cases, there is no specific therapy and management is mostly supportive. The management of seizures starts with classic AEDs but may also include VNS or the ketogenic diet when no contraindications exist.

## Other Metabolic Derangements

Electrolyte derangements in the form of hyponatremia, hypocalcemia, hypercalcemia, and hypomagnesemia may present with an encephalopathy and produce diffuse background slowing on EEG. They have rarely also been associated also with seizures and NCSE [12].

Hepatic encephalopathy is common in critically ill patients. Typically the EEG shows diffuse theta background slowing followed by characteristic generalized periodic complexes with triphasic morphology (triphasic waves) (Fig. 10). With increasing severity of hepatic failure, diffuse delta slowing appears [13]. Clinical seizures, NCS and NCSE have been described in patients in various stages of hepatic failure.

Uremic encephalopathy may also present with seizures and NCSE, especially late in the course of renal failure. The EEG is characterized by diffuse theta and

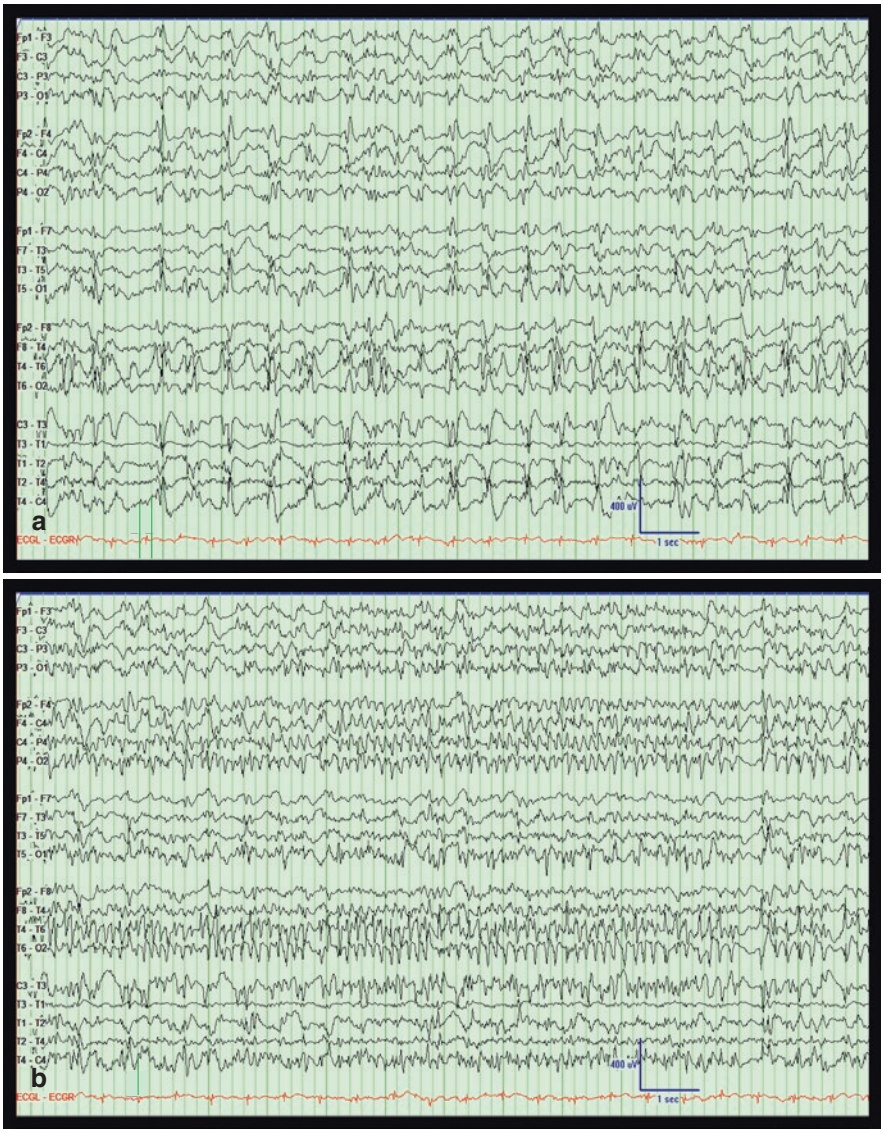


**Fig. 8** Pyridoxine-dependent epilepsy in a 7-year-old male child who presented in nonconvulsive status epilepticus for few days that was resistant to multiple AEDs and midazolam drip before he was found to have pyridoxine-dependent epilepsy. Figure (**a**) and (**b**) show his ongoing status epilepticus about 30 min prior to pyridoxine infusion. Figure (**c**) shows marked improvement of the EEG with cessation of the NCSE about 2 min after completion of the pyridoxine infusion and (**d**) shows the resolution of all epileptiform discharges 5 min after pyridoxine infusion

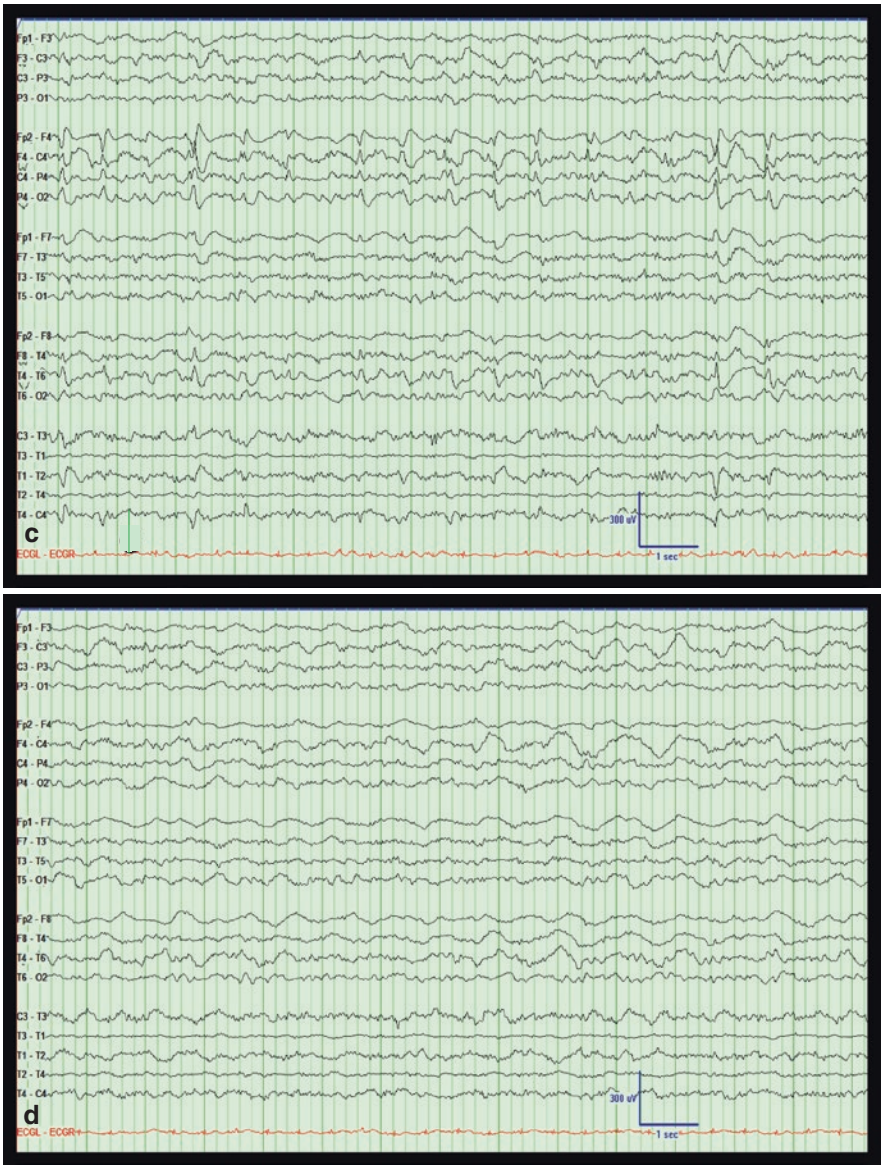


**Fig. 8** (continued)

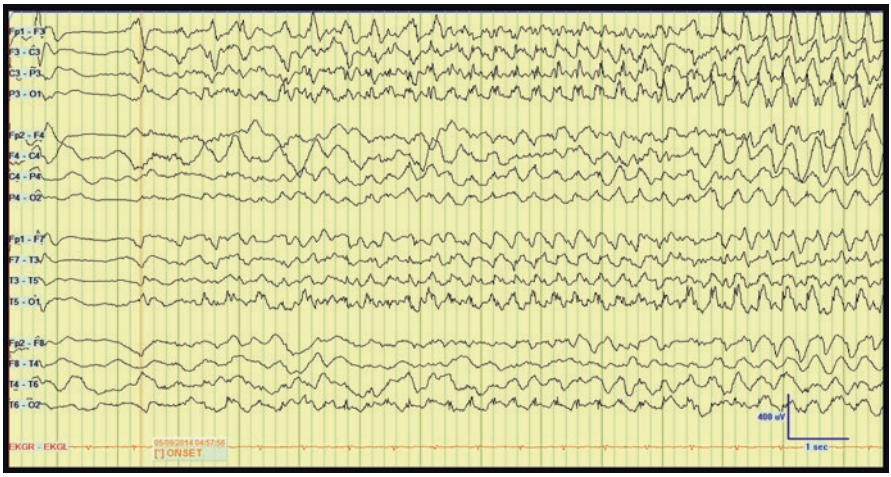


**Fig. 9** EEG in a child with POLG-related epilepsy who presented with recurrent nonconvulsive seizures and nonconvulsive status that were resistant to various AEDs and midazolam drip. The EEG shows a sample nonconvulsive seizure that is best developed over the left posterior quadrant

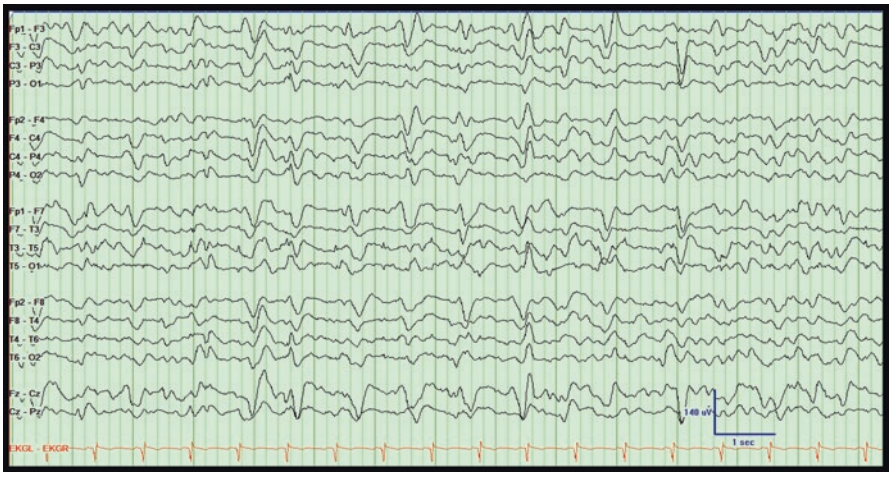


**Fig. 10** EEG showing generalized discharges with triphasic morphology typically seen in hepatic and other metabolic encephalopathies

delta slowing with development of generalized spike-wave discharges at 2–3 Hz later in the disease course. About 20% of these cases may show generalized periodic complexes with triphasic morphology.

## Conclusions

The presence of NCS and NCSE in critically ill neurologic patients has been well established necessitating the use of cEEG monitoring in this cohort of patients. The causes underlying these seizures are varied. Evaluation for an

autoimmune etiology and starting appropriate immunomodulatory therapy in combination with AEDs are essential to stop the seizures and hasten recovery. The identification of an infectious cause of acute seizures also permits timely treatment with antimicrobials and circumvents the damage caused by recurrent ongoing seizures. Finally, keeping in mind early and late-onset inborn errors of metabolism that may present with seizures in the absence of other common etiologies may permit initiation of the appropriate therapy when available and decrease the overall mortality and morbidity associated with these conditions.

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# Focal Neurologic Injury and Nonconvulsive Status Epilepticus/ Nonconvulsive Seizures

19

Leslie A. Rudzinski and Elakkat D. Gireesh

## Contents



L.A. Rudzinski, MD (✉)
Division of Epilepsy, Department of Neurology, Augusta University,
1120 15th St., Augusta, GA 30912, USA
e-mail: leslierudz01@gmail.com

E.D. Gireesh, MD
Division of Epilepsy, Department of Neurology, Florida Hospital Orlando,
615 E. Princeton St., #540 Orlando, FL 30912, USA
e-mail: gireesh.e@gmail.com



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## Introduction

Focal injuries in the intracranial space can lead to abnormal EEG patterns and epileptogenic activity in the brain resulting in convulsive and nonconvulsive seizures (NCS). Abnormal EEG changes consist of slowing of the physiological rhythms, reduction of the higher frequencies in the alpha and beta ranges, and increase in the delta frequency activity. Epileptogenic EEG changes span a range of activities including focal sharp waves, spikes, polyspikes, and evolving ictal activity, which occur in the form of rhythmic discharges. Also, in between these patterns frequently there can be an ictal-interictal continuum (IIC) consisting of periodic discharges (PDs) or rhythmic delta activity (RDA), which can be lateralized or generalized in distribution. The epileptiform discharges (spikes, sharp waves) can be either focal or broad based with unclear localization. As the epileptiform discharges become more frequent or evolve into seizures, the patients may present with a change in mental status. The seizures can be either convulsive or nonconvulsive in nature. The seizures with clinical manifestations, especially obvious features of convulsions, are usually diagnosed earlier than the nonconvulsive seizures. NCS can present with subtle clinical features and may be missed early on, and in some situations, the diagnosis is made only based on EEG monitoring. This is especially relevant in cases of lesions involving the non-motor cortex, where the clinical features are not obvious and diagnosis may be missed.

In general, nonconvulsive status epilepticus (NCSE) is generally divided into two categories: (1) absence status epilepticus, or generalized nonconvulsive status epilepticus, and (2) lateralization-related or focal nonconvulsive status epilepticus [1]. The focal lesions that we are going to discuss in this chapter commonly lead to lateralized EEG changes, and when epilepsy results from focal destructive lesions, it is usually focal in onset, although secondary generalization is possible.

## Acute Focal Neurologic Injury

### Acute Ischemic Stroke

Acute ischemic stroke is complicated by seizures in 5 % and status epilepticus (SE) in 1–10 % of cases. Acute stroke is the third leading cause of symptomatic SE after low antiepileptic drug (AED) levels and chronic stroke/brain tumor. In the older stroke literature, there is some variability in the incidence of poststroke seizures due to different study designs, small sample sizes, and grouping ischemic and hemorrhagic stroke cases together. In addition, many of these older studies only counted convulsive seizures or generalized convulsive SE (GCSE) based on caregiver reports and did not include NCS or NCSE because continuous electroencephalographic (cEEG) monitoring was not used. Instead, most EEGs in these older studies were performed postictally 24–48 h (and sometimes up to 7 days) after the seizures occurred. Therefore, several cases of NCS and NCSE were likely missed, so the

incidence of seizures in these older studies was lower than has been reported more recently. An older study using a cohort of 904 patients with either ischemic or hemorrhagic stroke found that seizures within the first 7 days of stroke occurred in 4.1 % of patients, and SE occurred in 1.1 %. Cortical infarct, cortical intracerebral hemorrhage (ICH), deep ICH, and subarachnoid hemorrhage (SAH) were associated with increased risk compared to deep infarction [2]. In a cohort of 700,000+ hospitalizations, 0.2 % of the acute ischemic stroke cohort developed GCSE, with female sex, African American race, renal disease, alcohol abuse, sodium imbalance, and hemorrhagic transformation associated with higher rates of GCSE [3]. A recent study selected patients based on high clinical suspicion for seizures and used cEEG as a diagnostic tool and monitored patients within the first week of ischemic stroke. In 56 patients with an admission diagnosis of ischemic stroke and clinical suspicion for seizures, 11 % had seizures (convulsive or nonconvulsive), while 9 % had NCS and 7 % had NCSE [4]. Variables such as the size of the infarct, mechanism of the infarct, and degree of clinical deficits on admission can predict the development of NCSE. In a cohort of 889 patients, NCSE was identified in 3.6 % of patients monitored with cEEG within the first week after stroke onset. Predictors of NCSE were large infarct size, large vessel infarcts, and relatively high National Institute of Health Stroke Scale Score (NIHSSS) at admission (mean, 13; range, 9–15) [5]. Early-onset SE after stroke appears to predict mortality. In a study of 180 patients with poststroke first-time seizure, early onset of SE after stroke (within 7 days) was associated with a higher mortality than late-onset SE (greater than 7 days) [6]. When compared to large vessel cerebral infarcts, there is little risk of seizures after lacunar infarcts [7].

## Acute Hemorrhagic Stroke/Intracerebral Hemorrhage

Seizures occur more frequently in patients with intracerebral hemorrhage (ICH) compared to those with acute ischemic stroke and are estimated to occur in 10–30 % of patients, with SE occurring in 1–21 % of patients. A study reported clinical seizures in 22 % of 65 patients with ICH. Lateralized periodic discharges (LPDs) were present in 21 % of patients with seizures and were seen on the postictal EEG performed within 24 h after the seizure. The study concluded that seizures were more frequently related to frontal lobar ICH [8]. Another study found that 4.2 % of 761 patients had seizures within the first 24 h of ICH. Lobar location and small ICH volume were predictors of seizures within the first 24 h, while lobar location and rebleeding were associated with seizures occurring within the first 30 days of ICH [9]. In a cohort of more than 700,000 hospitalizations, 0.3 % of the ICH cohort developed GCSE, with African American and Hispanic race, renal disease, coagulopathy, brain tumor, alcohol abuse, and sodium imbalance associated with higher rates of GCSE [3]. The incidence of NCS and NCSE in ICH is also higher than in acute ischemic stroke. cEEG monitoring detects more seizures, and its more widespread use over the last few decades has doubled the

incidence rate of seizures after ICH. In 45 patients with the admission diagnosis of ICH who underwent cEEG, 13 % had any type of seizure, while 13 % had NCS and 9 % had NCSE [4]. In patients with ICH, seizures are associated with progressive midline shift, and detecting them with cEEG and treating them with AEDs may improve clinical outcome. A study utilizing prospective cEEG reported NCS in 28 % of 63 patients with ICH (vs. 6 % of 46 patients with ischemic stroke). Seizures occurred in lobar hemorrhages more often than in subcortical hemorrhages. Seizures were associated with progressive midline shift on 48- to 72-h follow-up head computed tomography (CT) scans. Continuous EEG monitoring detected four times as many seizures as occurred clinically [10]. The majority of seizures after ICH are nonconvulsive, and most may be captured with cEEG within the first 48 h of recording. Seizures are also associated with hematoma growth. In 102 patients with ICH who underwent cEEG, 31 % had seizures and over half had NCS. NCS occurred in 18 % of the study population, and NCSE occurred in 7 %. NCS were twice as common in patients with expanding hemorrhages (growing by more than 30 % on the 24-h follow-up CT scan). In patients with NCS, the first seizure was detected within the first hour of recording in 56 % of patients and within 48 h in 94 %. There was a trend for worse outcome in patients with electrographic seizures and to a lesser extent with NCSE [11]. Most patients with acute ICH who have a decline in mental status and require admission to the neurological ICU should undergo cEEG monitoring for 24–48 h for NCS detection. An illustrative case is shown in Fig. 1.

## Acute Subarachnoid Hemorrhage

Acute subarachnoid hemorrhage (SAH) is complicated by seizures in 4–19 % of patients, and SE occurs in 10–14 % of patients. One study reported that seizures occurred in 19 % of 108 patients with an admission diagnosis of SAH undergoing cEEG. NCS and NCSE were present in 18 % and 13 % of this cohort, respectively [4]. NCSE has been associated with poor clinical outcome. In one study, NCS were observed in 15 % of 116 patients with SAH monitored with cEEG. NCSE occurred in 11 %. The clinical outcome was poor in 92 % of the 12 patients with NCSE. NCSE within the first 24 h had 100 % specificity and 100 % positive predictive value for poor outcome at 3 months (defined as a modified Rankin Scale Score $\geq$ 4) [12]. Seizures within the first 24 h after SAH may lead to poor scores on a severity scale upon initial presentation; however, these can achieve a good outcome. In this study, seizures were observed in 13 % of 425 patients with SAH. Early-onset seizures (within the first 24 h) negatively influenced the World Federation of Neurosurgical Societies grading regarding the severity of the SAH. Early-onset seizures were significantly associated with poor grades on this scale [13]. All SAH patients should be monitored with cEEG for at least the first 24–48 h for the detection of NCS and NCSE with longer duration monitoring used for the detection of delayed cerebral ischemia due to vasospasm after SAH.

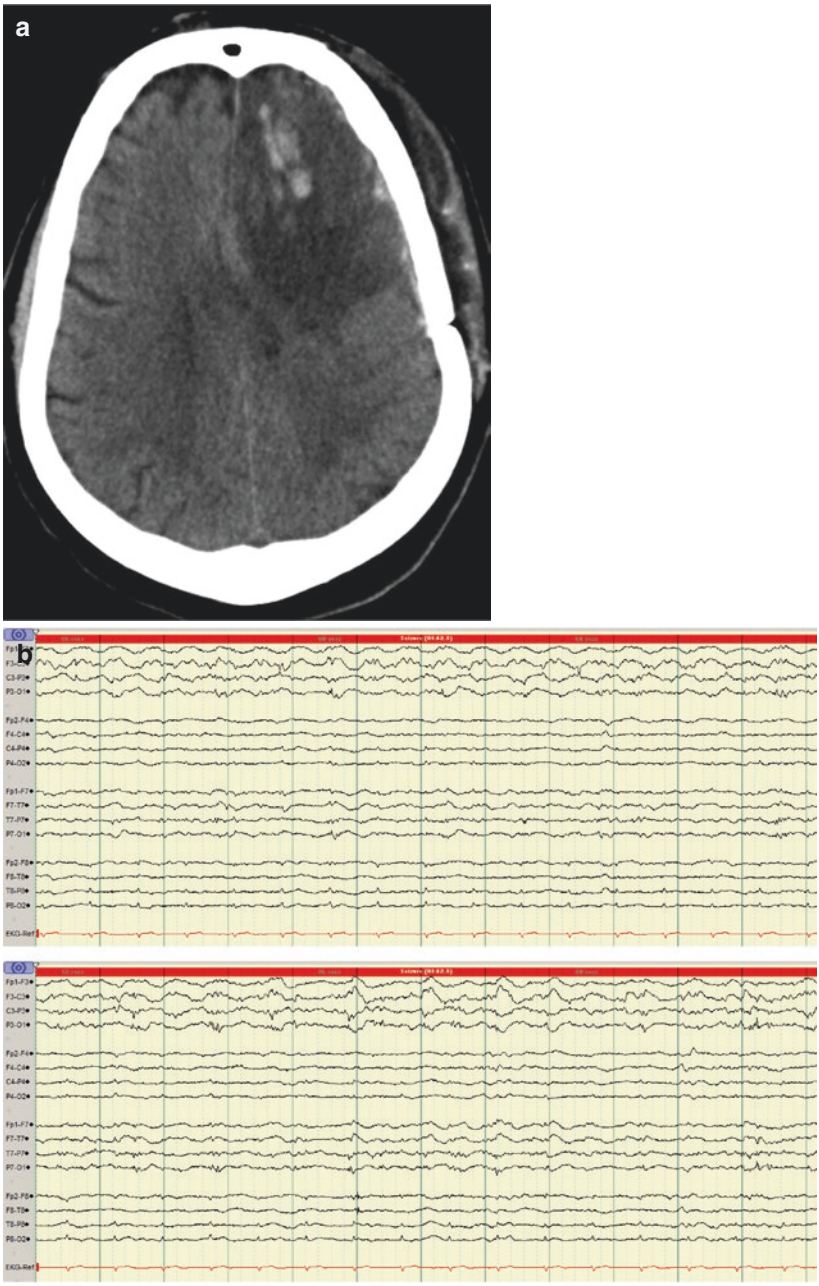


**Fig. 1** (**a**) Head CT of a 69-year-old male status post left frontal craniotomy for subtotal skull base meningioma resection with increasing ICH and edema in the left frontal and temporal lobes causing left-to-right midline shift. (**b**) The interictal EEG showed preceding continuous LPDs with spiky morphology independently over the left centrotemporal and left posterior temporal-parietal regions at a frequency of 0.5–1 Hz. The ictal discharge evolves up to 1.5–2 Hz and changes into a rhythmic delta frequency discharge plus superimposed fast activity over the left frontocentral region which slows down to 1 Hz then ends

## Acute Subdural Hemorrhage

Seizures and epileptiform discharges are relatively frequent in patients with acute subdural hemorrhage (SDH), and seizures can have a negative impact on early functional outcome. One study reported clinical seizures in 22 % of 134 patients with acute or acute-on-chronic SDH. Epileptiform discharges were present in 21 % of 134 patients. Seizures worsened early functional outcome in these patients [14]. In a smaller series based on the previous study, the EEGs of 24 patients who underwent evacuation for acute or acute-on-chronic SDH were analyzed. Eighty-seven percent of these 24 patients had epileptiform discharges on EEG, with 62 % of the discharges originating from the midline regions. Lateralized periodic discharges (LPDs) were present in 43 % of those patients with epileptiform discharges. NCS were present in 12 % of 24 patients, and the seizures were characterized as focal or multifocal in onset. Both LPDs and midline epileptiform discharges were associated with the degree of midline shift on neuroimaging. Poor early outcomes were associated with the presence of bilateral, bilateral independent, multifocal, and midline epileptiform discharges [15]. LPDs are known to be highly associated with focal-onset seizures. In a small case series of five patients with acute SDH who underwent surgical evacuation, focal motor or sensory seizures were present in all of these patients. In addition, all five patients had LPDs on EEG that were ipsilateral to the side of the SDH [16]. An illustrative case is shown in Fig. 2.

## Acute Traumatic Brain Injury

Seizures have been reported in 12–50 % of patients with traumatic brain injury (TBI), and SE occurs in 8–35 % of patients. cEEG monitoring is being used more often in these patients for the detection of subclinical electrographic seizures. One study reported that any seizure occurred in 18 % of 51 patients with an admission diagnosis of TBI undergoing cEEG. NCS and NCSE were present in 18 % and 8 % of this cohort, respectively [4]. Seizures are associated with increased intracranial pressure (ICP) and metabolic derangements and may cause worsening neuronal damage in patients with severe TBI. In another study using cEEG, 50 % of 20 patients with severe TBI monitored for seven days after injury had NCS. Thirty-five percent of these patients were in NCSE. Seizures were focal in onset with secondary generalization in 78 % of cases, and most were from the frontotemporal regions. There was an early peak seizure period at 29 h and a later peak seizure period at 140 h after injury.

NCS were associated with increased ICP, especially delayed increases in ICP beyond 96 h. The mean ICP was higher in the seizure group compared with the non-seizure group. The ICP nearly doubled with the occurrence of seizures. Metabolic derangements also occurred in the seizure group. The mean lactate/pyruvate ratio (LPR) was higher in patients with seizures, which is evidence that posttraumatic electrographic seizures negatively affect brain metabolism and may lead to permanent cellular injury. Animal models have shown that AEDs given to stop posttraumatic seizures

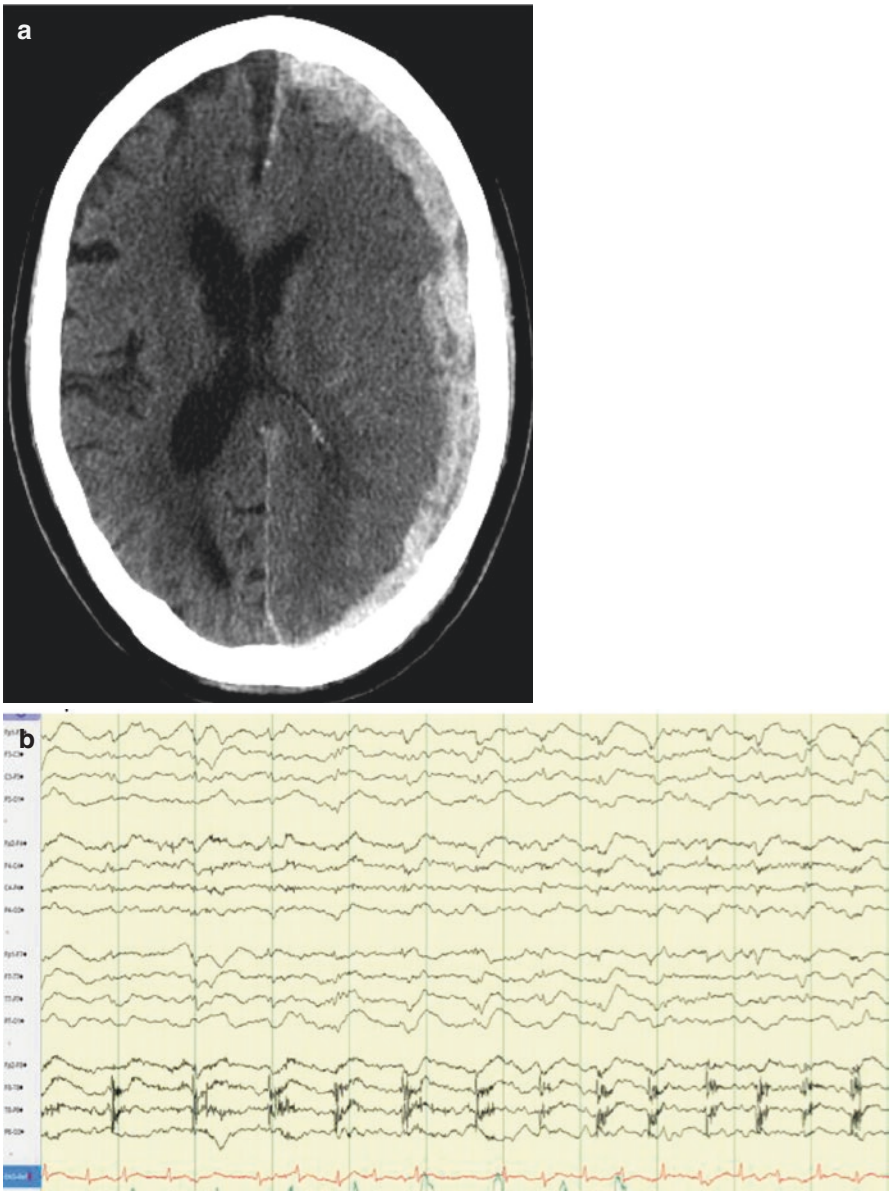


**Fig. 2** (**a**) Head CT of a 73-year-old male who presented with altered mental status and an acute left hemispheric SDH. (**b**) The ictal EEG shows ictal LPDs consisting of low-amplitude spikes with superimposed rhythmic delta activity at a frequency of 1 Hz over the left frontal region. The ictal LPDs correspond to rhythmic clonic right facial twitching which is seen on the EEG as muscle artifact over the right hemispheric electrodes, maximally involving the right temporal electrodes, which is time locked with the left frontal LPDs

improve outcome [17]. In fact, the current standard of care in patients with severe TBI is to give IV fosphenytoin for the first 7 days after injury to reduce the incidence of early posttraumatic seizures. In patients with severe TBI, phenytoin was associated with a 73 % decrease in the risk of seizures in the first week, but there was no protective effect from day 8 up to the end of the second year of the study. Phenytoin was thought to have an early suppressive effect but not a true prophylactic effect [18].

Seizures after moderate to severe TBI may be generalized or focal in onset with characteristic EEG patterns and clinical signs. SE in this population is associated with a high mortality rate with superimposed early hypoxic injury often present. Another study reported that 22 % of 94 patients with moderate to severe brain injury had seizures (clinical or electrographic), and 6 % of patients were in SE. Of patients with electrographic seizures, 55 % were of generalized onset, and 45 % were of focal onset. The electrographic patterns seen in SE patients consisted of secondarily generalized polyspike and wave, secondarily generalized repetitive spikes, and focal status epilepticus with clinical symptoms consisting of rhythmic facial twitching, eyelid fluttering, and irregular myoclonus. All patients with posttraumatic status epilepticus died, but the majority of these patients had early hypoxic injury. Therefore, status epilepticus in these cases with possible superimposed hypoxic-ischemic insult may have been a marker of severe injury and portended death. Some EEG patterns consisting of sudden-onset rhythmic epileptiform discharges that did not evolve were seen but not considered to be seizures because they did not meet the criteria [19]. These EEG patterns may now be characterized as on the ictal-interictal continuum, discussed elsewhere in the book.

## Acute Brain Abscess/Subdural Empyema

Brain abscesses may occur in isolation or in association with meningitis. EEG findings in patients with focal abscesses may include focal polymorphic delta frequency slowing, loss of faster frequency activity, and occasional epileptiform activity consisting of LPDs or focal spikes. Focal seizures may also occur [20]. Subdural empyemas may lead to focal seizures in at least 80 % of patients. The seizures are often related to underlying cortical vein thrombosis [21].

## Posterior Reversible Encephalopathy Syndrome

Posterior reversible encephalopathy syndrome (PRES) presents as altered mental status, headache, and visual disturbances resulting from vasogenic leakage associated with certain clinical conditions (e.g., eclampsia, hypertensive encephalopathy, neurotoxic substances, and immunosuppressants). The resulting edema affects the white matter and cortex usually in a posterior maximum, symmetrical distribution. Seizures are common in PRES. In a case series of 49 patients diagnosed with PRES, 78 % suffered from seizures. Two patients had epileptiform activity present on their EEGs, either LPDs or occipital sharp and slow waves. These two patients had a focal seizure presentation either with focal motor seizures or seizures affecting the

visual hemifield. The most frequent seizure type however was a single short "grand mal" seizure, with no seizures present beyond the first day. Focal interictal EEG abnormalities correlated with focal clinical seizures. Seizures did not recur beyond 24 h, and chronic epilepsy did not develop in these patients [22].

## Chronic Focal Injuries and EEG Changes

The major forms of chronic focal lesions that cause epileptiform abnormalities on EEG are tumors, trauma, old cerebrovascular events, arteriovenous malformations, and malformations of cortical development. The EEG abnormalities seen in these pathophysiological states are described below. While there is no clear one-to-one correspondence between the specific pathology and the abnormalities seen on the EEG, the propensity to cause different abnormalities varies depending on the underlying pathology and the anatomical location of the lesion.

### Tumors

Epileptic seizures are known to be a common presenting symptom in patients with brain neoplasms (between 15 and 100 % of patients with brain tumors). Recently, NCS or NCSE is increasingly being recognized as a cause of neurological worsening and less commonly as a presenting symptom of patients with brain tumors. In a case series involving 147 patients newly diagnosed with brain tumors, 38 % of the patients with a primary neoplasm and 20 % of patients with metastatic lesions had seizures as presenting symptom [23]. Oligodendrogliomas and grade 2 astrocytomas are more likely to present with seizures [23], and gliomas are thought to contribute to NCS and NCSE either at the onset or over the course of disease progression [24]. Patients with gliomas who have NCS can present with confusion, aphasia, and disorientation [25]. One recent study on patients hospitalized with a diagnosis of brain tumor demonstrated that 2 % of these patients had NCSE and 54 % had NCS. Treatment resulted in clinical improvement in 75 % of these patients [26]. The authors concluded that the NCSE may be underdiagnosed in patients with tumors because of the absence of obvious clinical manifestations. This study suggested that aggressive treatment of the NCS could improve clinical outcome in patients with tumors. Illustrative cases are shown in Figs. 3 and 4.

One of the major triggers for NCS noted in patients with intracranial neoplasms is fluctuation in AED levels. This can occur due to noncompliance or drug interactions. Anticancer drugs, including nitrosoureas, cyclophosphamide, vincristine, and methotrexate, interact with some older AEDs and can cause sudden changes in the medication levels. In some cases, patients with seizures related to brain neoplasms will have seizures triggered by an immediate cause such as systemic infection, brain tumor edema, acute exacerbation of pre-existing brain disease, alcohol use, or lack of sleep. Given these risk factors, patients with brain tumors presenting with alteration of mental status should be evaluated with an EEG early in the course of the workup. The pathophysiology of seizure development in patients with focal lesions

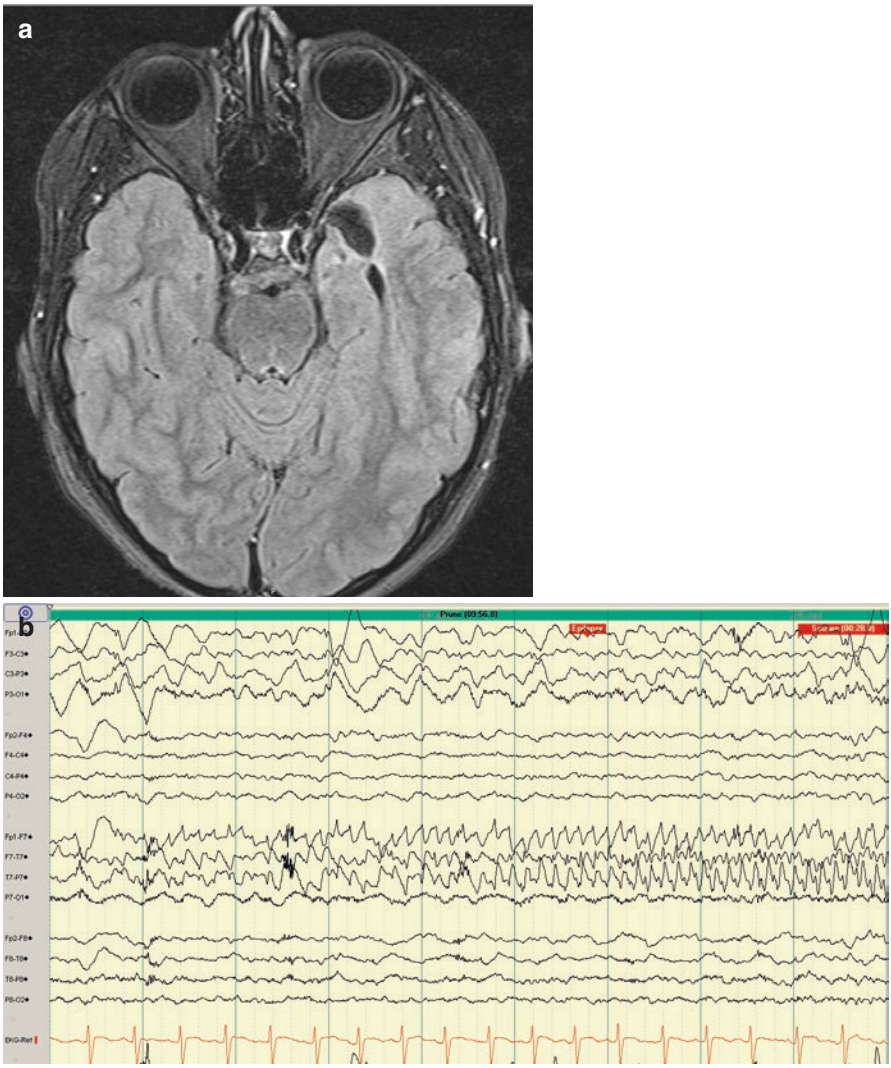


**Fig. 3** (**a**) MRI of a 10-year-old male with complex partial seizures and an epidermoid cyst over the left anterior temporal region which was resected 3 years ago. (**b**) The ictal EEG shows a seizure originating from the left temporal region consisting of a rhythmic theta frequency discharge

like tumors includes peritumoral amino acid disturbances, local metabolic imbalances, edema, disordered neurotransmitter and receptor balances, and pH alterations [27, 28].

As a result of the abovementioned processes in the brain, abnormal EEG patterns can be seen in the patients with brain tumors early in the course of the disease. EEGs performed in the evaluation of new brain tumors commonly show monomorphic or polymorphic delta activity with reduced fast activity. The presence of slow

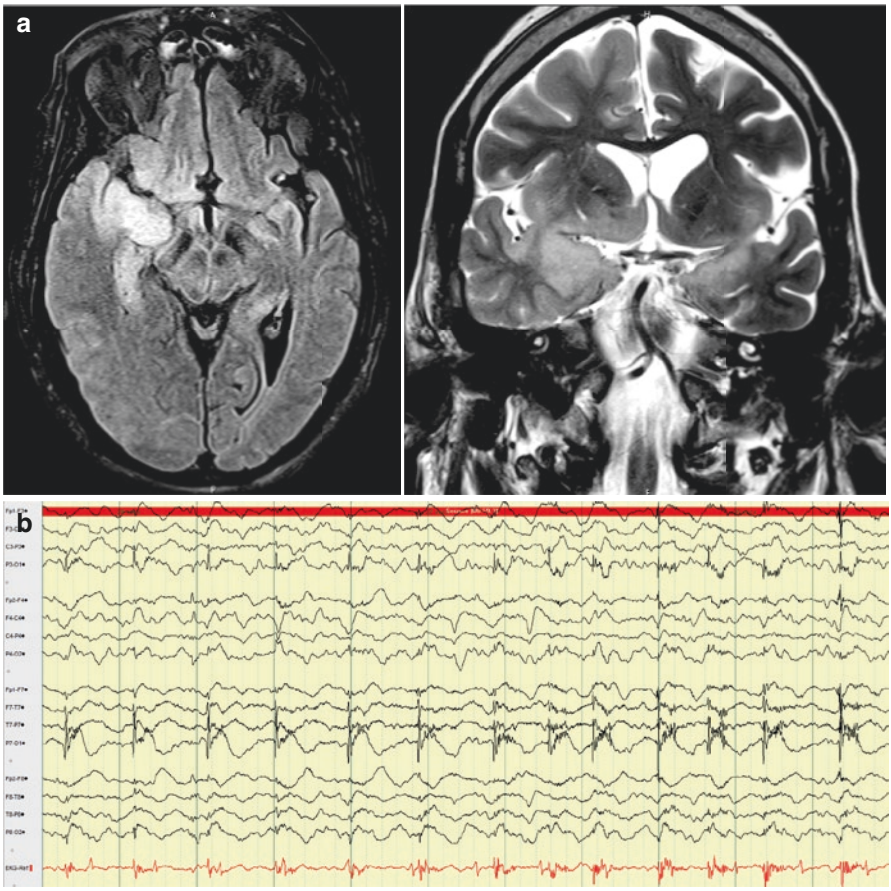


**Fig. 4** (**a**) Brain MRI (axial and coronal views) of a 72-year-old female with a history of new-onset epilepsy presenting as status epilepticus 3 months earlier who was readmitted with altered mental status and left upper-extremity weakness and developed convulsive status epilepticus. The MRI shows increased signal with mass effect involving the right frontotemporal region. Brain biopsy of this region confirmed anaplastic astrocytoma. (**b**) The ictal EEG shows ictal LPDs consisting of low-amplitude sharp waves with superimposed rhythmic delta activity at a frequency of 1 Hz over the right centroparietal region. The ictal LPDs correspond to rhythmic clonic twitching of the left neck, arm, and trunk which is seen on the EEG as muscle artifact over the left hemispheric electrodes, maximally involving the left parietal-posterior temporal electrodes, which is time locked to the right centroparietal LPDs

waves on the EEG signifies loss of function or disturbances of the surrounding region. Periodic discharges can be seen on the EEG as the tumor progresses and involves more areas of brain tissue. Sometimes focal delta activity or periodic discharges may be the only initial indication of a focal abnormality that triggers further workup. In one study, out of 282 patients with LPDs, 18 % had focal tumors. Depending on the location of the tumors, different types of intermittent rhythmic delta activity (IRDA) may be noted (frontal, FIRDA; temporal, TIRDA; occipital,

OIRDA). In addition, occipital tumors will be associated with a depression in the posterior-dominant rhythm. In the case of temporal gliomas, the delta activity is more continuous compared to the other locations.

EEG manifestations in patients developing NCS or NCSE depend primarily on the location of the tumor. The tumor itself may not produce much electrical activity, but the tissue surrounding it is capable of producing electrical activity. The patterns of EEG changes range from slow waves and PDs to frank seizures. In addition, high-grade tumors can cause local tissue necrosis and hemosiderin deposition (which is a trigger for epileptogenesis) while the tumor is present or sometimes long after it has been removed. Since the tumor itself may not contain functional neuronal tissue, the brain tissue adjoining the tumor usually produces the epileptiform discharges or NCS. Depending on the functional role of the cortex involved, this electrical activity may or may not produce clinical seizures.

An often-noted finding in ICU patients undergoing cEEG, especially with intracranial tumors, is the presence of PDs with or without NCS. In a study done on patients discharged from the ICU with these findings, it was demonstrated that among the patients who had PDs without NCS, 25 % of them developed seizures during the follow-up period (11.9 ± 6 months), compared to 61 % of the patients with NCS during the ICU stay [29]. In this population, 100 % of the patients with tumors had PDs. Also, patients with LPDs were ten times more likely to have focal lesions.

## Trauma

The EEG changes after trauma depend on the areas affected by trauma, the severity of the trauma, and the stage of healing after the trauma. Trauma to the white matter results mainly in slowing of the EEG rhythms with an increase in delta frequency activity. The EEG changes related to white mater injury usually persist for longer periods of time compared to changes seen after gray matter injuries. In the case of gray mater injuries, because of the significant neuroplasticity, the changes are usually dynamic with a normal or increase in the persistence of alpha activity in the early stages. This alpha rhythm is thought to represent the idling rhythms of the cortex and appears more persistent in the early stages of trauma, as the cortex is not functionally integrated into the rest of the brain. As the regeneration of the cortex improves and is better integrated into the rest of the cortex, the rhythm changes into more beta and theta activities. Previous studies on the EEG changes related to mild traumatic injuries showed that there will be a slowing of the posterior-dominant rhythm and increase in the theta rhythm in the early stages [30]. In an earlier study done on 344 patients admitted with head injury undergoing serial EEGs, up to 51 % of the patients continued to show the initial EEG abnormalities 3 days after injury, and the majority of EEG abnormalities resolved in 3 months [31]. Additional EEG changes related to focal damage to the brain include background slowing as well as PDs. Quantitative EEG studies have shown reduced power in all frequency bands, increased power in the delta frequency range, and changes in coherence and phase delays after concussions [32]. In addition to the milder EEG changes noted above, old trauma and related

pathophysiological changes, including hemosiderin deposition, can result in convulsive and nonconvulsive seizures [33]. As mentioned in the case of tumors, the nature of the seizures depends on the location of the injury. Regarding the epileptogenicity of head trauma, it is reported that TBI accounts for up to 20 % of symptomatic epilepsy. EEG changes and epileptiform discharges related to the specific areas affected may be expected in patients having posttraumatic epilepsy. Immediate posttraumatic NCS can result in both episodic and long-lasting increases in intracranial pressure and changes in the lactate/pyruvate ratio measured with microdialysis [17]. Also over the long term, NCS are associated with hippocampal atrophy.

## Cerebrovascular Accidents

Cerebrovascular events occurring in the form of either ischemic or hemorrhagic stroke can give rise to EEG abnormalities as well as seizures. In addition, SAH and chronic SDH can predispose to seizures. Although seizures immediately after stroke are common, seizures developing later are also frequently noted. Mild EEG changes including slowing of the background rhythms and increased delta activity are the most common findings after a cortical stroke. Additional findings such as periodic patterns in the form of LPDs or rhythmic delta activity (RDA) can be present on the side of the stroke.

### Ischemic Stroke

Prior ischemic strokes and related postischemic changes have been noted in many cases where patients presented with NCSE. Late-onset seizures, defined as seizures occurring after 2 weeks of onset of symptoms, peak between 6 and 12 months and carry a recurrence risk of about 90 % [34]. In a meta-analysis, the incidence of seizures was noted to be high in patients with cortical lesions compared to those with subcortical lesions [35]. NCS in the form of PDs or RDA is reported to be the cause of worsening of stroke symptoms in up to 22 % of patients who had recurrence of their initial stroke symptoms [36, 37]. Some illustrative cases are shown in Figs. 5, 6, and 7.

Regarding the changes in the background rhythm, one of studies done serially in patients with stroke demonstrated that the power in the alpha-frequency band is reduced over the affected side. Interestingly, the power improves over time (within months), but is reported to always be lower over the affected side. No significant sleep-related EEG changes are reported in patients with stroke. Another quantitative EEG study on patients who had stroke more than 12 months prior showed an increase in the power in the 1–9 Hz range over the affected hemisphere. The power involving the non-affected hemisphere was between 2 and 7 Hz. In addition, the power in the higher-frequency band (18–20 Hz) was lower over the affected side. Left hemispheric stroke patients show significantly greater frontal, central, parietal, and occipital slowing within the alpha and theta bands than controls. The right hemispheric group showed predominately frontal and parietal slowing in the delta

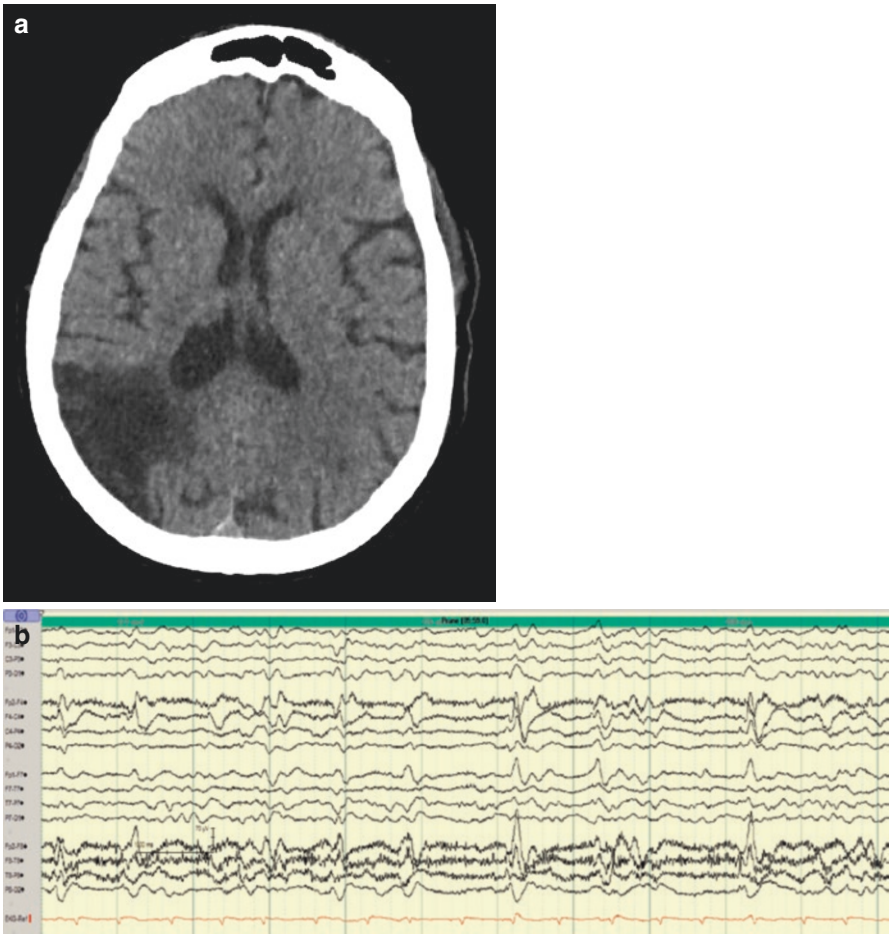


**Fig. 5** (**a**) Head CT of a 68-year-old female with previous history of ischemic right parietal infarct who was found down thought to be due to seizures. (**b**) The interictal EEG shows LPDs over the right hemisphere maximal over the frontotemporal electrodes

band, as well as global slowing in the theta band, and increased alpha in frontal, parietal, and occipital regions compared to controls [38].

## Hemorrhagic Stroke

Hemorrhagic strokes are thought to have a higher tendency to induce late-onset seizures compared to ischemic strokes. This is due to the increased epileptogenicity of hemosiderin deposition resulting from the bleeding. Apart from seizures, polymorphic delta wave activity appears ipsilaterally in patients with intracerebral hematoma and can last for a longer period over the course of recovery of the patient. The shift of the midline structures is thought to contribute to the slowing as well [39]. In cases of ICH, it is thought that the theta activity may be more prominent than seen in the ischemic strokes.

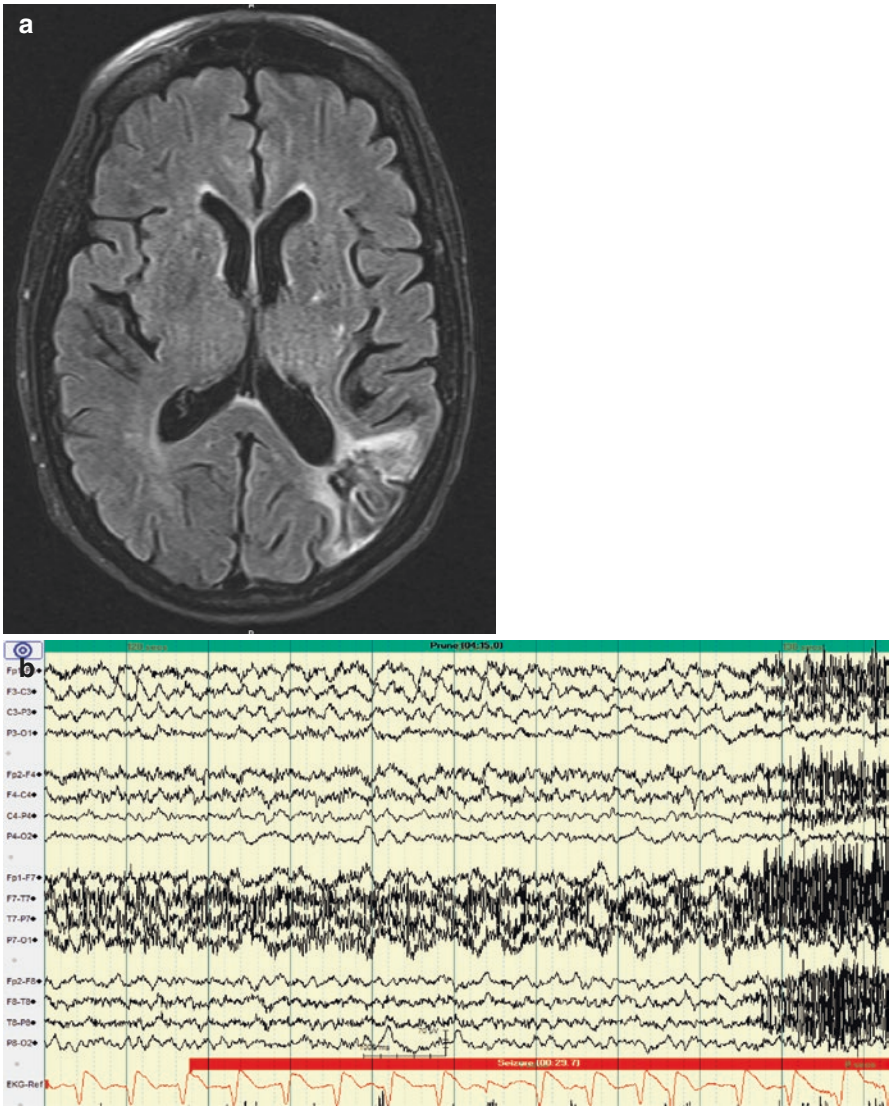


**Fig. 6** (**a**) Brain MRI of a 76-year-old female with history of an ischemic stroke over the left parietal region 8 weeks ago, presenting after collapse at home. (**b**) The ictal EEG shows a seizure consisting of an evolving theta frequency discharge over the left hemisphere, maximal over the frontocentrotemporal region

## Subarachnoid Hemorrhage and Subdural Hematoma

Both old SAH and chronic SDH are known to cause both convulsive and nonconvulsive seizures. The increased tendency of SAH to cause seizures is due to the epileptogenicity of the blood products. In study done on 876 patients who had SAH, 12 % developed epilepsy in 5 years [40].

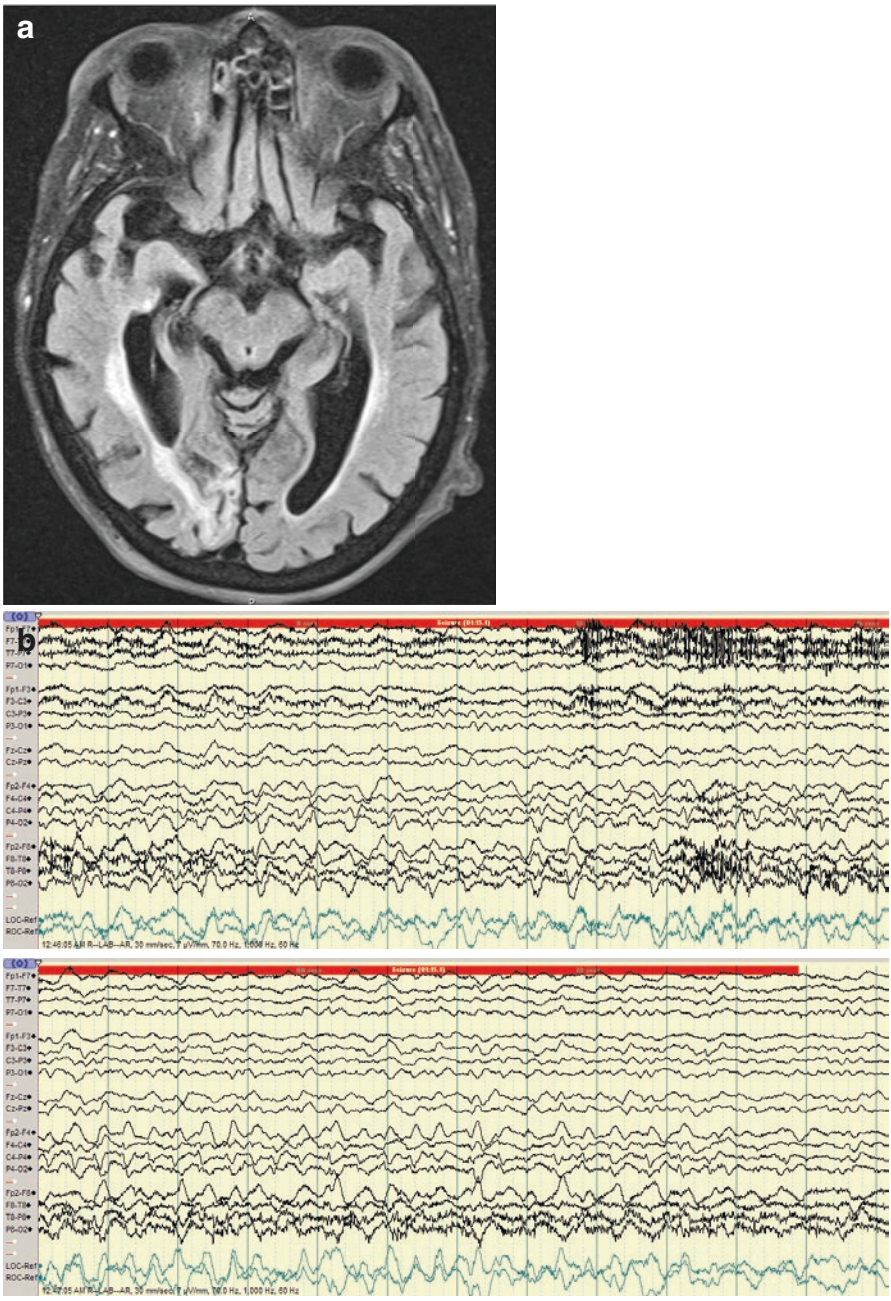


**Fig. 7** (**a**) Brain MRI of a 70-year-old female who presented with altered mental status and left upper-extremity weakness. The MRI shows global cerebral atrophy, ventriculomegaly, bilateral hippocampal atrophy, maximal on the right, and an old right mesial occipital stroke. (**b**) The interictal EEG showed right posterior temporal-parietal LPDs with sharp and slow wave morphology at a frequency of 1 Hz. The ictal discharge evolves in frequency up to 2 Hz and spreads to the right temporal region, increases in frequency up to 2.5 Hz and spreads to the rest of the right hemisphere then ends

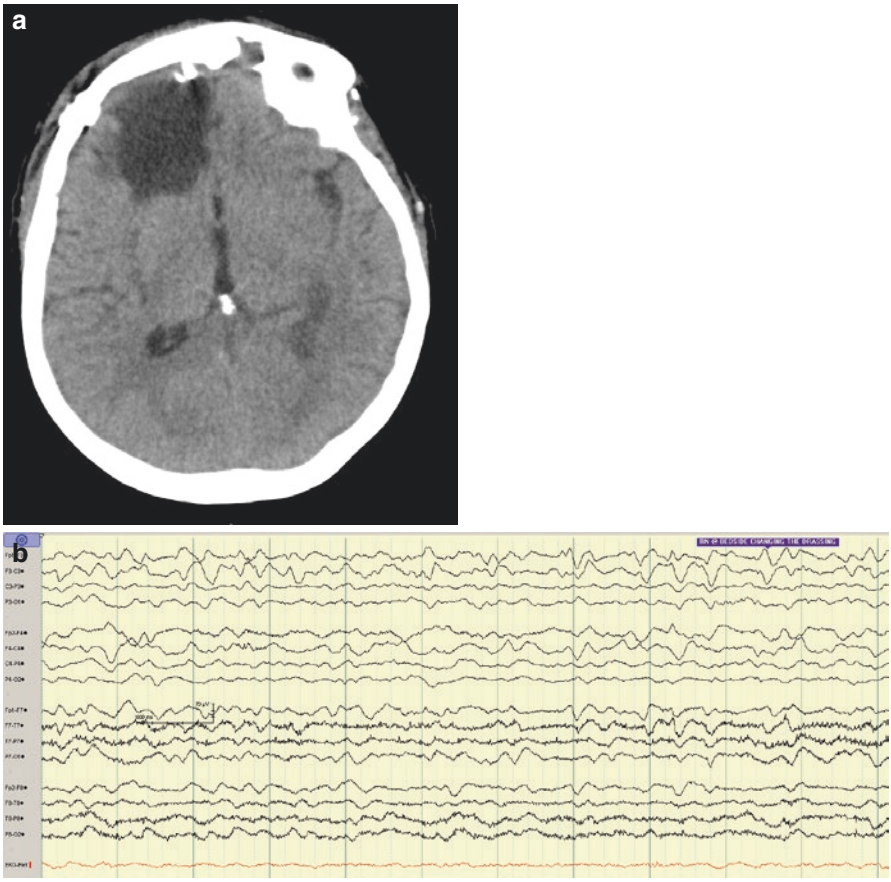


**Fig. 8** (**a**) Head CT of a 63-year-old female admitted for a ruptured arteriovenous malformation over the right frontal region. (**b**) The EEG after clipping shows theta and delta frequency slowing bilaterally and intermittent quasi-periodic lateralized discharges over the left frontal region

## Vascular Lesions: Arteriovenous Malformations and Cavernomas

Arteriovenous malformations (AVMs) are known to cause epilepsy, and seizures are frequently the presenting symptom. In one study, 30.7 % of patients with AVMs presented with seizures as their first clinical presentation. The EEG showed epileptiform abnormalities in 12.9 %. Another major abnormality noted was focal theta activity, which was present in around 16 % [41]. An illustrative case is shown in Fig. 8.

Epilepsy is a common presentation in patients with cavernous malformations. EEG abnormalities include spikes, sharp waves, and rhythmic theta activity. Intractability of the epilepsy related to the cavernoma is possibly related to the broad epileptogenic zone around the lesion. One study using stereo EEG suggests that the epileptogenic zone extends beyond the visible lesion in the case of cavernomas [42]. Depending on the location of the cavernoma, the clinical presentation will be a convulsive or nonconvulsive seizure.

**Table 1** Percentages of patients with nonconvulsive seizures and nonconvulsive status epilepticus based on etiology

| Etiology | % with NCS | % with NCSE |
|---|---|---|
| Acute ischemic stroke | 4–9 % | 1–10 % |
| Acute ICH | 10–30 % | 1–21 % |
| Acute SAH | 4–19 % | 10–14 % |
| Acute SDH | 12 % | – |
| Acute TBI | 12–50 % | 8–35 % |
| Brain tumors | 54 % | 2 % |
| Chronic ischemic stroke | 22 % | – |

## Malformations of Cortical Development and Focal Cortical Dysplasia

Malformations of cortical development (MCDs) are thought to arise from derangements in the cortical developmental process and result in both anatomical and pathophysiological changes. Focal cortical dysplasias (FCDs) are one of the most common types of MCDs and are highly associated with epilepsy. The exact reason why these tissues become epileptogenic is not clear but local interactions of dysmature cells with normal postnatal neurons are thought to play a role in developing epilepsy [43]. In a series of 20 patients with FCDs, the most common (60 %) pattern of interictal EEG activity was rhythmic 4–10 Hz medium voltage spikes or sharp waves lasting more than 1 s. In this study, up to 80 % of the patients had intermittent sharp waves. Among these patients, 70 % had fast activity at the onset of epileptic seizures [44]. Another study examined the clinical significance of polyspikes and their relevance in cortical dysplasia. It was noted that the etiology of epilepsy was more likely to be FCD in patients with regional polyspikes (35 %, 10 of 29 patients), compared to other regional epileptiform activity (5 %, 24 of 484 patients) [45].

### Conclusion

EEG and especially cEEG have proven to be useful tools in diagnosing NCS and NCSE in patients with acute and chronic focal structural lesions. The incidence of NCS and NCSE in acute structural lesions was underestimated before the widespread use of cEEG. Continuous EEG has allowed clinicians to detect NCS early in the evaluation of patients with acute or chronic structural brain lesions, thus determining a cause for altered mental status in these patients. NCS and NCSE also may be contributing to increases in ICP, increased midline shift, hematoma expansion, and increased metabolic stress in specific cases. The treatment of NCS and NCSE with AEDs may prevent secondary neuronal injury and improve clinical outcomes. Specific EEG findings can also aid clinicians in determining the type of chronic structural lesions present (gray vs. white matter injury, polyspikes in FCDs). It is useful for the electroencephalographer to be familiar with the incidence of NCS, NCSE, and specific focal findings seen with various structural lesions (Table 1) in order to provide the most reliable and clinically useful interpretation of the EEG in these challenging clinical situations.

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# Non-neurologic Causes of Nonconvulsive Status Epilepticus/ Nonconvulsive Seizures

20

Yara Nazzal and Jennifer L. DeWolfe

## Contents



## Introduction

Nonconvulsive status epilepticus (NCSE) is an underdiagnosed condition due to its minimal or inconspicuous clinical presentation. With increasing use of continuous electroencephalogram (EEG), NCSE has been diagnosed more frequently in critically ill patients. In 2012, the Neurocritical Care Society defined NCSE as seizure

Y. Nazzal, MD • J.L. DeWolfe, DO (✉)
Department of Neurology, University of Alabama at Birmingham, UAB Epilepsy Center, 1719 6th Avenue South, CIRC 312, Birmingham, AL 35294, USA
e-mail: ynazzal@uabmc.edu; jdewolfe@uab.edu



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activity on EEG that is continuous or recurrent without return to baseline between seizures for 5 or more minutes that is not associated with convulsive activity. In acutely ill patients, NCSE often follows convulsive status epilepticus and presents with severely impaired mental status with or without subtle motor movements as well as other positive or negative signs [1]. (See Chap. 5 for further NCSE classification). Nonconvulsive seizures (NCS)/NCSE have been reported in 8–21 % of critically ill patient populations [2–4]. Delayed diagnosis and treatment of NCSE may lead to increased mortality which has been reported to be as high as 52 % in critically ill patients [2, 5].

NCS/NCSE are most commonly attributed to acute medical or neurological problems, underlying epilepsy, and cryptogenic etiology. Patients with acute symptomatic etiology are typically caused by central nervous system infection followed by metabolic dysfunction and systemic infections [5, 6]. Continuous EEG performed in critically ill patients without a primary neurologic condition found NCS and periodic epileptiform discharges most commonly associated with sepsis and metabolic dysfunction [4]. This chapter reviews the non-neurologic etiologies of NCSE and NCS including metabolic and electrolyte derangements, glycemic dysfunction, thyroid and adrenal disease, systemic infection, and posterior reversible encephalopathy syndrome (PRES).

## Metabolic Causes of NCS/NCSE

### Hepatic Encephalopathy

Hepatic encephalopathy (HE) is a brain dysfunction that frequently presents as a complication of acute liver failure, advanced liver disease, or portosystemic shunting manifesting with neuropsychiatric signs and symptoms that may be subtle such as impaired attention and sleep disturbances or altered mental status with personality changes, confusion, asterixis, and then coma [7]. The pathophysiology of seizures in HE is not well defined and likely multifactorial. Hyperammonemia and possibly presence of short-chain fatty acids, mercaptans, and phenols may be contributing factors [8, 9].

The EEG in HE has been associated with nonspecific findings such as a slow background, an initial increase then decrease in amplitude, and triphasic waves [10]; however epileptiform abnormalities and electrographic seizures are infrequent [11, 12]. In a retrospective investigation of 81 encephalopathic patients with prior orthotropic liver transplantation, 29 % of the 47 patients who died had epileptiform abnormalities and clinical or subclinical seizures on EEG vs. 6 % of the 34 patients who survived. Of the 11 patients who underwent autopsy, 10 were found to have serious cerebral structural changes, suggesting that encephalopathy with EEG epileptiform abnormalities after liver transplant may be associated with poor prognosis [13]. Animal studies of HE have demonstrated that several neuronal cell death mechanisms may be activated [14]. A prospective study in liver transplant patients demonstrated improved cognitive function but persistent brain atrophy following

transplantation. Those with pre-transplant HE, diabetes, or alcoholic cirrhosis had lower posttransplant global cognitive scores, and pre-transplant HE was associated with smaller brain volumes [15]. These findings suggest that HE may be associated with neuronal loss [14, 15]. NCS/NCSE or HE should be considered in the differential diagnosis of altered mental status in patients with severe liver dysfunction. Although the incidence of seizures or NCSE in patients with HE is unknown [7, 8], case reports and retrospective studies suggest that seizures/NCSE may be rare and associated with a poor prognosis [9, 11, 16].

### Renal Impairment and Chronic Renal Failure

Chronic renal failure has been associated with NCS in critically ill patients. In a retrospective study of medical intensive care unit (MICU) patients undergoing continuous EEG without primary neurologic diagnosis, those with sepsis, chronic renal failure, and circulatory shock were significantly associated with NCS or periodic epileptiform discharges. Patients with NCS or periodic epileptiform discharges were associated with worse outcomes [4]. As in patients with HE, those with uremic encephalopathy may demonstrate similar nonspecific EEG findings of slow background and triphasic waves [12, 17].

Patients with renal failure and reduced creatinine clearance may be at increased risk of NCSE when exposed to medications or toxins, including use of beta-lactam antibiotics [17]. There are few published case reports/series of NCS/NCSE in chronic renal failure patients undergoing peritoneal dialysis [18] and hemodialysis [19]. A majority of those patients presented with acute confusion and were undergoing treatment with antibiotics for concomitant infections. (See Chap. 23 for Medication Induced NCS/NCSE.)

## Electrolyte Disorders and NCS/NCSE

### Hyponatremia

Hyponatremia has been documented in ~2.5% of hospitalized patients and may present with nausea, confusion, and agitation; however, severe decreases may be associated with seizures, coma, and death [20]. Symptoms as well as EEG changes are strongly associated with the rapidity of the change rather than the actual sodium level [20]. The EEG pattern manifests with generalized slowing and in more extreme cases, posteriorly dominant background slowing that persists after sodium has normalized. Less common patterns include paroxysmal high-amplitude rhythmic delta activity, triphasic waves, central high-amplitude theta frequencies, stimulus-induced delta activity, and rarely lateralized periodic discharges [10, 12, 20, 21]. The EEG in NCSE due to hyponatremia without a history of epilepsy demonstrates generalized seizure patterns on a slow background; however generalized patterns that subsequently lateralized, thus suggestive of a focal onset, have also been reported [20].

### Hypocalcemia

Like hyponatremia, acute hypocalcemia manifestations are more strongly associated with the rate of change rather than absolute number. They range from tetany to agitation, confusion, psychosis, and in up to 70% of patients, seizures [20, 21]. Infrequently, atypical absence and atonic seizures can be seen in hypocalcemia [21]. The EEG in hypocalcemic patients demonstrates generalized background slowing with paroxysmal theta/delta activity and hyperventilation-enhanced focal or generalized spike and spike-and-wave discharges. Hypocalcemic seizures in neonates have been associated with focal, rhythmic, high-voltage, and frontocentral epileptiform discharges that typically rapidly generalize. There are several case reports of NCSE solely or in part due to hypocalcemia, most of which were attributed to idiopathic or iatrogenic hypoparathyroidism, with associated EEG often demonstrating focal rhythmic epileptiform activity [21].

### Hypercalcemia

Hypercalcemia manifests with lethargy, confusion, and infrequently with coma. Because hypercalcemia results in reduced membrane excitability, seizures are rare and, if seen, may be due to calcitonin treatment, PRES, and vasoconstriction with epileptiform activity in the parieto-occipital regions [20]. Other EEG findings in hypercalcemic patients include generalized slowing with paroxysms of bifrontal theta/delta activity, prominent lambda waves and possible triphasic waves, and lateralized periodic discharges [20, 21].

## Endocrine Disorders and NCS/NCSE

### Hyperglycemia

Hyperglycemia may present with altered mental status, focal deficits, confusion, and seizures. Seizures, usually focal with or without altered consciousness, and NCSE are more common in nonketotic (vs. ketotic) hyperglycemia likely due in part to increased metabolism of gamma-aminobutyric acid, accumulation of lactate and adenosine, or concomitant electrolyte derangement. Hyperglycemic seizures may remain intractable to antiepileptic drugs until metabolic and glycemic abnormalities are corrected. Continuous EEG is indicated to distinguish between hyperglycemic encephalopathy and NCSE due to similarities in clinical presentation [20]. EEG changes are usually seen above 400 mg/dL with mixed slow and fast background, lateralized periodic discharges progressing to generalized medium-high-voltage delta/theta activity as serum concentrations increase. In patients with hyperglycemia-associated seizures, the EEG may demonstrate paroxysmal focal spike-and-wave discharges and focal medium- to high-voltage theta/delta transients, often in the parieto-occipital region suggestive of focal cortical irritability/cerebral dysfunction [20].

## Hypoglycemia

Hypoglycemia manifests with autonomic symptoms, focal neurological deficits, altered mental status, confusion, and coma depending on severity (usually below 70 mg/dL) and rapidity of the hypoglycemia onset. As with hyperglycemia, symptoms typically resolve with glycemic normalization; however, neurologic symptoms may persist and may not correlate with EEG changes [20]. Reported EEG changes in hypoglycemia include normal background, generalized theta slowing, focal theta slowing (predominance progressing from frontal to centrotemporal then parieto-occipital with decreasing blood glucose levels), and frontally predominant rhythmic delta activity. Epileptiform discharges may be more likely to manifest in diabetic patients and can be generalized, focal, and periodic and may be more common in the temporal and centrotemporal regions. Hypoglycemic focal and generalized NCS have been described in insulinoma patients presenting with complex partial seizures associated with focal evolution of theta and delta frequencies and sporadic intermixed temporal epileptiform discharges as well as evolution of generalized slow activity progressing to anterior spikes and sharp waves. Seizures were aborted with glucagon and resolved after insulinoma resection [20].

## Hyperthyroidism

Hyperthyroidism may present with subtle impaired cognition, sleep disturbances, anxiety, as well as more severe symptoms including severe encephalopathy, seizures, and coma that are more commonly observed during thyroid storm (up to 20 % mortality rate). As with some electrolyte disturbances, the level of thyroid hormone does not appear to correlate with the severity of EEG change, and thyrotoxicosis-related seizures may persist until euthyroid state is achieved [20]. Reported EEG changes in thyrotoxicosis or acute hyperthyroidism include faster posteriorly dominant rhythm (unique among the endocrine and electrolyte disorders in this chapter), increased fast activity and theta/delta frequencies, rare triphasic waves and prolonged responses, and higher voltages with photic stimulation. NCSE has been associated with near-continuous occipitally predominant bilateral synchronous spike-and-wave discharges. One case report demonstrated NCSE presenting with generalized 3–5 Hz rhythmic spike-and-wave discharges after levothyroxine treatment for misdiagnosed subclinical hypothyroidism [20, 22].

## Hypothyroidism

Central nervous system symptoms of hypothyroidism include mild cognitive slowing, memory impairment, myopathy, ataxia, and myxedema associated with stupor and coma. The background EEG in hypothyroidism can be normal or demonstrate low-voltage theta and delta frequencies, slow posteriorly dominant rhythm, poor/loss of reactivity, generalized periodic discharges, triphasic waves,

and rarely frontally predominant rhythmic delta activity. Although convulsive status epilepticus can be seen in hypothyroidism, there are rare case reports of NCSE often attributed to concomitant hyponatremia and one attributed to severely low triiodothyronine felt to have caused hypothalamic–pituitary–thyroid axis down-regulation [20, 23].

### Hypercortisolism

Seizures due to hypercortisolism typically occur in the setting of concomitant hypoglycemia and hyponatremia. Seizures due to PRES syndrome symptomatic of excessive exogenous corticosteroid treatment have been reported in a patient with adrenal insufficiency. Seizures and MRI changes resolved after bilateral adrenalectomy. Described EEG changes in hypercortisolism include normal background, theta/delta slowing, and excessive fast activity. Increased epileptiform discharges in patients with epilepsy have been described after corticosteroid treatment [20, 24].

### Hypocortisolism

Hypocortisolism can present with fatigue, abdominal pain, generalized weakness, hypotension, and coma; however, seizures are not commonly reported. The EEG findings in hypocortisolism can range from normal background to slowing of posterior dominant rhythm (PDR), loss of PDR blocking with eye opening, and generalized high-voltage delta activity with more severe disease. The etiology of these EEG changes may be due to concomitant electrolyte disturbances although one report of pure adrenocorticotropic hormone deficiency-associated NCSE was described with bifrontally predominant high-voltage rhythmic sharp and slow wave complexes [20, 25].

## Sepsis and NCS/NCSE

Infection is a common trigger of many seizure types, including NCS. Sepsis is frequently encountered in the ICU and may contribute to acute brain dysfunction that can lead to altered mental status, encephalopathy, and seizures, most commonly NCS [4, 26]. Reported possible mechanisms include disruption of the blood–brain barrier, endothelial activation, apoptosis, metabolic derangement, and increased excitatory neurotransmitter levels [27]. The EEG in critically ill patients with sepsis is frequently associated with background abnormalities (12–100 %) that correlate with the presence and severity of encephalopathy. Critically ill patients with sepsis are more likely to have epileptiform discharges and NCS vs. patients without sepsis. NCS has been reported in 10 % and NCSE in 8 % of septic ICU patients. Background slowing, triphasic waves (6–12 %), periodic discharges (10 %), and NCS are associated with higher mortality rates in septic patients [4, 26].

## Posterior Reversible Encephalopathy Syndrome and NCS/NCSE

PRES manifests with headache, seizures, and visual disturbances along with posterior subcortical vasogenic edema on neuroimaging and can result in irreversible neurologic damage or death if not promptly treated. PRES presents most commonly in acute hypertension, preeclampsia/eclampsia, renal disorders, and in the concomitant use of immunosuppressive and chemotherapeutic drugs. Seizures (convulsive > nonconvulsive) are frequent in patients with PRES. The EEG findings in PRES include occipital lobe seizures, lateralized periodic discharges with and without seizures, and NCSE [28]. (See Chap. 23 Medication Induced NCSE/NCS.)

**Conclusion**

Nonconvulsive seizures and nonconvulsive status epilepticus can be caused by a variety of non-neurological conditions including metabolic, electrolyte, and glycemic derangements as well as endocrine disorder, systemic infection, and PRES. In critically ill patients with such conditions, neurological symptoms, especially altered mental status, warrant consideration of NCS/NCSE as a possibility. Treatment often requires correction of the underlying condition, although antiepileptic drugs are often part of management as well.

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# Therapeutic Hypothermia in Children

# 21

Laurence Ducharme-Crevier and Mark S. Wainwright

## Contents



L. Ducharme-Crevier, MD
Ruth D. and Ken M. Davee Pediatric Neurocritical Care Program, Department of Pediatrics, Division of Neurology, no 51, Ann and Robert H. Lurie Children's Hospital of Chicago, Northwestern University Feinberg School of Medicine,
225 E. Chicago Ave, Chicago, IL 60611, USA
e-mail: lducharmecrevier@luriechildrens.org

M.S. Wainwright, MD, PhD (✉)
Ruth D. and Ken M. Davee Pediatric Neurocritical Care Program, Ann and Robert H. Lurie Children's Hospital of Chicago, Northwestern University Feinberg School of Medicine,
225 E Chicago Avenue, no. 51, Chicago, IL 60611, USA
e-mail: m-wainwright@northwestern.edu



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## Introduction

The clinical use of therapeutic hypothermia (TH) is established as a standard of care for neonates with perinatal asphyxia, for whom TH leads to improved neurologic outcome at 18-month recovery. TH has not proven effective in randomized trials of children with severe traumatic brain injury (TBI) or out-of-hospital cardiac arrest (CA). Despite a promising initial randomized-controlled study of TH in severe pediatric TBI [1], two further studies demonstrated decreased intracranial pressure during hypothermia but no difference in neurological outcome in children at 3 and 6 months of recovery and a possible increase in mortality in children treated with TH versus normothermia [2, 3]. The most recent study was stopped early for futility as safety concerns prompted for an interim analysis [3]. A study of TH for out-of-hospital CA in 260 children also showed no benefit at 1-year recovery [4]. In this chapter, we will discuss EEG monitoring in neonates after perinatal hypoxic ischemic encephalopathy (HIE) and in children in the context of CA, extracorporeal membrane oxygenation (ECMO), status epilepticus (SE), and acute liver failure. A summary of the effects of TH in neonates and children with respect to EEG changes during cooling and rewarming, the clinical applications of EEG in pediatrics, and its use for prognostication in pediatric brain insults is shown in Table 1.

**Table 1** Summary of EEG findings in neonates and children treated with therapeutic hypothermia

| Condition | Change during TH | EEG features during rewarming | Applications of EEG | EEG prognosis |
|---|---|---|---|---|
| HIE | Delay of onset of normal SWC<br>Decrease seizure activity | Seizure de novo | Seizure identification<br>Prognostication | Normal EEG background at any moment<br>Abnormal EEG background at 36 h<br>Presence of sleep–wake cycle |
| Cardiac arrest | Unknown | Stability of background<br>Seizures de novo | Seizure identification<br>Prognostication | Reactivity<br>Continuity |
| ECMO | Stable background | No modification | Seizure identification | Unknown |
| Status Epilepticus | Attenuation of ictal discharges<br>Low-amplitude burst suppression | No consistent pattern | Seizure identification | Unknown |
| ALF | Unknown | Unknown | Seizure identification | Unknown |

*TH* therapeutic hypothermia, *HIE* hypoxic ischemic encephalopathy, *SWC* sleep–wake cycle, *ALF* acute liver failure, *ECMO* extracorporeal membrane oxygenation

## Mechanisms of Therapeutic Hypothermia and Impact on EEG

Hypothermia following central nervous system (CNS) injury or ischemia may offer neuroprotection by targeting multiple underlying mechanisms involved in the pathologic effects of ischemia–reperfusion injury [5]. The acute ischemic phase initiates a toxic neuroexcitatory cascade with a release of excitatory amino acids and glutamate. A relative deficit of ATP leads to mitochondrial dysfunction and depolarization of neuronal cell membranes. The resulting high concentration of extracellular glutamate exposes neurons to a hyperexcitable state consisting of stimulation of NMDA receptors, influx of calcium, extracellular acidosis, increased synthesis of nitric oxide (NO), and reactive oxygen species (ROS). All these mechanisms result in neuronal injury and death. Hypothermia modulates the release of excitatory amino acids and reduces the oxidative and nitrosative stress. Hypothermia also significantly reduces cerebral metabolic rate and cerebral blow flow (CBF), thereby mitigating the injurious effects of the hyperemic response to cerebral ischemia. In the subacute state following cerebral injury, a CNS inflammatory response is initiated in response to release of proinflammatory mediators from ischemic tissue with activation of microglial cells and migration of systemic inflammatory cells. Hypothermia attenuates both the pro- and anti-inflammatory response to ischemia. Finally, hypothermia helps to maintain the integrity of the blood–brain barrier by inhibition of metalloproteinase activation, reduction of NO expression, and reduction of aquaporin-4 expression.

Hypothermia induces multiple physiological changes in neonates and children indirectly affecting CBF [6]. The cardiovascular system responds to the decrease in metabolic demand with bradycardia, decreased cardiac output, and global sympathetic tone. Despite these physiological variations, mild and moderate hypothermia does not impact hemodynamic stability. Hypothermia induces a reduction in cerebral and whole-body metabolism, prompting a reduction in $CO_2$ production and altering glucose metabolism, with a risk of neonatal hyperglycemia. Global CBF decreases by about 5 % for every °C reduction of body temperature.

The reduction in cerebral metabolism and CBF produced by hypothermia influence the EEG voltage. Animal and neonatal studies using amplitude-integrated electroencephalogram (aEEG) have demonstrated a stable voltage despite mild hypothermia up to 34 °C. In adult studies, within a few minutes after initiation of cooling, periodic, unilateral, bilateral, or dyssynchronous complexes may occur, superimposed on a continuous background [7]. With colder temperatures (16–33 °C), a reduction in the amplitude of the electrical activity can be seen, and eventually a burst suppression pattern is observed. Finally, electrocerebral silence occurs within an hour of cooling, with temperature ranging from 2.5 to 27.2 °C. In neonates, hypothermia also modifies the sleep pattern, producing a reduction in the time spent in deep sleep and a delay in the onset of normal sleep–wake cycling.

Patients undergoing TH often receive analgesia, sedation, and neuromuscular blockade that may confound the clinical exam. The use of these medications also influences EEG activity [8]. Multiple EEG changes have been described in adults

and children, and the EEG should be interpreted with this confounding factor in mind. Increased beta activity resulting in a wider field distribution and persistence of beta activity is often seen with the use of GABA agonists (barbiturates, benzodiazepines). Children are more susceptible than adults to this accentuation of beta activity. Background slowing with decreased amplitude and frequency of the alpha rhythm is related to many sedative agents and anticonvulsants. Opioid use in neonates has been reported to correlate with excessive spike and sharp transients, periods of background attenuation, and suppression and lack of trace reactivity.

## Neonates

### Animal Studies

In a preterm fetal sheep model mimicking preterm brain injury [9], umbilical occlusion was followed by immediate suppression of EEG intensity, remaining significantly suppressed during and after reperfusion. TH produced more pronounced suppression of EEG activity, lasting 9 h after occlusion.

### Use of EEG in Perinatal Asphyxia

Perinatal HIE associated with intrapartum asphyxia is a common cause of permanent disability and death in neonates. Moderate TH is an established, evidence-based therapy that improves the neurological outcome of a specific subpopulation of HIE patients. TH significantly reduces death or disability at 18 months, without any adverse events, in infants with moderate HIE [10]. In 2013, a Cochrane review identified 11 randomized-controlled trials of TH, involving 1505 late preterm and term infants with moderate and severe encephalopathy in the context of birth asphyxia. The entry criteria for TH for infants with HIE comprise gestational age $\geq$36 weeks and $\leq$6 h of age, Apgar score $\leq$5 at 10 min after birth or continued need for resuscitation 10 min after birth or pH <7.00 or base deficit $\geq$16 mmol/L within 60 min after birth, and moderate or severe encephalopathy on clinical examination. Infants receiving preferential head cooling must also demonstrate an abnormal background activity for at least 30 min or seizures detected by aEEG. Many different protocols exist, but TH for the neonate with HIE involves cooling to 32–34 °C within the first 6 h of life for 72 h, with gradual rewarming over the next 24 h. The method of cooling varies according to the institution (whole-body cooling with a blanket versus selected head cooling with a cooling cap).

The American Clinical Neurophysiology Society recommends that all neonates at risk for brain injury undergo continuous video EEG (vEEG) monitoring to assess for the presence of electrographic seizures and to evaluate suspicious clinical events [11]. Continuous bedside vEEG or aEEG are used in neonates suffering from HIE for many purposes: assessment of indication for neuroprotection with TH, monitoring of seizure activity, and evaluation of response to treatment with antiseizure

medications and to help determine prognosis. Multichannel vEEG study is the gold standard for accurate identification and quantification of seizures and analysis of background activity in this population. Most patients undergoing TH are monitored with aEEG, continuous vEEG, or periodic vEEG throughout the process of hypothermia and rewarming.

## Detection of Seizures Following Perinatal Asphyxia and Effects of Hypothermia

HIE is a common cause of neonatal seizures, which are an important predictor of neurological morbidities and mortality in this population. Prior to the era of TH, the incidence of seizures in neonates with moderate to severe HIE approached 90 % [12]. Despite the neuroprotective and anticonvulsant effects of TH, electrographic seizures are reported in about 50 % of infants undergoing TH following birth asphyxia, and SE occurs in up to 25 % of this population. TH may reduce the risk for electrographic seizures in neonates with HIE [12, 13].

Within the interval from birth to initiation of EEG monitoring (usually a few hours), about half of moderate to severe HIE patients have clinical events suspicious for seizure activity and most of these patients are treated with phenobarbital initially (78 %) [13]. Half of these patients continue to have further electrographic seizures while monitored by continuous vEEG. Interestingly, electrographic seizure onset while monitored by vEEG occurs at a median time of 13–18 h, but a small number of patients are in electrographic SE at the onset of recording [13]. Seizures may occur de novo during rewarming, but the reported incidence is variable. A 3-center observational study of 90 term neonates treated with whole-body TH for HIE who underwent continuous vEEG monitoring on the first day of life and continued for >24 h identified electrographic seizures in 48 % of cases [14]. Electrographic seizure onset occurred at a median of 19.9 h of life. Notably, treatment with phenobarbital prior to vEEG recording was not associated with risk for electrographic seizures, and only 4 % of the study population had seizure onset de novo during rewarming. The EEG of a 3-day-old infant with HIE and multiple focal electrographic seizures during rewarming is shown in Fig. 1.

Neonates with HIE undergoing TH have a lower seizure burden than normothermic neonates. Seizure burden is defined in this context as the total duration of electrographic seizures in seconds. For a similar population in terms of patient characteristics and HIE severity, cooled neonates have a lower seizure burden, but both groups develop a comparable number of seizure events. The mean duration of seizures and prevalence of SE are similar with regard to antiseizure medication before and after hypothermia initiation [12, 13]. Newborns with moderate HIE show a greater reduction in seizure burden with TH than those with severe HIE [12]. The mechanisms producing a decrease in seizure activity during TH and occurrence of seizure during rewarming may be multifactorial. TH may delay the evolution of CNS injury leading to a delay in onset of seizures. TH may also suppress seizure activity, and consequently, seizures occur later during the return to normothermia.

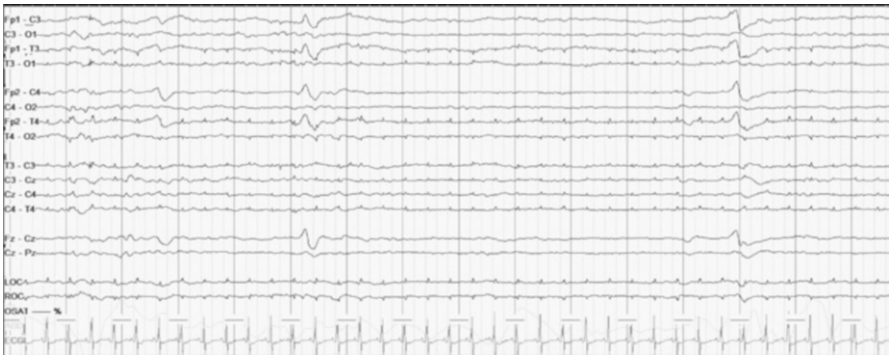

**Fig. 1** EEG of a 3-day-old infant, 39 postconceptional age, with hypoxic ischemic encephalopathy (HIE). The study was performed during rewarming. There are multiple focal electrographic seizures with onset from the left occipital region; excess multifocal sharp transients for age, maximal in the occipital regions; and excessively discontinuous background for conceptual age. These findings are suggestive of diffuse cerebral dysfunction and multifocal potentially epileptogenic foci with the dominant focus in the left occipital region

The use of TH for HIE has lead to a change in the duration of EEG monitoring. Normothermic neonates were previously monitored for the first 2 days of life, but infants undergoing TH are now often monitored through hypothermia and rewarming (approximately 4 days) [13].

An abnormal vEEG background is a risk factor for seizures following HIE [14]. An excessively discontinuous vEEG background at the onset of monitoring is associated with a 70 % risk of seizures. A severely abnormal, but not discontinuous, and normal vEEG background are associated with a 63 % and 12 % risk of seizures respectively. No perinatal clinical variable predicts the risk of electrographic seizures. Accordingly, vEEG monitoring remains an essential tool to assess seizure activity during TH in the asphyxiated newborn.

The relationship between seizure burden and the severity of CNS injury remains unclear, but it is possible that reducing the amount and duration of seizures with TH improves neonatal outcome. Seizure burden may reflect the severity of CNS injury or may contribute to and exacerbate underlying injury. Clinical recognition of seizures in this specific population is known to underestimate the real seizure incidence, as many neonatal seizures are subclinical. Accordingly, continuous vEEG monitoring allows prompt recognition and treatment of seizures. Importantly, there is no consensus regarding the threshold for treatment of electrographic seizures.

## Use of Amplitude-Integrated EEG in Perinatal Asphyxia

Multichannel vEEG remains the gold standard for background analysis and seizure detection, but its use in the neonatal intensive care unit is limited by availability and by the expertise required for application and interpretation. Amplitude-integrated EEG is a simplified alternative method allowing brain activity monitoring with 3–5

**Table 2** Classification of aEEG background in patients with hypoxic ischemic encephalopathy

| |
|---|
| *Pattern recognition classification* |
| 1. Flat tracing: very low voltage, mainly inactive (isoelectric) tracing with activity below 5 μV |
| 2. Continuous extremely low voltage: continuous background pattern of very low voltage around or below 5 μV |
| 3. Burst suppression: discontinuous background pattern with periods of very low voltage intermixed with burst of higher amplitude |
| 4. Discontinuous normal voltage: discontinuous trace, where the voltage is predominantly above 5 μV |
| 5. Continuous normal voltage: continuous activity with voltage of 10–25 μV |
| *Simplified aEEG classification* |
| 1. Normal amplitude is present when the upper margin of band of aEEG activity is >10 μV and the lower margin is >5 μV |
| 2. Moderately abnormal amplitude: upper margin of band of aEEG activity >10 μV and lower margin ≤5 μV |
| 3. Suppressed amplitude: upper margin of the band of aEEG activity <10 μV and a lower margin <5 μV, usually accompanied by bursts of high-voltage activity (burst suppression) |

electrodes attached to the scalp. The electrode application is simpler and aEEG interpretation is reliable for neonatologists and intensivists trained in its use. In a study comparing the use of continuous vEEG and aEEG in infants at risk for seizures, single-channel aEEG identified seizures in 56 % of cases. The ability to detect seizures using aEEG correlated with the duration of seizure, aEEG background, and skills of the interpreter [15]. Nevertheless, the sensitivity of aEEG to detect seizures during TH and following perinatal asphyxia remains controversial.

Amplitude-integrated EEG may be used as a tool to help in the selection of neonates for TH. In a study examining the predictive value of early aEEG (within the first 6–9 h) and clinical staging of encephalopathy among children with HIE, the strongest variables associated with a poor neurological outcome were a neurological exam compatible with severe HIE, followed by an abnormal aEEG (burst suppression, continuous low voltage or flat voltage) and a moderate HIE assessed by neurological examination [16]. Therefore, aEEG may be helpful for the selection of children with moderate HIE, as their early aEEG is more sensitive than the clinical examination for prediction of poor outcome in this population. This finding is important for this specific population, as infants with moderate HIE derive the greatest benefit from TH.

## EEG Background: Relation to Clinical Outcome and Impact of TH After HIE

Two scales are frequently used for the classification of aEEG background in HIE patients (Table 2). Approximately half of the infants with moderate to severe HIE undergoing TH present with burst suppression, continuous low voltage or flat

tracing for at least 1 h within the first 24 h of monitoring. Of these infants, 17 % have persistent abnormal background at 48 h of age [17].

In infants with HIE treated with TH, the predictive value of early background classification to predict neurodevelopmental outcome at 18 months is lower than for normothermic infants [18]. In infants with HIE not treated with TH, an abnormal aEEG pattern (burst suppression, low voltage or flat tracing) within 3–6 h of birth has a positive predictive value for poor outcome (death or disability) of 84 %, compared to 59 % in the hypothermia-treated infants ($p = 0.05$). At 36 hours, the odd ratio for an abnormal tracing to predict poor outcome is similar in both hypothermia and normothermia infants. A normal aEEG trace allows a much more accurate positive predictive value for good outcome in both normothermia and hypothermia infants (67 % and 100 % respectively). The degree of abnormality of the aEEG background and the presence of seizures during the 76-h interval after TH correlates with a poor outcome measured by the combined incidence of death and severe neurodevelopmental disability in survivors at 18 months of age (OR 2.06, $p = 0.05$ and OR 1.96, $p = 0.04$, respectively) [18].

In sum, in infants undergoing TH for moderate and severe HIE, a normal EEG at any time suggests a favorable outcome. Interpretation of an abnormal EEG should be delayed until 36 h to allow for a more accurate prognosis. Infants who do not recover a normal EEG background pattern in the first 48 h after HIE are more likely to have poor outcome, with a high mortality rate. The development of a sleep–wake cycle after TH also provides important prognostic information. The median time of onset of sleep–wake cycle in hypothermic neonates is 36 h. The failure to establish this cycle is a strong predictor of death and disability after HIE. The odds ratio for poor outcome increases by 1.05 for every 1 h delay in developing sleep–wake cycle [19].

## EEG Use During Therapeutic Hypothermia in Children

In contrast to HIE, there are no data supporting the use of TH in older children. While a wealth of preclinical data indicate its efficacy, studies in TBI or out-of-hospital CA have either shown no benefit (TBI and CA) or potential harm (TBI). For other conditions such as stroke, cerebral edema in acute liver failure, or diabetic ketoacidosis, there are insufficient data to make any recommendations about the efficacy of TH. At present, TH is recommended to support reduction in intracranial pressure in children with severe TBI. Accordingly, the published experience of EEG monitoring and TH in non-neonates is sparse.

### Cardiac Arrest

For the foreseeable future, TH will not be a standard for care for neurologic resuscitation after out-of-hospital pediatric CA [4]. In this study of 260 children, TH (2 days of cooling to 33.0 °C followed by 3 days of controlled normothermia) did not confer any benefit at 1 year recovery. A study of TH for in-hospital CA is in

progress. Two single-center prospective studies describe a small number of children with CA undergoing TH and concurrent EEG monitoring [20, 21]. Both studies observed children managed with the standard adult TH protocol after CA and specifically explored the correlation between vEEG background and clinical outcome. Monitoring consisted of continuous vEEG during hypothermia (24 h), rewarming (12–24 h), and the 24 h period following return to normothermia. Since EEG monitoring was initiated after TH, the impact of hypothermia on EEG background and seizure activity cannot be determined.

In these studies, approximately half of the patients had electrographic seizures, of which 2/3 presented in SE. The onset of seizures was variable and occurred any time beginning after 6 h of TH up to the start of rewarming. Most patients ultimately developed generalized electrographic seizures (at onset or after generalization of focal onset). Some patients not under neuromuscular blockade presented with myoclonic seizures and myoclonic SE. EEG background patterns during TH for CA have been characterized as normal for age (continuous and reactive tracings), mildly or moderately abnormal (slow and attenuated pattern, continuous but unreactive tracings), and severely abnormal (burst suppression and excessive discontinuity). A severely abnormal background is a positive predictive factor for seizure activity compared to a mildly or moderately abnormal background (sensitivity of 88 %, specificity of 100 %, and $p<0.01$). The presence of interictal epileptiform discharges also predicts presence of seizure activity (sensitivity 56 %, specificity 100 %, $p=0.01$). The EEG patterns during TH are diverse, ranging from reactive and continuous to discontinuous and (less commonly) attenuated and featureless.

EEG patterns during rewarming and normothermia are also variable. Of note, all initial EEGs during TH with a slow or attenuated but continuous background remained stable or improved over the rewarming and normothermia period. Patients with EEG showing discontinuous pattern remained with a similar pattern over time. The EEGs with an initial pattern of suppression had a most variable evolution. The majority worsened and none progressed to a normal background. These EEG changes during rewarming reflect a combination of the natural evolution of brain injury, TH, and the effects of therapies. Figure 2 illustrates a 2-month-old girl with a sudden CA of unknown origin cooled to 35.5 °C for controlled normothermia with multiple electrographic seizures and a discontinuous low-voltage record with slowing.

During hypothermia and normothermia, patients with continuous but unreactive EEG were 11 and 27 times, respectively, more likely to have a poor outcome than those with continuous and reactive tracings. Similarly, patients with discontinuous, suppressed, or burst suppression pattern were 35 and 18 times more likely to have a poor outcome than those with continuous and reactive tracings. Of note, only one patient with discontinuous, suppressed, or burst suppression pattern had favorable clinical outcomes. Patients with reactive and continuous EEG findings had a better survival rate compared to patients with discontinuous EEG or burst suppression pattern (60 % vs 29 %, $p<0.01$). A continuous and unreactive, discontinuous, or suppressed EEG was also correlated with unfavorable outcomes measured by mortality and Pediatric Cerebral Performance Category score.

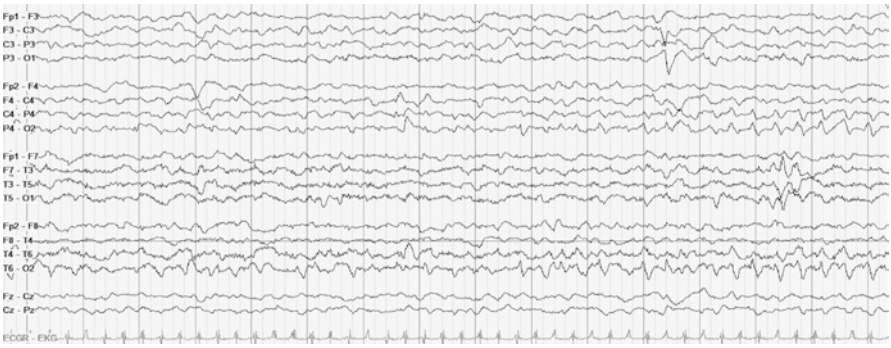


**Fig. 2** EEG of a 2-month-old girl with a sudden cardiac arrest of unknown origin, with temperature maintained at 35.5 °C for controlled normothermia. There are multiple electrographic seizures of left or right occipital onset and a discontinuous low-voltage record with slowing that shifts in laterality

A prospective randomized study of TH for in-hospital pediatric CA is in progress (https://www.thapca.org/index.html). The results of this study will determine whether there is any future role for TH for these patients. If so, the current experience suggests that the risk for electrographic seizures and SE is high for children undergoing TH after CA and is greater than that of other critically ill children. There is a good evidence to support the use of continuous EEG monitoring in these patients given both the increased risk for SE and the common use of pharmacologic paralysis. Initiation of the continuous EEG may be delayed to 6 h and even up to 12 h after the acute insult. Following TH, seizure burden during rewarming is considerable, and EEG should be continued at least 24 h after normothermia, as seizures occurring during the rewarming period may be prolonged. A limited electrode montage for seizure detection purposes may be efficient for monitoring and seizure screening, as most seizures are generalized. Importantly, the implication of different strategies for anticonvulsant medication treatment in this population has never been studied, and these studies did not address the issue of treatment of the electrographic seizures. EEG background changes during the evolution of brain injury following CA, including reactivity and continuity, provide important prognostic information (Table 1). The current literature on EEG changes with TH during CA does not allow to distinguish between the effects of TH, the evolution of brain hypoxic ischemic injury, and the response to medications including anticonvulsants.

## Extracorporeal Membrane Oxygenation

Infants undergoing ECMO are at high risk for ischemic, embolic, and vascular insults and seizures. As most of these patients are sedated and sometimes paralyzed, assessment of their neurological status with a physical exam is limited. A single study from the United Kingdom explored the effect of mild hypothermia on aEEG in infants undergoing ECMO for potential reversible respiratory or cardiac failure

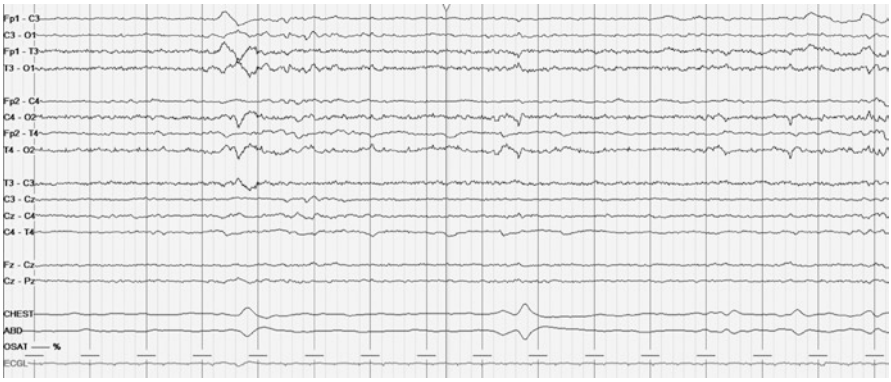


**Fig. 3** EEG of a 2-day-old neonate, 38-week postconceptional age, on ECMO for respiratory failure secondary to congenital diaphragmatic hernia and cooled to 34 °C for hypoxic ischemic encephalopathy (HIE). This abnormal study is consistent with a moderate to severe degree of diffuse cerebral dysfunction

[22]. In this study, 26 infants were divided into groups with different temperature goals (ranging from 34 to 37 °C). Initiation of aEEG within the first 6 h following ECMO cannulation and concomitant TH was achievable in most infants (85 %). Monitoring was pursued for 90–120 h in 80 % of subjects. By aEEG criteria, subclinical seizures were recorded in two patients; one of these patients was noted to have cerebral hemorrhage on cranial ultrasound 24 h later. In this study, there was no difference in aEEG voltage (upper and lower margins) during the last 6 h of cooling and the first 6 h of rewarming. An illustrative EEG of a neonate on ECMO for respiratory failure secondary to congenital diaphragmatic hernia and cooled to 34 °C for HIE demonstrates a moderate to severe degree of diffuse cerebral dysfunction (Fig. 3). In the context of a limited literature on the topic, no data correlate the EEG characterization and evolution to clinical outcome.

## Status Epilepticus

There is no standardized hypothermia protocol for refractory SE in children. In total, 13 children with diverse pre-existing comorbidities, etiologies, and duration of SE have been reported. All these patients had failed conventional treatment of seizure control with antiepileptic drugs. The largest case series in the pediatric population reported the use of mild to moderate hypothermia, ranging from 32 to 35 °C, to achieve seizure control [23]. All five children were monitored with continuous EEG and most demonstrated low-amplitude burst suppression within 2–13 h at goal temperature. The specific EEG changes during TH were variable and included progression from parieto-occipital to limited and attenuated posterior epileptiform activity, followed by low-amplitude burst suppression, rhythmic left central and midline spike and wave discharges progressing to burst suppression, slowing of electrographic burst frequency, and finally attenuation of ictal discharges. Similar to

the reported experience following CA and HIE, different EEG patterns also emerge during rewarming and no consistent pattern was observed. Overall, the efficacy of TH as a rescue therapy for refractory SE in children is unproven, and there are insufficient data to draw conclusions about EEG rhythms as indicators for prognosis for recovery or response to therapy.

## Acute Liver Failure

In children, only one case report explores the use of TH as a treatment of neurological complications of acute liver failure in neonate with herpes simplex virus-associated acute liver failure [24]. During hypothermia, EEG monitoring showed a slow and attenuated background with infrequent bitemporal epileptiform discharges. The day after rewarming, the EEG displayed intermittent runs of vertex spikes, consistent with subclinical seizures, and medical therapy of seizures was tailored accordingly. While the neurologic complications for acute liver failure are the primary determinant of outcome in children and EEG background abnormalities are a biomarker for poor outcome, there is no proven role for TH in children at present.

### Conclusion

TH in neonates with HIE is established as a standard of care, and EEG monitoring is an essential tool in the management of these patients, who are at high risk for electrographic seizures and SE. A growing body of literature supports the use of continuous EEG monitoring in pediatric neurocritical care including severe TBI, refractory SE, ECMO, CA, and coma. However, with the exception of HIE, none of these other conditions have evidence supporting the use of TH to improve outcome. Thus, our understanding of EEG changes during hypothermia is at present likely to be limited to HIE. In the longer term, studies using continuous EEG during TH will also require consensus on the definitions of specific EEG abnormalities across centers, standardized scoring systems for EEG severity, and better understanding of the relationship between anticonvulsant treatment and EEG changes. With further research on TH and better understanding of the conditions for which this promising therapy could be beneficial, EEG monitoring may help the clinician select appropriate patients, guide management, and provide essential information for neurological prognostication.

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# Medication-Induced Seizures and Status Epilepticus

22

Deepti Zutshi

## Contents



D. Zutshi, MD
Department of Neurology, Wayne State University,
4201 St. Antoine, UHC-8A, Detroit, MI 48201, USA
e-mail: dzutshi@med.wayne.edu



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## Introduction

Drug-induced seizures (DIS) were first described in the literature in the 1950s after the psychotropic drugs chlorpromazine and imipramine were observed to cause secondarily generalized tonic-clonic seizures [1]. In the mid-twentieth century, stimulants such as pentylenetetrazol and penicillin, which were described to have caused seizures in humans, were also used to create animal models for epilepsy research [2]. DIS are not considered to be epilepsy. The myriad of causes can be due to direct medication effect on brain receptors, withdrawal effects from antiepileptic medications and benzodiazepines, and medications causing electrolyte disturbances.

DIS can present with any phenotype. Generalized tonic-clonic seizures are seen more commonly in drug-induced seizures, whereas simple partial seizures are rare [2]. Convulsive as well as nonconvulsive status epilepticus (NCSE) secondary to drug intoxication has been reported in the literature. It is estimated that drug-induced seizures may result in status epilepticus 5–15 % of the time [3, 4]. The incidence of DIS of any phenotype is not clearly known. Commonly quoted figures from retrospective analyses include 0.08 % from the Boston Collaborative Drug Surveillance Program, which reviewed 32,812 patients, and 1.7 % from an outpatient neurology

clinic that reviewed 3155 patients [4, 5]. A prospective, observational study viewed all cases of DIS that were reported to the San Francisco Division of California Poison Control System over a 1-year period. Of the 121 patients included in the analysis, the causes for DIS in descending order were antidepressants (33.9 %), stimulants (including cocaine, MDMA, and amphetamine) (14.9 %), anticholinergics (9.9 %), isoniazid (INH) (6.6 %), antiepileptic drugs (AEDs) (11.6 %), and others (23.1 %). Twelve patients (10 %) had status epilepticus and ten of these patients were refractory to benzodiazepines [3].

The risk of developing DIS escalates in patients with a personal or family history of epilepsy or with a preexisting abnormal electroencephalogram (EEG). Breakdown of the blood-brain barrier (BBB) as can be seen in those with tumor, trauma, or cardiopulmonary bypass can also predispose toward DIS. Patients with an age greater than 50 years or less than 1 year are at higher risk as well as patients with reduced drug clearance secondary to renal failure or insufficiency. There is also a trend toward a higher risk of DIS in a patient with a baseline general illness (e.g., sepsis, hepatic encephalopathy) [2, 6, 7]. DIS may present a diagnostic challenge and suspicion should be kept in patients presenting with new onset seizures. A comprehensive medical history and physical examination should be undertaken. Patients with a known history of epilepsy should have drug levels drawn. There should be a low threshold for a toxic screen.

Patients who are comatose and not improving should be considered for electroencephalogram monitoring to evaluate for NCSE. In the intensive care setting, the incidence of nonconvulsive status epilepticus has been estimated to range from 8 to 37 % [8, 9]. In a study of over 200 patients who presented with coma and no overt signs of seizures and who underwent EEG, 8 % had electrographic status epilepticus. Of these patients, 5 % were from alcohol or AED withdrawal and another 11 % were of unknown etiology. The rest of the cases had some form of brain pathology, infection, or metabolic derangement [8].

Much of the literature of drug-induced NCSE or nonconvulsive seizures (NCS) is case reports or series that describe, rather than provide, EEG samples. Some describe NCSE as having generalized periodic discharges (GPDs) often with triphasic morphologies. These patterns often overlap with EEG findings seen in postanoxic injury, neurodegenerative disorders, and toxic/metabolic encephalopathies. As such, the question of whether these drug toxicities are truly NCSE or encephalopathy is a contentious issue among electroencephalographers. Most consider a true diagnosis of NCSE if (a) there is evolution of waveforms, (b) the frequency of discharges is 3 Hz or more, or (c) there is clinical or electrographic improvement with the administration of antiepileptic drugs (AEDs), usually in the form of benzodiazepines [9].

This chapter provides an overview of drugs and agents commonly associated with seizures. Those which are reported to cause NCS/NCSE are mentioned specifically. In the management of patients with known status epilepticus, care should be taken to avoid these agents if possible or to monitor for NCSE in the setting of clinical deterioration. Table 1 describes commonly prescribed medications that are associated with seizures.

**Table 1** Drugs that have been reported to cause seizures or status epilepticus

| Drug class | Drugs |
|---|---|
| *Analgesics* | Meperidine[a], opioids, tramadol |
| *Anesthetics* | |
| General anesthetics | Enflurane, isoflurane, sevoflurane |
| Intravenous anesthetics | Propofol, ketamine |
| Local anesthetics | Lidocaine, bupivacaine, procaine |
| *Antibiotics* | |
| Beta-lactams | Penicillins, cephalosporins[b] (all generations), carbapenems |
| Fluoroquinolones | Ciprofloxacin, levofloxacin |
| Antituberculosis | Isoniazid[a] |
| Nitroimidazole | Metronidazole |
| Antimalarials | Chloroquine, mefloquine |
| *Antidepressants* | |
| Tricyclic antidepressants | Imipramine[a], clomipramine, amoxapine, amitriptyline |
| Maprotiline (tetracyclic antidepressant) | Maprotiline |
| Bupropion | Bupropion |
| Selective serotonin reuptake inhibitors | Fluoxetine, sertraline, paroxetine |
| Lithium | Lithium |
| Typical antipsychotics | Chlorpromazine, haloperidol, trifluoperazine, pimozide, fluphenazine |
| Atypical antipsychotics | Clozapine[a], olanzapine, risperidone |
| *Antiepileptic drugs (AEDs)* | Benzodiazepines, carbamazepine, tiagabine, vigabatrin, lamotrigine, levetiracetam[b] |
| *Antihistamines* | Diphenhydramine, desloratadine |
| *Antineoplastic agents* | |
| Alkylating agents | Ifosfamide[b], cisplatin, chlorambucil |
| Antimetabolites | Cytarabine |
| Vinca alkaloid | Vincristine |
| *Beta-blockers* | Propranolol |
| *CNS stimulants* | Cocaine, theophylline[a], caffeine, methylphenidate, MDMA, other amphetamines |
| *Contrast* | |
| Intravenous | Iodinated contrast |
| Intrathecal | Metrizamide, iopamidol |
| *Immunosuppressants* | Cyclosporine, interferon alpha, methotrexate |
| *NSAIDs* | Aspirin, mefenamic acid |
| *Miscellaneous* | Allopurinol, cimetidine, thyrotropin-releasing hormone, bromocriptine, methyldopa, verapamil, insulin |

[a]Indicates higher potential to induce seizures

[b]Indicates drugs reported to cause nonconvulsive seizures or status epilepticus [2, 12]

## Antidepressants

Antidepressants can have anticonvulsant and proconvulsant properties depending on their effects on neurotransmitters. Higher levels of monoamines such as dopamine, noradrenaline, adrenaline, and serotonin can reduce the seizure threshold. As such monoamine oxidase inhibitors will decrease the seizure threshold. Dopaminergic chemicals will increase the seizure threshold, whereas dopamine receptor blocking agents, such as antipsychotics, will decrease the threshold. The noradrenergic system can both suppress and induce seizures, and its effect appears to be dose dependent, especially with tricyclic antidepressants, which can block presynaptic norepinephrine reuptake. There is also evidence that antidepressants may block the GABA receptor, another mechanism for decreasing seizure threshold. Furthermore, long-term use of antidepressants can downregulate α-adrenergic receptors resulting in a delayed exacerbation of seizures. The role of serotonin in seizure exacerbation is controversial with animal models showing both proconvulsant and anticonvulsant properties [10]. In general, selective serotonin reuptake inhibitors (SSRIs) are considered to carry a lower risk of seizures than tricyclic or tetracyclic antidepressants [6].

### Bupropion

Bupropion is a monocyclic antidepressant and indicated for smoking cessation. The incidence of seizures has been reported to be 0.2–0.4 % [10]. At least half of these patients had predisposing risk factors for epilepsy. There appears to be a dose-dependent increase for the risk of seizures, especially over 450 mg per day. The seizures also seem to occur within 6 weeks of starting the medication. Long-acting forms of bupropion (IR and ER) have resulted in seizures, usually with overdose, with reported incidence of 21 %. Treatment with clonazepam has been suggested as efficacious in treating bupropion-induced seizures [11].

### Tetracyclic Antidepressants

Maprotiline and amoxapine are tetracyclic antidepressants introduced in the early 1980s. Maprotiline was reported to cause seizures in 0.4 % of the manufacturer's clinical trial of 6100 patients. It has a strong lipophilic affinity and high brain concentrations that block the presynaptic uptake of norepinephrine. Unlike tricyclic antidepressants, the pro-convulsive effects of maprotiline appear to be more immediate, usually within 1 week of starting the medication [10]. Amoxapine intoxication is associated with an incidence of seizures as high as 36 % with some suggestion of severe, prolonged seizures [12].

### Tricyclic Antidepressants (TCAs)

TCAs are traditionally prescribed for the treatment of depression and other mood disorders but currently have a broader scope of use in peripheral neuropathy and headaches. Animal studies and in vitro studies show that tricyclic antidepressants have convulsive and anticonvulsant properties due to an increase in biogenic amines such as norepinephrine and serotonin [10]. Since imipramine was first introduced to the market in 1958, tricyclic antidepressants have been known to cause seizures. In the early clinical trials for imipramine, the rate of seizures was 4 %. Other studies, of which only one was prospective, showed an incidence of seizures of 1–2 % [1, 10]. In cases of TCA overdose, generalized tonic-clonic seizures have been reported in 4 % of cases [12]. Traditional first-line treatment with benzodiazepine, phenytoin, or phenobarbital has been reported to be effective in these cases. Electroencephalograms performed on patients taking tricyclic antidepressants have shown activation or aggravation of abnormal waveforms in patients with a known history of epilepsy or who had preexisting abnormal EEGs. They were not shown to generate new abnormal EEG activity [6].

### Selective Serotonin Reuptake Inhibitors (SSRIs)

SSRIs are generally considered to have a lower risk of seizures among antidepressants and may even have anticonvulsant properties. However, case reports and small case series of seizures associated with the use of fluoxetine, sertraline, and paroxetine have been reported. The risk associated with SSRIs is considered to be about 0.2 % [6]. The use of fluoxetine in combination with tricyclic antidepressants and bupropion has been known to also cause seizures [2].

## Antipsychotics

Approximately 1 % of all patients on antipsychotic drugs will have seizures related to drug use. Risk factors predisposing patients to have seizures while on antipsychotic drugs include a history of epilepsy, electroconvulsive therapy, history of a brain lesion from trauma, tumor or previous surgery, treatment with two or more antipsychotic agents, or a large dose of antipsychotic medications [2]. Chlorpromazine and clozapine have a higher incidence of causing seizures and changes on EEG. Haloperidol, fluphenazine, pimozide, and trifluoperazine have a lower seizure potential among the antipsychotic drugs. The newer generation antipsychotics, such as olanzapine and risperidone, have had reports of drug-induced seizures in the literature but are generally considered to be less epileptogenic [6].

### Clozapine

Clozapine is a dibenzodiazepine derivative with a high affinity for the D4 receptor and a low affinity for the D2 receptor. It is used in the treatment for refractory schizophrenia. During clinical trials, 2.8 % of 1418 patients had seizures with a

10 % cumulative risk after 10 years of treatment [13, 14]. Doses greater than 600 mg/day are associated with the highest rate of seizures. It is estimated that the incidence of seizures at a dose of 600–900 mg/day is 5 %, for 300–599 mg/day the risk is 3–4 %, and for doses less than 300 mg/day, the risk is 1–2 % [13, 15]. Seizure types including generalized tonic-clonic seizures, myoclonic seizures, and 3 Hz status epilepticus have been described in the literature. In a series of 5629 patients exposed to clozapine, 1.3 % had generalized tonic-clonic seizures and 33.8 % of these patients had recurrent seizures. The average number of days from the start of treatment to developing seizures was 42. Patients who were successfully weaned from their total dosage had no recurrence of their seizures [13].

There appears to be affinity of the drug for the temporal regions and these are where the EEG changes are usually found. Another mechanism that has been proposed includes kindling models in the hippocampi [15]. In a series of 12 patients who underwent EEG recording, eight showed interictal epileptiform abnormalities. Two of these patients did not experience clinical seizures [16]. In another retrospective study of 283 patients who had EEGs performed prior to, during and after treatment with clozapine, 61.5 % showed abnormalities [17]. However, these findings were not predicative of clinical seizures. The application of EEG screening prior to the use of clozapine has not been established and is controversial [15].

Among the psychiatric community, the general trend for treatment of clozapine-induced seizures is to first attempt to reduce the dose. If the seizure is recurrent or if the patient is refractory to reduction of the clozapine, then an AED may be considered. Valproic acid appears to be the antiepileptic drug of choice as drug-inducing AEDs such as phenytoin, phenobarbital, and carbamazepine lower the levels of clozapine. Furthermore, carbamazepine in conjunction with clozapine has a higher risk of bone marrow suppression. Other treatment options include lamotrigine, gabapentin, and topiramate [2, 15].

## Lithium

Lithium is proposed to have proconvulsant and anticonvulsant properties. Seizures have been reported in cases of therapeutic serum levels as well as lithium poisoning [12, 18]. EEG may show diffuse slowing or generalized periodic discharges [19].

## Phenothiazines

The aliphatic phenothiazines which include chlorpromazine, promazine, and triflupromazine have a much higher risk of seizures then the piperazine phenothiazines (fluphenazine, prochlorperazine, perphenazine) [12]. In a 4-year prospective study following 859 psychiatric patients on chlorpromazine without risk factors for epilepsy, 1.2 % developed seizures. Those receiving doses greater than 1000 mg/day had a seizure incidence of 9 %, whereas doses less than 1000 mg per day had a seizure incidence of 0.5 % [6, 12, 20]. In comparison to the phenothiazines, other classes of antipsychotics including haloperidol, pimozide, quetiapine, olanzapine, and risperidone are considered to have lower epileptogenic potential [6, 12].

## Antiepileptic Drugs (AEDs)

Antiepileptic drugs can also cause a paradoxical increase or exacerbation of seizures. Risk factors for this include young children with epileptic encephalopathies, patients on polytherapy, or patients with multiple seizure or seizure types. There may be multiple causes of AEDs inducing seizures. Drug-drug interactions can lead to an increase or decrease in the serum level of other drugs. Incorrect selection of the AED may worsen a particular type of epilepsy syndrome. A classic example of this is the use of carbamazepine in a patient with primary generalized epilepsy which can exacerbate seizures or induce new seizure types including typical and atypical absence, atonic, tonic, myoclonic seizures and absence status epilepticus. Toxic levels or overdose of certain AEDs can cause a paradoxical worsening of seizures as can be seen with phenytoin or carbamazepine. Electrolyte abnormalities as a secondary effect of some drugs can lead to seizures such as carbamazepine or oxcarbazepine causing hyponatremia. A sudden cessation or rapid withdrawal of medication may cause drug-induced seizures such as can be seen with benzodiazepines or barbiturates. Changes in the absorption or bioavailability of the active metabolite may cause seizures. An example is worsening seizures in a pregnant woman taking lamotrigine or levetiracetam due to increased relative clearances.

### Benzodiazepines

The most common cause of benzodiazepine-inducing seizures is rapid withdrawal. However, the use of benzodiazepines may precipitate tonic seizures or status. Case reports and case series of children with Lennox-Gastaut syndrome given intravenous benzodiazepines causing absence status or tonic status epilepticus have been reported. The EEGs in these five patients showed numerous slow spike-waves, which peaked concomitantly with serum levels of the benzodiazepines [21, 22].

### Carbamazepine

Carbamazepine is well recognized to worsen or induce seizure activity in primary generalized epilepsies. EEGs in these cases have shown an increase of generalized spike-wave discharges. Myoclonic status has been reported in a case of Angelman syndrome. Worsening atypical absence and tonic seizures in patients with benign epilepsy with centro-temporal spikes (BECTS) have also been reported after carbamazepine use. Case reports have also been published on carbamazepine causing status epilepticus, which was reversible by lowering the dose [2, 23].

### Lamotrigine

The use of lamotrigine in myoclonic epilepsies is well known to aggravate myoclonus. Myoclonic status induced by lamotrigine in a child with Lennox-Gastaut syndrome has been reported. Worsening of absence seizures in BECTS has also been reported [22].

### Levetiracetam

Levetiracetam has also been shown to induce or worsen seizures in patients. In a series of 70 adults and 44 children with refractory epilepsy, levetiracetam was used as adjunctive treatment. In the adult group, 18 % of patients had an increase in their seizure frequency and three adults had status epilepticus within 4 weeks of starting levetiracetam. In the children subgroup, 43 % had an increase in seizure frequency at a dose greater than 30 mg/kg/day [24].

### Tiagabine

Multiple case reports have been reported of tiagabine causing absence status in idiopathic generalized epilepsies as well as focal NCSE. These cases of status were generally in patients taking over 40 mg/day. However, a case of tiagabine with a dose as low as 20 mg/day may also result in focal status [25]. The pathophysiology is theorized to be due to higher doses blocking GABA reuptake and depleting intercellular GABA [22, 25].

### Valproic Acid

A case of valproic acid inducing tonic status has been reported in the literature in a patient with mild cognitive impairment [26]. Focal NCSE has been reported secondary to hyperammonemic encephalopathy due to valproic acid 4 days after initiation of treatment [27]. Multiple case reports on the carbapenem class of antibiotics inducing seizures in patients on valproic acid treatment with and without a history of epilepsy have also been published. Drops in VPA concentrations can be as high as 58 % after initiation of carbapenems [28].

### Vigabatrin

Vigabatrin can aggravate absence seizures in patients with childhood absence epilepsy. It can also induce myoclonic seizures and status in myoclonic epilepsies [22].

## Antibiotics

Since the advent of penicillin, antibiotics in the class of beta-lactams and fluoroquinolones have been reported to induce seizures by lowering the seizure threshold [29]. Risk factors for seizures induced from antibiotics include renal insufficiency, age greater than 50 years, high doses or serum levels, and alterations of the blood-brain barrier (tumor, stroke, cardiopulmonary bypass surgery) [7]. Seizure types can include tonic-clonic seizures as well as nonconvulsive seizures or status epilepticus

[7]. In general, patients who have antibiotic-induced seizures do not require chronic AED treatment, and if they do, then short-term treatment can be considered.

In a retrospective review of 112 consecutive patients, who were diagnosed with status epilepticus, 10 % were attributed to antibiotic usage. These patients had comorbidities including hepatic failure (41.7 %), renal failure (50 %), and abnormal brain lesions diagnosed on MRI (77.8 %). The most common antibiotics in these cases were cephalosporins and fluoroquinolones, sometimes used in combination [30].

Beyond the direct effects of antibiotics on the central nervous system as described below, antibiotics may also induce seizures by altering serum levels of AEDs. For example, carbapenems can reduce levels of valproic acid as much as 66 % as published in a case report. Chloramphenicol can increase the levels of phenytoin and clarithromycin. Erythromycin and isoniazid (INH) may increase carbamazepine levels. As such, recommendations are to monitor levels of AEDs prior to starting antibiotics [7].

## Carbapenems

Carbapenems are a class of beta-lactam antibiotics with broad-spectrum coverage and are used commonly in the setting of hospital-acquired infections. Imipenem/cilastatin has been reported to cause seizures in up to 20 % of patients who have renal dysfunction and an organic brain lesion [7]. Like fluoroquinolones and β-lactams, the epileptogenicity of the carbapenems is thought to be due to the binding of GABA receptors. Various prospective trials for imipenem suggested seizure rates of 0.2–0.9 % due to the drug itself. With other confounding factors such as the use of multiple antibiotics, a history of seizures or continued seizures despite stopping the carbapenem, the incidence was closer to 3 % [10]. In a meta-analysis looking at carbapenems and seizures, carbapenems were more epileptogenic than competitor antibiotics (odds ratio of 1.87, 95 % confidence interval 1.35–2.59). Imipenem was specifically more epileptogenic and this was a dose-dependent effect. Patients receiving $\leq 2$ g/day had a risk difference (RD) of three patients per 1000 with seizure, whereas patients receiving $>2$ g/day had an additional eight patients per 1000 with seizure. The meta-analysis showed no significant difference in seizure risk between imipenem and meropenem, even though meropenem is considered less epileptogenic of the two [30, 31].

## Cephalosporins

Cephalosporins are used for surgical prophylaxis and for the treatment of pneumonia, strep throat, staphylococcal infections, sexually transmitted diseases (STDs), and urinary tract infections. Seizures have been reported with each generation of cephalosporins. The cephalosporins act as GABA inhibitors and may increase glutamate levels [29]. Increased risk of seizures is associated with reduced creatinine

clearance and organic brain lesions. The third- and fourth-generation cephalosporins (e.g., ceftazidime and cefepime, respectively) seem to have a higher incidence of seizures [10, 29, 32].

The onset of seizures is generally 3–21 days after starting treatment. Cefepime in particular has been reported to cause NCSE in the setting of an elderly patient recovering from renal failure [29, 33]. Furthermore, cefepime has also been reported to cause cortical myoclonus. EEGs in cefepime-associated seizures may frequently show generalized discharges that are often of triphasic morphology. These have been interpreted as NCSE [32]. As mentioned in the introduction, these cases are often challenging to distinguish between true NCSE and encephalopathy.

## Fluoroquinolones

Fluoroquinolones are used to treat urinary and respiratory tract infections, STDs, and gastrointestinal and soft tissue infections. Many case reports of seizures induced from ofloxacin, ciprofloxacin, norfloxacin, and alatrofloxacin have been reported. Fluoroquinolones bind to GABA receptors in the brain and possibly act as an agonist on the NMDA receptor causing CNS activation [10]. The incidence of seizures with fluoroquinolones is estimated to be 0.1–0.5 %. Ciprofloxacin is estimated to induce more seizures than levofloxacin (0.5 % vs. 0.1 %, respectively) [7].

## Isoniazid

Isoniazid is used in the treatment of tuberculosis. Intoxication with ingestion of over 35–40 mg/kg generally produces a syndrome of seizures, metabolic acidosis, respiratory depression, and coma roughly 30–120 min after ingestion [34]. INH is thought to produce seizures by depleting pyridoxine, a required cofactor for the production of GABA by glutamic acid decarboxylase. Case reports of status epilepticus with overdoses have been reported. However, therapeutic doses of 14 mg/kg/day twice a week produce seizures in 1–3 % of patients [12]. Treatment with IV pyridoxine can be used to terminate seizures [34, 35]. In severe cases of renal failure, dialysis may be considered as well.

## Metronidazole

Metronidazole is used to treat gastrointestinal, skin, vaginal, joint, and respiratory infections. A case report of a patient with treatment of the drug resulting in NCSE and death has been reported [36]. In a systematic review of the literature, of 64 patients with metronidazole-induced neurological toxicity, 15 % had seizures [37]. Prolonged use is thought to lead to a higher risk of seizures [7, 36]. In general, cessation of the antibiotic is associated with improved prognosis.

### Penicillins

Penicillins are well known to induce seizures in patients and have been used in the creation of animal models. Penicillins bind to the GABA receptor and block its activation. A case report of newer generation penicillin antibiotics such as piperacillin/tazobactam inducing NCSE has also been reported [38].

### Antimalarials

Chloroquine and mefloquine are well known to induce seizures, particularly in patients with a known history of epilepsy, even with prophylactic doses. The mechanism of seizure induction is unclear, although the reduction of GABA concentrations by inhibiting glutamate dehydrogenase has been proposed [2, 39].

## Anesthetics

Anesthetics can also have proconvulsant and anticonvulsant properties. Risk factors include a history of epilepsy and oxygen toxicity. Patients with epilepsy are routinely asked to have clearance prior to surgery. Management to avoid anesthetic-related seizures include avoiding drugs known to reduce the seizure threshold, continued use of the patient's AEDs to maintain serum levels, avoidance of electrolyte disturbances, and possible use of prophylactic AEDs in patients at high risk, such as those with organic brain disease [2].

### General Anesthetics

Of the general anesthetics, enflurane, isoflurane, and sevoflurane have all been reported to cause seizures including myoclonic and tonic-clonic seizures [2]. In a systematic review of 129 patients without risk factors for epilepsy, the incidence of seizures due to sevoflurane was 0–12 % and usually occurred within the first 90 min of induction. EEG changes showed epileptiform activity in 80–100 % of cases. The mechanism of epileptogenesis is thought to be a strong inhibitory effect on GABA activity [10]. Enflurane use has been associated with delayed seizures as well as EEG abnormalities that can persist for several days [12]. Nitrous oxide has also been linked to inducing seizures [12].

### Intravenous Anesthetics

Intravenous anesthetics can also have paradoxical proconvulsant properties. Propofol, used in the induction of anesthesia, has been reported to cause focal and

generalized seizures, usually within the first 33 min of infusion. Risk factors include organic brain lesions [2, 10]. Ketamine is an intravenous NMDA receptor antagonist used as an anesthetic. It has also been reported to cause tonic and tonic-clonic activity. Subdural depth electrodes recording in the limbic and thalamic regions have shown subcortical seizure activity that is not always seen on the surface electrode with ketamine use in these patients [12].

### Local Anesthetics

In general, local anesthetics may induce seizures if taken as an overdose, if unintentionally infused into a blood vessel, or if absorbed through the mucosa (oropharyngeal applications). Lidocaine in doses<4 mg/L is an anticonvulsant but in higher and cumulative doses is known to produce seizures. Its mechanism is to close chloride channels in the synapse which hyperpolarizes the membrane. In cases of liver failure or congestive heart failure, lidocaine can accumulate in the brain due to increased cerebral blood flow from hypoxia or hypercapnia. Treatment with IV succinylcholine and non-rebreather mask with 100% oxygen has been recommended rather than the use of benzodiazepines in lidocaine-induced seizures. Epidural anesthetics in high doses that have inadvertently been injected into a blood vessel have also been reported to cause seizures [2, 12].

## Antineoplastic Agents

### Alkylating Agents

Ifosfamide is used in the treatment of lymphoma and solid tumors. It is associated with complications such as hemorrhagic cystitis and myelosuppression. However, in doses greater than 1.5 g/m$^2$/day, it may cause neurotoxicity. Case reports of NCSE occurring within 72 h of infusion have been reported. The EEG shows generalized periodic discharges with triphasic morphology and spike and wave discharges in up to 65% of patients. Discontinuation of ifosfamide generally leads to reversal of the neurological dysfunction [40].

Cisplatin is used in the treatment of solid tumors. It is well known to cause ototoxicity, nephrotoxicity, and neurotoxicity in the form of peripheral axonal sensory neuropathy. However, case reports of encephalopathy and focal seizures have been reported [41].

Chlorambucil is a nitrogen mustard and is used to treat chronic lymphocytic leukemia, Hodgkin and non-Hodgkin lymphoma, and Waldenstrom macroglobulinemia. In a retrospective study of 91 patients treated for nephrotic syndrome and without risk factors for epilepsy, seven developed seizures [12]. In doses greater than 5 mg/kg, generalized tonic-clonic seizures were more likely to occur [12]. The toxicity is thought to be due to by-products of the drug and acts like chloral hydrate or ethanol on the CNS [10].

### Antimetabolites

Cytarabine given in high doses intravenously may lead to seizures, encephalopathy, or an acute cerebellar syndrome in up to 14 % of cases [42].

### Vinca Alkaloids

Vincristine has the potential to cause seizures, possibly by the inappropriate release of antidiuretic hormone thereby producing hyponatremia. Some children have been reported to have seizures without hyponatremia [12].

## Antiarrhythmics

Lidocaine has been discussed earlier. Beta-blockers (propranolol and metoprolol) in therapeutic doses have been shown to have anticonvulsant properties. However, in high doses or overdoses, they can cause seizures. This may be due to hypoglycemia and bradycardia or because of their high permeability in the brain and changes in the membrane stabilization of neurons [2]. Quinine overdose has also been reported to cause seizures and usually presents with respiratory depression and coma. Treatment with intravenous benzodiazepine usually results in the control of these seizures [12].

## Immunosuppressants

### Cyclosporine

Cyclosporine is an immunosuppressant used in allogenic bone marrow transplant. In retrospective studies of patients with no risk factors, seizure risk ranged between 0.5 and 3.9 %. Most seizures occurred 2–180 days after starting treatment. Risk factors include high serum concentrations of the agent and younger age. Abnormal EEGs were found in 13 of 21 patients in a cohort of adults and children receiving cyclosporine [10]. The cause of seizures may be direct brain tissue damage [12].

### Interferon Alpha (IFN-alpha)

IFN-alpha is used as an antiviral agent in chronic viral hepatitis as well as an immunomodulatory agent in cancers of the lymphatic and hematopoietic organs. A seizure incidence of 0.7 % was found in two studies of 11,241 and 311 patients. Other studies quote seizure incidences ranging from 1 % in adults up to 4 % in children on therapeutic doses [43]. IFN-alpha is thought to cause hyperexcitability as evidenced by the fact it may stimulate spontaneous and evoked electrical activity when it crosses the blood-brain barrier [10].

### Methotrexate

Case reports of methotrexate inducing seizures in high doses, especially in young children, have been published. There may be increased risk with cranial irradiation. Status epilepticus after intracranial perfusion of methotrexate has also been reported. The exact mechanism is unknown, but increased BBB permeability, elevation of biogenic amines to lower the seizure threshold, and the degeneration of astrocytes have been postulated as causes for CNS toxicity [44].

### Tacrolimus

Tacrolimus is a calcineurin inhibitor used in organ transplantation to prevent rejection. The incidence of seizures associated with tacrolimus after transplantation may range from 9 to 20 % [45, 46]. Phenotypes generally involve secondary generalized tonic-clonic seizures, though focal seizures and status epilepticus have also been reported [46]. Isolating seizures to tacrolimus alone is difficult in these patients due to the severity of their underlying disease, other immunosuppressants, and renal and liver failure. Posterior reversible leukoencephalopathy syndrome may also be present concomitantly, producing its own increased risk for seizures [45]. Reducing the dose of tacrolimus, switching to another type of immunosuppressant, or starting AEDs may be warranted to prevent recurrent neurological complications [45].

## Analgesics

### Opioids/Meperidine

Opioid analgesics such as morphine and fentanyl can precipitate seizures and this effect can be successfully treated with naloxone. These are generally reported in children, specifically neonates. Meperidine, an opioid analog, showed in two studies of 510 sickle cell children and 67 adults with cancer, has a combined seizure incidence of 2.1 % [10]. Neither set of patients had previous risk factors for seizures. In this cohort, there was a higher incidence of seizures in the cancer population than in children (14.9 % and 0.4 %, respectively). The mechanism is thought to be the accumulation of the metabolite normeperidine, which is toxic to the CNS and has twice the proconvulsant activity [10, 12]. Seizures have been reported with both intramuscular and intravenous use. The use of a patient-controlled analgesia pump also increases the risk of seizures. Other risk factors include renal dysfunction, older age, and high accumulated doses due to chronic use, estimated to be greater than 0.8 mg/L [12, 47]. Giving naloxone in these cases can exacerbate seizure activity by blocking the anticonvulsant effects of meperidine, thus allowing normeperidine to exert a greater proconvulsant effect [47].

### Tramadol

Tramadol, a synthetic opioid analog that blocks the synaptic reuptake of serotonin and norepinephrine, is associated with reduction of the seizure threshold. In a 2.5-year retrospective chart review of patients presenting solely with tramadol poisoning to the California Poison Control System, seizures occurred in 13.7 % of 190 patients. Doses ranged as low as 200 mg up to 5000 mg. Seizures occurred within the first 6 hours in 84.6 % of patients. Single seizures were seen 80.8 % of the time. Multiple seizures were seen 11.5 % of the time. No patients were reported to have status epilepticus [48].

## CNS Stimulants

### Cocaine

Cocaine exerts its effect on GABAergic neurons by blocking sodium currents and increases serotonin levels by blocking its reuptake, which then increases excitatory processes. There is also some suggestion that it has a kindling effect after chronic use. It has been well known to induce seizures since the 1970s. Concomitant use of other stimulants and drugs can also predispose toward having seizures. A systematic review found seizure prevalence rates ranging from 0.9 to 10.4 %, a wide range due to diverse variables between studies [49]. In chronic users, lifetime seizure prevalence ranged from 1.8 to 18.1 %. In patients with a history of epilepsy, the incidence of seizures ranged from 4.6 to 6 % of patients [49]. Clinical phenotype is commonly generalized tonic-clonic seizures but NCSE has been reported [2]. Treatment of cocaine crisis usually involves beta-blockers to treat the tachyarrhythmias and benzodiazepines or phenobarbital for seizures [12].

### Methylphenidate

Methylphenidate is an amphetamine-like stimulant used to treat attention deficit hyperactivity disorder (ADHD), postural orthostatic tachycardia syndrome (POTS), or narcolepsy. The use of methylphenidate in patients with abnormal EEGs or epilepsy is controversial, and multiple surveillance articles do not show an increased risk of seizures in these patients [50].

### Methylxanthines

Theophylline is a methylxanthine used in the treatment of bronchospasms in reversible airway obstructive diseases such as asthma or chronic bronchitis. Aminophylline is used in asystolic cardiac arrest or peri-arrest bradycardia. Including caffeine,

these agents were also used to prolong seizures in electroconvulsive therapy for depression. These drugs act as proconvulsant by inhibiting the adenosine A1 receptor, which regulates hippocampal excitability. They also work by blocking production of GABA by antagonizing the enzyme pyridoxal kinase. They have also been found to increase cyclic GMP that maintains epileptic discharges and directly inhibits the GABA-A receptor. In addition, theophylline potentiates preexisting brain hyperexcitability [51]. Furthermore, blockade of adenosine A2 receptors causes vasoconstriction and leads to cerebral hypoxia that may contribute to neurological toxicity [12].

High doses of theophylline (above 20 mg/L) are known to cause arrhythmias and convulsions, including generalized and focal seizures and status epilepticus. Treatment failure to benzodiazepines and phenytoin has been well documented [51]. In a study of 78 cases of theophylline seizures, more than 90 % were refractory to diazepam with or without phenobarbital or phenytoin. The most efficacious AED may be phenobarbital but this has not been evaluated [12]. Risk factors include children under the age of 5 or elderly patients, a history of epilepsy, encephalitis, organic brain disease, and alcohol withdrawal [12]. Seizures are associated with a poor prognosis. High caffeinated beverages, such as "energy drinks," are reported to have resulted in seizures and arrhythmias [52].

### 3,4-Methylenedioxymethamphetamine (MDMA)

MDMA (ecstasy) is a phenethylamine stimulant which increases serotonin, dopamine, and norepinephrine levels. Toxicity with overdoses of MDMA may lead to seizures, hyponatremia, hyperthermia, autonomic crisis and even renal and liver failure, strokes, and death. Chronic use of MDMA induces damage and alters hippocampal processing leading to long-term effects of learning and memory, and in animal models, a proconvulsant effect toward limbic seizures can be observed [53].

## Nonsteroidal Anti-inflammatory Drugs (NSAIDs)

Aspirin toxicity in children due to salicylic acid accumulation leads to decreased glucose as well as a metabolic acidosis. In salicylate intoxication, seizures are most likely secondary to depleted glucose storage in the brain tissue despite normal serum glucoses [12]. Treatment with benzodiazepines is the first-line choice in these cases.

Mefenamic acid is an NSAID used in the treatment of menstrual pain or perimenstrual headache. Over one-third of patients who overdose on mefenamic acid present with seizures. Other NSAIDs have a lower incidence of seizures [54]. It has a short half-life of about 2 h and seizures have been described to occur within the first few hours after ingestion [12].

## Intravenous Contrast

Iodinated contrasts are used in angiography, urography, or computer tomography studies. The incidence of seizures in three large retrospective studies found seizure rates of 0.2–0.5 % of cases. Most seizures occurred within 30 min of infusion. The majority of the cases had a history of seizures or organic brain disease. In patients with brain metastases, up to 19 % have seizures after being given IV contrast [12]. The mechanism may be the high iodine content directly irritating the neuronal membrane when there is a leaky BBB. Prophylactic use of diazepam may be used in patients with known history of brain tumors, primary or metastasized [12].

Intrathecal use of metrizamide and iopamidol used for myelography, cisternography, and ventriculography has also been associated with seizures and status epilepticus [55]. The incidence ranges up to 0.6 % of patients given metrizamide [56]. Treatment with benzodiazepines appears to be effective in managing seizures induced by these radiographic contrasts [12].

## Vaccines

In the mid- to late twentieth century, there was a concern that pertussis vaccination (part of the diphtheria, tetanus, and pertussis) had a high risk of seizures and encephalopathy. The risk was reported as high as 1 in 1750 children, though many of these were febrile convulsions [57]. More recent large-scale studies found a small risk of febrile seizures (1 per 19,496 vaccinations) and afebrile seizures (1 case in 76,133 doses of DTaP) [58].

## Antihistamines

H1 antagonists are known to have some anticonvulsant response in animal models but also have been reported to induce seizures from their central anticholinergic effect, especially in patients with a history of epilepsy [2]. First- and second-generation antihistamine agents such as diphenhydramine and desloratadine, respectively, have been reported to cause seizures. Diphenhydramine is also known to cause sodium channel blockade when taken in high doses. Case reports of seizures occurring in children have been published [12]. One case of status epilepticus in an adult patient who overdosed has also been reported [59].

## Treatment of Drug-Induced Seizures

The treatment of drug-induced seizures depends on the prompt identification of the cause. In general, most seizures are self-limiting and single. About 15 % of drug-induced seizures may result in status epilepticus requiring more aggressive care [4]. First-line treatment should be to discontinue the drug if possible. Second-line

treatment would be to use agents such as benzodiazepines to terminate seizures. Failure of benzodiazepines to control seizure activity should result in the use of AEDs such as phenytoin, valproic acid, or phenobarbital.

An understanding of the medication and their various toxicities and drug-drug interactions can also help reduce the incidence of iatrogenic drug-induced seizures or worsening of seizures. For example, certain medications should be avoided in patients who are elderly, have a history of epilepsy, and have organic brain disease, in children with a history of febrile seizures, or patients who have renal insufficiency. Avoiding rapid infusion or higher than recommended doses may also help to prevent seizures, e.g., carbapenem infusions, isoniazid, theophylline, anesthetics, and meperidine [4]. In drug-withdrawal seizures, particularly with benzodiazepines and barbiturates, a slow wean would reduce the risk of seizures.

In certain specific drugs, other methods of removing the drug would be of benefit. For example, in tricyclic antidepressant poisoning where metabolic acidosis potentiates arrhythmias and toxicity, alkalinizing the urine by bicarbonate would increase TCA excretion [4]. Isoniazid overdose, which is commonly associated with seizures, can be treated with high doses of pyridoxine [4, 34]. In drug-induced hypoglycemia caused by insulin overdose, correction of the underlying metabolic derangement would be appropriate. Theophylline, lithium, and salicylate poisonings may require hemodialysis to remove the drug from the body [4]. Cocaine-induced seizures are generally short and quite responsive to phenytoin, whereas amphetamines are longer seizures and often resistant to phenytoin. In patients taking clozapine-induced seizures, first reducing the daily dose should be considered. In the setting of recurrent seizures with clozapine, many consider adding an AED for prophylaxis.

Patients in the intensive care unit represent a challenging cohort in drug-induced seizures. Severe systemic illness and other comorbidities may limit the choice of medications. In cases of clinical neurological deterioration in the form of encephalopathy, subtle motor signs, or psychosis, consideration for NCS or NCSE should be undertaken. Diagnostic tools such as continuous EEG monitoring may help to elucidate underlying neurological processes.

## Conclusion

A variety of drugs are associated with an increased risk of seizures. The mechanisms for inducing seizures are varied including direct effects on neuronal excitability and indirect effects due to systemic factors. The seizures may take on various semiologies including tonic-clonic, myoclonic, and status epilepticus including NCSE. Management requires prompt recognition of both the seizure and the underlying etiology. In comatose or encephalopathic patients, a high degree of suspicion is necessary to establish the diagnosis as it may not be clinically apparent. While immediate treatment often resembles that for seizures or status epilepticus due to other etiologies, recognition of the responsible agent can aid treatment by allowing for early removal of the offending agent and, in some cases, suggesting specific treatment modalities.

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# Super Refractory Status Epilepticus

# 23

Joseph Zachariah, Jeff Britton, and Sara Hocker

## Contents



J. Zachariah, DO • J. Britton, MD • S. Hocker, MD (✉)
Department of Neurology, Mayo Clinic, 200 1st St SW, Rochester, MN 55902, USA
e-mail: Zachariah.Joseph@mayo.edu; Britton.Jeffrey@mayo.edu; hocker.sara@mayo.edu



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## Introduction

Earlier definitions of status epilepticus (SE) were based on the duration of seizures, but newer definitions rely more on a pragmatic staging based on treatment failures (Table 1). Refractory status epilepticus (RSE) is defined as SE that continues despite administration of both benzodiazepines and an appropriately dosed second-line antiseizure drug. Depending on the semiology of the seizures and comorbidities of the patient, this stage may be treated with further antiseizure drugs or anesthesia. When seizures recur upon weaning the anesthetic agent, typically after 24 h of seizure suppression, or in the rare cases where seizure control cannot be achieved with anesthesia, status epilepticus is considered to be super refractory (SRSE). The incidence of status epilepticus has been increasing, from 3.5 to 12.5/100,000 population between 1979 and 2010. During this time hospital mortality has not changed [1].

Approximately 30–50 % of status epilepticus episodes progress to RSE [2, 3] and ~15 % of these progress to SRSE [2]. Peak incidence of SE is in a bimodal distribution with ages less than 1 and greater than 60 years. RSE does not discriminate between basic patient demographics such as age, sex, or gender. New-onset RSE without an obvious cause after initial investigations has been termed NORSE or new-onset refractory status epilepticus. This may represent a unique group of patients who are more likely to have an antibody-mediated cause.

As with seizures and status epilepticus, RSE may be simplistically categorized as convulsive or nonconvulsive and focal or generalized. These delineations have treatment implications. Convulsive seizures are easily recognized and must be controlled emergently. At the refractory stage of convulsive SE, the standard treatment is anesthesia which is highly effective at achieving seizure suppression. The semiology of nonconvulsive status epilepticus is highly varied and thus may be diagnosed after some delay when seizures are identified on the electroencephalogram (EEG) with limited or fluctuating clinical correlates. Patients may have subtle behavioral changes, confusion, or automatisms as well as an altered level of consciousness. Patients in NCSE may exhibit subtle rhythmic jerks, eye fluttering, or gaze deviation. The optimal treatment of refractory nonconvulsive status epilepticus is not well established. Compared with focal status epilepticus, generalized status epilepticus may warrant more aggressive treatment. Yet, paradoxically, both focal motor seizures and nonconvulsive status epilepticus predict development of refractoriness [3].

**Table 1** Stages of status epilepticus

| | |
|---|---|
| Stage 1: early SE | Seizure lasting 5 min *or* two or more seizures without recovery of consciousness between |
| Stage 2: established SE | Ongoing SE after appropriately dosed benzodiazepine |
| Stage 3: refractory SE | Ongoing SE after failure of benzodiazepines and an appropriately dosed second-line antiseizure drug (typically fosphenytoin, valproic acid, phenobarbital, lacosamide, or levetiracetam) or SE requiring an anesthetic agent for control |
| Stage 4: SRSE | Ongoing SE despite use of an anesthetic drug *or* recurrence of SE upon weaning of anesthesia |

*SE* status epilepticus

Forty percent of generalized convulsive SE evolves into nonconvulsive status epilepticus by the time anesthetic agents are initiated [4]. Nonconvulsive seizures after control of convulsions should be suspected in patients who do not regain consciousness within 15–30 min of the cessation of convulsions. While certain variables may suggest a prolonged postictal period, such as high doses of benzodiazepines or barbiturates or underlying cognitive impairment or structural brain disease in the setting of prolonged convulsions, these are unreliable, and only EEG can ensure adequate seizure control in this setting.

Seizures become refractory when there is excessive excitatory stimulation with glutamate via N-methyl-D-aspartate (NMDA) receptors and insufficient inhibition via Ð-aminobutyric acid (GABA). Receptor trafficking with an increase in glutamatergic receptors and a reduction in GABA receptors is thought to contribute to pharmacoresistance and perpetuation of seizures. Additionally, mitochondrial failure, electrolyte disturbances due to compromise of the blood–brain barrier, and changes in gene expression may all play a role in the development of refractoriness.

## Etiology

While the epidemiology of SRSE is not well described, it is likely to be very similar to that of RSE. Between 38 and 60% of episodes of refractory status epilepticus occur in patients with epilepsy [4, 5], among whom precipitating factors include low antiseizure drug levels, changes in drug regimen, drug intoxication or withdrawal, systemic infection, metabolic derangement, or progression of the underlying disease responsible for their epilepsy. RSE which develops in the absence of underlying epilepsy is most commonly due to acute encephalitis, stroke, brain tumor, traumatic brain injury, or drug or alcohol withdrawal. Myoclonic status resulting from hypoxic ischemic injury will be discussed in Chap. 18. A more comprehensive list of etiologies is shown in Table 2. Identification of the etiology is important for both treatment and prediction of outcome.

**Table 2** Etiologies

| |
|---|
| Structural |
| Traumatic brain injury |
| Hemorrhagic or ischemic stroke |
| Venous sinus thrombosis |
| Hypoxic ischemic brain injury |
| Polymicrogyria |
| Heterotopias |
| Schizencephalies |
| Cortical dysplasias |
| Autoimmune conditions |
| N-methyl-D-aspartate (NMDA) encephalitis |

(continued)

**Table 2** (continued)

| |
|---|
| Glutamic acid decarboxylase (GAD) antibody |
| Voltage-gated potassium channel (VGKC) antibody |
| Voltage-gated calcium channel (VGCC) antibody |
| $GABA_A$ receptor, $GABA_B$ receptor antibody |
| Alpha-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA) receptor antibody |
| Leucine-rich glioma inactivated protein 1 (LGI1) antibody |
| Contactin-associated protein-like 2 (Caspr2) antibody |
| Dipeptidyl-peptidase-like protein-6 (DPPX) antibody |
| Metabotropic glutamate receptor 5 (mGluR5) antibody |
| Hashimoto encephalopathy |
| CNS lupus |
| Central nervous system infections |
| Viral encephalitis |
| Meningitis |
| Abscess |
| Empyema |
| HIV |
| Creutzfeldt–Jakob disease |
| Cat-scratch disease |
| Progressive multifocal leukoencephalopathy |
| CNS tumors |
| Primary CNS tumors |
| Metastatic CNS tumors |
| Hereditary diseases |
| Mitochondrial encephalopathy, lactic acidosis, and stroke-like episodes |
| Myoclonic encephalopathy with ragged red fibers |
| Neuropathy, ataxia, and retinitis pigmentosa |
| Leigh syndrome |
| Mitochondrial spinocerebellar ataxia and epilepsy (MSCAE) |
| Occipital lobe epilepsy |
| Alper's disease |
| Maple syrup urine disease |
| Porphyria |
| Wilson's disease |
| Leukodystrophies |
| Systemic conditions |
| Sepsis |
| Electrolyte or glucose derangements |
| Hyperammonemia |
| Organ failures |
| Acid–base derangements |
| Drug intoxication or withdrawal |
| Alcohol |

**Table 2** (continued)

| |
|---|
| Cocaine |
| Ecstasy |
| LSD |
| Amphetamines |
| Medication effects |
| Cephalosporins |
| Supratherapeutic AED levels |
| Tigabine |
| Valproic acid |
| Carbamazepine |
| Chemotherapeutic agents |
| Ifosfamide |
| Cisplatin |
| Calcineurin inhibitors (posterior reversible encephalopathy syndrome or tacrolimus toxicity) |
| Epilepsy (patients with a history of seizures) |
| Any factor listed above |
| *Or* |
| AED noncompliance |
| Subtherapeutic AED levels |
| Inappropriate AED choice |
| Progression of underlying neurologic disease |
| Cryptogenic |

*CNS* central nervous system, *AED* antiepileptic drug

## Structural Injury

Cerebrovascular disease makes up the most common etiology of SE in Western countries [6]. Acute and remote strokes and hemorrhages account for almost 50 % of the cases of SE and 30–35 % of cases of RSE [3, 7]. In contrast, SRSE due to stroke or hemorrhage was found in only 3–7 % of cases from India and China, respectively [8, 9]. Traumatic brain injury is also a common cause of SE that is refractory to treatment [10]. Six percent of RSE cases were related to traumatic injuries [5]. Apart from acute structural damage, developmental malformations such as polymicrogyria, heterotopias, schizencephalies, and cortical dysplasias can also lead to refractory seizures.

## Iatrogenic Causes

Antibiotics such as fluoroquinolones and cephalosporins have long been known to cause neurological problems. The theory behind these effects lies in the molecular similarity between cephalosporins and bicuculline, a GABA receptor antagonist

[11]. Supratherapeutic doses of tiagabine, valproic acid, and carbamazepine as well as chemotherapeutic agents such as ifosfamide, cisplatin, and tacrolimus have been reported to paradoxically cause seizures likely through systemic effects (see Chap. 23).

## Infectious Etiologies

The most common cause of SRSE in developing countries is encephalitis, accounting for 67–69 % of the cases in two SRSE studies from India and China, respectively [8, 9]. In contrast, a study from Berlin with 36 cases of RSE revealed 22 % with an etiology of encephalitis [7]. Each of these studies labeled patients as presumed encephalitis based on the definition from the California Encephalitis Project, encephalopathy plus one or more of the following: fever, CSF pleocytosis, focal neurological deficit, or EEG or MRI changes suggestive of encephalitis. A responsible infectious agent was identified in less than 30 % of the patients in these studies. Other potential infectious etiologies include meningitis, brain abscess, and empyema.

## Hereditary Diseases

Several mitochondrial diseases have been related with SE such as mitochondrial encephalopathy, lactic acidosis, and stroke-like episodes (MELAS); myoclonic encephalopathy with ragged red fibers (MERRF); neuropathy, ataxia, and retinitis pigmentosa (NARP); Leigh syndrome; mitochondrial spinocerebellar ataxia and epilepsy (MSCAE); occipital lobe epilepsy; and Alper's disease. Once mitochondrial patients have SRSE, it is usually related to the progression of disease, and the prognosis is typically poor. Along with mitochondrial diseases, inborn errors of metabolism such as maple syrup urine disease, porphyria, Wilson's disease, and several of the leukodystrophies have been associated with seizures.

## Systemic Conditions

Systemic conditions such as sepsis, hyperammonemia, organ failures, electrolyte or acid–base derangements, and hypo- or hyperglycemia can result in SRSE. The elderly have a higher incidence of SRSE of metabolic etiology than younger adults (26 % vs 2 %) [8]. Treatment for SRSE on the other hand can complicate treatment of the underlying systemic cause.

## Autoimmune, Paraneoplastic, and Neoplastic Conditions

Autoimmune refractory epilepsies usually associated with limbic encephalitis include anti-neuronal antibodies to glutamic acid decarboxylase (GAD),

voltage-gated potassium channels (VGKC), voltage-gated calcium channels (VGCC), and NMDA receptors. These patients have CSF pleocytosis and MRI features suggestive of limbic encephalitis such as mesial temporal or hippocampal signal changes. Patients in whom autoimmune limbic encephalitis is suspected may benefit from a trial of immunosuppression. The remaining list of known antibodies are as follows: $GABA_A$ receptor, $GABA_B$ receptor, alpha-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA) receptor, leucine-rich glioma inactivated protein 1 (LGI1), contactin-associated protein-like 2 (Caspr2), dipeptidyl-peptidase-like protein-6 (DPPX), and metabotropic glutamate receptor 5 (mGluR5).

Intracranial tumors whether primary brain tumor or metastatic cancer can undoubtedly lead to refractory seizures. Tumors in the limbic areas and frontal and temporal lobes have a higher epileptogenicity. The pathophysiology of seizure propagation is more than local irritation. The mechanisms resulting in seizure generation are thought to be the results of primary injury by tumor microinvasion into surrounding tissue or due to ischemia as a result of direct compression. The secondary mechanisms of seizure propagation include loss of the integrity of the blood–brain barrier, high extracellular glutamate, reduced GABAergic neurotransmission, and electrolyte alterations in extracellular peritumoral space [12].

Several paraneoplastic etiologies of SRSE have been discovered; the most well known of which is anti-NMDA receptor encephalitis. NMDA encephalitis more commonly affects women and half of women with this entity have an ovarian teratoma. Resection of the tumor is generally related to favorable outcomes. Patients present with a constellation of neuropsychiatric symptoms ranging from anxiety, psychosis, and mutism to memory impairment, insomnia, and seizures. Treatment consists of aggressive immunosuppression and treatment of any associated malignancy.

## Epilepsy

Between 38 and 60 % of RSE patients have a prior history of epilepsy [4, 5]. Risk factors for the generation of SRSE in these cases include subtherapeutic AED levels, progression of primary CNS disease, or the addition of any of the other acute causes that may affect patients without epilepsy. Inadequate AED coverage is the cause of up to 10–31 % of SE admissions [3, 13]. A 30-patient SRSE study reports 13 % of cases to be due to inadequate AED levels [8]. SE in the setting of low AED levels has the lowest mortality rate of 4 % [6].

## Drug and Alcohol Use

It is common knowledge that alcohol intoxication as well as withdrawal can cause seizures and is the etiology in 8–10 % of RSE cases [7, 8]. Super refractory SE

due to alcohol intoxication or withdrawal has not been reported in the literature. Drug intoxication with ecstasy and amphetamines can lead to seizures as well, but cocaine intoxication can theoretically lead to vasculitis and thus refractory seizures.

### Cryptogenic

Preliminary data from the global audit of SRSE suggests that cryptogenic etiologies are the most commonly listed cause of SRSE (https://www.status-epilepticus.net/). New etiologies of autoimmune states are discovered on a regular basis. Anti-NMDA receptor encephalitis, currently the main cause of autoimmune encephalitis-related refractory epilepsy, was discovered only as recently as 2007. The latest discovery is of a $GABA_A$ antibody [14]. As new discoveries continue to occur, the percentage of the cryptogenic cases will continue to decline.

## Diagnostic Evaluation

After achieving seizure control, evaluation begins with a focused history and examination. Important historical features include circumstances at seizure onset (prodromal illness, motor vehicle accident, or party suggesting substance abuse), medical history (epilepsy, neoplasms, autoimmune conditions), and active medications (cephalosporins, fluoroquinolones). The patient should be examined for signs of trauma, meningismus, and focal neurological deficits. In nearly all episodes of status epilepticus, a comprehensive laboratory evaluation including antiseizure drug levels, serum electrolytes, glucose level, urine and serum toxicology screens, troponin, lactate and creatine kinase levels, and a head computed tomography (CT) scan is warranted. Because cardiopulmonary complications are commonly associated with status epilepticus, a screening chest X-ray and electrocardiogram would aid in evaluation for aspiration, ischemic changes or development of a prolonged QTc, or other stress-related changes. When laboratory evaluation and neuroimaging do not yield an etiology for SRSE, workup continues with CSF analysis for infection and autoimmune and paraneoplastic conditions. This basic workup will identify the most common causes of SE. In addition to this evaluation, mitochondrial studies are occasionally conducted in younger patients. A stepwise approach to the evaluation of RSE etiology is presented in Table 3.

The ability to perform continuous EEG (cEEG) monitoring is a cornerstone of SRSE treatment as anesthetic agents are titrated against the EEG. Occasionally, the EEG can provide clues to the etiology of the seizures. Periodic lateralized epileptiform discharges (PLEDs) will point the practitioner to a focal intracranial lesion, while the so-called extreme delta brush suggests possible autoimmune encephalopathy, specifically anti-NMDA receptor encephalitis. PLEDs or generalized periodic epileptiform discharges (GPEDs) are a frequent finding after prolonged and untreated seizures.

**Table 3** Diagnostic evaluation

| |
|---|
| *First line:* |
| Blood glucose |
| Electrolyte panel |
| Complete blood count |
| Liver function test |
| Serum ammonia |
| Serum and urine toxicology screen |
| Alcohol level |
| Troponin |
| Creatine kinase |
| Lactate |
| CT head |
| Chest X-ray |
| EKG |
| *Second line:* |
| Continuous EEG monitoring |
| CSF analysis: |
| Cell count and differential |
| Protein and glucose |
| Bacterial, viral, and fungal gram stain, cultures, and smear |
| Viral and fungal serologies (in appropriate situations) |
| MRI brain with and without contrast |
| *Third line:* |
| Serum and CSF paraneoplastic panel |
| Thyroperoxidase antibody |
| CSF cytology |
| N-methyl-D-aspartate receptor antibodies |
| Voltage-gated potassium channel antibodies |
| Glutamic acid decarboxylase 65 antibodies |
| *Fourth line:* |
| CT chest/abdomen/pelvis |
| CT body positron emission tomography |
| Testicular and pelvic ultrasounds (male and female) |
| Exploratory surgery for ovarian teratoma |

*CT* computed tomography, *EEG* electroencephalogram, *CSF* cerebral spinal fluid, *MRI* magnetic resonance imaging

## Treatment

Excessive glutamatergic activity from seizures is thought to trigger a cascade of electrolyte imbalances, oxidative stress, and mitochondrial dysfunction. These processes result in neuronal cell damage within a few hours of the seizure, which is the

principle that drives urgent treatment. Rapid identification and treatment of the underlying etiology is critical to resolution of SRSE; however, as previously discussed, a substantial portion of patients may undergo an exhaustive diagnostic search with no identified etiology.

Widely accepted treatment recommendations for SRSE are based on small, retrospective case series and general consensus. However, anesthetic drugs used for long-term suppression of seizures in this setting can also have detrimental effects, leading some experts to reexamine their protocols. The first-line treatment for status epilepticus is benzodiazepine administration. Proven second-line therapies include fosphenytoin, valproic acid, or phenobarbital. Less established options include levetiracetam and lacosamide. Anesthetics should be considered once second-line medications fail [5]. Clinicians should progress through this protocol rapidly in convulsive status epilepticus where it is not advisable to await completion of the second-line agent to begin intubation, initiation of mechanical ventilation, and induction of an anesthetic drug. In nonconvulsive seizure types, it is often reasonable to await true failure of the second-line agent or even trial a third- or fourth-line non-anesthetic antiseizure drug prior to committing the patient to anesthesia. Any patient requiring an anesthetic drug for seizure control requires continuous EEG monitoring and admission to an intensive care unit. Table 4 provides the overall treatment algorithm, mechanism of action, recommended dosing, and adverse effects of commonly used anesthetic agents for SRSE.

## ICU

The basis for intensive care monitoring is to meet the medical and nursing needs of these complex patients. These needs include mechanical ventilation and aggressive pulmonary hygiene, hemodynamic and cEEG monitoring, and meticulous nursing care to avoid the myriad complications that can occur in an immobilized sedated patient.

## Anesthetics

Anesthetic infusions commonly used in SRSE include benzodiazepines, propofol, barbiturates, and ketamine. Benzodiazepines bind and enhance the $GABA_A$ receptor. The benzodiazepine of choice in inducing anesthesia is midazolam with the benefit of a rapid offset and lack of accumulation. Cardiovascular depression, eventual tolerance from downregulation of GABA receptors, and unclear clearance in patients with renal failure are its main disadvantages. Benzodiazepines such as lorazepam or diazepam are delivered in propylene glycol solutions, and prolonged infusions can result in propylene glycol toxicity, which consists of elevated anion gap, hyperosmolarity, and severe metabolic acidosis.

Propofol is considered to be a modulator of the $GABA_A$ receptor. A major advantage of propofol is its rapid clearance despite prolonged use as well as the welcomed absence of significant drug–drug interactions. Propofol has a faster offset and less

**Table 4** Treatment algorithm for SE and SRSE

| | | | |
|---|---|---|---|
| *First line: early status epilepticus* | | | |
| **Benzodiazepines** | **Loading dose** | | |
| Lorazepam- | 0.1 mg/kg IV, in divided doses | | |
| Midazolam | 10 mg IM | | |
| Diazepam | 0.2 mg/kg PR | | |
| *Second line: established status epilepticus* | | | |
| **Antiepileptics** | **Loading dose** | | **Maintenance** |
| Fosphenytoin | 20 mg/kg at 150 mg/min | | 5 mg/kg/d in divided doses |
| Levetiracetam | 1–3 g IV | | Up to 4 g total daily |
| Valproic acid | 20–40 mg/kg at 3–6 mg/kg/min | | Up to 7.5–15 mg/kg in divided doses |
| *Third line: refractory status epilepticus* | | | |
| **Anesthetics agents** | **Loading dose** | | **Maintenance** |
| Midazolam | 0.2 mg/kg | | 0.05–2 mg/kg/h |
| Propofol | 1–2 mg/kg | | 30–200 mcg/kg/h |
| Pentobarbital | 5–15 mg/kg | | 0.5–5 mg/kg/h |
| Ketamine | 0.5–4.5 mg/kg | | <5 mg/kg/h |
| *Fourth line: super refractory status epilepticus* | | | |
| If seizures are uncontrolled: | | | |
| Consider either switching to an alternative anesthetic agent or combining a second agent with the first if seizures occur upon weaning attempt: | | | |
| Resume anesthetic infusion at prior dose ± additional bolus depending on seizure semiology and urgency to treat | | | |
| Consider alternative anesthetic agents or adjunctive therapies | | | |
| *Adjunctive therapies: (limited evidence for all)* | | | |
| **Treatment** | **Dose** | **Adverse events** | **Contraindications** |
| Hypothermia | 32–36 degrees | Acid–base and electrolyte imbalance, coagulation disorder, arrhythmia, ileus | Coagulation disorders |
| Magnesium | Infusions of 2–6 g/h to maintain serum level >3.5 mmol/l | Hypotension, arrhythmia, weakness | Myasthenia gravis, kidney failure |
| Ketogenic diet | 3:1 or 4:1 ketogenic ratio to attain ketosis | Acidosis, hypoglycemia | β-Oxidation or pyruvate carboxylase deficiency |
| Surgical resection | Focal or lobar resection, subpial transection, corpus callosotomy | Any complication of surgery | Lack of an identifiable surgical focus |
| Electroconvulsive therapy | 5–8 daily sessions | Arrhythmias, increased ICP, requirement of holding AEDs for treatment | Intracranial tumors, recent stroke, myocardial infarction |

(continued)

**Table 4** (continued)

| *Adjunctive therapies: (limited evidence for all)* | | | |
|---|---|---|---|
| **Treatment** | **Dose** | **Adverse events** | **Contraindications** |
| Vagal nerve stimulator | 0.25–1.75 mA | Asystole, cough, bradycardia | Prior neck surgery |
| Immunosuppression | Prednisolone 1 g daily ×3 days followed by 1 mg/kg/day | Ileus, psychiatric disorders | Infections |
| | Immunoglobulins 2 g/kg administered over 5 days | Coagulation disorders | History of clotting, IgA deficiency (leads to anaphylaxis) |
| | Plasma exchange – 5-day course | Active infection, severe thrombocytopenia, hypotension | Hypocalcemia, anaphylactoid reactions, hypotension |

cardiorespiratory depression compared to barbiturates and benzodiazepines. However, prolonged use of propofol at high doses can lead to propofol infusion syndrome (PRIS) which is a rare but frequently fatal constellation of hypoxia, severe metabolic acidosis, rhabdomyolysis, renal failure, and cardiovascular collapse. Other disadvantages include drug-induced involuntary movements that can closely mimic seizures.

Barbiturates enhance the action of the $GABA_A$ receptor and have been historically favored for use in RSE due to their high efficacy. They have the added properties of producing a degree of hypothermia and immunosuppression. They are currently preferred as a second- or third-line anesthetic agent due to the prolonged half-life, numerous drug interactions, and serious common systemic adverse effects including infections, ileus, hypotension, and cardiovascular depression.

Ketamine acts by NMDA receptor antagonism, which decreases the excitability of the brain. It has been gaining favor as a third- and fourth-line agent in SRSE. As the other anesthetics primarily act on GABA receptors and as GABA receptors are downregulated with time, a novel mechanism of action is theoretically attractive. The adverse effect of hypertension is generally welcomed as cardiovascular depression is common with the other anesthetic agents.

Infusion rates of anesthetics should be used at the minimum dose that controls clinical and electrographic seizures. The drug is titrated against the EEG background, and weaning often commences 24 h after achieving seizure control with careful monitoring of the continuous EEG. There is no consensus regarding the rate of weaning anesthetics but it is generally done over 12–24 h. Further discussion on weaning of anesthetics can be found in Chap. 29.

## Immunosuppression

Immunosuppression is used in antibody-mediated, vasculitic, and some other inflammatory etiologies, and it is often used empirically in cryptogenic cases of

SRSE as many of these are thought to be antibody mediated. Options for immunosuppression include steroids, IVIG, or plasma exchange and later transition to a steroid-sparing agent such as rituximab or cyclophosphamide.

### Polypharmacy

The desire to frequently alter the patient's AED regimen should be avoided. Rapid weaning of medications can lead to unpredictable AED levels considering inter-AED drug–drug interactions which can in turn lead to more seizures. There is no evidence favoring specific polytherapy, and so any decision to change ongoing regimens should be undertaken with caution and implemented slowly. The use of multiple agents with differing mechanisms of action, described as rational polypharmacy, has been suggested to be useful in animal models in SE [15].

### Alternative Therapies

Alternative therapies with varying degrees of success include hypothermia, ketogenic diet, resective surgery for lesional epilepsy, and electrical stimulation therapies such as deep brain stimulation, vagal nerve stimulation, or electroconvulsive therapy. These interventions will be discussed in Chap. 30.

## Complications

In addition to the treatment-related adverse events mentioned above, patients admitted for SRSE will be subject to various neurological and systemic complications as a consequence of the seizure itself. MRI can demonstrate irreversible changes of laminar necrosis as well as mesial temporal sclerosis after prolonged seizures. Reversible changes include signal changes in the thalamus, basal ganglia, and contralateral cerebellum. The contralateral cerebellum is involved through pathways of crossed cerebellar diaschisis otherwise known as the corticopontocerebellar pathway. Laminar necrosis is theorized to occur due to cytotoxic edema from excessive excitatory amino acid release [16]. Serial imaging can reveal cerebral atrophy that results from prolonged seizures [2] and is likely the result of excitotoxic injury to the neurons. The significance of these radiographic changes is not well established. Epileptogenesis is not infrequent in patients who recover from SRSE. Sixty-nine percent of patients who recover go on to suffer medically refractory seizures [17] likely as a result of structural damage and glial scarring. SRSE affects nearly every organ system. Systemic complications include cardiac arrhythmias, hypotension, venous thromboembolism, infections, and critical illness neuropathy and myopathy, among others. While these complications are common to any patient that remains in the intensive care setting for weeks to months, they appear to be more common in the setting of RSE even after adjusting for length of stay [3].

## Outcome

The heterogeneous etiologies of SRSE, numerous treatment options, and various serious adverse effects of treatment make accurate prognostication challenging. Type and duration of status, premorbid APACHE 2 scores, anesthetic choice, and even age have not been shown to reliably influence prognosis [10]. Although age is a well-known predictor in SE, it is not shown to be a strong predictor in RSE or SRSE. The variation in mortality estimates in various studies likely stem from the studies' length of follow-up, the use of anesthetics, the ratio of convulsive vs NCSE, and the variable exclusion of myoclonic status due to hypoxic ischemic injury. Although studies examining outcomes have been largely underpowered, etiology has consistently impacted prognosis. As previously mentioned, SRSE due to AED noncompliance in patients with pre-existing epilepsy has the lowest mortality at 4 %. Patients with NMDA encephalitis produce NMDA antibodies which are not destructive to the CNS. Therefore, these patients may have a favorable outcome despite months of SRSE. On the other hand, SRSE as a result of glioblastoma multiforme or progression of mitochondrial disease portend a poor prognosis.

Convulsive SE is thought to foreshadow a worse prognosis than NCSE [10]. This has been postulated to be due to more excitotoxic injury to the brain as well as increased systemic complications due to the massive sympathetic outpouring during the convulsions. Prolonged convulsive seizures are undoubtedly taxing to the body with excessive lactic acidosis, rhabdomyolysis and secondary renal failure, aspiration pneumonia, as well as cardiopulmonary stress.

Although the mortality in SRSE is generally high, some patients may have good functional recovery after weeks to even months of general anesthesia for SRSE. Sixty percent of patients survive SRSE. Among those who survive, 60 % stabilize or improve their functional status over time [10]. A significant minority of survivors (22 %) are able to achieve independence [17], and 10 % return to their premorbid functional status [17]. The high mortality rates in SRSE patients are largely driven by either changes in the goals of care or complications of treatment and critical illness. Therefore, the relationship between duration of SRSE and outcome might be a result of accumulating systemic complications rather than the seizure itself. [5] Transition to palliative care is usually guided by family members or medical staff after bearing witness to weeks or months of refractory seizures and when treatment options have been exhausted.

## Representative Cases

### Case 1

A 47-year-old woman presented with status epilepticus in the setting of progressive encephalopathy following a flu-like illness. Her symptoms began with headache, malaise, and poor oral intake. CSF analysis showed no white blood cells, glucose 71 mg/dL, protein 28 mg/dL, and negative polymerase chain reaction (PCR) titers for influenza A and B, herpes simplex virus, Epstein–Barr virus, and varicella-zoster virus.

The next day she experienced two witnessed generalized tonic–clonic seizures. She was loaded with fosphenytoin and underwent a noncontrast CT scan of the head followed by an MRI of the brain, blood and urine cultures, and repeat CSF analysis, all of which were normal. She experienced a flurry of recurrent seizures necessitating admission to the intensive care unit where she was noted to have myoclonic pelvic jerking and twitching of the eyelids which abated with repeated doses of midazolam. Brief 40 s seizures were noted on EEG monitoring, though there was no correlate with her pelvic jerking and facial twitching. Midazolam was replaced with a pentobarbital load and infusion when seizures broke through 2 mg/kg/h of midazolam.

A repeat CSF analysis remained unremarkable for basic chemistry as well as *Borrelia burgdorferi* IGM, IGG, *Rickettsia rickettsii*, *Anaplasma phagocytophilum*, and *Leptospira* serologies. Autoimmune encephalitis and paraneoplastic antibody panels including voltage-gated potassium channel and anti-NMDA receptor antibodies were negative. A repeat contrasted brain MRI/MRA demonstrated nonenhancing symmetric T2 hyperintensity in the mesial temporal lobes, amygdala, and subinsular region, suggestive of paraneoplastic limbic encephalitis, and a 5-day course of methylprednisolone was completed and followed with weekly pulse steroids. A CT of the chest abdomen and pelvis, transvaginal ultrasound, and finally a CT positron emission tomography scan of the body showed no masses or areas of increased metabolic uptake concerning for malignancy.

As she continued to have seizures, plasmapheresis was performed in addition to increasing her antiepileptic coverage, which included valproic acid, levetiracetam, and phenobarbital infusion. Despite these measures, intermittent breakthrough seizures continued. She was started on isoflurane in an attempt to reduce her dose of phenobarbital and achieve better seizure control. Felbamate and lacosamide were trialed but subsequently discontinued due to skin rashes. Adjunctive hypothermia and ketamine infusions did not improve seizure control. She ultimately required neuromuscular blockade to improve synchrony with the mechanical ventilator and reduce her myoclonic jerking. Continued aggressive attempts at immunosuppression including weekly rituximab failed to reduce her seizure frequency. Repeat brain MRI performed approximately 3 months after presentation revealed global cerebral atrophy with hyperintensities in bilateral hippocampi suggestive of significant neuronal cell loss secondary to damage from ongoing seizure activity (see Fig. 7).

Systemic complications during her admission included a ventilator-associated pneumonia, lower extremity deep venous thrombosis, bacteremia and sepsis requiring vasopressors, urinary tract infection, lacosamide-associated rash, ventricular bigeminy secondary to a central line, heparin-induced thrombocytopenia, stress-induced cardiomyopathy, critical illness polyneuropathy, and ileus. Three months after presentation, her family decided to transition to comfort care and then she died shortly thereafter. Autopsy revealed widespread variable microglial activation, focal marked neuronal loss and gliosis, mild perivascular chronic inflammation, acute hypoxic encephalopathy, and generalized cerebral edema with a final diagnosis of probable autoimmune limbic encephalitis. An antibody was never identified.

The continuous cEEG findings are shown in Figs. 1, 2, 3, 4, 5, and 6. Examples of the patient's cEEG on Hospital Day 1 upon transfer to our institution are shown in Fig. 1. The EEG showed multifocal lateralized periodic

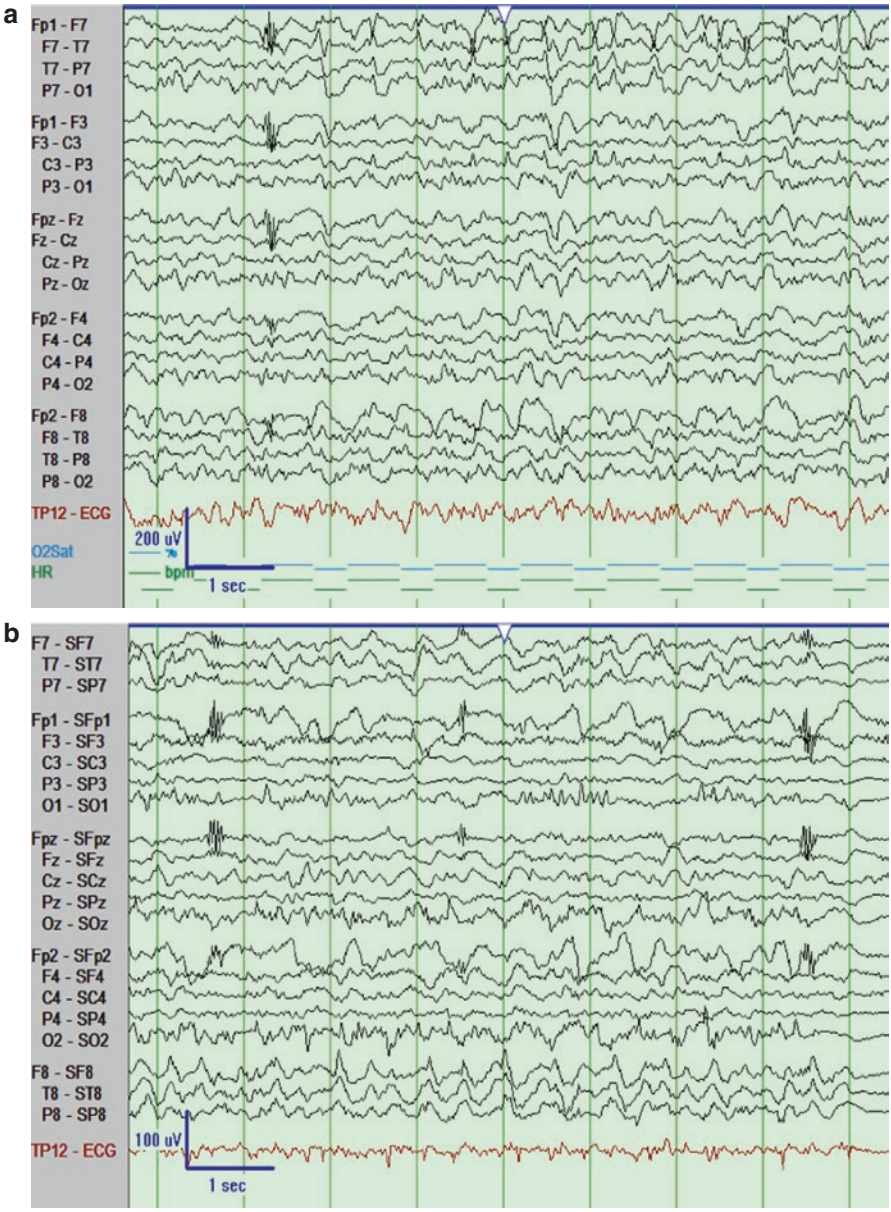



**Fig. 1** EEG on Hospital Day 1 showing multifocal epileptiform abnormalities and electrographic seizures. (**a**) Lateralized periodic discharges noted left frontal (F3). (**b**) Seizure discharge noted consisting of rhythmic sharp activity at F8 (longitudinal Laplacian montage). (**c**) Bursts of rhythmic high-frequency activity left occipital region (O1). (**d**) Electrographic seizure activity consisting of rhythmic spikes left frontotemporal region (F7)

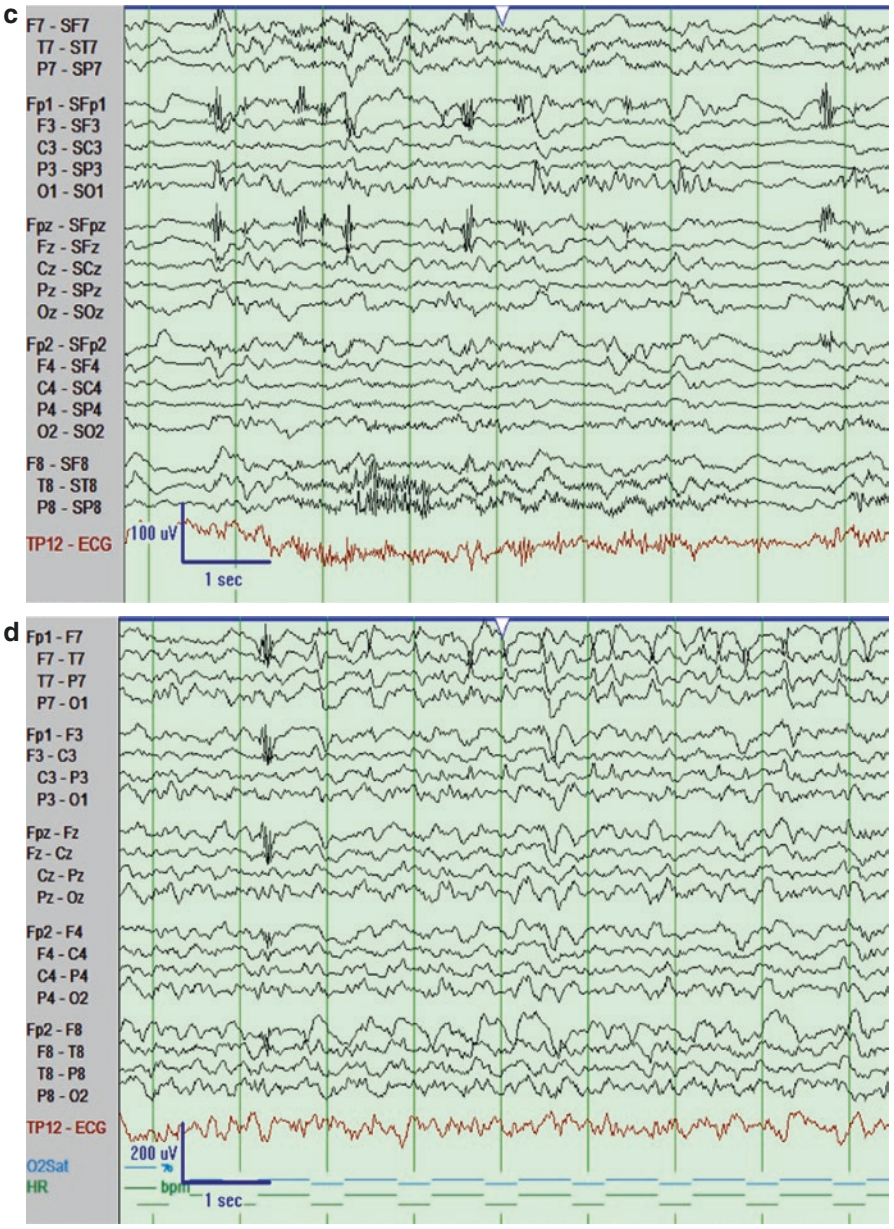



**Fig. 1** (continued)

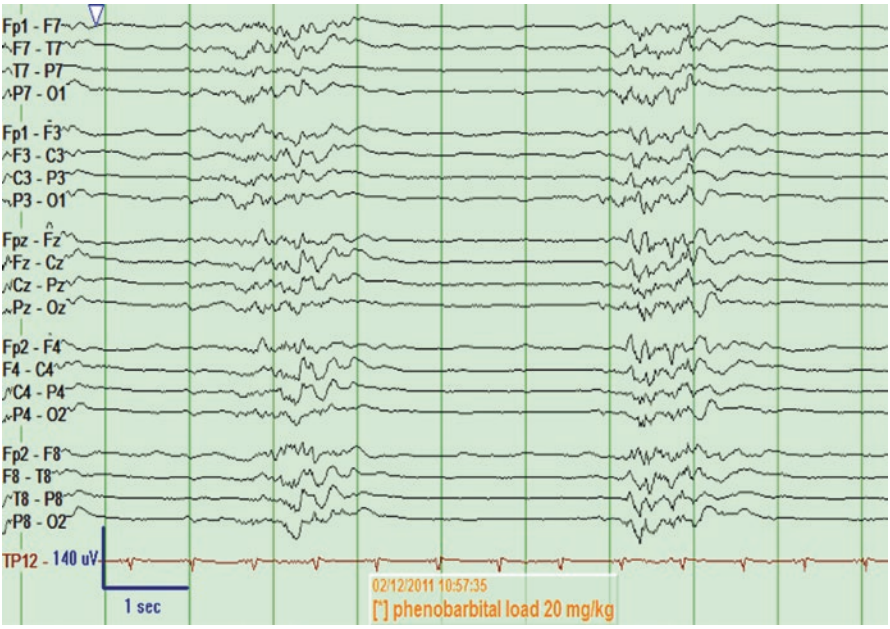



**Fig. 2** Burst–suppression pattern following administration of 20 mg/kg phenobarbital on Hospital Day 2

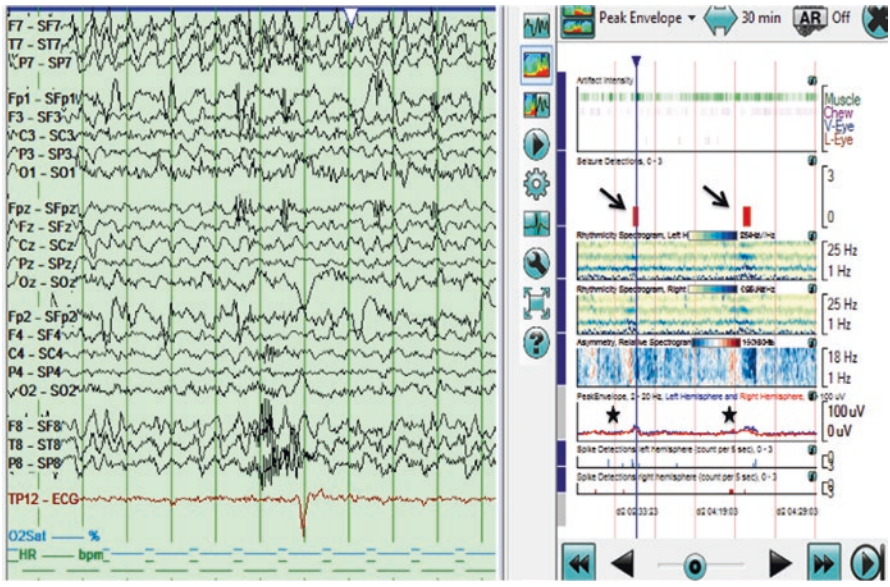



**Fig. 3** Routine EEG with compressed sweep of 15 mm/s showing electrographic seizures predominantly involving left temporal derivations. Quantitative EEG trending software display shows seizure detection marked by red bar in seizure detection tool (*arrows*) and by transient rises on the peak envelope tool, which reflects detection of increases in amplitude during seizures (indicated by *stars*)

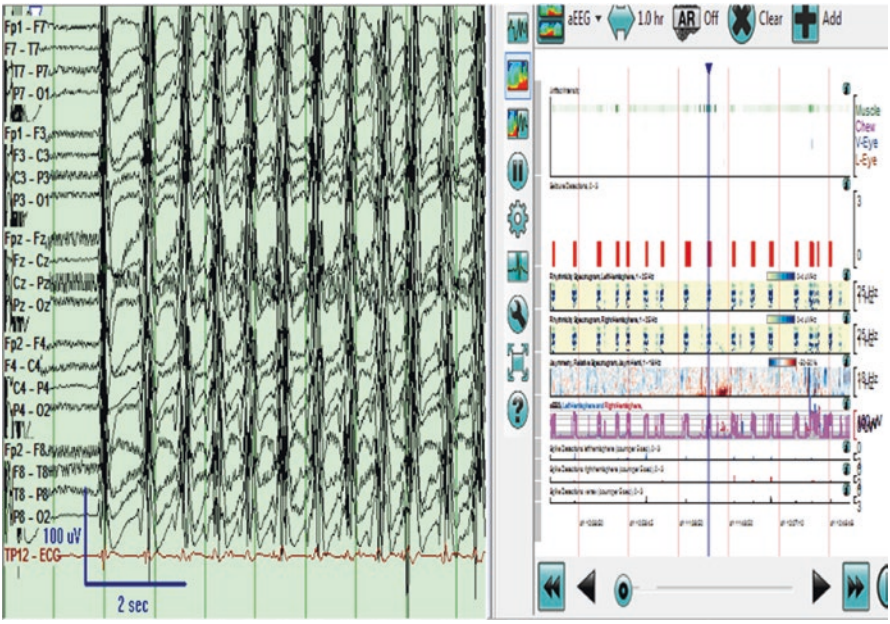



**Fig. 4** EEG from Hospital Day 10 during attempt to reduce sedation showing onset of generalized electrographic seizure discharge on raw EEG. Quantitative EEG trending software shows 16 seizure detections in a 1-h period

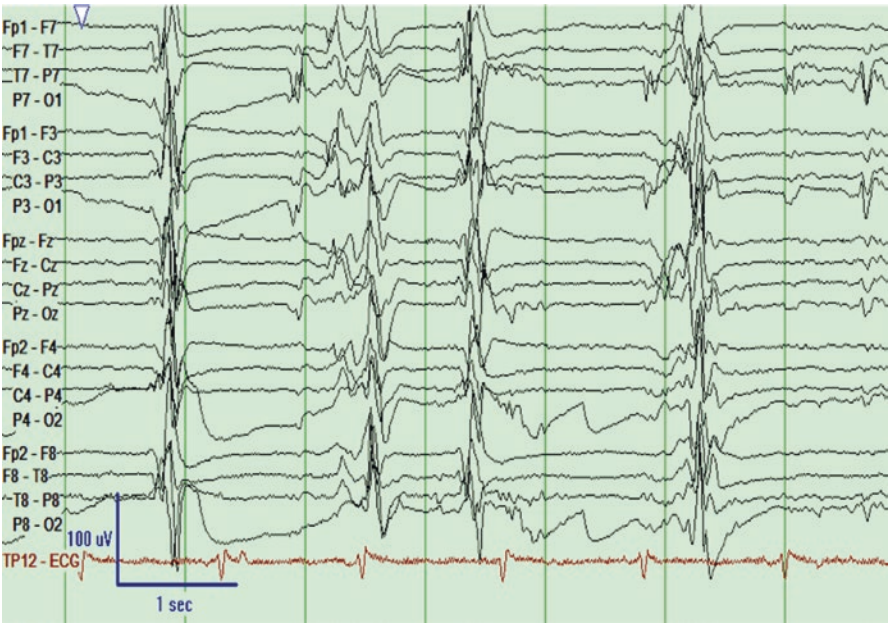



**Fig. 5** EEG Hospital Day 35 showing intermittent generalized and left posterior temporal sharp complexes. Electrographic seizures suppressed

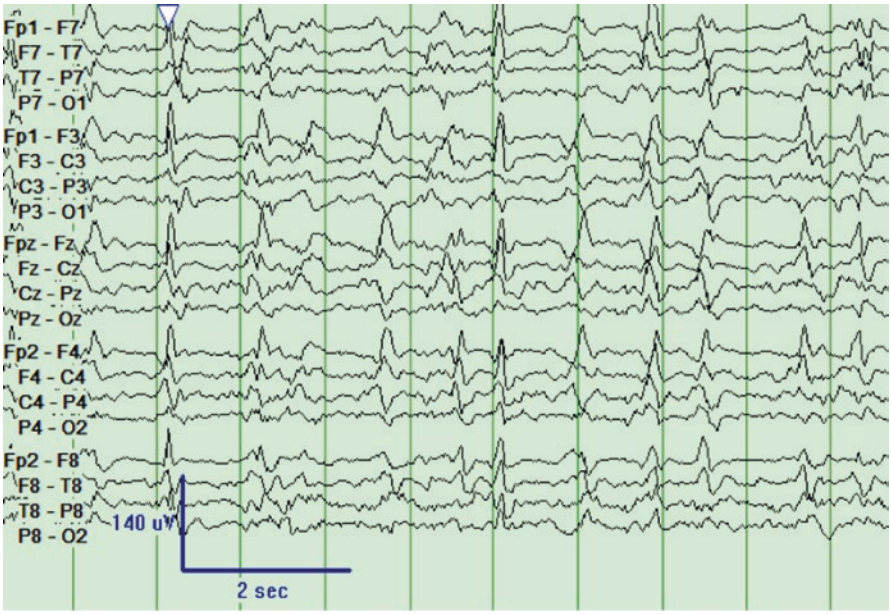



**Fig. 6** EEG on Hospital Day 58 shows generalized periodic discharges (GPDs)

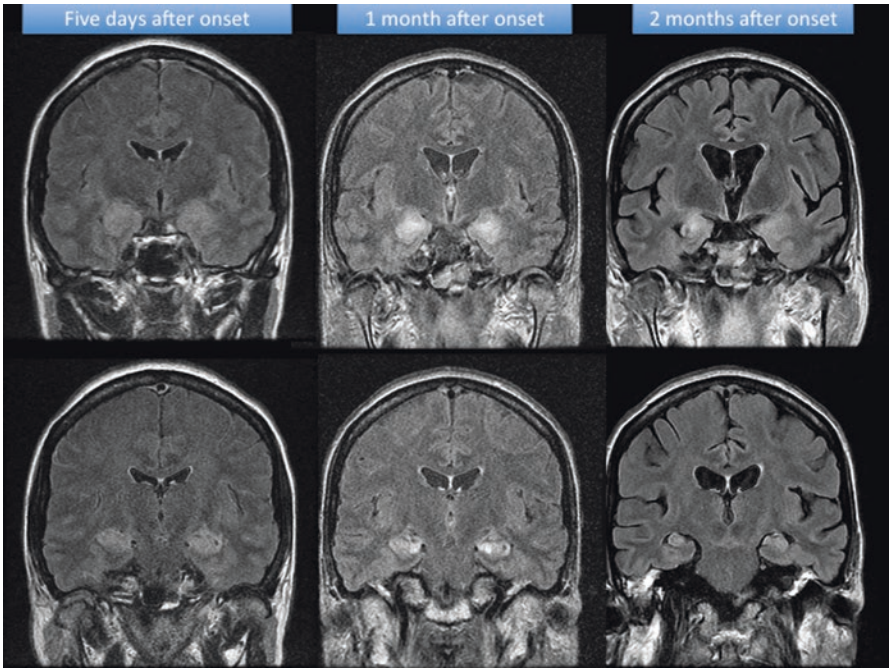



**Fig. 7** Serial FLAIR-weighted coronal MRI images of the brain showing high signal involving the medial temporal structures initially. Progressive atrophy is apparent at 1 month and 2 months after onset of status epilepticus

discharges localized independently in the left frontal, right and left frontotemporal, and occipital head regions. These findings were consistent with a widespread encephalopathic etiology. The patient exhibited a number of clinical features such as pelvic thrusting that were not directly correlated in time with the discharges. This electromechanical dissociation suggested a subcortical as opposed to cerebral origin for these clinical features. Given the continued electrographic seizures and clinical events, phenobarbital was administered, leading to a discontinuous, and in her case, burst–suppression pattern (Fig. 2). Despite treatment with several anticonvulsants and phenobarbital administration, seizures continued to occur. A left temporal seizure discharge is noted in Fig. 3. Quantitative EEG trending software facilitates following efficacy of therapy. The quantitative EEG in this patient (Fig. 3) indicated that seizures were continuing to occur at a rate of 4 per hour. During the patient's treatment, sedation was decreased periodically in order to determine if seizure potential had ceased. An example of the patient's cEEG from Hospital Day 10 shows continued seizures (Fig. 4). The seizures at this point were more widespread when compared to the distribution of the discharges at admission, suggesting the development of synchrony between the multifocal regions previously generating the seizures at admission. Quantitative EEG showed seizures occurring at a rate of 16 per hour at that point in the patient's care. The cEEG on Hospital Days 35 (Fig. 5) and 58 (Fig. 6) showed continued generalized and lateralized periodic discharges. Anesthetic therapies were required to prevent seizure recurrence.

## Case 2

A 22-year-old woman with a history of right-sided focal seizures presented with worsening seizures. Her seizures began at age 15 with right-sided focal seizures with an EEG demonstrating interictal epileptiform discharges arising from the left occipital region. MRI at the time was unremarkable. These seizures were originally controlled on phenobarbital and valproic acid with occasional breakthrough seizures a few times per year characterized by flashing lights.

She developed gradually progressive gait ataxia, tremor, dysarthria, and diplopia. MRI showed significant cerebral and cerebellar atrophy. She also developed persistent twitching of the left head, shoulder, arm, and leg which started to become painful. Lacosamide was added to her regimen of phenobarbital and valproic acid without benefit. As the focal motor seizures became more prominent and painful and EEG monitoring showed persistent right posterior lateralized periodic discharges, she was intubated and started on a midazolam infusion. As her movements were controlled, phenobarbital was increased and midazolam slowly weaned. Her jerking movements resurfaced, and the midazolam infusion resumed in addition to phenobarbital and lacosamide.

Valproic acid was discontinued because of a recently discovered family history of mitochondrial disease and was replaced with levetiracetam. EEG continued to demonstrate right-sided PLEDs, and clonazepam was started with the goal of liberating her from the midazolam infusion. Continuous EEG started to show

stimulus-induced rhythmic, periodic, or ictal discharges (SIRPIDs) in addition to PLEDs, while her clonic activity became progressively multifocal. This prompted initiation of ketamine. Her EEG then returned to baseline PLEDs and her ketamine was discontinued. A ketogenic diet was initiated although she never achieved ketosis due to the many medications and their carbohydrate contents. Intravenous methylprednisolone was attempted but did not impact favorably on her EEG. A repeat MRI of the brain performed after 3 weeks of SRSE revealed diffuse cortical atrophy, bilateral mesial temporal sclerosis, and FLAIR signal hyperintensities in bithalamic nuclei. Muscle biopsy showed cytochrome C-negative muscle cells, suggesting mitochondrial cytopathy. A chromosomal array showed 530 kilobase duplication at 10q26.3. Further DNA testing was sent and pending when she underwent single-photon emission computed tomography (SPECT) imaging to evaluate for a possible resectable seizure focus, but the results were inconclusive, and she was not deemed a candidate for surgical or DBS intervention.

Her hospital course was complicated by a urinary tract infection, ventilator-acquired pneumonia, acute respiratory distress syndrome (ARDS), anemia requiring transfusion, thrombocytopenia, pressure ulcers, *C. difficile* colitis, and adynamic ileus. Despite aggressive therapy, she had persistent myoclonic activity and dyscognitive features with abnormal mental status despite complete liberation from anesthetic agents for 10 days. After extensive discussions, her family decided to pursue comfort measures upon which she passed away with hospice care.

The cEEG findings in this patient are shown in Figs. 8, 9, 10, 11, 12, and 13. The cEEG at admission showed polyphasic lateralized periodic discharges over the right posterior head region (Fig. 8). The patient showed intermittent left upper extremity jerks, which were not in synchrony with the discharges. Rhythmic right upper extremity jerks were also noted. The lateralized periodic discharges were polyphasic in morphology, suggesting some degree of asynchrony of the underlying epilepsy network generator. The cEEG also showed rhythmic activity during stimulation and cares (Fig. 9). These discharges had the characteristics of SIRPIDs (stimulus-induced rhythmic, periodic, or ictal discharges) and had no clear clinical correlate. Further maturation of the lateralized periodic discharges occurred by Hospital Day 3. This was suggested by the conversion of polyphasic to bi- and triphasic morphology (Fig. 10). These periodic discharges would emerge and resolve in a periodic manner as shown on the quantitative EEG trend display (Fig. 11). These continued as did the patient's multifocal clonic activity, prompting sedation with several agents including ketamine. The periodic discharges would resolve following administration of sedative agents (Fig. 12a) and convert to a discontinuous (Fig. 12b) and sometimes a burst–suppression pattern. The patient's status epilepticus did not resolve despite several interventions. Lightening of anesthetic treatment would result in reemergence of the periodic discharges. Over time, the individual complexes became longer in duration compared to baseline as shown in Fig. 13.

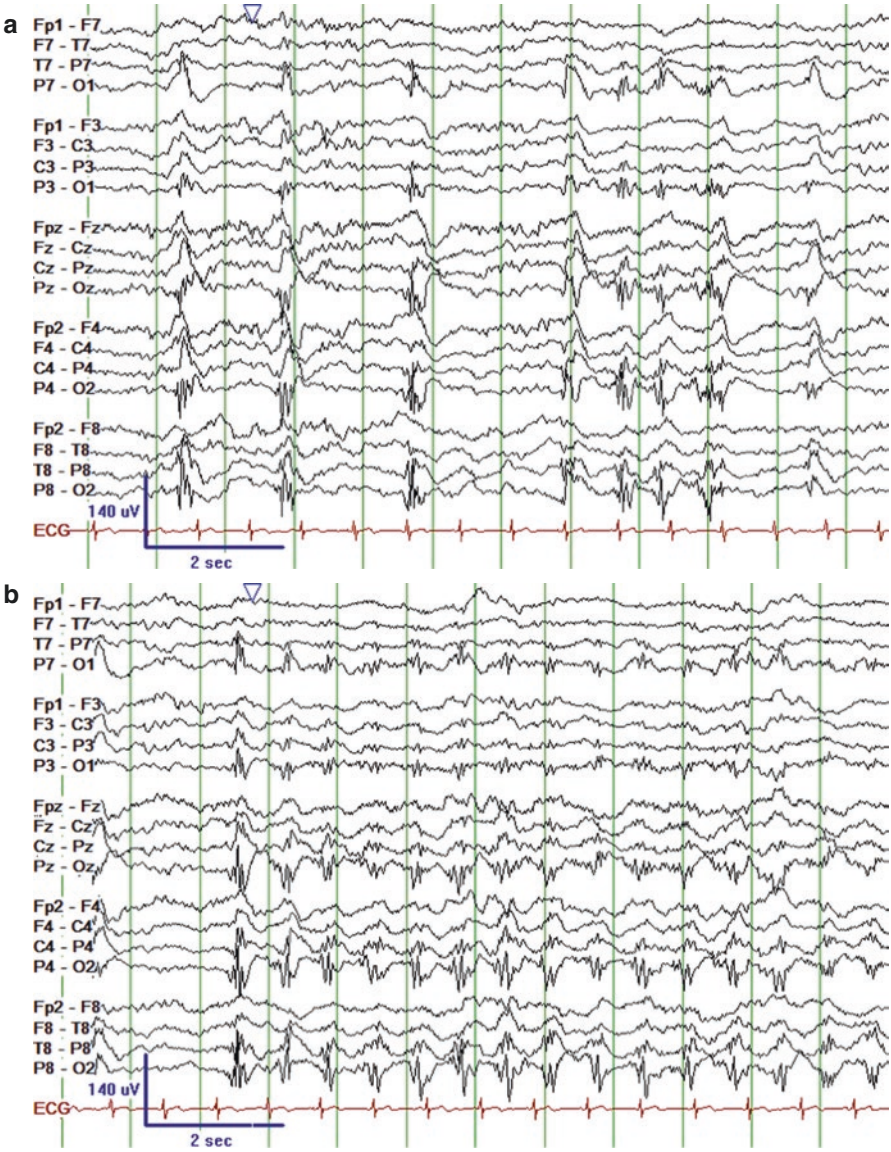



**Fig. 8** EEG on admission in Case 2 with focal status epilepticus. (**a**) EEG shows quasiperiodic polyphasic right posterior lateralized discharges. (**b**) EEG shown with compressed sweep of 15 mm/s showing train of polyphasic lateralized discharges which were maximal over the posterior head region

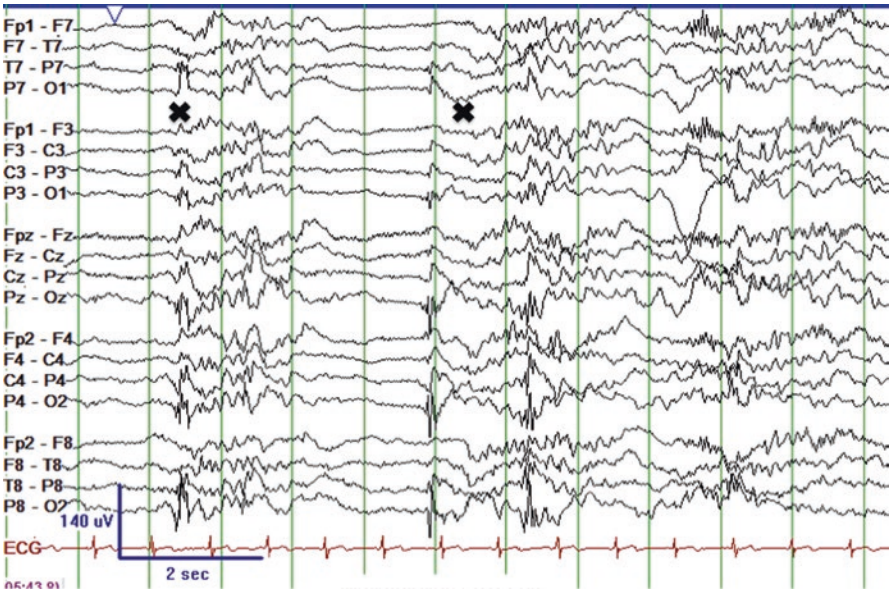



**Fig. 9** During cares, the lateralized periodic discharges become associated with bursts of rhythmic theta (marked by Xs)

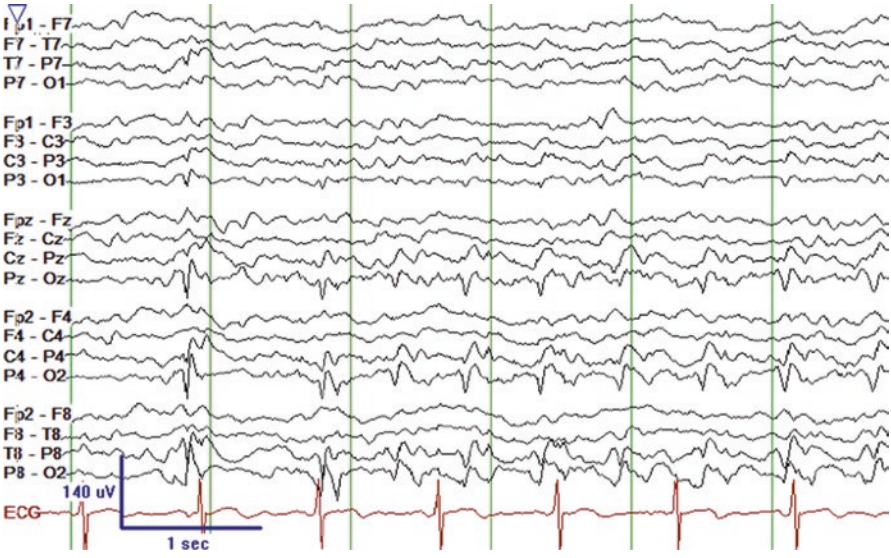



**Fig. 10** EEG on Hospital Day 3. Right occipital lateralized periodic discharges have become bi- and triphasic, as opposed to polyphasic, suggesting greater synchrony within the neural network underlying it

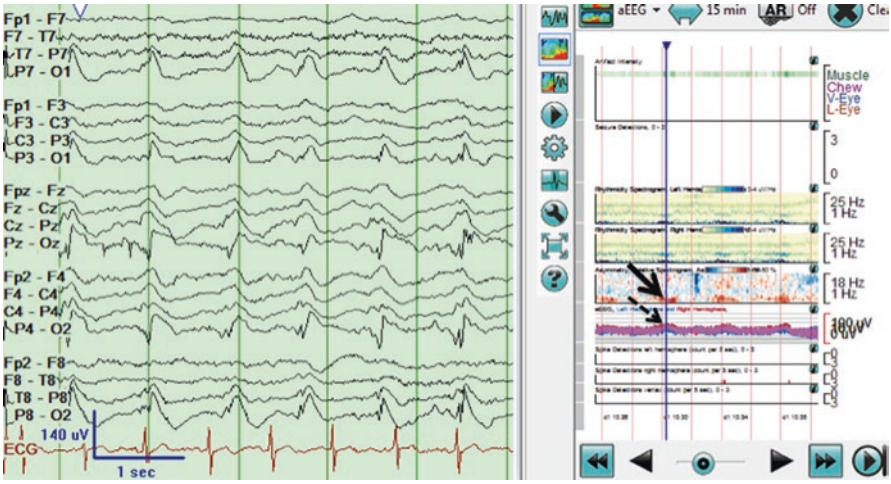



**Fig. 11** Lateralized periodic discharges primarily involving the right occipital regions. Quantitative EEG trends show transient deflections in the rhythmicity spectrogram (*solid arrow*) and amplitude-integrated EEG tool (*dashed arrow*)

## Case 3

A 53-year-old man who fell down the stairs secondary to alcohol intoxication was found by his wife the next morning and noted to be confused and poorly responsive. A CT head showed a large subdural hematoma with the right frontal and temporoparietal intraparenchymal hemorrhages. Following successful drainage of the subdural hematoma, the patient was noted to be intermittently mute. In addition, nursing staff noted the patient to exhibit intermittent jerking of the left face, thumb, and fingers. An emergency EEG showed polyphasic periodic lateralized epileptiform discharges ("poly-PLEDs") over the right posterior temporal–occipital region. Poly-PLEDs are typically present in acute or subacute conditions as opposed to chronic focal cerebral lesions. Over time, the area of cerebral damage gives rise to more synchronous discharges, and poly-PLEDs may evolve to less complex biphasic or triphasic PLEDs. This EEG was also notable for the presence of iterative discharges seen in the same derivations as the poly-PLEDs. PLEDs occurring in association with iterative discharges are referred to as "PLEDs plus." Clinical seizures occur at a higher prevalence in patients with PLED plus compared to those with PLEDs alone. Prolonged EEG monitoring should be considered in patients with PLEDs plus, given the risk of subclinical electrographic seizures in these cases. In addition to poly-PLEDs and PLEDs plus, frequent electrographic and clinical seizures were present in this patient, justifying a diagnosis of focal NCSE. He was conscious in between seizures and had not required ventilator support. Non-sedating therapies for status epilepticus were utilized initially including levetiracetam, phenytoin, lacosamide, and low-dose lorazepam, which were unsuccessful. An IV

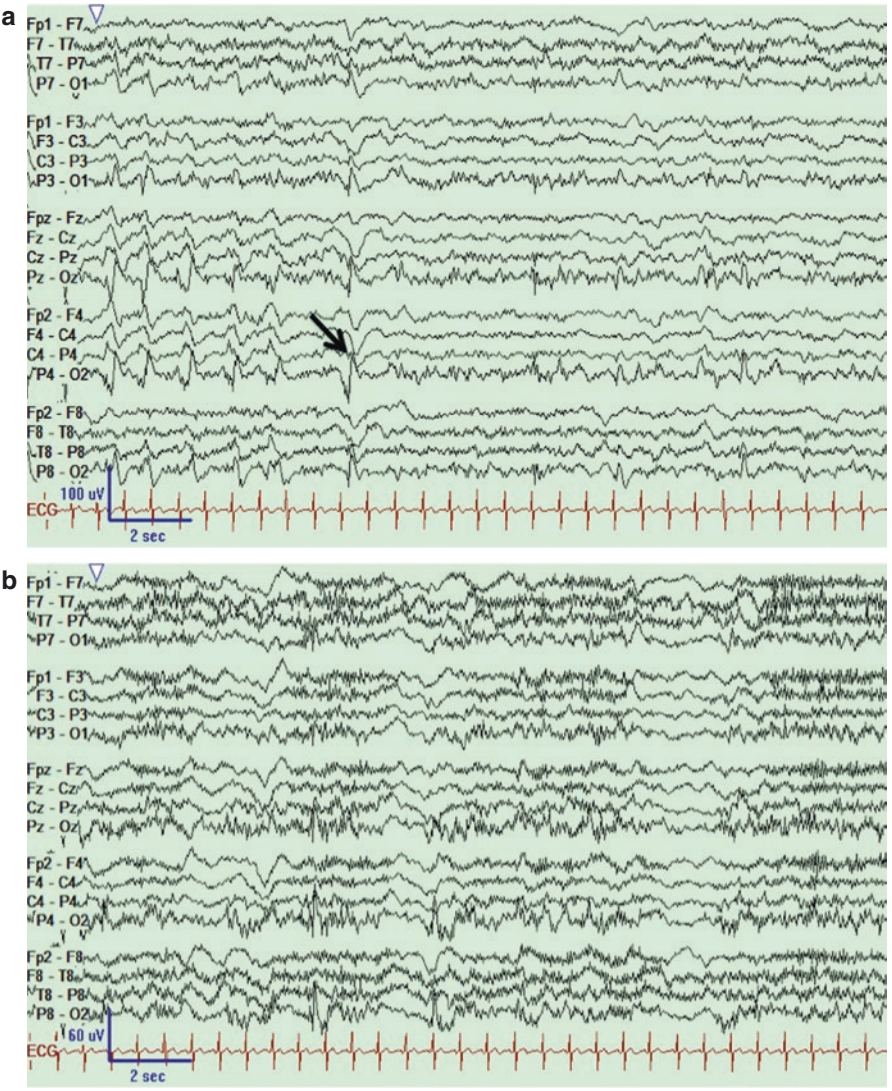



**Fig. 12** cEEG during induction of sedation with ketamine. (**a**) The EEG initially shows attenuation of right occipital lateralized periodic discharges (*arrow*). (**b**) The EEG progresses to a discontinuous pattern following ketamine infusion

infusion of phenobarbital at a subanesthetic dosage of 5 mg/kg resulted in definitive suppression of seizures in this case.

The cEEG findings in this patient are shown in Figs. 14, 15, 16, and 17. The CT head in this patient showed a moderate-sized right subdural hematoma and bleeding in the right cerebral parenchyma (Fig. 14). An emergency EEG showed intermittent lateralized periodic discharges localized to the right

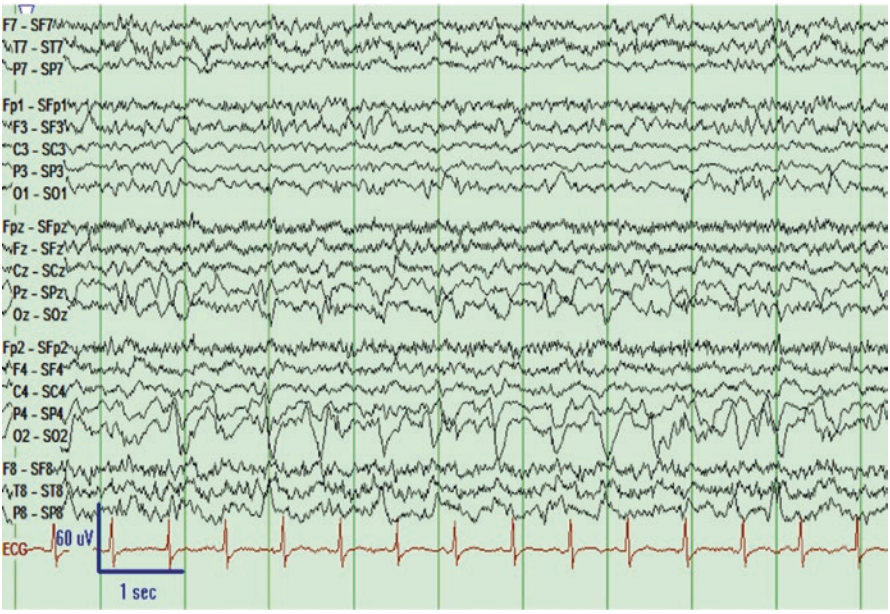



**Fig. 13** EEG with reduction of sedation shows resumption of right occipital lateralized periodic discharges

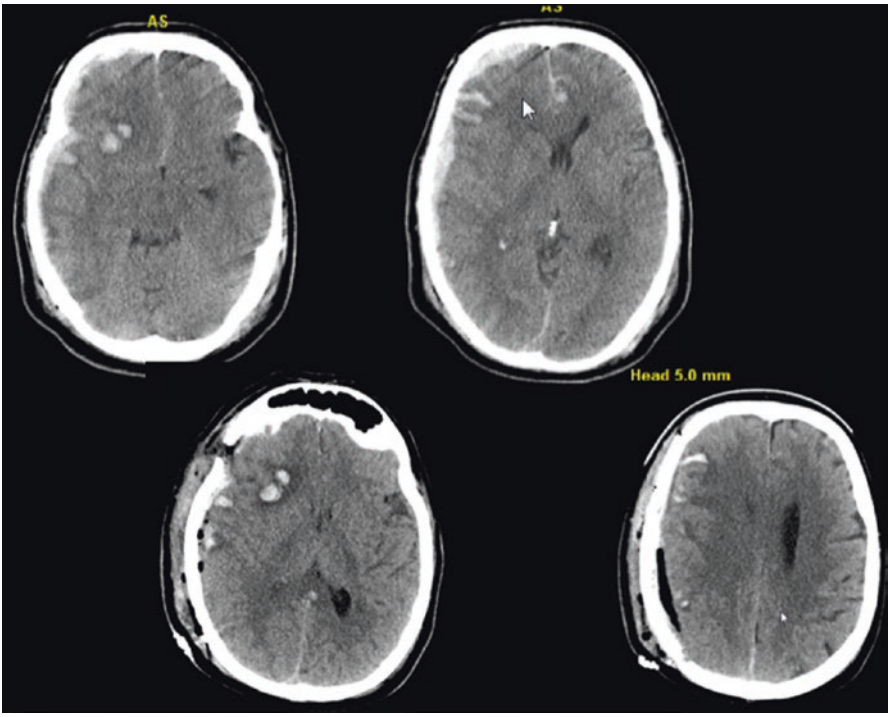



**Fig. 14** CT head imaging showing a right hemispheric subdural hematoma and right frontotemporal parenchymal contusion

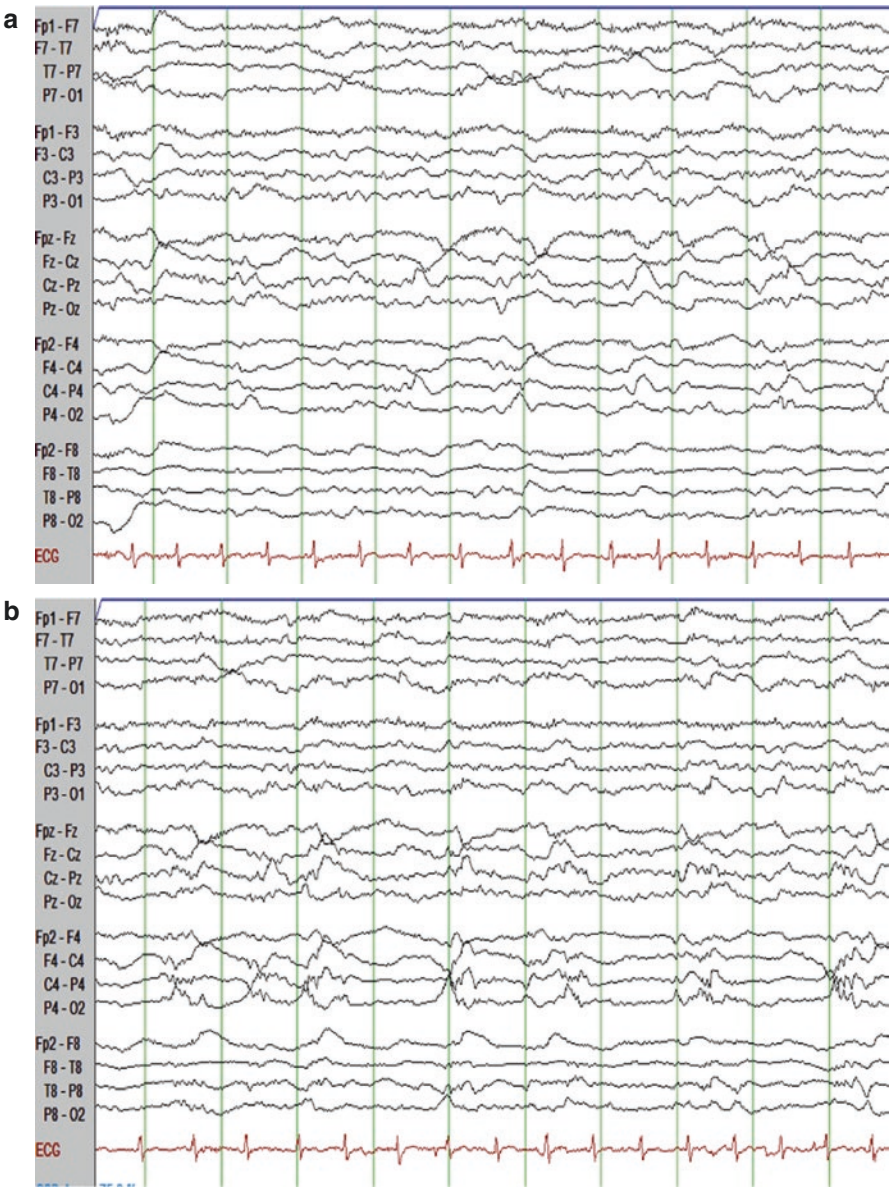



**Fig. 15** Emergency EEG in Case 3. (**a**) Subtle onset of intermittent lateralized periodic discharges in the Cz-Pz and C4–P4 derivations. (**b**) Further evolution of periodic discharge in right centroparietal region. The morphology of the periodic discharges has evolved from subtle rounded complexes to polyphasic potential which show phase reversal at C4–P4

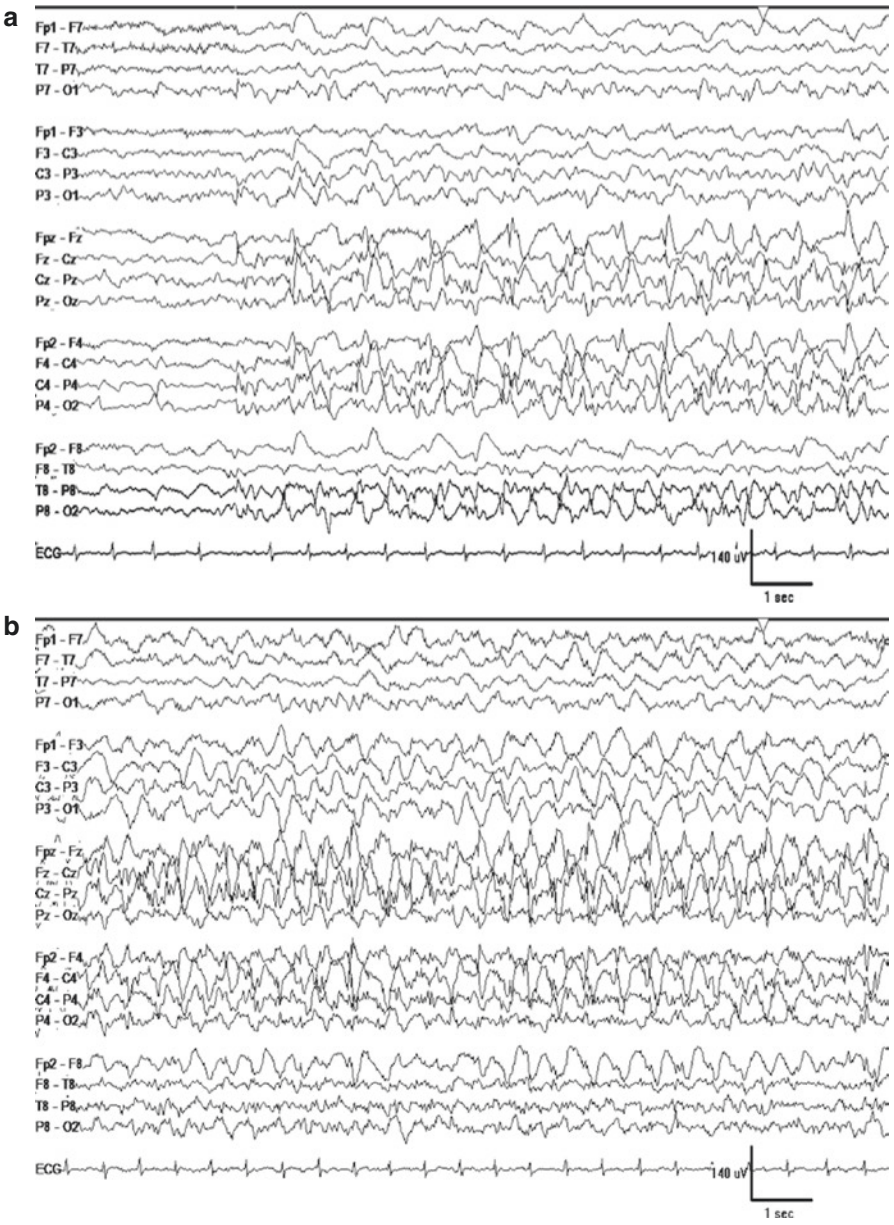


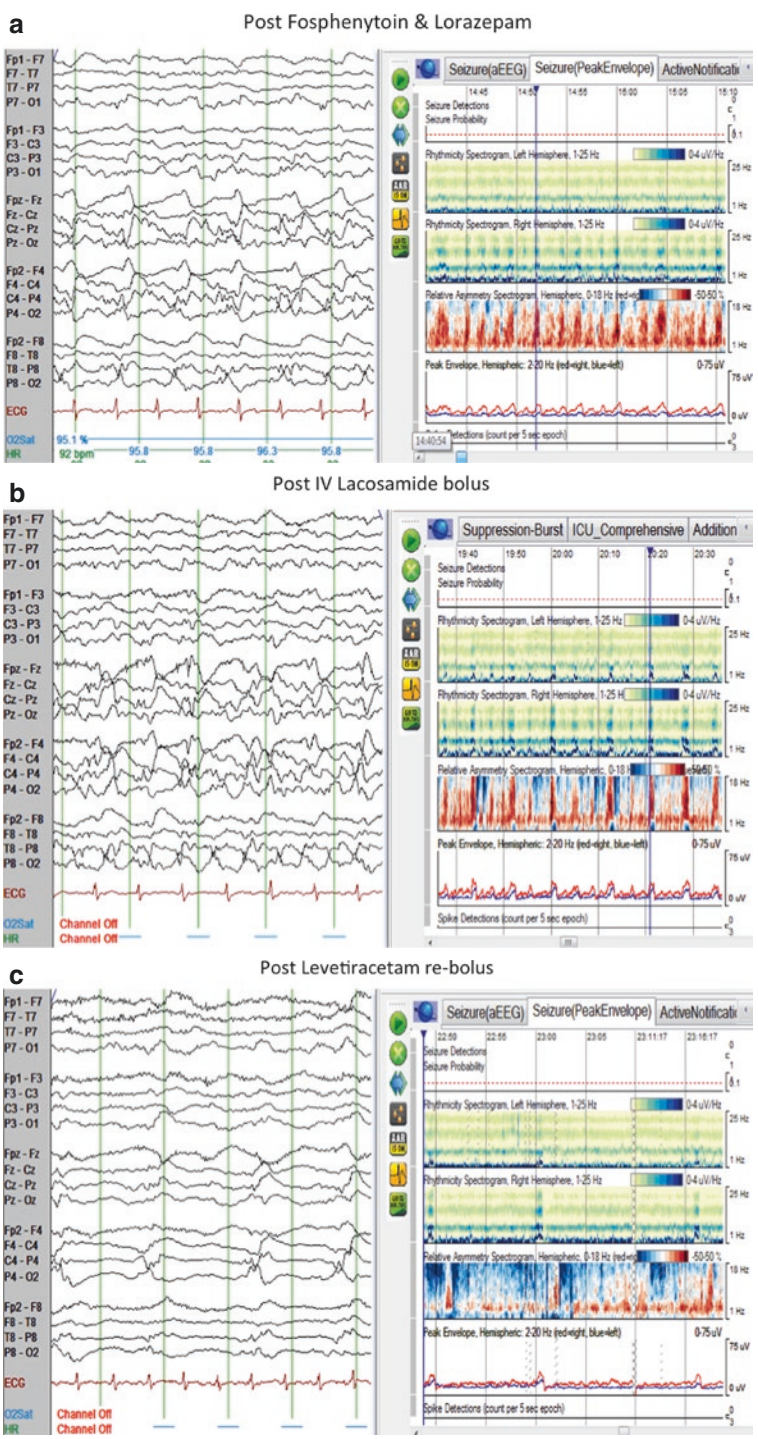

**Fig. 16** Recorded seizures on cEEG in Case 3. (**a**) Onset of seizure discharge that consists of onset of rhythmic activity showing phase reversal at P8 with a field also involving the right and midline frontoparietal regions. (**b**) Continued seizure discharges manifested by rhythmic activity involving right and midline centroparietal derivations with spread to the left parasagittal regions

centroparietal region (Fig. 15), which was anatomically concordant with the imaging findings. The features of the EEG were concerning for the potential for seizures, and cEEG was recommended. cEEG showed frequent seizure discharges (Fig. 16), some of which were subclinical and some of which were associated with focal motor seizures involving the left face and upper extremity. Several seizures were noted per hour. Trials of several non-anesthetic medications were administered in order to try to avoid the need to intubate the patient who was relatively easy to arouse, somewhat conversant between seizures, and breathing spontaneously. cEEG and quantitative EEG trend software were utilized to monitor seizure frequency following each intervention (Fig. 17). The seizures were eventually controlled following phenobarbital administration at a dose of 5 mg/kg.

## Areas of Need/Future Directions

Progress in SRSE research is slow because of the rarity of the disease. A multinational database of RSE and SRSE patients is currently being compiled at https://www.status-epilepticus.net/. There are a few ongoing studies of hypothermia and ketogenic diet in SE and RSE, respectively (ClinicalTrials.gov, study NCT01359332 and NCT01796574). An American multicenter pilot study of compound SAGE-547, an allosteric modulator of $GABA_A$ receptors, is ongoing and scheduled to complete in June 2015 (ClinicalTrials.gov, study NCT02052739). Work is needed in many areas including (1) identification of the causes of cryptogenic status epilepticus, (2) use of rational polypharmacy, (3) optimal patient and drug selection for the use of anesthetic agents, (4) elucidation of the prognostic implications of brain atrophy development, and (5)

**Fig. 17** Utilization of cEEG and quantitative EEG in monitoring the effects of therapeutic intervention. (**a**) Lorazepam and fosphenytoin previously led to a temporary suppression of seizure activity; however, seizures returned as shown in this figure. Quantitative EEG trend shows a seizure rate of 21 seizures per 30 min epoch. (**b**) Quantitative EEG shows modest reduction of seizure rate from 21 to approximately 13 seizures per 30 min epoch following the administration of IV lacosamide. (**c**) cEEG and quantitative EEG show further reduction in seizure rate to three seizures per 30 min epoch following administration of levetiracetam. The seizure rate ultimately returned to near baseline within a few hours. Phenobarbital subsequently led to termination of the patient's seizures


a
Post Fosphenytoin & Lorazepam
b
Post IV Lacosamide bolus
c
Post Levetiracetam re-bolus
Fp1 - F7
F7 - T7
T7 - P7
P7 - O1
Fp1 - F3
F3 - C3
C3 - P3
P3 - O1
Fpz - Fz
Fz - Cz
Cz - Pz
Pz - Oz
Fp2 - F4
F4 - C4
C4 - P4
P4 - O2
Fp2 - F8
F8 - T8
T8 - P8
P8 - O2
ECG
O2Sat
HR
Channel Off
Seizure(aEEG)
Seizure(PeakEnvelope)
Suppression-Burst
ICU_Comprehensive
Addition
Seizure Detections
Seizure Probability
Rhythmicity Spectrogram, Left Hemisphere, 1-25 Hz
Rhythmicity Spectrogram, Right Hemisphere, 1-25 Hz
Peak Envelope, Hemispheric: 2-20 Hz (red-right, blue-left)
Spike Detections (count per 5 sec epoch)

understanding of the role of inflammation in the development of seizure refractoriness.

**Conclusion**

SRSE is defined as the persistence or recurrence of seizures despite 24 h of general anesthesia. Risk factors for refractoriness include traumatic brain injury, stroke, encephalitis, brain tumors, AED noncompliance in patients with epilepsy, and drug intoxication or withdrawal. Apart from etiology, there are no reliable predictors of outcome. In addition to the established treatment, there are several alternative or adjunctive treatment options that have anecdotal success but remain poorly studied. Mortality is generally due to transition to palliative care or complications related to treatment. Prognosis can be favorable in up to 20 % of patients despite weeks or months of seizures.

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# Critical Care Considerations

# 24

Elie Dancour, Amy C. Jongeling, and Jan Claassen

## Contents



E. Dancour, MD • A.C. Jongeling, MD • J. Claassen, MD, PhD (✉)
Columbia University College of Physicians and Surgeons,
177 Fort Washington Ave, Milstein 8 Center Room 300, New York, NY 10032, USA
e-mail: eliedancour@gmail.com; acj2121@cumc.columbia.edu; jc1439@cumc.columbia.edu



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## Introduction

Electroencephalography (EEG) provides the ability to continuously monitor the brain at the bedside and in the critical care unit. Continuous EEG (cEEG) is indicated in convulsive or nonconvulsive status epilepticus, acute stroke with alteration of mental status, traumatic brain injury (TBI), and post-cardiac arrest but may be useful in other situations as well. Invasive (depth) EEG monitoring and quantitative analysis techniques expand the monitoring capabilities of cEEG. With continuous improvements and advances in neurocritical care, cEEG is acquiring an important role in decision-making, but those who use it must be aware of special considerations that may add variability to the data, including medication side effects, artifacts that may mimic seizures, and the effects of structural lesions. Other practical issues must also be considered including maintaining high-quality recordings and interpreting controversial data. While imaging modalities such as computed tomography (CT), magnetic resonance imaging (MRI), Doppler ultrasound, and the neurological exam – standards of intensive care medicine – provide only a snapshot in time; cEEG provides uninterrupted brain monitoring at the bedside.

## cEEG in the ICU

### Types of EEG in the ICU

There are many different types of EEGs that can be ordered in the ICU setting which should be dictated by the clinical needs of the patient while taking into consideration practical aspects such as resources, quality of the recording, and availability of technologists and neurophysiologists to interpret the data. Routine or "spot" EEGs are usually recorded for 30–60 min and provide a snapshot in time; serial routine EEGs can be used in the absence of the availability of cEEG to attempt to track changes in brain activity or seizure frequency over time. The advantage conferred by serial routine EEGs over a single EEG is to provide more of a pattern that can be correlated to the overall clinical picture and trajectory of the patient's clinical status, much like plotting multiple points on a line. However, the most complete picture will be obtained with cEEG with or without quantitative EEG (Chaps. 12–13, and 16) as well as cEEG with depth electrodes, with or without multimodality monitoring (discussed below).

### Indications for cEEG in the ICU

The most common indication for cEEG monitoring in the ICU is for the detection of subclinical seizures, including nonconvulsive status epilepticus (NCSE). Studies have shown that in patients who have had a clinical seizure without return to

baseline within 20 min, 20–48 % will have nonconvulsive electrographic seizures (NCSz) and 14 % will be in NCSE. In a neurocritical care unit, up to one-third of patients will have NCSz, and most of these patients will be in NCSE. NCSz should be considered in any ICU patient with an abrupt and unexplained change in consciousness. Studies have estimated that up to 10 % of patients in a medical ICU – especially those with sepsis – may be in NCSE [1]. Another indication for cEEG monitoring in the ICU is to evaluate the treatment efficacy of anticonvulsant therapies in patients with NCSE or NCSz. Ability to track changes in seizure frequency and promptly detect resolution of status epilepticus while making small adjustments in medication doses decreases the risk of overtreating or adding unnecessary medications. cEEG monitoring in the ICU is also indicated for the management of burst suppression in anesthetic coma, assessment of level of sedation, and detection of ischemia, particularly in the setting of subarachnoid hemorrhage (SAH) and resultant vasospasm [2].

## Indications for cEEG in the ICU, Surface and Depth with Multimodality Monitoring

Invasive EEG with depth electrodes has been used for many years to stereotactically localize lesions in preparation for the surgical removal of epileptogenic areas. Novel monitoring techniques including multimodality monitoring for intracranial pressure, cerebral perfusion, and cerebral blood flow, used in conjunction with cEEG to monitor comatose patients with severe TBI, have broadened knowledge about complex brain pathophysiology. This method of intracerebral monitoring has many promising applications for more precise diagnosis, detection of evolving brain injury, prevention of secondary brain injury from vasospasm, and even tailoring treatment to individual needs after TBI [3].

Studies suggest that depth electrodes inserted into the cortex may augment or corroborate data obtained from surface electrodes as well as improve the signal-to-noise ratio of EEG: for example, myogenic artifact from shivering often obscures surface EEG recordings. Further applications may include clarifying EEG changes that raise the suspicion for seizures that are not frankly detected by surface electrodes: an example of this includes rhythmic slowing on the surface EEG that correlates with periodic epileptiform discharges on the depth electrode. Depth electrodes may also be used for detecting changes that indicate secondary complications (e.g., ischemia secondary to vasospasm) [3]. However, the significance of depth-only findings requires further investigation, and currently, management decisions should not be made solely on these findings but instead should be correlated with clinical impression. Figures 1, 2, 3, 4, 5, and 6 demonstrate examples of seizures and in some cases NCSE captured with depth electrodes on cEEG.

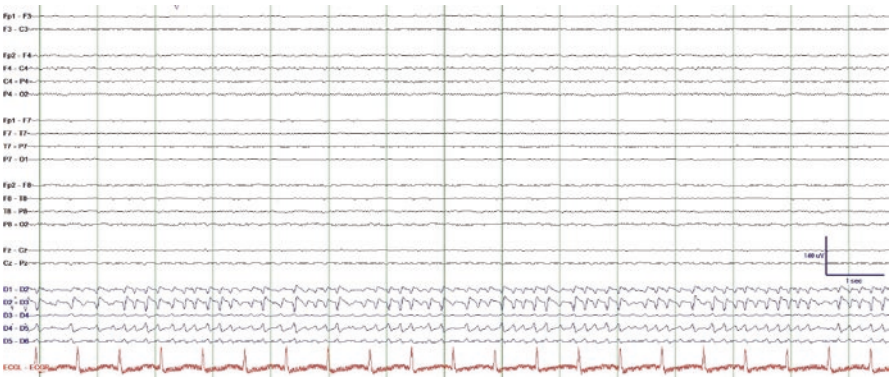

**Fig. 1** cEEG demonstrating NCSE only detected with depth electrodes (*D leads*) in a 59-year-old woman with refractory status epilepticus despite pentobarbital, midazolam, levetiracetam, valproate, and phenytoin. Note the relative lack of activity at the surface electrodes

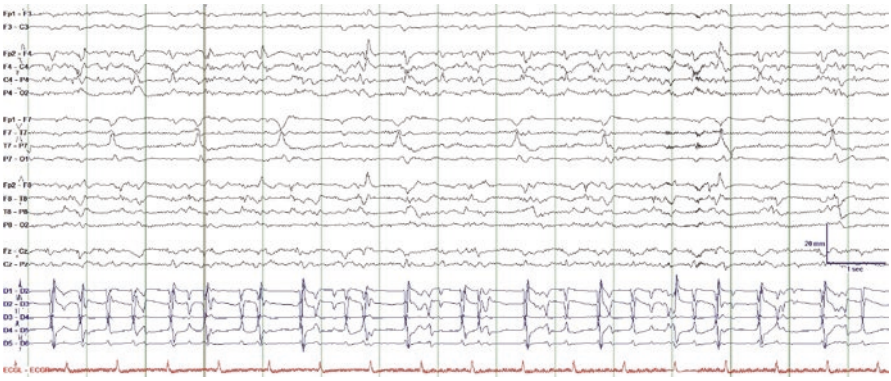

**Fig. 2** cEEG from the same patient as in Fig. 1 demonstrating NCSE on scalp electrodes with depth electrode correlate (*D leads*)

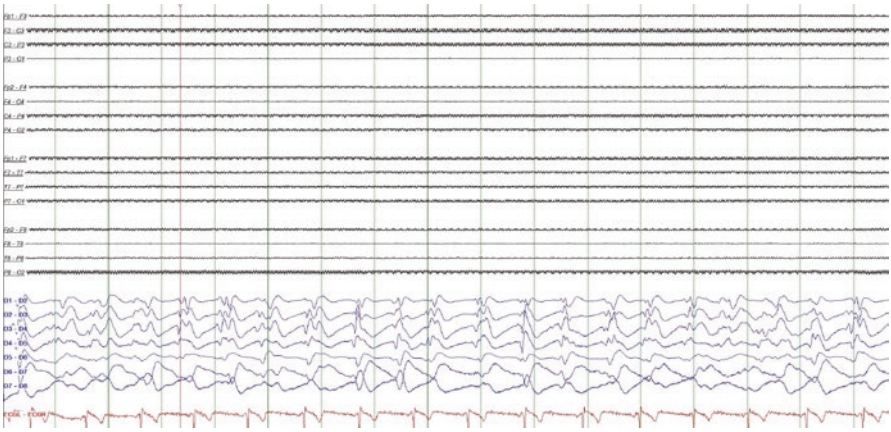

**Fig. 3** cEEG demonstrating NCSE only detected with depth electrode (*D leads in blue*) in a 64-year-old man with nontraumatic SAH. Note the relative lack of activity at the surface electrodes

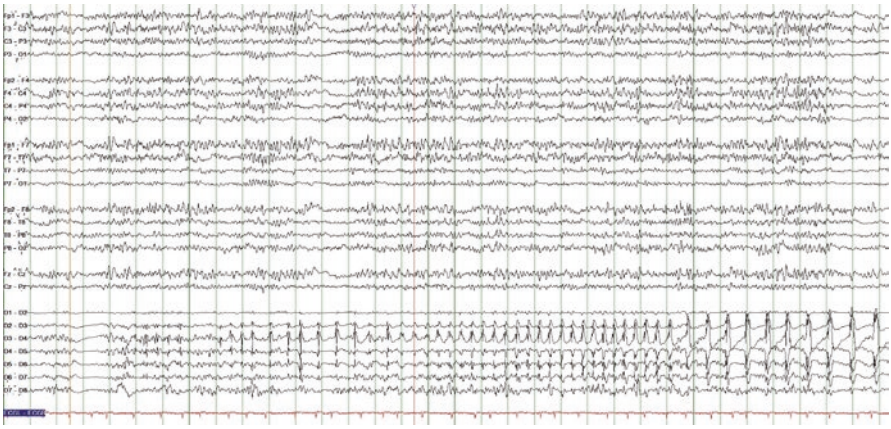

**Fig. 4** cEEG demonstrating electrographic seizure captured only with depth electrode in a 74-year-old woman with nontraumatic SAH (*D leads*). Note the relative lack of activity at the surface electrodes

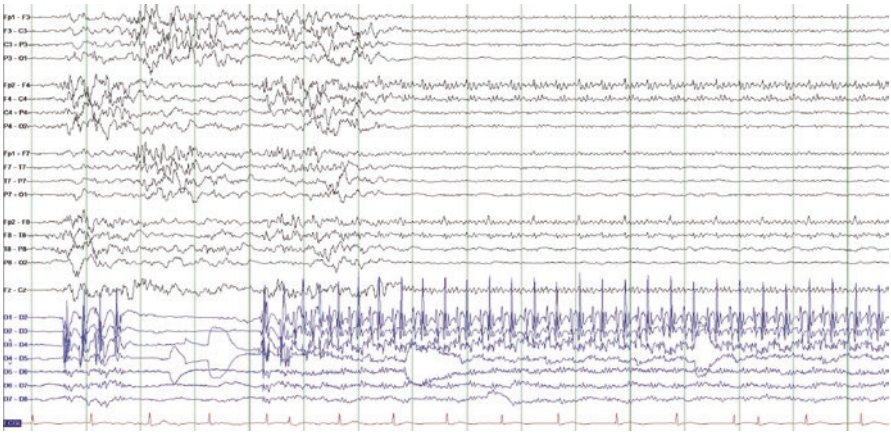

**Fig. 5** cEEG in a 66-year-old woman with a right frontal inflammatory lesion, demonstrating NCSE in the right frontal depth electrode (*D leads*, *blue*), with only a subtle correlate on the scalp electrodes

## Neurocritical Care ICU Considerations

### Status Epilepticus in the Intensive Care Unit

Status epilepticus is common in all types of acute brain injury and is not restricted to patients with a previous history of epilepsy or those admitted for seizures. It is estimated that approximately 150,000 cases of generalized convulsive status epilepticus (GCSE) occur annually in the United States [4]. Most seizures occurring in the ICU setting are nonconvulsive and will remain undetectable unless EEG monitoring is employed. The astute clinician may notice some subtle signs that may raise the

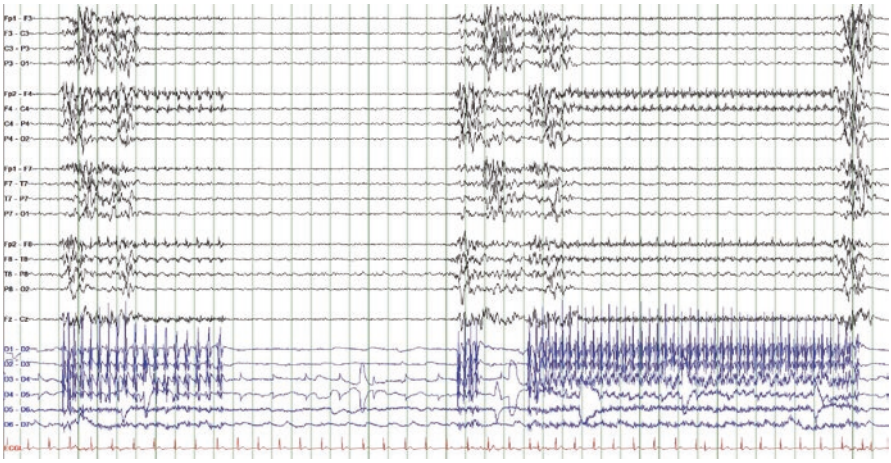

**Fig. 6** cEEG from the same patient as in Fig. 5, expanded view showing electrographic seizures on the depth electrode (*D leads*, *blue*) with subtle scalp correlate

suspicion for NCSz such as face and limb myoclonus, nystagmus, eye deviation, pupillary abnormalities, and autonomic instability, while many patients will have purely electrographic seizures without any overt signs [3, 5]. cEEG is therefore necessary to make the diagnosis of NCSE. As more ICUs employ cEEG, the epidemiology of seizures is becoming better understood. Generalized seizures complicate about 8 % of general ICU admissions with another 10 % having electrographic seizures. NCSz are seen in 48 % and NCSE in 14 % following clinical control of GCSE with benzodiazepines. In the neurocritical ICU setting, up to 34 % will have NCSz, and up to 76 % of those will go into NCSE [6, 7]. The subset of patients undergoing hypothermic protocols for coma after cardiac arrest have a seizure frequency of 20–30 % (excluding clinical myoclonus), most of which are NCSE [4, 8].

The recognition of NCSE has increased exponentially in the past 40 years [9]. The underlying etiologies for GCSE and NCSE are usually similar and include structural lesions, infections, metabolic derangements, toxins, withdrawal, intake of psychotropic drugs, and epilepsy, all of which are commonly encountered in the ICU setting either on their own or in conjunction with other medical problems.

## Diagnostic Considerations

A single self-limited seizure in the ICU should prompt a diagnostic workup although it may not always require anticonvulsant therapy to prevent recurrence. For example, drug withdrawal, intoxication, and electrolyte disturbances are known causes of seizures for which the treatment is to address the primary underlying etiology. Renal failure, hepatic failure, as well as CNS infections are other common causes of seizures in the ICU which may or may not require anticonvulsant therapy. Toxicity from beta-lactam antibiotics is a commonly overlooked cause of seizures, especially in patients with renal failure. Hyposmolarity has the potential to exacerbate conditions which

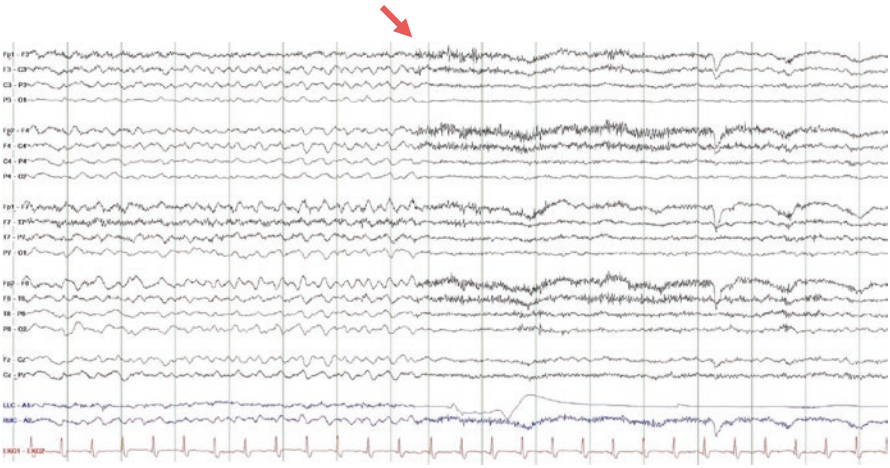

**Fig. 7** cEEG demonstrating NCSE before and after benzodiazepine trial (*red arrow*) in a 59-year-old liver transplant patient with sepsis. The improvement in the EEG background was associated with a dramatic clinical improvement

may cause seizures but should only be accepted as the sole cause of seizures when it develops acutely (over the course of hours), in which case it usually also produces intracranial hypertension. Chronic hyposmolarity causes weakness, fatigue, and confusion, but not usually seizures unless concomitant conditions are present [10].

Hypo- and hyperglycemia, hyponatremia, hypocalcemia, uremia, liver dysfunction, hypertensive encephalopathy, and sepsis have all been associated with NCSE; the incidence of which has been shown to vary from 5 to 22%. Acute renal failure and sepsis have especially been linked to increased electrographic seizures [10]. Certain periodic discharges, such as those with triphasic morphology, are more closely related to underlying systemic metabolic abnormalities (e.g., triphasic waves in hepatic encephalopathy) and are not considered to be epileptiform, while the significance of lateralized periodic discharges (LPDs, formerly known as PLEDs or periodic lateralized epileptiform discharges) remains controversial. At times a benzodiazepine trial may be warranted to attempt to differentiate ictal from non-ictal EEG patterns in critically ill patients (Fig. 7). In a benzodiazepine trial, a bolus of a fast-acting benzodiazepine is administered to a comatose patient with an EEG pattern suspicious for NCSE. However, almost all periodic discharges, including those with triphasic morphology, are attenuated by benzodiazepines; therefore, a benzodiazepine trial is nondiagnostic unless accompanied by a clinical improvement.

## Seizure Prophylaxis in the Neurocritical ICU

Prophylactic antiepileptic treatment should be started in the ICU patient that has had one provoked or unprovoked seizure if even one more seizure would adversely affect the patient's condition. For example, the acute hypertension that accompanies most generalized convulsions could prove detrimental for a patient suffering from

raised intracranial pressure, and therefore antiepileptic drug (AED) treatment should be initiated after the first seizure. In other patients, it may be wise to hold off on initiating AED treatment after the first seizure when taking into consideration possible side effects, drug interactions, and sedative effects of those medications.

Most clinicians will choose to start an AED after the second seizure. In recent years, there has been a proliferation of IV AEDs available to the intensivists, so that options other than the traditional fosphenytoin can be considered, including IV valproate, levetiracetam, and lacosamide. Benefits of choosing phenytoin and valproate include monitoring serum concentrations, as they are readily available. However, ICU patients often have very low serum albumin concentrations and require therapies that compete for protein-binding sites, so unbound (free) concentrations may be needed to guide therapy [11]. Concomitant conditions must be taken into consideration. Valproate should be avoided in patients with liver failure, for example. Levetiracetam and lacosamide have fewer interactions than phenytoin and valproate with other hepatically metabolized medications but must be carefully dosed in patients with renal failure.

## Management of Status Epilepticus

The emergent and potentially fatal nature of status epilepticus makes the initiation of treatment to terminate the seizures mandatory before the clinician can investigate their etiology. First and foremost, patients presenting in GCSE need attention to the basics of life support. While the best way to manage airway problems in GCSE is to terminate the seizures pharmacologically, often endotracheal intubation will be required due to the sedating nature of the pharmacological agents used to terminate the seizures [11]. In these cases, the drugs typically used for sedation – such as propofol and etomidate – will often terminate seizures briefly. If neuromuscular junction (NMJ) blockade is used, the sedative and anticonvulsant effect will usually wear off prior to the NMJ blockade, and therefore, patients may go back to having seizures while still paralyzed and without any overt signs except perhaps pupillary dilation. These patients should be treated as if they are still in GCSE and placed on cEEG to detect ongoing seizure activity [11, 12].

Most patients will be hypertensive in the first 30 to 60 min of GCSE; however antihypertensives are not recommended as almost all of the parenteral anticonvulsants (except ketamine) will lower blood pressure. Sedative drugs used for intubation (except etomidate) and positive-pressure ventilation will decrease preload and further cause hypotension as well. Conversely, if the patient is found with low blood pressure on presentation, this is suggestive of GCSE or NCSE ongoing for more than 60 min, unless a concomitant condition is causing hypotension. Saline resuscitation or vasopressor support should be considered at this point [11, 12].

NCSE in the ICU setting is associated with high morbidity and mortality, although experimental models and pathologic studies showing neuronal damage from status epilepticus were performed on convulsing patients. No randomized controlled study has conclusively proven that treating NCSz or NCSE alters the amount

of neuronal damage; therefore, it is technically unclear if treating this phenomenon is beneficial. There is overwhelming evidence, however, in the form of elevated neuron-specific enolase (NSE) [13], that NCSz and NCSE have the potential to damage the brain. Elevations in NSE can also be seen after stroke, global cerebral ischemia, and coma. Elevated brain interstitial glutamate, lactate-pyruvate ratio, elevated intracranial pressure in NCSE lasting greater than 96 h, brain tissue hypoxia, increasing mass effect, and hippocampal atrophy on follow-up MRI are all evidence that NCSz and NCSE cause brain injury [14].

It can take a substantial amount of time to note clinical improvement in patients who have had NCSE once it is aborted. Therefore, lack of clinical improvement immediately after the resolution of the suspected electrographic pattern does not exclude NCSE. The general approach to the patient in SE should focus on the following: (1) terminating SE, (2) preventing its recurrence, (3) treating its complications, and (4) determining and managing its etiology.

### Termination of Status Epilepticus

Studies have compared lorazepam, phenobarbital, diazepam, and phenytoin to phenytoin alone and determined that lorazepam was most likely to terminate convulsive SE. It was statistically significantly more likely to terminate SE than phenytoin although not statistically superior to the other agents [15]. It has emerged as the drug of choice for the initial treatment of SE because it is also faster and more convenient to administer than the other drugs tested. The dose of lorazepam studied was 0.1 mg/kg; lower doses may be efficacious but have not been systematically studied. At all time points studied, patients randomized to receive lorazepam were more likely to have stopped clinical seizure activity than those who received diazepam (or placebo) [15]. Confounding these studies, however, is the use of EEG. Further investigations in these studies went on to show that many of the patients who were no longer clinically seizing after "successful treatment" of SE were in fact still in NCSE. Thus, it is likely that studies only looking at clinical symptoms overestimate the efficacy of treatment. Recent studies have compared prehospital administration of IM midazolam with IV lorazepam, testing the theory that a rapidly absorbed IM drug would yield the same success rates as an IV drug because the IM drug could be administered more rapidly. The dose of midazolam was 10 mg and for lorazepam was 4 mg, and if patients weighed between 13 and 40 kg, the doses were halved. The study showed that the more rapidly administered midazolam was superior at terminating SE than lorazepam, likely because of the ease with which it could be given [16]. Most clinicians still agree, however, that if an IV line is already in place (such as in the inpatient setting), then IV lorazepam should be administered.

One of the most important confounding factors in assessing the efficacy of treatment of SE is the latency from seizure onset to treatment. Studies have investigated this based on the EEG pattern at the time treatment was initiated [11]. Table 1 shows the likelihood of terminating SE based on the initial EEG pattern, while Figs. 8, 9, and 10 demonstrate different SE patterns. While it is difficult to know the time of seizure onset, the progression from one EEG pattern to the next is well established and provides an estimate of the latency to treatment. For example,

**Table 1** Likelihood of successful overt status epilepticus termination in relation to initial EEG pattern

| Pattern | % treated successfully |
|---|---|
| Discrete seizures | 75 |
| Waxing and waning | 30 |
| Continuous (invariant) pattern | 24 |
| Brief suppressions | 8 |
| Burst suppression | 7 |

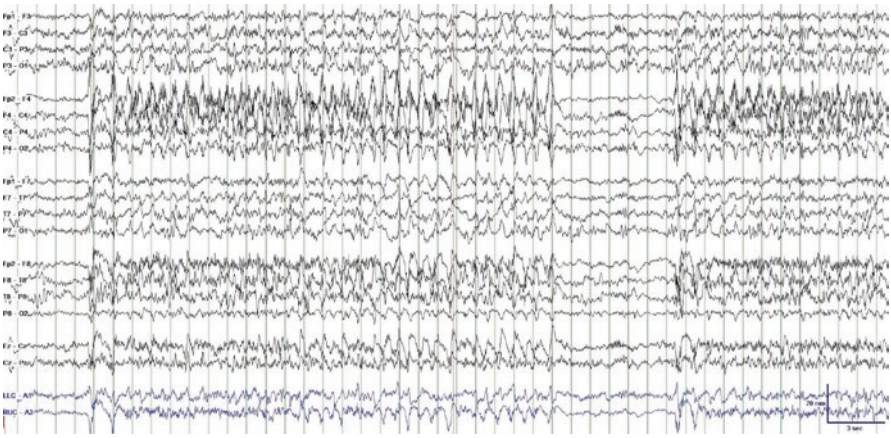

**Fig. 8** cEEG demonstrating SE, waxing-and-waning pattern

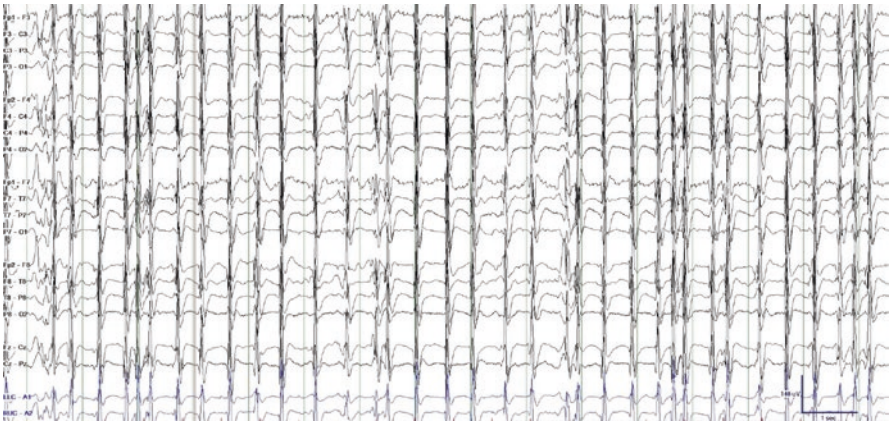

**Fig. 9** cEEG demonstrating SE, invariant pattern

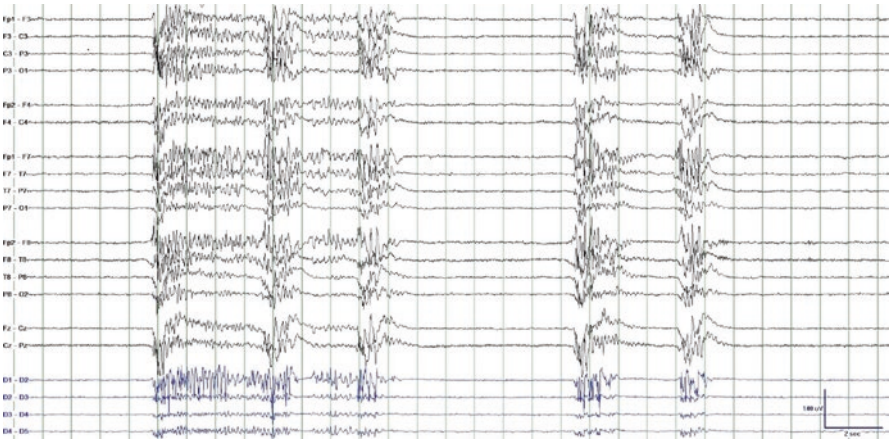

**Fig. 10** cEEG demonstrating NCSE, burst suppression pattern in both the surface and depth electrodes (*D leads*, *blue*)

**Table 2** Response rates for subsequent antiepileptic drugs (overt status epilepticus patients only)

| Initial agent | Drug | Response rate (%) |
|---|---|---|
| Lorazepam | Lorazepam | 64.9 |
| | Phenytoin | 7.2 |
| | Phenobarbital | 2.1 |
| Phenobarbital | Phenobarbital | 58.2 |
| | Phenytoin | 3.3 |
| | Lorazepam | 2.2 |
| Diazepam plus phenytoin | Diazepam and phenytoin | 55.8 |
| | Lorazepam | 3.2 |
| | Phenobarbital | 2.1 |
| Phenytoin | Phenytoin | 43.5 |
| | Lorazepam | 13.9 |
| | Phenobarbital | 3 |

patients with a burst suppression pattern likely have been seizing for longer than those with a waxing-and-waning pattern. Patients classified as having subtle SE most likely have been experiencing seizures for a long period of time or have a catastrophic underlying condition, which helps to explain their poor response rates to any of the conventional antiepileptic drugs [11].

Available data shows that only the first anticonvulsant has a reasonable chance of terminating SE (Table 2) and does not have any implications on preventing recurrence [15]. While fosphenytoin is the only AED to be approved by the US Food and Drug Administration (USFDA) for the termination of SE, it is not superior to

phenytoin as a first- or second-line agent. It is used because it carries a lower risk of complications related to intravenous infusion, although complications like bradycardia and hypotension are still possible. Other second-line agents with published data include valproate, levetiracetam, lacosamide, and topiramate (given enterally as no parenteral form is currently available). There is insufficient data to recommend one over the other at this time. However, the clinician should be familiar with the reasons to choose one agent over another, e.g., side effects or interactions with other medications.

Regarding second-line agents, many believe that if SE has lasted through the time that it took to administer and assess the efficacy of the first-line AED, a more definitive treatment should be employed for the second-line treatment – usually an anesthetic agent (summarized in Table 3). Endotracheal intubation and mechanical ventilation should be started prior to the anesthetic agent. At this point, cEEG is necessary because these agents will usually terminate all movements before

**Table 3** Conventional second-line agents for terminating status epilepticus

| Agent | IV loading dose | Maintenance | Adverse effects | Comments |
|---|---|---|---|---|
| Valproate | 20 mg/kg to 40 mg/kg at 5 mg/kg/min | 4 mg/kg to 6 mg/kg every 6 h | Hepatic toxicity, thrombocytopenia, pancreatitis, induction of autoimmunity | Avoid in pregnancy or after head trauma; numerous drug interactions |
| Levetiracetam | 1 g to 6 g at 2 mg/kg/min to 5 mg/kg/min | 10 mg/kg to 15 mg/kg every 12 h | Accumulates when creatinine clearance is diminished | Minimal drug interactions |
| Lacosamide | 200 mg to 400 mg over 15 min to 30 min | 200 mg every 12 h | Somnolence, atrial fibrillation | Interactions with antiretroviral rugs |
| Topiramate | Not available for IV use; 400 mg enterally every 3 h to 4 h up to 2 g | 300 mg every 6 h | Sedation, metabolic acidosis | Numerous drug interactions |
| Midazolam | 0.2 mg/kg over 5 min | 0.2 mg/kg/h to 2.0 mg/kg/h | Hypoventilation, hypotension | Tachyphylaxis occurs rapidly |
| Propofol | 1 mg/kg to 5 mg/kg (depending on blood pressure and other drugs used) over 5 min to 10 min | Up to 15 mg/kg/h (increasing risk of propofol infusion syndrome above 5 mg/kg/h) | Propofol infusion syndrome (acidosis, rhabdomyolysis), hypotension, immunosuppression | Lipid vehicle is a substantial calorie source |

(continued)

**Table 3** (continued)

| Agent | IV loading dose | Maintenance | Adverse effects | Comments |
|---|---|---|---|---|
| Pentobarbital | 5 mg/kg to 10 mg/kg at 50 mg/min; slow infusion for hypotension | 0.5 mg/kg/h to 5 mg/kg/h | Acidosis from glycols in vehicle, hypotension, immunosuppression, prominent negative inotrope at higher doses | May become unavailable; substitute phenobarbital at a loading dose of 20 mg/kg |
| Ketamine | 1 mg/kg to 3 mg/kg over 2 min to 5 min | 0.5 mg/kg/h to 10 mg/kg/h | Hypotension may develop in patients who have exhausted their intravascular catecholamine stores | Raises blood pressure in about 70 % of cases. Increased intracranial pressure reported in the past was a consequence of carbon dioxide retention, not an issue with controlled ventilation |
| Isoflurane or desflurane | Requires assistance of an anesthesiologist | | | Newer delivery devices may facilitate intensive care unit use |

abolishing GCSE, and the only way for the intensivist to titrate the anesthetic agent to resolution of status epilepticus is via cEEG monitoring. Vasopressor and inotropic support is almost always necessary, as is support of core body temperature since anesthetic agents will often lead to poikilothermia. Enteral feeding may be possible, but parenteral nutrition may be required if an ileus develops. Infections are common, at least in part due to immunosuppression.

Seizures do not respond to first- and second-line therapy in 9 % to 40 % of patients in SE, and this condition is known as refractory status epilepticus (RSE) when there is no recovery of consciousness or return to baseline for at least 30 min. Among these patients, 10 % to 15 % fail to respond to third-line therapy and are considered to have super-refractory SE (SRSE) when seizures are ongoing or SE recurs 24 h or more after continuous infusion of an anesthetic agent [17]. The term also applies to seizures or SE that recurs upon reduction or withdrawal of anesthetic agents within 48 h. These patients are not well studied, and in the absence of randomized clinical trials, treatment remains controversial. Many protocols recommend the use of continuous IV pentobarbital (cIV-PTB) as a third-line therapy for SRSE refractory to propofol or midazolam; however, its use traditionally has been replaced with midazolam given lower rates of hypotension. One retrospective single-center study found that cIV-PTB was effective at treating SRSE: 90 % of the

31 patients studied were seizure-free after treatment [17]. In that study, underlying etiology leading to SRSE was the only variable predictive of poor outcome, and cIV-PTB was found to be relatively safe in the ICU setting except in cases of acute hemodynamic instability. Withdrawal seizures, however, were common (occurring in 48 % of the patients) and were only detected when all the patients were maintained on cEEG monitoring. Withdrawal seizures from weaning off cIV-PTB can be controlled with phenobarbital successfully.

### Titration of Anesthetic Agents Using cEEG

It is common practice to use cEEG monitoring to titrate anesthetic agents for the control of status epilepticus to a background burst suppression pattern. The optimal level of background EEG suppression and the optimal duration of this suppression has not been adequately studied, but it is clear that titration to a burst suppression pattern on EEG is insufficient to prevent seizures, as they often recur once anesthetic agents are withdrawn. Reasonable goals are freedom from electrographic seizures for a maintenance period of 12–24 h, after which the dose of anesthetic agent can be tapered [11]. It remains unclear whether there is a "tolerable" amount of electrographic seizures that are allowed during this off-titration period. Taper of anesthetic agents should be done while the patient is maintained on cEEG for detection of withdrawal seizures for a period of at least 24 h, though no studies have effectively shown this amount of surveillance time to be superior to that of other protocols.

### Other Forms of SE Encountered in the Critical Care Setting

While more rarely encountered, other forms of SE may be encountered in the neurocritical care setting and are worth mentioning. Epilepsia partialis continua (EPC), defined as prolonged spontaneous regular or irregular clonic muscular twitching affecting a limited part of the body, sometimes aggravated by action or sensory stimuli can be considered one type of simple partial status epilepticus, most often resulting from an underlying inflammatory lesion (e.g., Rasmussen's encephalitis). Simple partial status epilepticus can occur as seizures return when prolonged use of anesthetic agents is withdrawn [9]. Absence SE is a form of generalized status epilepticus which does not appear to damage the brain so the aggressive addition of anesthetic agents to terminate this type of SE should be carefully considered [11]. And while complex partial SE appears to damage the brain, it does so to a much lesser degree than GCSE, and therefore, a trial of the non-anesthetic AEDs should be attempted first. Regarding NCSE in the setting of critical illness, the appropriate treatment remains to be defined.

### Prevention of Recurrence of SE

There is little data to guide the choice of AEDs to prevent the recurrence of SE – traditionally the anesthetics mentioned above are used. When an underlying epileptogenic stimulus is present (such as an active infectious or inflammatory CNS state), some institutions have found that phenobarbital is efficacious at doses of 100–150 mcg/mL [11].

### Outcomes in SE

As there is no maximal duration of definitive treatment for SE, there is wide variability for outcomes. One small study found that as many as 10 % of patients recovered despite long duration of SE (although were dependent on others for all ADLs), leading those authors to conclude that the length of SE itself should not lead to discussions of goals of care, but rather catastrophic underlying etiology [17]. Therefore, if a patient has a treatable underlying etiology such as encephalitis in which inflammation will eventually end, treatment should continue even if it takes months. Serial MRIs showing progressive destruction or inability to tolerate the treatment, in addition to underlying catastrophic etiology, are reasons to terminate treatment [11].

## Secondary Complications of SE

The major complications of SE are those inherent to critical care medicine and immobility and include deep vein thrombosis (DVT), pulmonary embolism (PE), central-line-associated bloodstream infections, catheter-related urinary tract infections, and decubitus ulcers. Many of these leave the patient susceptible to sepsis [10]. Complications specific to SE include hyperthermia, rhabdomyolysis, and cerebral edema involving a seizure focus. Hyperthermia and rhabdomyolysis generally cease to be a problem once clinical convulsions cease, even if electrographic seizures are still present. Edema from a single-seizure focus usually does not cause shift or herniation but, as it is vasogenic in nature, will usually respond to steroids if clinically warranted.

## Managing the Etiology of SE

While termination of SE is of the utmost importance, there are many cases where treating the etiology is equally important. A good example is that of SE secondary to bacterial meningitis, in which case-empiric antibiotics are started at the same time as AEDs. Many studies have shown that the most common cause of SE is withdrawal from alcohol, benzodiazepines, or barbiturates, in which case the management is clearly that of managing withdrawal symptoms.

### Stroke

Seizures or SE arising as a consequence of stroke can be more problematic when compared to other underlying etiologies. When the cause is intraparenchymal or subarachnoid hemorrhage, the diagnosis will be apparent from imaging (discussed below), but ischemic causes may escape consideration when presenting with clear-cut generalized seizures. Diffusion-weighted magnetic resonance imaging is most helpful in these cases. Seizures or SE may also be caused by venous sinus thrombosis, in which case magnetic resonance venography (MRV) or computed tomography with venous-phase imaging (CTV) is needed.

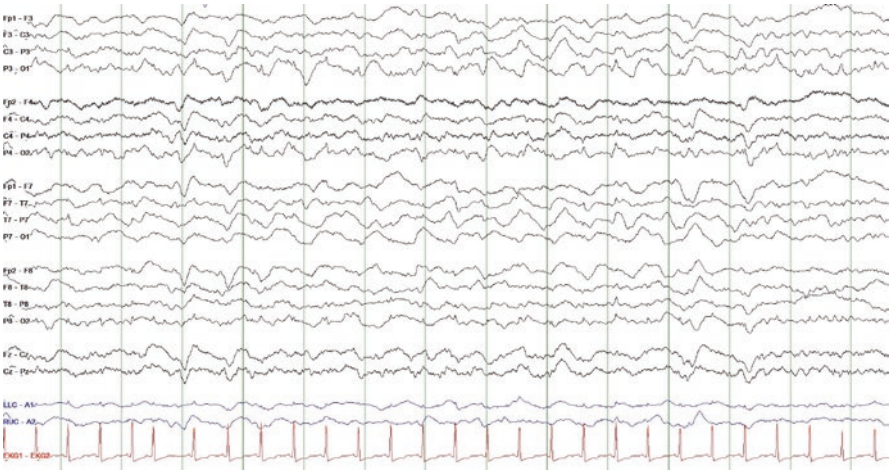

**Fig. 11** EEG demonstrating left-sided lateralized rhythmic delta activity (LRDA) in a 75-year-old woman with a large ischemic stroke who had a clinical correlate of episodic aphasia that resolved after treatment with an AED

One high-powered study showed that seizures occurred in 9 % of those with ischemic cortical infarcts and that 3–4 % occurred in the first 24 h post-stroke. Early-onset seizures, defined as within the first 2 weeks after the ischemic event, occurred in 5 % and late-onset seizures (greater than 2 weeks) occurred in 4 % of those studied. 55 % or more of those with late-onset seizures went on to develop epilepsy [18]. In another study looking at 177 patients with ischemic stroke monitored by cEEG, a 7 % incidence of seizures in the first 24 h post-stroke was reported, with more than 70 % of those being nonconvulsive [19]. Unexplained encephalopathy or an abrupt decline in mental status or neurological exam immediately after ischemic stroke warrants cEEG monitoring to assess for subtle nonconvulsive seizures.

Cerebral infarction may result in several EEG changes including lateralized periodic discharges, unilateral polymorphic delta, lateralized rhythmic delta activity, loss of fast activity, loss of sleep spindles, and focal voltage attenuation. These EEG findings have been shown to reflect change in cerebral blood flow (CBF) and decreased cerebral metabolism as demonstrated by positron emission tomography [20]. Figures 11 and 12 demonstrate EEGs from patients with large cortical ischemic strokes found to have lateralized rhythmic delta activity on EEG after seizures. Figure 13 shows an EEG of a patient found to have left frontal waxing and waning seizures after an ischemic stroke to the same region.

## Subarachnoid Hemorrhage

In patients with subarachnoid hemorrhage (SAH), seizures may occur at the time of the bleed, within the first few weeks after the bleed, or long after hospital discharge. While the underlying mechanisms are different, they are all associated with poor

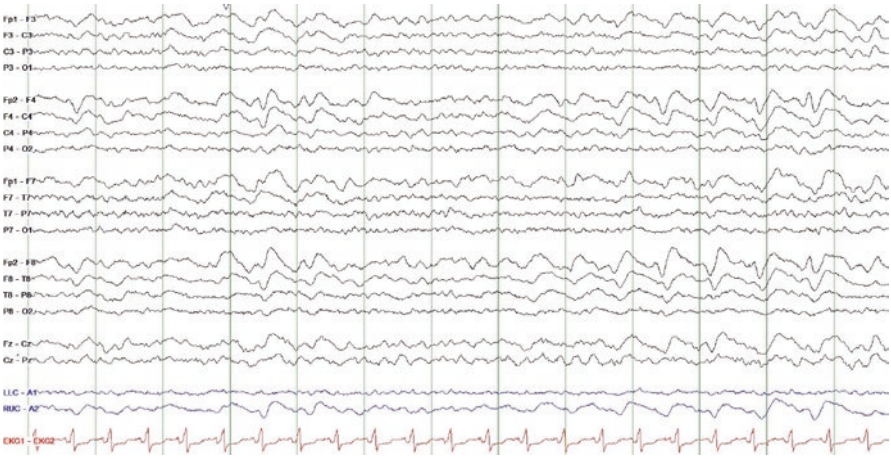

**Fig. 12** EEG demonstrating right-sided lateralized rhythmic delta activity (LRDA) in a 75-year-old man with a large ischemic stroke without clinical seizures

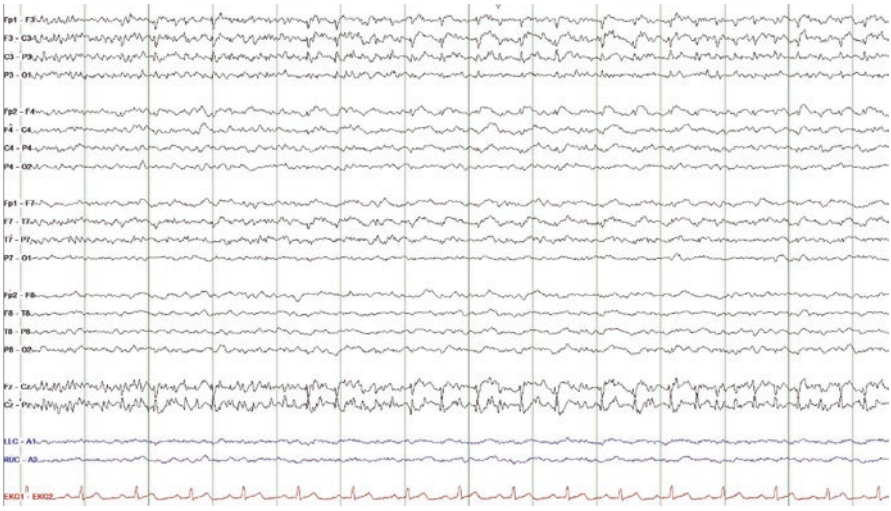

**Fig. 13** EEG from an 81-year-old man with a large left frontal ischemic stroke found to have a waxing-and-waning pattern of NCSE (cyclic seizures every 5–6 min)

outcomes. Studies have found rates of 4–9 % for convulsive seizures at the time of the initial bleed, while more recent studies utilizing cEEG have shown that those numbers were likely underestimating the incidence of electrographic seizures following SAH, especially in comatose patients. In one recent series looking at 108 SAH patients who underwent cEEG for altered mental status or suspicion of seizures, 19 % had seizures. Most of these were NCSz, and 70 % of all patients with seizures had NCSE [6]. Figures 14, 15, and 16 demonstrate EEG findings in patients

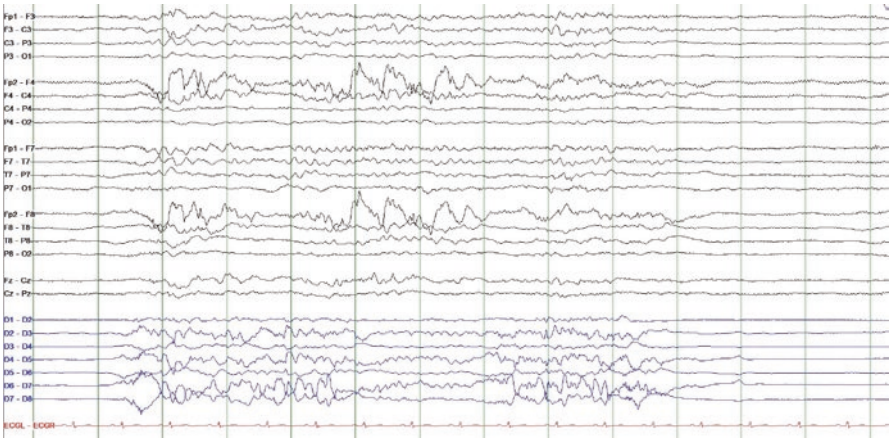

**Fig. 14** cEEG in a 51-year-old woman with nontraumatic SAH demonstrating burst suppression pattern on both the scalp and depth electrodes (*D leads*, *blue*)

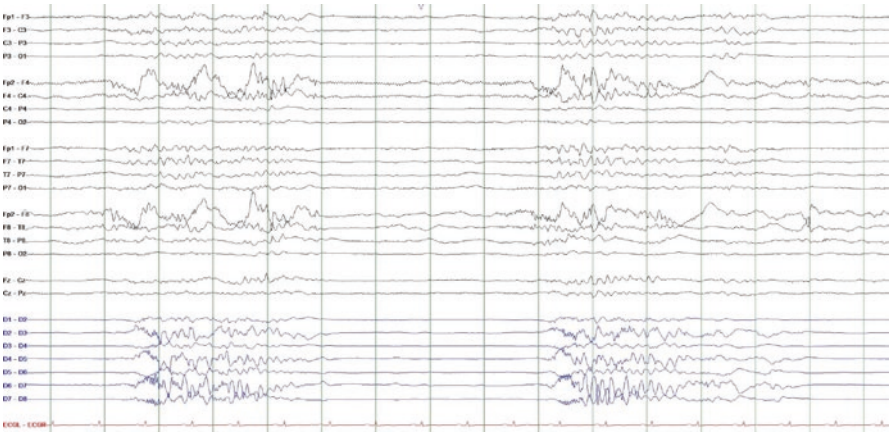

**Fig. 15** cEEG in a 23-year-old woman with nontraumatic SAH demonstrating burst suppression pattern on both the scalp and depth electrodes (D leads, blue)

with nontraumatic SAH who developed seizures, while Fig. 17 demonstrates seizures captured after a traumatic SAH.

Quantitative EEG can be used in the neurocritical care setting for the detection of delayed cerebral ischemia (DCI) in the setting of subarachnoid hemorrhage although the parameter that best correlates with clinically significant ischemia remains controversial. Most authors agree that a ratio of fast over slow activity (e.g., alpha over delta or relative alpha variability) is the correct approach. Some other qEEG parameters that have been shown to correlate with DCI include trend analysis of total power (1–30 Hz), variability of relative alpha (6–14 Hz/1–20 Hz), and post-stimulation alpha-delta ratio (PSADR, 8–13 Hz/1–4 Hz). Indeed, these parameters

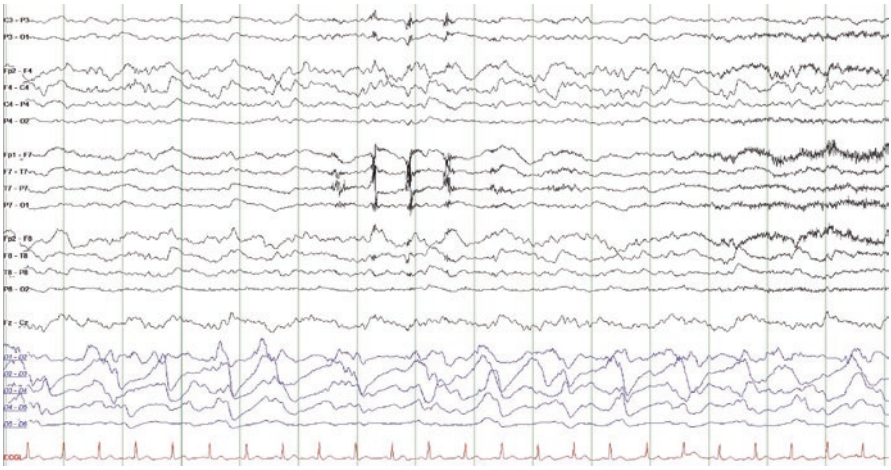

**Fig. 16** cEEG in a 38-year-old man with nontraumatic SAH and ICH demonstrating slowing on both scalp and depth electrodes (*D leads*, *blue*)

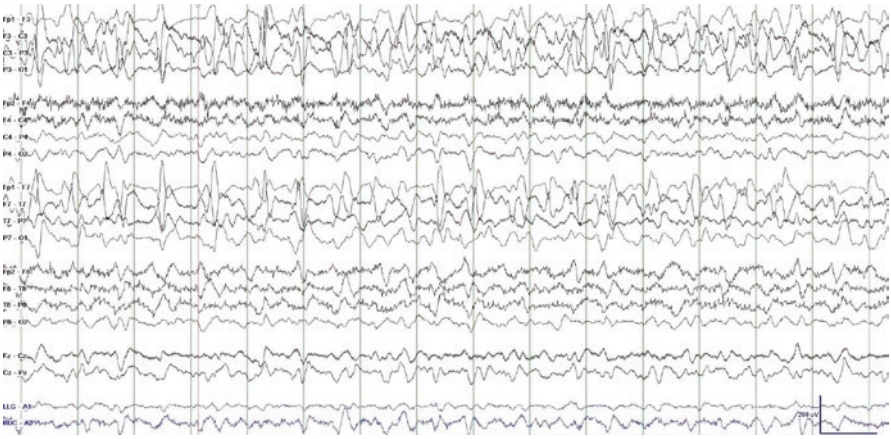

**Fig. 17** cEEG demonstrating seizure activity in a patient with a traumatic SAH

reflecting focal or global ischemic insults on the EEG may detect changes up to 2 days prior to any clinical changes, highlighting their importance [21–23].

## Intracerebral Hemorrhage

Intracerebral hemorrhage (ICH) has been associated with a rate of inhospital convulsive seizures as high as 3–19 %. One prospective multicenter study found an almost twofold increase in the risk of seizures following ICH (all types) when compared to ischemic strokes. 57 % of seizures after ICH occurred in the first 24 h.

Early-onset seizures (less than 2 weeks) occurred in 8 % while late-onset (greater than 2 weeks) occurred in 3 %. All patients with late-onset seizures after ICH went on to develop epilepsy [18]. Two studies using cEEG showed that 28–31 % of patients with ICH have NCSz [24, 25]. One of these studies found that NCSz were associated with increased cerebral midline shifting and with a trend toward worse outcomes, even after controlling for hemorrhage size [24]. In another study of patients with ICH, NCSz were associated with expansion of hemorrhage volume and mass effect, again with a trend toward worse outcomes. Periodic epileptiform discharges (PEDs) were an independent predictor of poor outcome [25].

## Subdural Hemorrhage

Subdural hemorrhages (SDH) are caused by the tearing of bridging veins. This causes accumulation of blood in the subdural space and produces mass effect over the brain tissue. It is usually due to head trauma involving acceleration. In one consecutive series of 1868 adult patients with head injuries who developed early posttraumatic seizures (EPTS), defined as a seizure within the first week after trauma, 34 % of patients were found to have a subdural hemorrhage on CT scan. The study showed that not only was subdural hemorrhage a strong independent risk factor for EPTS, it was also found to be the second strongest overall risk factor, following chronic alcohol abuse, for the development of seizures [26].

In one small study of five patients with SDH and focal seizures, EEG was performed for alteration of consciousness, and it was found that the majority of patients had LPDs prior to hematoma evacuation. Factors possibly involved in the development of LPDs may include compression of the underlying cerebral cortex, cerebral injury or contusion, shift of midline structures, and altered vasculature with compromised blood flow [27]. While neuroimaging studies showed that the hematomas were successfully evacuated, LPDs persisted when they had been present prior to evacuation. The clinical seizures were on the side of the body contralateral to the evacuated hematoma and occurred 1–6 days after the evacuation. The seizures resolved 1–3 days after treatment with antiepileptic drugs, and the patients were continued on maintenance therapy. Figure 18 demonstrates an EEG showing right-sided LPDs done on a patient with a SDH prior to evacuation. These findings should raise the awareness of the intensivists to the possibility of epileptic complications in acute SDH. Even in the absence of clinical seizures, a disturbance in cerebral electrical activity may be present. EEG should therefore be performed in patients who fail to recover full alertness or develop focal deficits before or after SDH evacuation despite absence of SDH recurrence or stroke on brain imaging [28].

## Infection and Autoimmunity

Herpes simplex virus (HSV) encephalitis was considered the most common cause of treatable encephalitis causing seizures until the advent of PCR for the virus showed that many cases of NCSE associated with focal areas of increased T2 signal on MRI

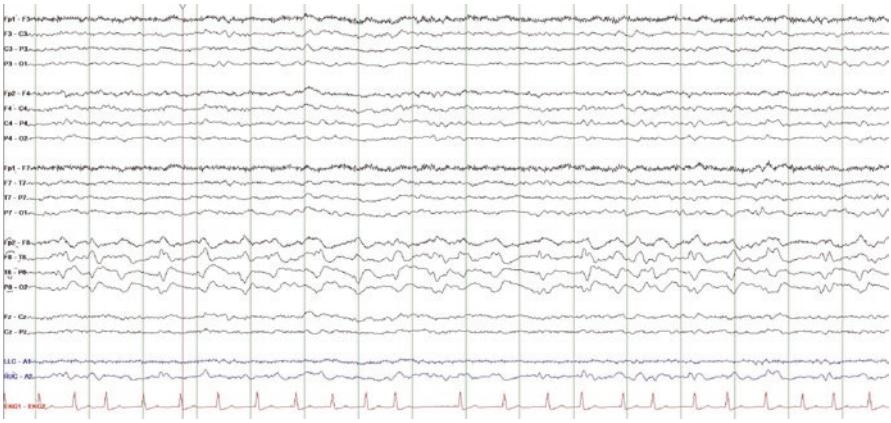

**Fig. 18** EEG performed on a 90-year-old man with traumatic right greater than left bilateral subdural hematomas (not evacuated), who developed seizures. Note the right-sided sharp lateralized periodic discharges (LPDs)

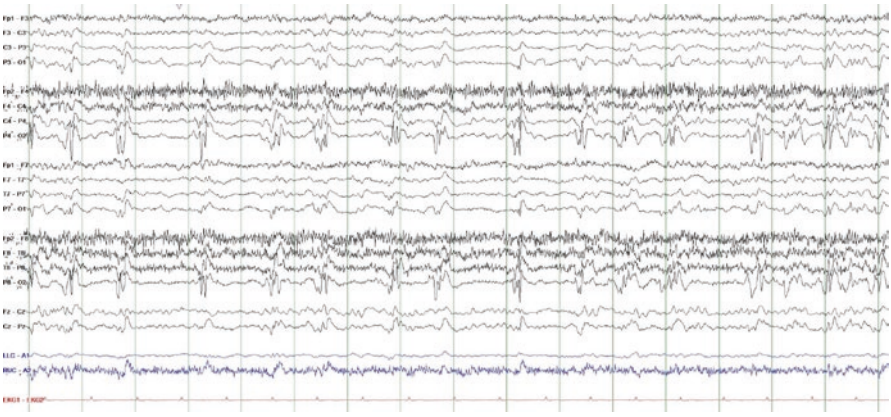

**Fig. 19** Right-sided characteristic sharp lateralized periodic discharges (LPDs) seen on EEG in a 52-year-old woman with HSV encephalitis

were, in fact, not due to HSV at all. It remains, however, the most commonly identified sporadic cause of viral encephalitis (90% are type 1 and 10% are type 2) and is particularly important in neonates where encephalitis may be part of a disseminated infection. Seizures occur in approximately 40% of patients with encephalitis due to HSV type 1 and may be the presenting symptom [29]. It often manifests on EEG with characteristic lateralized periodic discharges as shown in Fig. 19. Despite advances in sequencing techniques, however, one large retrospective study looking at 1151 patients with encephalitis found that of the 43 patients with SE unresponsive to standard antiepileptic therapy who required general anesthetic coma for management, an infectious etiology in the pediatric age group was usually not established, and outcomes were generally poor [30]. Therefore, guidelines continue to recommend starting acyclovir while waiting for PCR results. If PCR results are negative, a

paraneoplastic or autoimmune workup should be started emergently. While there are greater than 20 separate causes of autoimmune encephalitis, some manifest with common phenotypes, such as the characteristic orofacial dyskinesia often associated with anti-NMDA receptor antibody-mediated encephalitis or the faciobrachial dystonic seizures associated with anti-voltage-gated potassium channel (anti-VGKC) antibody-mediated encephalitis. NMDA receptor antibody-mediated encephalitis is unique among the described autoimmune encephalitides in having a specific associated EEG pattern, described as extreme delta brush [31], illustrated in Figs. 20 and 21. Figure 22 shows an EEG of a patient with anti-NMDA receptor antibody-mediated encephalitis who developed frontal seizures. Confirmatory diagnosis, including workup for neoplastic lesions such as ovarian teratomas or small cell lung

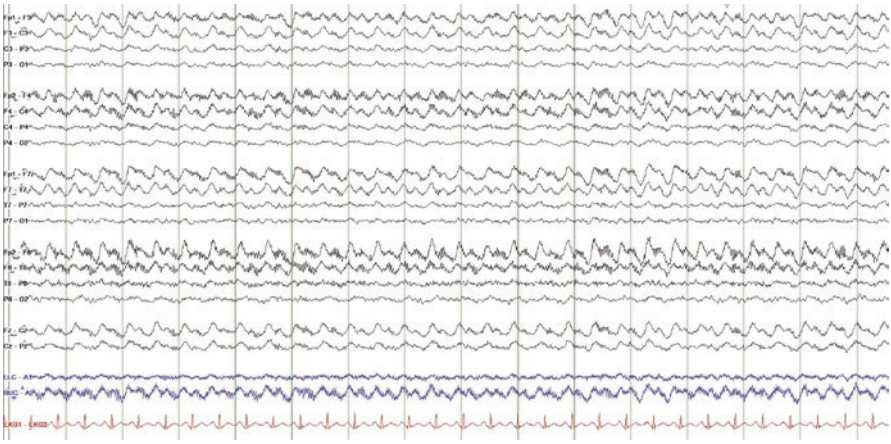

**Fig. 20** Characteristic finding of extreme delta brush on EEG of a 25-year-old man with anti-NMDA receptor antibody-mediated encephalitis

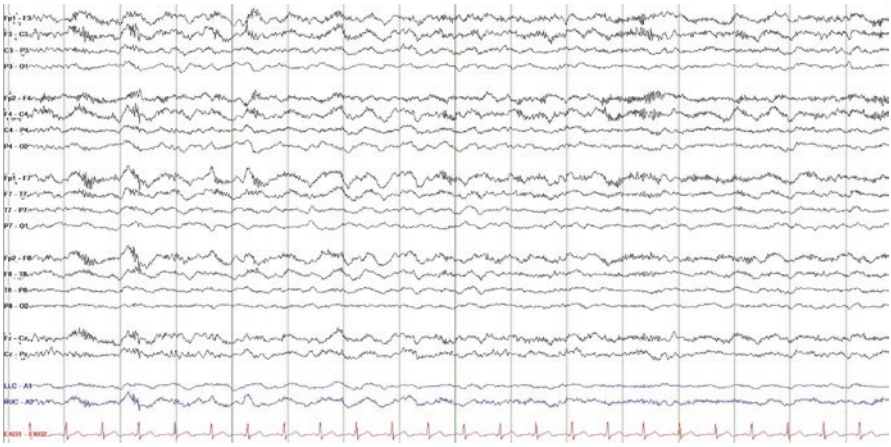

**Fig. 21** Characteristic finding of extreme delta brush on EEG of a 31-year-old woman with anti-NMDA receptor antibody-mediated encephalitis

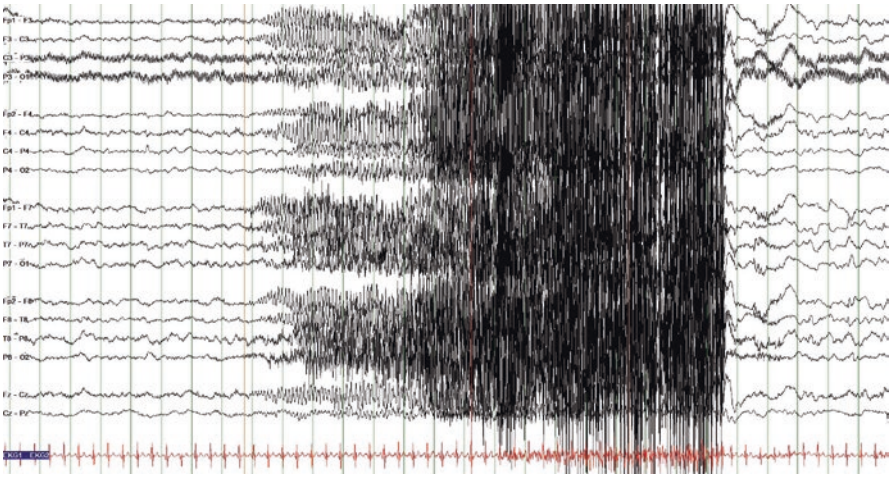

**Fig. 22** EEG of the same patient in Fig. 21, after developing frontal seizures

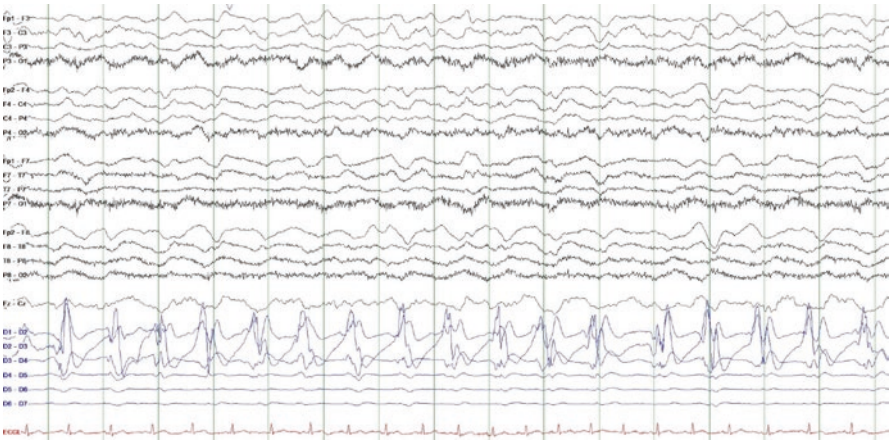

**Fig. 23** EEG of 44-year-old man with a left frontal toxoplasma lesion with only rhythmic slowing on scalp EEG, found to have seizures on the depth electrode (*D leads*, *blue*)

cancer, is necessary. Many of the autoimmune encephalitides will require long courses of cytotoxic or immunomodulatory drugs [32]. Other infections must also be considered as part of the differential. Figure 23 illustrates the EEG of a patient with toxoplasmosis who was found to have seizures on depth electrodes.

## Traumatic Brain Injury

Seizures occurring after traumatic brain injury (TBI) elicit a pathophysiologic response at a time when the brain is most vulnerable. Post-traumatic seizures give rise to increased levels of extracellular glutamate, exceeding the concentration

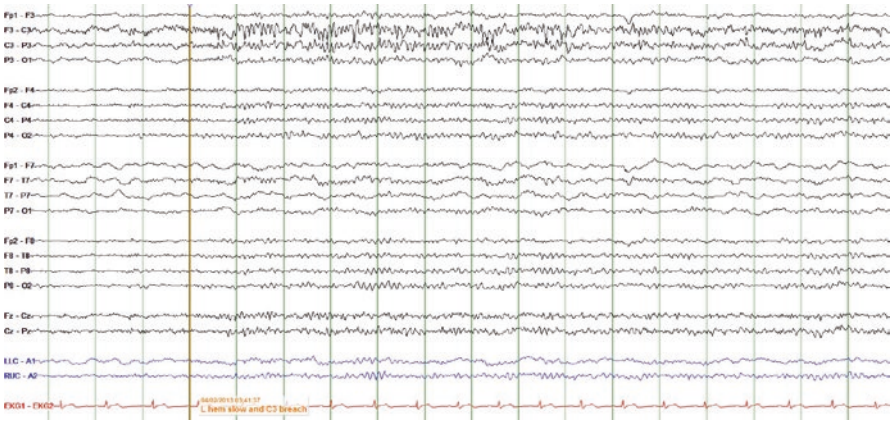


**Fig. 24** cEEG in a young man status-post craniotomy after stroke. Note the left-sided breach rhythm over C3

known to induce cell death and continuing for days after the initial injury. In addition, seizures increase glucose metabolism in the acute phase of injury, resulting in a metabolic drain on already stressed tissue. Seizures increase vasogenic edema within the areas of injured brain and result in increased intracranial pressure [33].

The rates for convulsive seizures in TBI ranges from 15 to 22 %, and although the rate for NCSz is less well studied, rates between 18 and 28 % have been reported. cEEG monitoring is crucial in these cases to follow the clinical course, titrate sedative medications, manage elevated intracranial pressure, and diagnose secondary complications such as seizures. The goal remains to individualize therapy once secondary brain injury is detected as well as to prevent further injury from etiologies like focal ischemia [33]. As a caution, craniotomy defects creating breach artifacts on EEG (Fig. 24) as well as subgaleal hemorrhages creating EEG attenuation patterns must be recognized.

High-dose barbiturates, benzodiazepines, or propofol infusions are often needed to manage intracranial pressure in TBI patients and cEEG should be used as an end point for the termination of seizures. A simple two-channel left and right hemisphere recording is enough to titrate the therapeutic dose to burst suppression (an often-sought goal in TBI), monitor for steady-state conditions, and avoid unnecessarily high doses, which may result in significant cardiovascular side effects.

## Cardiac Arrest

Early and accurate prognostication is important in order to give appropriate information to caretakers and those involved in decision-making in cases of cardiac arrest patients who have survived the event but remain comatose. The best indicator of a good recovery after a cardiac arrest is for a patient to wake up and follow commands, to make spontaneous intentional movements, or to move as a response to painful stimuli when sedation and analgesia have been turned off. A significant number of

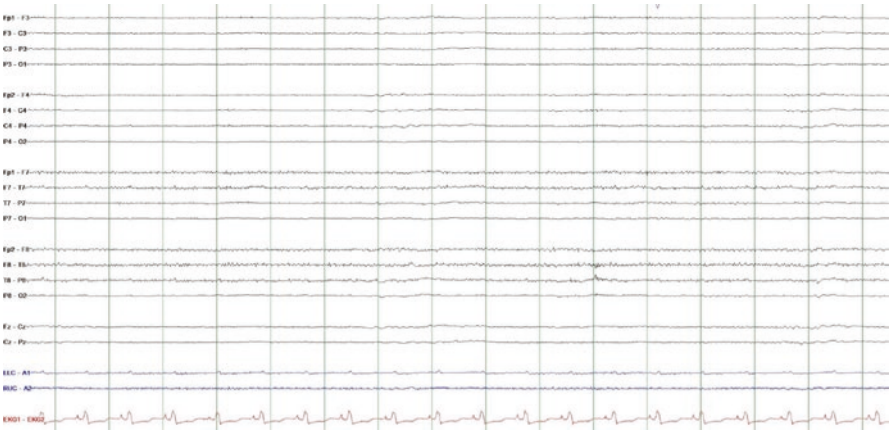

**Fig. 25** Diffuse background voltage attenuation on EEG in a 48-year-old woman with cardiac arrest

patients, however, develop electrographic seizures immediately after cardiac arrest. In fact, most seizures occur within the first 8 h of cEEG monitoring and within the first 12 h after resuscitation from a cardiac arrest. Outcomes have been shown to be poor in those who experience convulsive and nonconvulsive status epilepticus post-cardiac arrest [34, 35]. Therapeutic hypothermia has been shown to improve outcomes in patients resuscitated from cardiac arrest. However, NCSE may result in a prolonged, persistent coma. As more cardiac arrest patients undergo induced therapeutic hypothermia for neuroprotection, cEEG is becoming an ever-increasingly invaluable tool for identifying NCSz or NCSE, especially during the rewarming phase. It has been shown that 20–35 % of patients can have NCSz or NCSE following cardiac arrest. In patients treated with hypothermia, cEEG monitoring during the first 24 h after resuscitation can be used to predict both good and poor neurological outcomes. Continuous patterns within 12 h are generally predictive of good outcome, while isoelectric and low-voltage EEGs after 24 h may herald catastrophic neurological outcomes. While several authors stress the importance of a multimodal approach to accurately predict outcomes using somatosensory evoked potentials, biochemical markers in peripheral blood, and brain imaging, EEG remains of paramount importance in the decision-making algorithm [34, 35]. Studies have proposed implementing cEEG with a simplified montage using only two channels of the original EEG to monitor cerebral function in patients with cardiac arrest. While it is a convenient and dynamic approach to continuous monitoring, it has yet to be compared with the gold-standard multichannel EEG [34]. Figure 25 demonstrates the low-voltage readings seen on EEG in post-cardiac arrest patients.

## Conclusions

The importance of focal findings and pattern recognition on cEEG in the critical care unit lies in generating the appropriate differential diagnosis. The etiologies mentioned above manifest with common EEG patterns and provide the intensivists with invaluable information for both diagnosis and management: lateralized

rhythmic delta activity (LRDA) may be seen in acute strokes; lateralized periodic discharges (LPDs) can be seen in HSV encephalitis; frontal intermittent rhythmic delta (FIRDA) can be seen with increased ICP and the development of hydrocephalus in SAH; alpha or beta coma can be seen in patients being treated with barbiturates or benzodiazepines; generalized slowing can be seen in various metabolic encephalopathies; triphasic waves can be seen in metabolic encephalopathies; and burst suppression can be induced medically with benzodiazepines, propofol, and pentobarbital in the treatment of SE or can be seen in post-cardiac arrest.

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# Prognostication in Adults

# 25

Joao McONeil N.M. Plancher and Brandon Foreman

**Contents**



## Introduction

The neurophysiology of the central nervous system can be evaluated by electroencephalography (EEG) and evoked potentials (EP). Both provide an extension of the neurological examination by assessing electrical function through critical pathways to the cortex. In the critically ill, these pathways may be disrupted reversibly or

J.M.N.M. Plancher, MD
Department of Neurology and Rehabilitation Medicine, University of Cincinnati College of Medicine, 260 Stetson Street Suite 2300, Cincinnati, OH 45219, USA
e-mail: planchjl@ucmail.uc.edu

B. Foreman, MD (✉)
Division of Neurocritical Care, Department of Neurology and Rehabilitation Medicine, University of Cincinnati College of Medicine, Cincinnati, OH 45267, USA
e-mail: foremabo@ucmail.uc.edu



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irreversibly as a result of primary injury, sedation, temperature modulation, or secondary injuries. EEG and EP data in the critically ill provides a window both into current brain functioning and, particularly in patients who are comatose, may provide additional information to help guide decision-making.

Neurophysiologic data has been linked with a variety of outcome endpoints, and timing is crucial. Just 12 h after cardiac arrest, for instance, more than half of patients who eventually have a good outcome do not have a continuous, normal amplitude background – yet at 24 h after cardiac arrest, this same finding becomes 96% specific for poor outcome [1]. While studies after cardiac arrest often utilize the cerebral performance category score (CPC) [2], the Glasgow outcome score (GOS) [3] and the modified Rankin score (mRS) [4] are commonly used in other populations, often with distinct thresholds for what is considered a "good" or "poor" outcome (see Table 1). Outcome measures may be assessed at discharge or after

**Table 1** Commonly used outcome measures

| Score | Cerebral performance category (CPC) [2] | Glasgow outcome scale (GOS) [3] | Modified Rankin score (mRS) [4] |
|---|---|---|---|
| 0 | | | No symptoms at all |
| 1 | Good cerebral performance: conscious, alert, able to work, and lead a normal life. Might have minor psychological or neurological deficits (mild dysphasia, non-incapacitating hemiparesis, or minor cranial nerve abnormalities) | Death | No significant disability despite symptoms: able to carry out all usual duties and activities |
| 2 | Moderate cerebral disability: conscious, sufficient cerebral function for part-time work in sheltered environment or independent activities of daily life (dress, travel by public transportation, food preparation). Such patients may have hemiplegia, seizures, ataxia, dysarthria, dysphasia, or permanent memory or mental changes | Persistent vegetative state | Slight disability: unable to carry out all previous activities but able to look after own affairs without assistance |
| 3 | Severe cerebral disability: conscious, patient dependent on others for daily support (in an institution or at home with exceptional family effort), because of impaired brain function. Has at least limited cognition. This category includes a wide range of cerebral abnormalities, from patients who are ambulatory but have severe memory disturbance or dementia precluding independent existence, to those who are paralyzed and can communicate only with their eyes, as in the locked-in syndrome | Severe disability (conscious but disabled): dependent for daily support by reason of mental or physical disability, usually a combination of both | Moderate disability: requiring some help but able to walk without assistance |

**Table 1** (continued)

| Score | Cerebral performance category (CPC) [2] | Glasgow outcome scale (GOS) [3] | Modified Rankin score (mRS) [4] |
|---|---|---|---|
| 4 | Coma/vegetative state: not conscious, unaware of surroundings, no cognition. No verbal and/or psychological interaction with environment | Moderate disability (disabled but independent): independence to a greater degree than merely activities of daily living | Moderately severe disability: unable to walk without assistance and unable to attend to own bodily needs without assistance |
| 5 | Brain death: certified brain dead or dead by traditional criteria | Good recovery: resumption of normal life, despite minor neurological and psychological deficits | Severe disability: bedridden, incontinent, and requiring constant nursing care and attention |
| 6 | | | Dead |

several months or even years. This chapter makes an effort to clarify the outcome measures and their time frame, but it should be noted that few studies address withdrawal of care, a major confounder of any study of outcome, particularly in the critically ill and those with brain injuries [5].

## Continuous Electroencephalography (cEEG)

Widespread use of continuously recorded EEG (cEEG) has led to evolving insights into the function of the brain after injury and the use of EEG for prognosis. cEEG is noninvasive and has excellent time resolution, which can be used to capture brief periods of reactivity over seconds, nonconvulsive seizures (NCSz) over minutes, or trends in variability over hours or even days. Historically, EEG has been qualitatively "graded" in order to be used for prognostic purposes based on intermittent EEG recordings over time after diffuse brain injuries [6, 7]. With the recognition of the high incidence of nonconvulsive seizures [8] and the standardization of terminology used for critical care EEG [9], the past decade has seen a shift away from using cEEG to provide a definitive prognosis in non-anoxic brain injury and toward a more descriptive approach to evaluating the cEEG and its evolution over time.

### Status Epilepticus

#### Generalized Convulsive Status Epilepticus

cEEG plays a crucial role in the management and prognosis of patients who present with generalized convulsive status epilepticus (GCSE). After GCSE has been treated, cEEG is indicated after 20 min if there has been no improvement in

neurological exam and after 60 min if the patient has not returned to baseline [8, 10]. Nearly half of patients undergoing cEEG after GCSE will continue to have nonconvulsive seizures, and 14 % have nonconvulsive status epilepticus (NCSE) [11]. NCSE after convulsive status epilepticus in one study was associated with an OR 1.66 for poor outcome defined as death or dependency within 30 days after cessation of SE, even after controlling for age and etiology [11]. In patients with "subtle status epilepticus," an electromechanical dissociation resulting in NCSE specifically after prolonged GCSE, 30-day mortality has been found to be substantially higher than in those who initially present with GCSE (65 % vs 27 %). cEEG is required to make the diagnosis of NCSE, and successful treatment with an initial agent reduces mortality by half [12].

### Nonconvulsive Status Epilepticus

The duration of NCSE and delays to its diagnosis have been significantly associated with mortality at hospital discharge in critically ill patients, even after controlling for etiology, age, and length of stay [13]. In the adult neurological ICU, 11/12 patients with subarachnoid hemorrhage (SAH) who developed NCSE had poor outcome, defined as mRS >3 at 3 months [14]. Patients with traumatic brain injury (TBI) who experience NCSE have higher average intracranial pressures and periods of metabolic crisis [15]. While functional outcomes in one small cohort were similar between patients with and without NCSE after TBI as measured by the extended GOS and the disability rating scale (DRS), hippocampal atrophy on MRI developed at 6 months in those with NCSE [16].

In patients admitted to the surgical ICU, NCSE and nonconvulsive seizures (NCSz) together was "found" to have an OR 10.4 for poor outcome, defined as a GOS 1–3 at discharge. The presence of NCSE was associated with coma and prior clinical seizure and was independently associated with outcome once age and etiology were controlled; two-thirds in the cohort had sepsis [17]. In the medical ICU, 8 % of patients with coma had NCSE in a retrospective analysis, but no mortality differences were seen between those with and without NCSE [18]. A more recent prospective observational study in the medical ICU demonstrated that 11 % of those with severe sepsis, three-quarters of whom were comatose, developed NCSE. In that cohort, NCSE did not appear to independently impact mortality or functional and cognitive outcome measures at 1 year [19]. In children admitted to a general ICU, the probability for neurological decline by hospital discharge increased by 1.13 for each 1 % increase in *seizure burden*, the number of minutes of electrographic seizure activity per hour [20]. To date, studies that have examined NCSE in adults have been largely underpowered to adequately detect changes in functional or cognitive outcomes based on sample size.

## Nonconvulsive Seizures

NCSz refer to discrete electrographic seizures. A precise definition of what constitutes NCSE vs NCSz is not well established, and some studies merge patients with

NCSz and NCSE; others merge NCSz with ictal–interictal patterns, described in the next section. Despite this, there is clear evidence to suggest that isolated NCSz, even those that occur in a small region of the brain recorded only using intracortical recordings, result in increases in heart rate and blood pressure and may result in increased intracranial pressure and metabolic demand with reciprocal changes in brain tissue oxygen and regional cerebral blood flow [21]. After SAH, NCSz have been independently associated with poor functional outcome defined as mRS 4–6 at 3 months, even after controlling for age, bleed severity, delayed cerebral ischemia, and inflammatory response [22]. After intracerebral hemorrhage (ICH), NCSz appeared to worsen neurological function and increase midline shift, although overall functional outcome at hospital discharge was not affected [23, 24]. Interestingly, nonconvulsive seizures appear to occur in patients with an intermediate-severity brain injury; while patients with seizures are at higher risk for poor outcome in general, they tend to do better than those who have markedly severe background attenuation or lack reactivity in patients with SAH or with severe sepsis [19, 22].

## The Ictal–Interictal Continuum

Critically ill patients may exhibit a variety of periodic or rhythmic patterns during cEEG that do not fulfill typical definitions of NCSz [25]. The interactions between neuronal injury and metabolic dysfunction manifest as abnormal patterns on cEEG which cannot be easily classified, falling somewhere on an ictal–interictal continuum [26]. Periodic discharges (PDs) are commonly associated with acute brain injury and may be acute, prolonged [27], or even chronic [28]. PDs are clearly associated with electrographic seizures [27, 29–31], but their relationship with outcome is less clear. In the medical ICU, the presence of PDs or NCSz has retrospectively been associated with poor outcome defined as GOS 1–3 at hospital discharge [32], although in a prospective study of medical ICU patients with severe sepsis, PDs or NCSz had no impact on 1-year survival or functional and cognitive outcomes [19]. In the setting of central nervous system infection, 48% had either PDs or NCSz with sixfold odds increase for poor outcome at discharge, defined as severe disability or worse [33]. In the surgical ICU, PDs were not independently associated with hospital discharge outcome, although 97 % of patients with PDs lasting longer than 24 h had poor outcome compared with 58 % of patients with transient PDs [17]. In comatose neurological ICU patients, however, prolonged PDs lasting more than 5 days in a row were found to have no impact on mortality [27] compared to intermittent or no PDs.

Of the PDs, lateralized periodic discharges (LPDs) are the best studied. Case series have demonstrated instances of increased regional glucose metabolism or blood flow in the region of LPDs, mirroring changes seen during seizures. After GCSE, LPDs on cEEG have been associated with poor outcome: more than half of those with LPDs died or were dependent at discharge [34]. After intracranial hemorrhage and SAH, LPDs were found to be independent predictors of poor outcome,

defined as GOS 1–2 at discharge or mRS 4–6 at 3 months, respectively [14, 24] (see Fig. 1). Although overall mortality rates in patients with LPDs are between 25 and 41 %, much of the mortality associated with LPDs appears to be related to the underlying etiology, and case–control studies are lacking.

Generalized periodic discharges (GPDs), which include triphasic waves, are associated with mortality rates between 30 and 47 %, but when age, etiology, and level of arousal were controlled, there was no association with poor outcome, was found defined as death or vegetative state at hospital discharge [29]. Bilateral independent periodic discharges (BIPDs) have been highly associated with poor outcome, with a mortality of 61 % compared to 29 % in patients with LPDs. Nearly three-quarters of patients with BIPDs were comatose (vs 24 % of patients with LPDs), and with such a small sample size, it is likely that injury severity

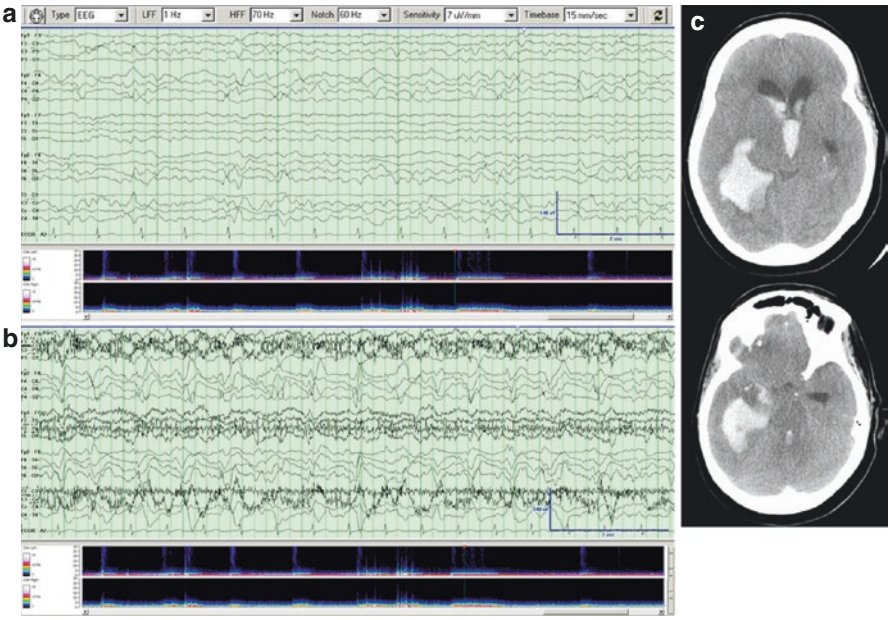


**Fig. 1** Stimulus-induced lateralized periodic discharges after poor-grade subarachnoid hemorrhage. A 61-year-old comatose woman post-bleed day 8 after modified Fisher 2, Hunt–Hess 4 subarachnoid hemorrhage requiring craniotomy and clipping of a right posterior communicating artery aneurysm. With stimulation, the focal delta frequency slowing seen over the right hemisphere (pictured in **a**) becomes periodic, with frontally predominant blunted sharp waves at 1Hz (SI-LPDs; pictured in **b**). Compressed spectral array (at the bottom of each EEG left hemisphere is above the right hemisphere) demonstrates increased delta power over the right (*bottom half*) more than the left (*top half*) after stimulation multiple times throughout the 24-hr period. (**c**) Extent of the subarachnoid hemorrhage. The patient remained in a persistent state of unresponsive wakefulness and was eventually sent to hospice care 6 weeks after discharge from the hospital

accounted for much of the mortality [31]. Further studies of BIPDs are needed to fully assess their prognostic importance.

## Burst Suppression

Burst suppression (BS) has long been associated with diffuse brain injuries and is caused by a loss of normal cortical inhibition with hyperexcitable bursting interrupted by refractory periods [35]. Prognosis is strongly dependent on etiology: traditionally, BS has been associated with poor outcome after cardiac arrest but in other cases may be seen transiently during deep anesthesia. Asymmetric bursts in particular may point to structural lesions in the corpus callosum [36, 37]. Background suppression, on the other hand, refers to either a low-voltage record of predominantly theta or delta frequencies without reactivity or an isoelectric recording [38]. The prognosis associated with this pattern is typically poor once the effects of sedative medications or metabolic dysfunction (e.g., severe sepsis, uremia, hypercalcemia, thyroid or adrenal failure, hypoglycemia) are ruled out [39]. However, much of the literature on burst suppression and background suppression is focused on anoxic brain injury, and the majority are from the pre-hypothermia era.

Burst suppression may be induced therapeutically, as in refractory intracranial pressure or refractory status epilepticus. The prognosis in these cases is usually considered poor as a result of the underlying etiology, although maintenance of BS induced for treatment of refractory status epilepticus for >72 h may help improve overall seizure control and perhaps even survival [40, 41]. In one series of patients requiring pentobarbital for refractory status epilepticus, 90 % of whom had BS on cEEG, one in ten had minimal or no disability at 1 year [41], and in a series of patients with TBI requiring pentobarbital titrated to BS for refractory intracranial pressure, 24 % survived to good recovery defined as GOS 4–5 at 1 year [42].

Spontaneous BS may be observed in critically ill patients, many of whom require sedation and analgesia as part of their critical care. In neurological ICU patients with ICH, the presence of BS does not significantly portend poor outcome, defined as GOS 1–2 at hospital discharge, once clinical and radiologic predictors are controlled [24]. This appears to be true across neurological ICU patients, regardless of etiology [43]. In the operating room and in some ICUs, BIS monitoring (Covidien; Boulder, CO) is performed via a device designed to process the crossed bispectrum of raw frontal EEG into a simple-to-read number between 0 and 100. Using the BIS, anesthesiologists have reported on a large cohort of patients from two prior clinical trials, 28 % of whom experienced > 5 min of anesthesia-related BS during elective surgery under general anesthesia. Patients who experienced BS were older and had higher preoperative comorbidity. After controlling for these factors, those with both anesthesia-related BS and intraoperative hypotension had three times the risk for 90-day postoperative mortality [44]. Another study found that each hour spent in BS intraoperatively increased mortality at 1 year by 24 %, and each minute spent with

a systolic blood pressure < 80 mmHg increased mortality at 1 year by 4 % [45]. Among medical ICU patients, 62 % of whom had sepsis, those with BS had double the hazard ratio for 6-month mortality than those without BS after controlling for age, comorbidities, and illness severity [46].

## EEG Background: Variability and Reactivity

The background frequency content of the cEEG is typically reported descriptively: attenuated delta frequency slowing, predominant theta/delta frequencies, organized posterior dominant alpha, etc. Some frequency changes are important for the interpretation of cEEG in the critically ill, such as declining faster frequencies in the setting of inadequate cerebral perfusion, and particularly focal findings such as focal delta frequencies or asymmetry in the EEG related to stroke. Quantitative analysis of the frequency spectra provides useful objective information [47] and may have a role in predicting certain outcomes, as described in Chapter 15. However, the overall background frequency mix is largely nonspecific. Prior attempts to develop grading systems to reflect prognosis after diffuse brain injury have used overall background frequency patterns and their reactivity [6, 7]. However, with the use of continuously recorded EEG, the importance of dynamic parameters such as reactivity and state changes has been more heavily emphasized. As an example, the prognosis of frequency-dominant patterns such as alpha or theta coma, best studied after hypoxia, is predicated on their reactivity [48] and frequently evolves over several days to different patterns altogether [49].

Reactivity refers to a reproducible change in the EEG background as a result of stimulation (see Fig. 2). Although reactivity has received attention as a prognostic

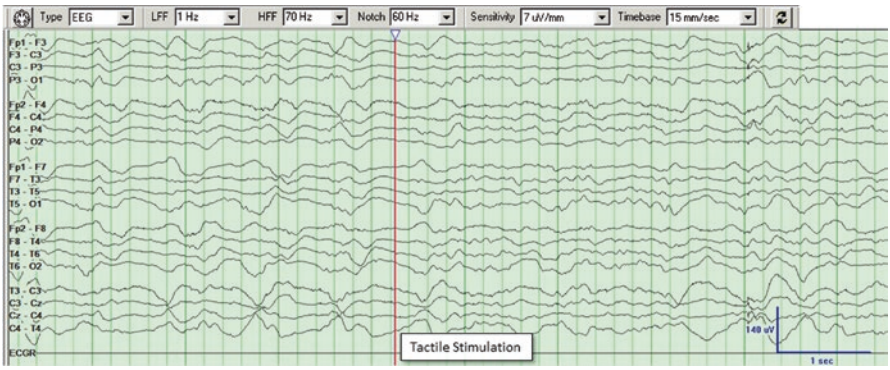


**Fig. 2** Reactivity in a comatose patient with toxic metabolic encephalopathy. A 55-year-old woman in coma 4 days after presenting with ethylene glycol toxicity. cEEG demonstrated severe diffuse background slowing. Stimulation, as marked, produced an attenuation of delta amplitude and an increase in theta frequencies. Termed desynchronization, this is a form of reactivity. The patient regained consciousness several days later and was discharged with mild disability (Glasgow Outcome Scale score 5)

marker after cardiac arrest, the *reproducibility* of this finding is confounded by a lack of standardization of stimulus type and stimulus strength, inter-rater agreement on EEG changes, the effects of confounders such as sedation, and the timing of stimulation during the sleep–wake cycle. The kappa between expert raters for background reactivity in one study of routine EEG segments from patients with a clear "awake" state ranged broadly 0.33–0.95 [50]. Of practical importance in the ICU, the method of stimulation for a given patient needs to take into account other injuries, for example, hearing impairment from canal obstruction following trauma or surgery or sensory loss after cervical spinal cord injury. Caution should be used when applying background EEG reactivity to prognostic decision-making in the clinical setting. Within 48–72 h of TBI, one study used auditory clicks and nasal septum stimulation to elicit one of several categories of EEG reactivity: slow waves, attenuation, no reactivity, and uncertain. Increasing slow-wave activity (so-called paradoxical reactivity) was associated with GOS 4–5 (good recovery) at 18 months post-injury in 90 %. In those without EEG reactivity, 93 % had severe disability or worse; notably, 78 % with uncertain reactivity had good recovery or moderate disability [51]. After SAH, all patients with a poor outcome, defined as mRS >3 at 3 months, lacked EEG reactivity to any alerting stimuli; however, more than half of patients' reactivity was not reported [14]. After ICH, reactivity was not found to be an independent predictor of outcome in multivariate analysis [24]. In patients with severe sepsis, a standardized stimulation protocol was used to define reactivity, which was absent in patients with continuous sedation, circulatory shock, and coma. Patients without reactivity had a mean survival time of 3 months compared with 8 months for those with EEG reactivity, although 13 % of survivors at 1 year had lacked reactivity in the ICU, and no differences were seen in functional outcome between those with and without EEG reactivity [19].

In a special case of reactivity, stimulation may produce ictal–interictal discharges. These stimulus-induced rhythmic, periodic, or ictal discharges (SIRPIDs) have been described in 22 % of patients undergoing cEEG on an inpatient neurology service [52]. SIRPIDs are thought to be related to dysregulated afferent input into hyperexcitable cortex and appear to be associated with the development of seizures. They are seen significantly more frequently after ICH, convulsive status epilepticus, and TBI [52, 53]. After ICH, focal SIRPIDs are independently associated with poor outcome, defined as GOS 1–2 at hospital discharge [24]; after SAH, SIRPIDs do not appear to be predictive of outcome [14]. The impact of SIRPIDs on outcome in general has not been adequately studied.

Variability refers to spontaneous changes in EEG over time, as opposed to reactive changes to a stimulus. A lack of variability – a "monotonous" EEG – has been described after brain injury using raw EEG [54] and using compressed digital spectral array [55] in association with poor outcome defined as death or unresponsive wakefulness. The presence of variability may refer to a simple biphasic EEG that alternates from one abnormal pattern to another over time, to more complex and definitive state changes with a behavioral correlate, or to variability in specific background frequencies during EEG. In a foundational study of states in comatose critically ill patients, all patients with a biphasic or invariant nighttime recording died [54].

In patients with TBI, variability has been quantified using the percentage of 6–14 Hz frequencies in the background EEG. The degree of variability in the first 72 h after TBI significantly correlated with discharge and 6-month GOS, and when added to a prognostic model of outcome that included standard clinical covariates, the alpha variability significantly improved the predictive ability of the model [56, 57]. After SAH, the presence or absence of state changes or spontaneous variability does not appear to independently predict outcome [14]. However, the alpha variability declines in patients with SAH a mean of 2.9 days prior to the onset of vasospasm [58].

Cyclic alternating patterns (CAP) are a specific form of variability described after brain injury. CAP refers to periodic bursts of delta frequencies in the absence of stimulation (hence, not reactivity). These patterns mimic normal sleep microarchitecture and appear independent of other alternating physiologic patterns, such as Cheyne–Stokes breathing. In one series of patients with CAP, 7 of 11 patients experienced good outcome (complete recovery or minimal dependency) after a follow-up period of several months [59] (see Fig. 3). In another cohort 1–2 weeks after traumatic injury, CAP was described in six patients, none of whom had a good outcome. This may have been related to the persistence or delayed presentation of CAP or a lack of overlying sleep transients which were not reported in the former series [60].

## Sleep

Sleep is frequently abnormal in critically ill patients with or without brain injury [61, 62]. In one series, only 30 % of critically ill patients had normal sleep at any point during cEEG [61]. The majority of patients in the ICU have state changes that do not fit the standard definitions of sleep as defined by the American Academy of Sleep Medicine. The term “atypical sleep” has been used to describe periods of behavioral or electrographic sleep-like states in these patients, who lack typical sleep transients such as K-complexes or sleep spindles [63]. After TBI, patients with typical sleep features have favorable prognosis: the presence of K-complexes or sleep spindles had a positive predictive value of 86 % for no or only mild disability at more than 1-year follow-up [60], and increasing spindles have been seen prior to recovery of consciousness and have been correlated to the duration of coma [54].

On the other hand, EEG that does not include typical sleep features correlates with worse injury severity, coma, impending sepsis, and delirium [62–65]. In a series of patients with SAH, 85 % lacked sleep architecture during the first 24 h of cEEG, which was the only independent predictor of an outcome of mRS 4 or worse at 3 months, with an OR 10.4 [14]. In hospitalized encephalopathic patients, 62 % of patients had no identifiable typical sleep transients. The presence of K-complexes was an independent predictor of good outcome, defined as GOS 5 at hospital discharge with an OR 2.8 [66]. In unsedated, awake but encephalopathic patients with no brain lesions, both vertex waves and K-complexes increased the odds for good outcome significantly; sleep spindles were not significantly associated with outcome in this group, which may represent distinct pathology compared to patients with TBI.

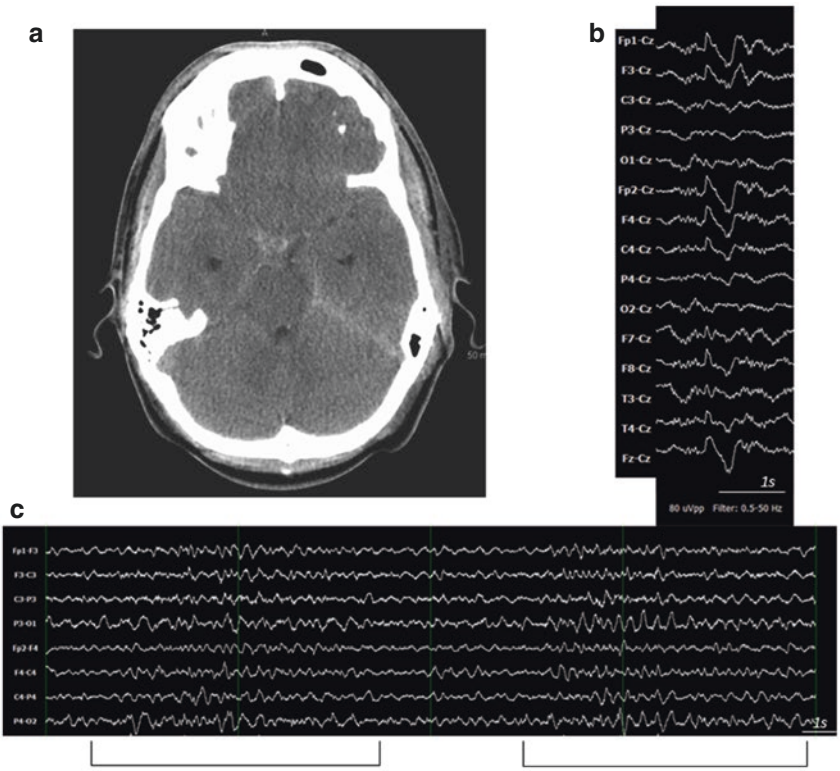


**Fig. 3** Cyclic alternating patterns and sleep transients in a comatose patient after traumatic brain injury. A 24-year-old man post-trauma day 2 from a high-speed motor vehicle collision. Injuries included subarachnoid hemorrhage and Barrow A (*direct*) left carotid–cavernous fistula. Initial Glasgow Coma Scale score was 5 on scene with unilateral pupillary nonreactivity on arrival to the neurological intensive care unit. Multiple intracranial pressure crises required sedation and limited examination. (**a**) Admission CT with traumatic subarachnoid hemorrhage. (**b**) Clear K-complex; diffuse background beta frequencies in the setting of propofol sedation makes distinguishing clear sleep spindles impossible. (**c**) A cyclic alternating pattern with paradoxical bursts of high-amplitude delta slowing (*denoted by brackets*), not apparently related to specific stimulation. At follow-up 5 months post-injury, Glasgow Outcome Scale score was 5

## Evoked Potentials

Evoked potentials (EPs) extend the neurological exam by providing standardized afferent input and recording the time-averaged cortical responses to those inputs. Typical evoked potentials include somatosensory evoked potentials (SEPs), brainstem auditory evoked potentials (BAEPs), and event-related potentials (ERPs). See Fig. 4; Table 2 outlines the short-latency waveforms and their relevant anatomy. Although EPs are not typically continuous measures, they can provide serial, noninvasive bedside assessments of the brainstem and thalamocortical tracts and are

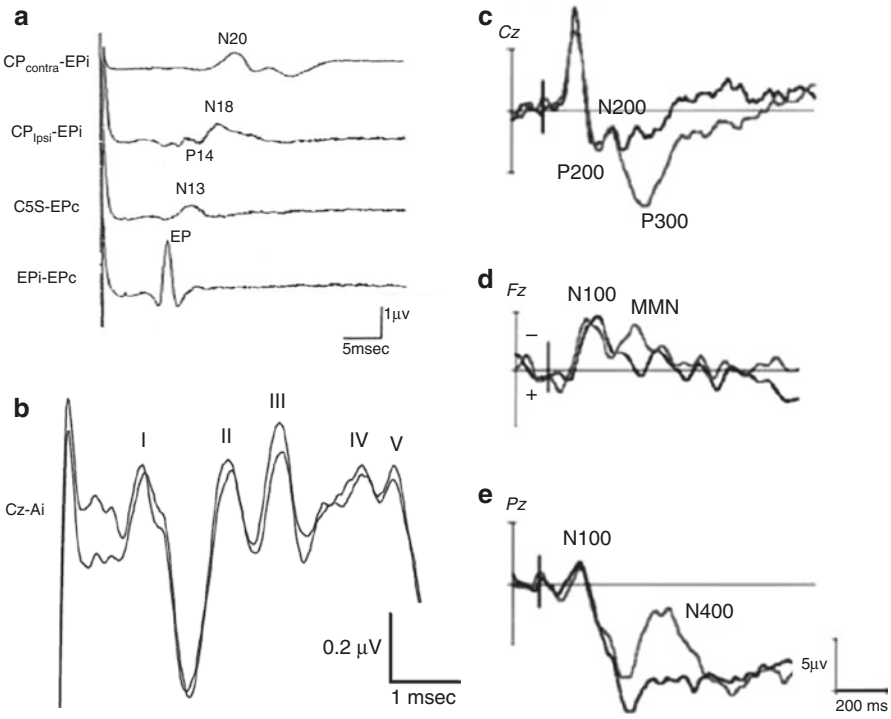


**Fig. 4** A composite of normal short-latency and long-latency potentials. Short-latency potentials: (**a**) somatosensory evoked potentials and (**b**) brainstem auditory evoked potentials. Long-latency potentials: (**c**) P300, (**d**) the N100 and mismatch negativity, and (**e**) the N400 (Waveforms adapted and modified from the originals found in Legatt [87] and Vanhaudenhuyse, et al. [83])

relatively robust to the effects of sedation, paralytics, and therapeutic temperature modulation [67]. Although much of the focus on evoked potentials has been in the postanoxic brain injury population, literature exists on their use in other forms of brain injury.

## Somatosensory Evoked Potentials

SEPs are short-latency potentials that assess the integrity of the dorsal column–lemniscal tracts by recording the cortical response to stimulation of the median or tibial nerves. SEPs may be graded 1–6 based on relative symmetry (see Table 3) or reported as latencies from stimulus onset. Bilateral absence of cortical response (grade 1) is traditionally considered a robust indicator of severe brain injury. In a large meta-analysis including adults and children, only 12 of 777 patients with bilaterally absent cortical responses had an outcome better than severe disability, with a false positive rate of <0.5 % excluding children and those with surgically amenable traumatic lesions [68]. Nonetheless, sensitivity was around 50 % to predict either a

**Table 2** Relevant anatomy and waveforms for short-latency evoked potentials

| Potential | Recording site | Anatomy | Notes |
|---|---|---|---|
| Median SEP | | | |
| N9 | Erb's point (supraclavicular fossa) | Antidromic conduction through motor fibers (C8,T1) and orthodromic sensory fibers (C6, C7) via brachial plexus | Robust to brachial plexus avulsion but may be affected by sensory peripheral neuropathy |
| N13 | Cervical spine (C5) | Dorsal horn; axon collaterals of the fibers near the root entry zone in the lower cord | Latency between N13 and P14 is an indicator of cervical cord to brainstem transmission |
| N20 | Contralateral cortex (C3 or C4) | The response of neurons in the hand area of the contralateral primary somatosensory cortex to thalamocortical afferents | Abnormalities may be graded based on appearance (see Table 3); loss reflects either diffuse cortical injury or anesthetic effect |
| Central conduction time (CCT; P14-N20) | Centroparietal cortex (C3 and C4) | Subcortical connections from the spinal cord–brainstem junction (caudal medial lemniscus) to the cortex via the thalamus and its afferents | Central latencies increase linearly with hypothermia and with declining blood flow |
| BAEP | | | |
| I | Central midline (Cz) to ipsilateral ear (Ai) | Auditory nerve compound action potential | Stimulus intensity or sound polarity may elicit wave I; if not, may be a problem with sound transmission or cochlear nerve function |
| II | | VIII nerve to cochlear nucleus | Not always present in normals |
| III | | Caudal pons at the superior olive and trapezoid body | I-III latency and III-V latencies are typically reported |
| IV | | Upper pons (lateral lemniscus) | Not always present in normals |
| V | | Midbrain (inferior colliculus) | I–V latency is robust to effects of stimulus intensity; latencies increase linearly with hypothermia and with decreased blood flow |

favorable or unfavorable outcome, and with an inter-rater agreement of 0.52 [69], the reliability of SEPs for definitively predicting outcome may be limited.

Timing further complicates the use of SEPs: the transient absence of SEPs has been documented in patients who later regain consciousness, particularly early during the course of TBI [70]. The SEP has even been shown to recover prior to clinical

**Table 3** Grading of somatosensory evoked potential responses

| Grade | SEP response |
|---|---|
| 1 | Absent N20; N13/P14 waveforms normal |
| 2 | Unilateral absence of N20; preserved side abnormal, defined as prolonged latency (CCT > 7.2ms) or decreased latency (<0.9 μV) |
| 3 | Unilateral absence of N20; preserved side normal |
| 4 | Bilaterally abnormal signals |
| 5 | Unilateral abnormal N20; preserved side normal |
| 6 | Bilaterally normal N20 |

Data modified from Sun et al. [73] and Houlden et al. [74]

recovery in some patients with an absent N20 < 48 h after TBI [71]. It is worth noting that *recovery* of SEPs does not necessarily imply an inevitable clinical recovery. But, the positive predictive value of SEPs to detect poor outcome, defined as unresponsive wakefulness or death, ranges from 0.67 to 1.0 across studies, lowest in those that performed SEPs < 48 h from injury [72]. SEPs performed on or after post-trauma day 3 appear to be more stable over time, and the presence of grade 6 (bilaterally present and normal) SEPs has been reported to be 98 % specific for favorable recovery, defined as GOS 5 at 1 year [73]; a grade 5 or 6 SEP (see Table 3) has been associated with an OR 5.3 for good recovery or moderate disability at 1 year [74]. The combination of cEEG reactivity and SEP after TBI is an alternative approach: 98 % of patients were correctly categorized as having good outcome (GOS 4–5) at 18 months post-TBI when SEP, EEG reactivity, and GCS at 48–72 h were considered [51].

A study using continuous SEPs to monitor comatose patients after SAH has demonstrated declining amplitude and increasing latency 24–48 h prior to increases in ICP related to vasospasm and ischemia [75]. Early deterioration of the SEP between days 1 and 3 of monitoring increased the odds of dying by nearly one-third in this study. Additional evidence suggests a prolonged conduction time occurs as blood flow declines below the ischemic threshold, possibly explaining this connection [76]. After ischemic stroke, SEPs may be helpful in comatose patients following basilar artery thrombosis when combined with BAEPs – if both are absent, the outcome in one small series was invariably poor, defined as locked-in or dead [77]. There is no consistent prognostic value in SEPs for ischemic stroke at other locations, although it should be noted that SEPs may be attenuated, prolonged, or absent in the setting of contralateral lacunar infarcts. There is no evidence yet linking the abnormalities seen in SEPs to outcome in severe sepsis [78].

## Brainstem Auditory Evoked Potentials

BAEPs are short-latency potentials that reflect the auditory pathway from the auditory nerve to the midbrain. If wave I is absent, the prognostic value of the BAEP is lost, as no stimulus is registered at the cochlear nucleus, potentially from

mechanical damage to the auditory apparatus. The absence of waveforms *after* wave II or prolonged III–V inter-peak latencies, which reflect central conduction, has been reported after TBI to be correlated with irreversible brain injury [79], but BAEPs have been less frequently studied in this population relative to SEPs. After stroke, BAEPs in the first 24 h following hemispheric infarction are significantly more likely to be normal in those who do not require decompressive hemicraniectomy [80]. In brainstem stroke, initial BAEPs significantly correlated with an outcome better than locked-in or dead [77]. A variety of abnormalities have been reported after pontine ICH: the presence of normal amplitude waves I–V on at least one side was noted in two of three survivors with good outcome, described as moderately disabled or better, in one series [81]. In a cohort of patients with SAH or ICH, the combination of BAEP and SEPs yielded a predictive power of 96% with an RR 223 for poor outcome, defined as vegetative or dead [82].

## Event-Related Potentials

ERPs are long-latency potentials that measure the cortical response to complex, distributed afferent networks after stimulation, typically auditory. This differs from short-latency potentials that measure responses through simple, defined anatomic pathways. Several ERPs have been reported after brain injury, including the N100, the first negative peak after an auditory stimulus; mismatch negativity, a negative potential at 100–250ms; the P300, a positive wave at 300ms; and the N400, a negative potential at about 400ms. Mismatch negativity and the P300 are responses to an unexpected sound within the context of a repetitive or predictable stimulus, but while the P300 requires attention, expectation, working memory, and decision-making, mismatch negativity reflects a more conserved auditory network which does not require attentional capacity.

Most of the literature on ERPs extends from the anoxic brain injury population. Comprehensive review of existing literature suggests that while the N100 may not be fully reliable as a prognostic marker, mismatch negativity and the P300 appear to confer a higher probability for good outcome [83]. In one study of comatose post-traumatic patients 8 days after injury, the P300 had a predictive value of 94% for favorable 6-month extended GOS. Addition of either a present P300 or a present SEP increased the sensitivity for excellent recovery at 6 months to 100% [84]. Interestingly, the tone or sound chosen for the test may impact presence or amplitude of these potentials – a simple tone will elicit ERPs less frequently and at lower amplitude than an attention-grabbing stimulus such as a patient's name or a family member's voice.

The N400 is a response to an unexpected speech pronunciation or word, indicating higher-order cognitive processing. Although potentially useful to predict recovery of consciousness [85], its use has been largely restricted to patients in a persistent state of unresponsive wakefulness, and it has not been reported after acute brain injury. The combination of long-latency EPs together may allow for a comprehensive assessment of complex thought or even consciousness and therefore have the

potential to predict outcome measures such as recovery beyond a state of persistent unresponsive wakefulness [86]. Adequate sensitivity and specificity testing in the acute phase after brain injury will be important prior to using any ERP to predict outcome in the ICU setting.

**Conclusions**

In patients with neurological injury, neurophysiological tests such as EEG and evoked potentials can provide significant information about the current state of neural pathways and the long-term prognosis for recovery. However, these tests are dependent on several factors, especially the specific mechanisms of injury and the timing of the tests (relative to the timing of the neurological injury). Furthermore, there is potential for variability in the interpretation of neurophysiological tests. These studies may be most helpful when used in combination and should always be interpreted in conjunction with clinical information and the physical examination.

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# Prognostication in Pediatrics

# 26

Alejandra M. Stewart and Kevin E. Chapman

**Contents**



## Introduction

Continuous electroencephalographic (cEEG) monitoring has increasingly become a standardized strategy in the evaluation of critically ill pediatric patients [1]. cEEG is essential for the identification of nonconvulsive seizures (NCS) and nonconvulsive status epilepticus (NCSE) and contributes pertinent data for the evaluation of altered mental status. The literature has reported high rates of NCS and NCSE in critically

A.M. Stewart, MD • K.E. Chapman, MD (✉)
Department of Pediatrics and Neurology, Children's Hospital Colorado, University of Colorado – Denver, Denver, CO, USA
e-mail: kevin.chapman@childrenscolorado.org



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ill patients that would otherwise be missed without this testing modality. cEEG can be a valuable tool in directing clinical management and treatment but also provides useful data associated with prognosis and potential comorbidities [1].

Evoked potentials (EPs) have been used to predict short-term outcome in critically ill children, including brainstem auditory evoked potentials (BAEPs), visual evoked potentials (VEPs), and somatosensory evoked potentials (SEPs). EPs have the added advantage of not being as sensitive to therapeutic hypothermia and sedative medications as cEEG in most cases (Table 1). Unfortunately, there is no single neurophysiologic modality that has ideal prognostic power. This chapter reviews the use of cEEG and other neurophysiologic studies in the prognostication of survival and neurologic comorbidities in specific high-risk neonatal and pediatric populations, including hypoxic-ischemic encephalopathy (HIE), congenital heart disease (CHD), extracorporeal membrane oxygenation (ECMO), stroke, and traumatic brain injury (TBI).

## EEG Features in Critically Ill Pediatric Populations

EEG is readily available in most centers and frequently used to evaluate the etiology of altered mental status in critically ill children. In critically ill children with altered mental status, there is a high incidence of nonconvulsive seizures (NCS) or nonconvulsive status epilepticus (NCSE) ranging from 7 to 47 %, depending on the study population [1]. In general, there is some disagreement whether NCSE and NCS, regardless of etiology, are both associated with worse clinical outcomes. Some studies evaluating short-term outcomes have found higher mortality and neurologic morbidity in patients with NCS or NCSE. There are fewer long-term outcome studies, but those performed report that there may be a lower quality of life or neurocognitive outcome in patients with NCSE, but not NCS alone. About 1/3 of critically ill patients who have seizures on cEEG will later develop epilepsy regardless of etiology. This is more commonly seen in patients with NCSE than NCS recorded during cEEG monitoring.

The challenge in many of these studies is to determine the effect size of NCSE or NCS on outcome. The underlying etiology likely plays the largest role in outcome, while NCS and NCSE likely play a smaller but potentially important role. Given the uncertainty about the impact of NCS and NCSE, it would be difficult to ignore these if encountered during cEEG. However, there is no data to support that aggressively treating NCS or NCSE leads to improvement in outcome. In fact, recent studies have demonstrated an increased relative risk for death in refractory status epilepticus patients receiving anesthetic therapy compared with those that do not. This has raised concerns that, at some point, the treatment may be more harmful than the continued presence of electrographic seizures. A randomized study to evaluate the impact of NCS and NCSE would be challenging to perform since equipoise between treatment and nontreatment arms may not exist based on observational studies.

cEEG background features can evolve over time and are dependent on factors such as sedation or other co-administered medications. cEEG features that were

**Table 1** Comparison of various neurophysiologic tests used for prognosis in pediatric patients

| | Routine EEG | aEEG | cEEG | VEP | BAEP | SEP |
|---|---|---|---|---|---|---|
| Availability | Common | Common | Tertiary care centers | Tertiary care centers | Tertiary care centers | Tertiary care centers |
| Sensitivity to medications | Sensitive | Sensitive | Sensitive | Sensitive | Resistant | Fairly resistant |
| Predictive value for outcome or seizures | Limited for intermittent seizures. Background may provide prognostic information | May detect NCS/NCSE. Background may provide prognostic information | Gold standard for detecting NCS/NCSE. Background may provide prognostic information | Low | May be predictive in HIE and TBI (limited data) | May be predictive in HIE and TBI |
| Cost | Low | Low | High | Low | Low | Low |
| Advantage | Provides real-time data | Rapid analysis of cEEG | Provides real-time data | Helpful in evaluation of conversion with visual loss | Evaluates the brainstem | Evaluates cortical and brainstem function |
| Interpretation | Formal training | Can be performed by bedside staff | Formal training | Formal training | Formal training | Formal training |
| Disadvantage | Sampling error may miss intermittent events | 1. Can miss subtle seizures<br>2. Used in prognosis mainly in newborns | Sensitive to environment, muscle, medication artifact | Technically difficult to perform in younger children | No reliable information about cortical function | Best predictive power after 3 days of brain injury |

*aEEG* amplitude-integrated EEG, *cEEG* continuous EEG, *VEP* visual evoked potentials, *BAEP* brainstem auditory evoked potentials, *SEP* somatosensory evoked potentials

reported in early studies that had poor prognosis include electrocerebral silence, severe background attenuation, excessive background discontinuity, lack of reactivity, and periodic or multifocal epileptiform discharges.

## Hypoxic-Ischemic Encephalopathy

Hypoxic-ischemic encephalopathy (HIE) is caused by a diffuse sustained hypoxic or ischemic brain injury in a variety of conditions, including perinatal asphyxia, cardiac arrest (CA), nonfatal drowning, severe hypotension, smoke inhalation, and carbon monoxide poisoning among others. HIE is one of the most common indications for a neurology consultation and cEEG monitoring in neonatal and pediatric intensive care units. HIE severity can vary from a mild case of a clinically transient postischemic confusional state with complete recovery and minimal or no irreversible brain tissue damage to a far more severe case of ischemic brain injury that clinically presents with multiple brain infarcts, deep comatose state, and cortical brain damage. Severe HIE is often fatal, but survivors of severe HIE often have lifelong chronic neurologic deficits. NCS and NCSE are commonly associated with HIE [1]. In the limited studies available, about 1/3 of patients with HIE who undergo cEEG will be found to have NCS.

The presence of epileptiform discharges and background activity was prospectively studied in children with HIE in one study using daily EEGs for 3 days. The background was classified as isoelectric, low voltage, slow, burst suppression, or discontinuous. Reactivity to sensory stimulation was also assessed. The study found that the presence of either discontinuous activity or epileptiform discharges had a positive predicted value (PPV) for poor outcome of 100 % (95 % CI of 56–100 %, $P = 0.05$ and sensitivity 27 % and 54 %, respectively), while lack of reactivity, defined as no change in frequency or amplitude of the background in response to external stimuli, or high-voltage slow waves less than 2 Hz had a PPV of 96 % (95 % CI of 76–100 %, $P = <10^{-5}$) [2].

The background EEG features could be influenced by body temperature, for which discontinuity in such a setting has an unreliable significance. During deep therapeutic hypothermia, the EEG can demonstrate discontinuity followed by an isoelectric pattern; however, these EEG abnormalities are not reported with moderate hypothermia at 32–34 degrees centigrade.

In a prospective study of 35 children managed with a standardized clinical therapeutic hypothermia (TH) protocol after cardiac arrest, two samples of continuous EEG recordings were scored and categorized using a simple standardized method at onset of hypothermia and then after 24 hrs. EEG category 1 consisted of continuous and reactive tracings. EEG category 2 consisted of continuous but unreactive tracings. EEG category 3 included those with any degree of discontinuity, burst suppression, or lack of cerebral activity. During hypothermia, patients scoring a 2 or 3 on cEEG had an odds ratio of 10.7 and 35, respectively, for a poor outcome compared those scoring a category of 1. During normothermia, patients with a cEEG category of 2 had an odds ratio of 27 for a poor outcome compared to patients of

category 1, and patients with a cEEG category of 3 had an odds ratio of 18 for a poor outcome compared with category 1 patients. During hypothermia, a score of 2 or 3 had a PPV for a poor outcome of 88 %, and during normothermia, the PPV was comparable for a poor outcome at 91 % with scores of 2 or 3. Given the similarity between normothermia and hypothermia, it is likely that the presence of a discontinuous or unreactive EEG cannot be explained by the decrease in body temperature alone and the presence of the EEG patterns during hypothermia can be useful in predicting poor outcome [3].

Since EEG is such a dynamic test, an EEG demonstrating prompt recovery over hours in comatose children has a better clinical outcome in terms of morbidity and mortality. The development of reactivity or normal background structures, such as sleep spindles, in comatose patients may suggest a lower degree of injury and a better prognosis.

Alpha coma (AC) is defined as an EEG pattern with an unreactive alpha (8–13 Hz) frequency as the primary EEG background feature in comatose patients (Fig. 1). AC is well recognized in adults and is associated with a poor prognosis following cardiac arrest. In children, there are limited studies regarding this pattern. The underlying pathophysiology of AC is thought to be due to interruption of reticulothalamocortical pathways from alpha-generating cortical neurons. This may be the same in children, but the immature brain may produce variable responses to such deafferentation. Clinically, the AC EEG patterns in comatose children can have more variety in background frequencies (alpha, theta, spindle, and beta

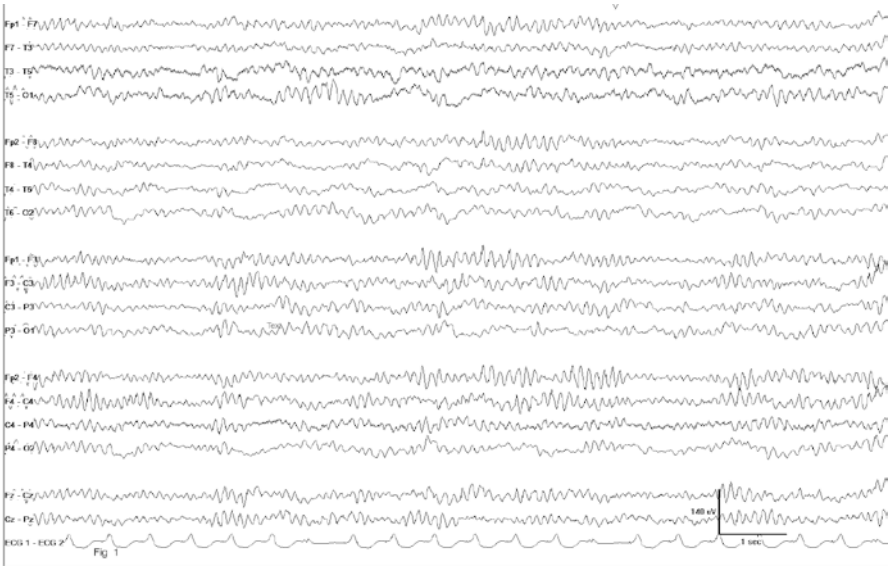

**Fig. 1** A 15-year-old male with a history of a complex congenital heart disease, who presented with cardiac arrest. Bipolar montage shows diffuse medium amplitude 8 Hz activity that is not reactive to stimulation consistent with alpha coma. [Low frequency filter, 1 Hz; high frequency filter, 70 Hz; notch, 60 Hz; sensitivity, 7μv/mm; time base, 30 mm/s]

frequencies) possibly due to the immaturity of the young brain [4]. Alpha coma may be seen in about 30 % of comatose pediatric patients with HIE. When encountered, establishing the presence or absence of any reactivity is important. In the few published reports of AC, the mortality is high, approaching 40–50 %. However, these numbers are generally better compared with the adult population and may support that children may tolerate HIE better than adult patients. The prognosis is highly related with the underlying etiology of the AC.

Postanoxic myoclonus status epilepticus (MSE) is a commonly encountered symptom in adults after an anoxic event. This is typically seen within the first 24 h after hypoxic or anoxic brain injury and is associated with a very unfavorable prognosis. The incidence is estimated to be between 30 and 37 % of comatose adult survivors after cardiopulmonary resuscitation. There may be an additive detrimental effect of anoxic neocortical damage after cardiorespiratory arrest and prolonged myoclonic seizures [5]. Postanoxic MSE is occasionally seen in pediatric patients; however, there are no literature reports in terms of incidence and mortality related with postanoxic MSE and children. The EEG changes in patients with postanoxic myoclonus vary, but the majority shows bursts of generalized spikes and polyspikes activity. Other patterns include burst suppression, generalized low-voltage slow activity, periodic complexes, and alpha coma. In some instances, it can be challenging to determine if the myoclonus is of cortical origin when significant muscle artifact is dominating the EEG. In these instances, a brief trial of a neuromuscular blocker, such as rocuronium, can suppress the myogenic artifact allowing better interpretation of the EEG (Fig. 2).

Postanoxic MSE should be differentiated from chronic postanoxic nonepileptic myoclonus or Lance-Adams syndrome (LAS), which presents in survivors of hypoxia. LAS refers to intermittent myoclonic jerks that are induced by movement, startle, and tactile stimulation. These myoclonic jerks may lead to postural lapses, ataxia, and dysarthria. There is no consistent electrographic seizure discharge on EEG during this myoclonus, differentiating it from epileptic myoclonus. LAS can cause severe disabilities, and treatment during rehabilitation therapy is especially challenging [6]. This is more commonly observed in adults, and reports on the incidence in children are lacking. In the absence of a hypoxic event, myoclonic status epilepticus may not necessarily be associated with high mortality. MSE encountered in patients with idiopathic generalized epilepsy is typically reversible with standard treatment (benzodiazepines, valproate), and a full recovery is expected.

In adults with HIE, the American Academy of Neurology (AAN) practice parameter cites three EEG patterns prognostic of poor outcome. The first is myoclonic status epilepticus within the first 24 h after the event. The second is generalized suppression of the background to less than 20 μV. Finally, a burst-suppression pattern with generalized epileptiform activity or generalized periodic complexes on a flat background is strongly, but not invariably, associated with poor outcome [1]. A similar practice parameter is not available for children; however, as reviewed above,

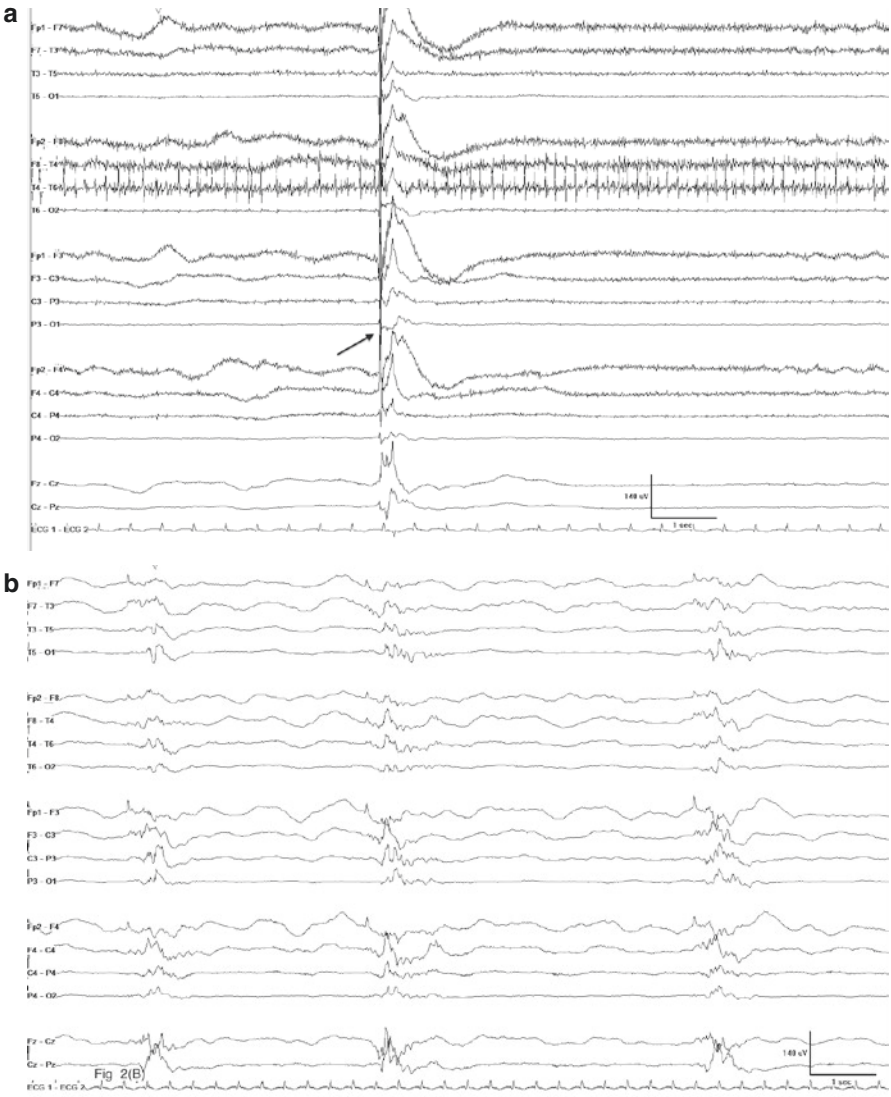


**Fig. 2** A 13-year-old female presented with anoxic brain injury secondary to intentional suffocation. She was noted to have recurrent myoclonic jerks concerning for seizures. (**a**) Postanoxic myoclonus status epilepticus. Bipolar montage shows a background characterized by diffuse suppression pattern with a burst high of amplitude fast activity with superimposed muscle artifact (*arrow*). (**b**) EEG recorded after the patient received a neuromuscular blocking agent to suppress muscle artifact. Bipolar montage shows a background without muscle artifact and a burst-suppression pattern. This supports that the clinical myoclonus is epileptic. [Low frequency filter, 1 Hz; high frequency filter, 70 Hz; notch, 60 Hz; sensitivity, 7μv/mm; time base, 30 mm/s]

similar patterns are typically associated with a poorer prognosis in children. Further studies are needed to elevate the significance of the data to the level where a practice parameter could be created [7].

Other complementary tools to cEEG could be helpful for early seizure identification and background changes, including quantitative electroencephalography (qEEG) such as density spectral array (DSA). These techniques may provide information about subtle changes, such as vasospasm, that are easily overlooked with raw EEG data. Since qEEG tends to display data on a compressed time scale, it can provide trend data at the bedside to help determine response to therapy and improvements in background activity that may portend a better prognosis.

Evoked potentials (EPs) are another neurophysiologic modality that can be used to help determine prognosis after HIE. EPs are reproducible time-locked signals generated in the central nervous system and neural structures in response to a sensory stimulus. Typically, these electrical signals are serially repeated and averaged to produce waveforms that can be analyzed for amplitude and latency from the stimulus. Between the stimulus and recording electrode, absent or delayed waves suggest an anatomical or functional interruption in the conduction pathway. Brainstem auditory evoked potentials (BAEPs), visual evoked potentials (VEPs), and somatosensory evoked potentials (SEPs) have been used to predict short-term outcome after severe acute TBI and HIE in comatose children. Some EPs, such as BAEPs, have the advantage of not being as sensitive to therapeutic hypothermia and sedative medications as cEEG. Somatosensory evoked potentials (SEPs) have demonstrated a strong predictive value for outcome, especially in cases of nontraumatic pediatric coma. The absence of the N20 response following median nerve stimulation bilaterally has been associated with an unfavorable outcome (death, vegetative state, or severe disability resulting in dependence) in nearly all patients following severe HIE with a sensitivity ranging from 63 to 75 %. These studies are typically performed for prognostic purposes 3 days after the injury to improve predictive value. There is limited data on BAEPs and VEPs in pediatric patients with coma. However, some studies have evaluated both of these modalities, generally in multimodality evaluations with SEPs and/or EEG. Absent VEPs (flash stimulation) or BAEPs suggest a poor prognosis; however, there is variable sensitivity and specificity. This can be improved by combining various neurophysiologic techniques. The absence of multimodality evoked potentials would suggest a greater risk for poor outcome and a higher sensitivity and specificity than any single evaluation.

Brainstem auditory evoked potentials (BAEPs) may provide prognostic information for comatose patients with absent BAEPs being associated with a poor prognosis. However, some studies suggest that early BAEPs may not be as reliable in predicting outcomes due to the limited area being tested. It is important to recognize that BAEPs measure primarily the integrity of the auditory pathway in the brainstem pathway and that there are many conditions in which normal BAEPs can be associated with severe brain damage rostral to the brainstem. Also, BAEPs can be

normal until a few hours before death in severe brain injury, but repeated testing in such cases will often show some deterioration.

## Perinatal Asphyxia

In the full-term neonate, a leading cause of neurologic impairment is severe neonatal hypoxic-ischemic encephalopathy. The development of hypoxia is most commonly associated with intrauterine disturbances of gas exchange across the placenta but may also occur with respiratory failure at the time of birth. Congenital heart disease with severe right-to-left shunt or persistent fetal circulation may occur associated with perinatal asphyxia. Therapeutic hypothermia (TH) has been shown to improve outcome by alleviating brain injury in neonatal asphyxia and has shown utility in multiple animal model studies. In the newborn population (near term and term), the benefit of TH was established by randomized clinical trials (RCT), demonstrating a reduction of brain injury secondary to HIE; subsequently, it has become standardized strategic care in the neonatal intensive care unit (NICUs).

Currently, there is a variety of EEG monitoring protocols related with whole-body versus selective head TH, depending on the institution's resources [1]. Full-head EEG monitoring was not required in the pivotal neonatal cooling trials, but 72h of amplitude-integrated EEG (aEEG) was used. aEEG involves a trend analysis of either one or two channels of EEG to evaluate for moderate or severe encephalopathy. With this technique, the raw EEG data is separated into its components then compressed and displayed as a single tracing. This allows for prompt analysis of EEG data and assists in seizure recognition at bedside. This test is easier to apply than a full EEG and allows staff who are not formally trained as neurophysiologists to interpret simplified EEG data. However, low-amplitude, brief, and focal seizures outside of the region covered can be missed due to the limited scope of recording. Amplitude-integrated electroencephalography has not been approved for use in older children. Currently, it is mainly used for prognosis and seizure identification in the NICU. Abnormal aEEG performed in the first few days of life is predictive of a persistent encephalopathy and poor neurologic outcome in term infants with HIE. A recent meta-analysis pooled multiple studies to determine the utility of aEEG in predicting neurodevelopmental outcome in full-term infants with HIE. Amplitude-integrated EEG had a relatively high sensitivity (0.93) and specificity (0.90) for predicting a poor outcome with an abnormal aEEG tracing performed in the first week of life [8].

Conventional EEG tracings can be predictive of neurological outcome, especially when used serially or followed over time. Infants who progress to a normal tracing by 8–12 h of age have better outcomes than those infants whose tracings remain abnormal or worsen during the monitoring period. As in older children, a burst-suppression pattern in patients without sedation suggests a poor prognosis for neurologic outcome. In a meta-analysis study, it was found that EEG had a sensitivity of 0.90 and specificity of 0.83 for predicting poor outcome [8].

Evoked potentials have also been utilized to help predict poor outcome in neonates with HIE. Technically, VEPs in newborns are more challenging to perform and waveforms are more variable and difficult to reliably interpret. However, VEPs can reliably predict outcome with a sensitivity of 0.90 and a specificity of 0.92. SEPs appear to have more varied outcomes but generally can be predictive of outcome, especially when combined with other tests [8].

## Cardiac Arrest

Every year, about 16,000 children in the United States experience an out-of-hospital cardiac arrest (CA) with less than 10% surviving. About 2% of children suffer a cardiac arrest during admission to pediatric ICUs, with about 25% of inhospital arrest patients surviving. Multiple studies demonstrate the benefits of therapeutic hypothermia (TH) following cardiac arrest in adult and neonatal HIE. However, there is limited TH efficacy data in older children after CA. During moderate hypothermia, the EEG patterns may evolve and worsen as a result of multifactorial additive effects including the continuous evolving brain insult, temperature regulation, and sedatives. Improved outcome is seen in patients with reactivity, improvement in the background activity over time, and a lack of background suppression or attenuation. NCS occur in nearly 50% of patients suffering CA with associated HIE undergoing cEEG with about 1/3 experiencing NCSE. These seizures often occur during the rewarming period or later necessitating a longer duration of monitoring to capture these events. TH may be working as an anticonvulsant or may delay some of the complex changes that induce seizures after CA. The exact duration of monitoring to capture seizures is unclear but at least 24 h after rewarming would capture most of these seizures. Background EEG features during TH tend to evolve over time with mild abnormalities prone to improve, while severe abnormalities tend to worsen. This may allow for the determination of an early prognosis in the course of TH to help guide who may benefit from TH [15].

## Nonfatal Drowning

Drowning refers to hypoxic-ischemic brain injury caused by respiratory impairment from submersion or immersion in liquid. It differs from cardiac arrest (CA) in two main ways: first, submersion fluids may be with a lower-than-normal brain and body temperature, which may decelerate neural tissue injury or death; second, cerebral blood flow stops immediately in CA, while in nonfatal drowning the flow continues for a period of time; however diminished oxygen is delivered and adds to neuronal injury. Consequently, the duration of submersion may not reliably predict neurologic results, and therefore after drowning rescue, the neurologic status at that moment should not be considered as a final predictor of outcome. Drowning may cause hypoxic-ischemic injury with similar prognostic findings as discussed above. Seizures are present in about 50% of patients with a mortality rate of about 25%.

cEEG can be useful to help determine prognosis and to identify electrographic seizures. A gradual worsening of EEG background, such as the development of burst suppression, is associated with a poor clinical outcome, while a gradual improvement in EEG may suggest a better prognosis. The presence of myoclonic seizures, status epilepticus, or bilaterally absent N20 on SEPs is highly predictive of a poor outcome.

## Congenital Heart Disease

Surgical outcomes for infants and newborns afflicted with congenital heart disease can potentially result in devastating brain injury. Changes in perfusion and oxygenation during heart surgery can have significant effects on vulnerable developing cerebral white matter. There is a highly complex physiology seen in the neonates compared with older children that often requires a more technically challenging surgery. These children are at high risk for neurologic injury and may have profound neurologic deficits, developmental disabilities from injury to visual and motor areas, as well as an increased incidence of behavioral difficulties during childhood years [9]. With deep hypothermic circulatory arrest (DHCA) during cardiac surgery, there is an anticipated lessening of EEG activity followed by reappearance of EEG background activity during rewarming. cEEG has been used clinically to monitor central nervous system function intraoperatively during open-heart surgery; however, the value of EEG changes during surgery as a predictor of acute and long-term outcome is still unknown.

In the postoperative period, frequent clinical seizures have been reported in neonates and infants who underwent surgery for congenital heart disease. It is known to have an increased rate of NCS and NCSE occurring in 8–25 % of patients. There is also a relatively high occurrence of EEG abnormalities ranging from 23 to 85 % in this group, with background slowing and epileptiform activity being most commonly encountered. Patients with coexistent genetic conditions appear to be at particular risk for seizures with about 40 % experiencing a seizure. Other risk factors for acute neurologic events, including seizures, are a longer duration of DHCA and aortic arch obstruction. The NCS long-term outcome is still unclear. Early postoperative electrographic seizures were found with a near 11-point decrease in the psychomotor development index on the Bayley scales of infant development at 1 year of follow-up after heart surgery. They also had an increased risk for possible or definite MRI abnormalities [10]. Other studies of differing cardiac pathology have demonstrated similar findings of an increased risk of developmental impairment or higher mortality rates in patients with NCS or NCSE. Some studies suggest that an improvement in the EEG background during this period is associated with a better possibility of normal development.

The utility of evoked potentials in predicting outcome in children with CHD has been evaluated in various studies. At baseline, BAEPs and SEPs generally show a higher rate of abnormalities compared to controls. In limited studies of neonates and infants undergoing open-heart surgery, the presence of abnormal

somatosensory evoked potentials can be predictive of neurologic outcome 1 year after the procedure. An absence of cortical potentials or bilaterally increased conduction times correlates with an abnormal neurologic examination at a 1-year follow-up.

## Extracorporeal Membrane Oxygenation

In patients with severe cardiorespiratory failure and an inability to maintain adequate systemic perfusion with standard life support, a cardiopulmonary bypass technique, known as extracorporeal membrane oxygenation (ECMO), is frequently performed. This bypass interrupts normal venoarterial circulation through the body with ligation of the right common carotid artery and internal jugular vein. Using this procedure, there is a substantial risk for seizures, stroke and diffuse hypoxic cerebral injury. Diffuse ischemic cerebral brain injury could happen prior to or during the bypass due to impairment of cerebral autoregulation or difficulty in initiating ECMO. Cardiopulmonary resuscitation prior to ECMO initiation has been reported to increase the risk of neurologic complications in patients of all ages. During right common carotid artery cannulation, it is possible to develop cerebral reperfusion injury from pressurized blood flow to brain tissue damaged during initial cerebral hypoperfusion. Focal brain injury may present either as an acute cerebral infarct secondary to an emboli or thrombosis from the ECMO circuit or as cerebral hemorrhaging as a relatively common complication from systemic heparinization. Neurologic complications are common during ECMO and with a high risk of mortality and long-term morbidity. Long-term studies of ECMO survivors report that neurologic disabilities occur in 10–30 % of patients. The CNS complications were seen more often in patients with prematurity, underweight, cardiopulmonary arrest, and severe hemodynamic instability prior to ECMO initiation.

In patients undergoing ECMO, NCS have been reported an incidence rate of 2.1–17 %, while NCSE occurs in about 10 %. The occurrence of NCS and NCSE is related with a high risk of death in this group. Numerous studies showed that survivors of ECMO who developed seizures during or before ECMO have substantially lower intelligence and developmental scores with higher rates of cerebral palsy and language impairment. A burst-suppression pattern during ECMO has been related with an unfavorable prognosis and a higher risk of neonatal death. However, there is some literature that suggests that EEG background severity during ECMO did not predict academic and achievement testing at school age. Since the right internal carotid is ligated during ECMO, a higher degree of EEG background abnormalities in the right hemisphere would be anticipated. However, this is unclear as some studies have suggested that there is no consistent laterality.

SEPs recorded in children receiving ECMO are not consistently altered by right carotid artery and jugular vein cannulation, suggesting that ECMO may not affect the tests' predictive value. SEPs may be used to evaluate baseline neurologic function prior to initiating ECMO in pediatric patients and repeated during ECMO to detect changes, but there are limited studies discussing its utility in predicting

long-term outcome specifically in patients undergoing ECMO. Some studies have attempted to predict outcome using a combination of neurophysiologic studies, such as EEG and EPs, but these studies are limited and too small to draw conclusions.

## Stroke

The incidence of pediatric stroke is 1.3–1.6 children per 100,000 (children aged 1 month to 18 years) every year in developed countries. It is a significant cause for disability affecting motor and cognitive functioning in children. Stroke can be classified into acute ischemic stroke (AIS), intraparenchymal hemorrhagic stroke, and cerebral venous thrombosis subtypes.

### Acute Ischemic Stroke

Acute ischemic stroke is an estimated 2.3 to 8 in 100,000 children a year and is significantly lower than in adults. In children, the causes differ considerably from those found in adults, and risk factors in children include cardiac disease, infection, vasculopathy, trauma, and hematological disorders [11]. The utility of EEG for prognosis in children with AIS has not been studied compared with adult AIS. In adult AIS, EEG may complement the physical examination in predicting who may have a poor outcome, as the degree of focal slowing generally correlates with the clinical deficit. Adult patients with contralateral background abnormalities have a higher risk of impaired consciousness and poor outcome, while worsening EEG changes may suggest the development of significant edema or mass effect.

Clinical seizures have been reported in multiple studies as a common symptom in children with AIS occurring in 19–44 % at presentation. Children younger than 3 years of age have a higher risk to present with seizures compared with older children. Systematic studies evaluating the utility of cEEG in patients with AIS are lacking. In retrospective studies of critically ill children undergoing cEEG, 70 % of patients with ischemic stroke and altered mental status developed nonconvulsive seizures. However, these patients were studied due to clinical concern for seizures suggesting a potential ascertainment bias. Given the high incidence of subclinical seizures in critically ill children with altered mental status, it is reasonable to strongly consider cEEG in children with AIS and unexplained altered consciousness.

The effect of seizures at presentation on the clinical course of patients with AIS is unclear; however, multiple studies have demonstrated a trend toward longer hospitalization and durations of ICU care. There is considerable variability in the incidence of remote epilepsy following AIS with studies suggesting a rate of 7–29 %. Some of this variability may relate to duration of follow-up, since there appears to be an increased recurrence of seizures over time. The occurrence of acute seizures

may increase the risk of epilepsy to about 25 %; however, it is unknown if this accounts for subclinical seizures on EEG. Increased use of cEEG in the ICU setting will hopefully clarify the effect of acute seizures on the development of remote epilepsy.

In adult studies, absent or low-amplitude SEPs have reliably correlated with poor functional motor outcome in AIS. In contrast, evoked potentials have not been studied as a means to predict outcome in pediatric patients.

## Perinatal Arterial Ischemic Stroke

Perinatal arterial ischemic stroke (PAIS) refers to stroke occurring between 20 weeks of fetal life and 28th postnatal day validated by neuroimaging or neuropathology studies. PAIS occurs in approximately 1 in 3500 live births. PAIS is a common cause of congenital hemiplegia, mild to severe motor dysfunction, ranging from hand weakness to quadriplegia. There is very limited literature on EEG anomalies predicting outcome in patients with PAIS. The EEG often shows an asymmetry of the background, which may correlate with larger stroke volume, and ipsilateral sharp waves. There appears to be a high occurrence of seizures (about 25 %) and a high seizure burden in patients with PAIS. Subtle clinical signs, such as cycling movement or sucking, may be seen in some seizures; however, as in HIE, most seizures are subclinical (~80 %). The high incidence of subclinical seizures may be attributed to the electroclinical dissociation seen in neonates following treatment with anticonvulsants. Unfortunately, studies are often limited due to a lack of multichannel recordings. There is some limited data to suggest that the presence of an abnormal background and epileptiform activity is associated with a higher risk of hemiplegia in PAIS. The risk of long-term epilepsy is relatively high and appears to vary based on the duration of follow-up. In studies with longer follow-up, nearly 50 % continued to have epilepsy.

## Intraparenchymal Hemorrhagic Stroke

Intraparenchymal hemorrhagic stroke (IHS) is generally secondary to vascular brain malformation and accounts for approximately half of all strokes in childhood. There is a relatively high incidence of seizures ranging from 31 to 48 % reported in multiple studies of children with intraparenchymal hemorrhagic. There is little data in regard to epidemiology and the risk of epilepsy in the long-term outcome. In a prospective study that was conducted with newborn and children with intracranial hemorrhage, it was noted that 60 % of patients in the neonatal period and 1/3 of patients in childhood had acute seizures, which is higher than the rate in AIS. At 2 years post-injury, the risk of developing epilepsy was 15 % and appeared lower in perinatal hemorrhage than in older children. In this study, only emergent treatment of elevated intracranial pressure (ICP) was a significant risk factor for developing epilepsy [12].

## Cerebral Venous Sinus Thrombosis

Cerebral sinus venous thrombosis (CSVT) occurs in 0.67 cases per 100,000 children a year, with about 40 % appearing in neonates. Neonates are more likely to present with seizures occurring in 70–80 %, while seizures occur in 20–40 % of children and adolescents. In neonates, seizures are generally associated with a worse neurologic outcome. Epilepsy develops in about 20 % of cases of CSVT. No studies relating outcome to EEG or EP findings in CSVT were found.

## Traumatic Brain Injury

Included among the most leading causes of acquired disability and death in infants and children is traumatic brain injury (TBI). Seizures are common, and regularly happen within 7 days of injury. The incidence of post-traumatic seizures (PTS) in pediatrics patients varies from 5 to 65 %. This wide variability is likely due to earlier studies not utilizing cEEG. In studies looking at severe TBI in children, 20–40 % of patients have PTS. Younger children (less than 2 years of age) and subjects with abusive head trauma appear to be at particularly high risk. The presence of a subdural or epidural hematoma also increases the risk of post-traumatic seizures [13]. As in other acute injuries, electrographic seizures without clinical signs are common and seen exclusively (no clinical seizures) in 30–40 % of patients with seizures. Due to the high rate of electrographic seizures, cEEG for at least 24 h is recommended for all children with moderate to severe TBI. If seizures are recorded, it is recommended to continue the monitoring until the patient is seizure-free for at least 24 h. A repeat EEG should be considered for persistent or worsening encephalopathy of uncertain etiology.

The significance of post-traumatic seizures, especially those that are solely electrographic, is unclear. In rodent studies, electrographic seizures are associated with increased neuronal injury, increased mortality, and impaired long-term motor and social functioning. Studies in children with TBI are limited; however, adult studies have found that electrographic seizures may cause an increase in intracranial pressure, an increase in brain lactate and pyruvate ratios, and an elevation in neuron-specific enolase, a biomarker for neuronal injury. With these factors interacting in the injured brain, an increase in the amount or extent of damage could be expected. Indeed, an increase in the incidence of hippocampal atrophy has been associated with PTS [14]. In children, early clinical PTS have been associated with a worse outcome score compared to children without seizures.

Early studies evaluating the risk of post-traumatic epilepsy (PTE) in children after traumatic brain injury with frequencies ranging from 11 to 33 %. The risk is highest within the first year of injury, but the risk continues to remain elevated 10 years after the injury. The presence of early seizures and the severity of brain injury are strong predictors of who will develop PTE. Other predictors of increased seizure risk include length of hospital stay, skull fractures, and a family history of epilepsy [13].

EEG background patterns can be prognostic of outcome in TBI. The presence of background reactivity, EEG variability, or the presence of sleep structures correlate with an improved neurologic outcome. Quantitative EEG techniques have also been evaluated with decreased variability or significant interhemispheric asymmetry being associated with worse outcome. More studies using these novel techniques are necessary to clarify their clinical utility.

Evoked potentials have been used to help predict outcome in children following TBI. There is high mortality associated with the absence of BAEPs recorded in the first 72 h after hospital admission. In children with absent SEPs and BAEPs, no child improved and all died. However, some studies suggest caution in predicting unfavorable outcomes in children with an absence of SEPs in both TBI and HIE.

**Conclusion**

This chapter reviewed the literature related to the use of continuous EEG and other neurophysiologic studies to aid in prediction of survival and comorbidities in specific high-risk neonatal and pediatric populations, including hypoxic-ischemic encephalopathy, congenital heart disease, extracorporeal membrane oxygenation, stroke, and traumatic brain injury. With the greater use of cEEG in clinical practice, it is important that the practitioners understand the utility and limitations of the test for prognostication in critically ill pediatric patients. The presence of NCS and NCSE tends to suggest a worse outcome, but it remains unclear if treatment can alter this risk factor. Evoked potentials may provide complementary data about outcome but are more likely to be predictive when used in combination with other clinical factors. Further studies evaluating the utility of neurophysiologic monitoring in predicting the long-term outcomes of critically ill pediatric patients need to be undertaken. The development of models utilizing multiple clinical and neurophysiologic factors to predict long-term outcome would be useful for families and care teams to guide clinical management and expectations.

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# Part III

# Treatment

# Treatment of Status Epilepticus with Nonsedating Antiepileptic Drugs

27

Mariam Wasim and Aatif M. Husain

**Contents**



M. Wasim
Department of Neurology, Duke University Medical Center, Durham, NC, USA

A.M. Husain, MD (✉)
Department of Neurology, Duke University Medical Center, and Neurodiagnostic Center
Veterans Administration Medical Center, Durham, NC, USA
e-mail: aatif.husain@duke.edu



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## Introduction

The treatment of status epilepticus (SE) has evolved considerably over the last 20 years. The recognition of the many patients who have nonconvulsive SE (NCSE) and nonconvulsive seizures (NCS) and the availability of newer antiepileptic drugs (AED) have prompted this evolution of the treatment paradigm. This chapter will provide a brief overview of the various definitions of SE, how the definition of status has evolved over the years, and how this impacts the approach to treatment. The difference between NCSE and NCS will be discussed in terms of their classification and how this impacts the aggressiveness of treatment. This chapter will focus on treatment with nonsedating (AEDs); sedating AEDs will be discussed elsewhere.

Treatment with nonsedating AEDs is important in the initial management of seizures since the efficacy of treatment is monitored by cessation of clinical seizure activity and patient's return to baseline mentation. Treatment with sedating medications can confound the clinical picture and make it difficult to assess the efficacy of AEDs. Side effects of sedating AEDs include respiratory depression, which often leads to intubation requiring further sedation and the inability to monitor improvement clinically.

## Definitions

### Nonconvulsive Seizures

Nonconvulsive seizures are defined as seizures that have subtle or no clinical phenomena associated with altered consciousness lasting a minimum of 10 s [1]. Subtle clinical features may include twitching of limbs or facial muscles, nystagmus, agitation, catatonia, and psychosis [2].

### Status Epilepticus

Status epilepticus most recently is defined as five min or more of continuous clinical and/or electrographic seizure activity or recurrent seizure activity without recovery or return to baseline between seizures [3]. SE can be classified into generalized convulsive SE (GCSE) or nonconvulsive SE based on the presence of convulsions or rhythmic jerking of limbs.

The definition of SE has evolved over the past half century. In the 1960s, the International League Against Epilepsy (ILAE) defined SE as a "seizure [that] persists for a sufficient length of time or is repeated frequently enough to produce a fixed and enduring epileptic condition" [4]. The length of time was mentioned as "sufficient" without a time limitation. The definition also did not include the absence of recovery in between repeated seizure activity until the 1980s. The risk

of neuronal damage with continued seizure activity was studied in animal models which showed excitotoxic neuronal damage with continuous seizure activity of 30 min or more. After this, the definition proposed by the Working Group on Status Epilepticus evolved to include continued seizure activity for more than 30 min without recovery in between episodes [5]. This time criterion was applied to define SE for several years. However, further research in animal models suggested that permanent neuronal damage and pharmacoresistance may occur before 30 min have elapsed [6]. One animal study demonstrated that self-sustaining SE can occur after brief (15 min) electrical perforant pathway stimulation (PPS). The neuronal damage observed in these animals was similar to that observed in the 30-min PPS group suggesting the need for earlier treatment [7]. Successive research studies and guidelines used a shorter duration to define SE. This trend led to the development of an "operational" definition of SE where a patient was treated as being in SE although they may not be in established SE as previously defined [8, 9]. The definition was then modified in the late 1990s stating that GCSE refers to >5 min of continuous seizures or two or more discrete seizures between which there is incomplete recovery of consciousness [9]. This definition still only addressed SE limited to conditions with clinical seizure activity. With the improvement and increased availability of EEG, continued electrographic seizures were observed in up to one-third of patients who were in GCSE and had clinically stopped convulsing [10]. This was defined as nonconvulsive SE, and the presence of electrographic seizure activity has since been included in the definition of SE by the Neurocritical Care Society [3, 5].

### Generalized Convulsive Status Epilepticus

GCSE is defined as continuous or repeated generalized tonic-clonic movements or rhythmic jerking of the extremities in a patient with impaired consciousness. There may be focal findings such as focal limb weakness after cessation of convulsions, known as Todd's paralysis [6]. GCSE is a neurological emergency associated with considerable morbidity, mortality, and cost. Treatment algorithms have been developed for the early, aggressive treatment of GCSE and are discussed elsewhere.

### Nonconvulsive Status Epilepticus

NCSE is defined as ongoing or intermittent electrographic seizure activity without obvious convulsions for at least 30 min in a patient with impaired consciousness and without recovery in between episodes. Other terms have also been called NCSE and include complex partial SE (CPSE), typical absence SE (TASE), or tonic SE. The diagnosis of NCSE is completely dependent on electroencephalography (EEG). EEG criteria for diagnosis of NCS and NCSE have been established but not validated. The EEG criteria for NCSE are shown in Table 1. Although EEG criteria have been proposed for the diagnosis of NCSE, there remain difficulties in the practical implication of these criteria. Response to treatment does not always indicate the presence of an epileptic cause. For example, treatment with benzodiazepine may improve some encephalopathic EEG patterns such as triphasic waves [11].

**Table 1** Criteria for nonconvulsive seizures and nonconvulsive status epilepticus

| |
|---|
| A pattern satisfying any of the primary criteria and lasting ≥10 s (for NCS) or ≥30 min (for NCSE) |
| Primary criteria |
| 1. Repetitive EDs[a] occurring at ≥3 Hz |
| 2. Repetitive EDs[a] occurring at <3 Hz AND the secondary criterion |
| 3. Sequential, rhythmic, periodic, or quasiperiodic waves at ≥1 Hz and typical spatiotemporal evolution[b] |
| Secondary criterion |
| 1. Significant improvement in clinical state or appearance of previously absent normal EEG patterns correlating temporally with administration of a rapidly acting AED. Resolution of the EDs leaving diffuse slowing without clinical improvement and without appearance of previously absent normal EEG patterns would not satisfy the secondary criterion |

Adapted from Hirsch [1] and Beniczky [46]
*NCS* nonconvulsive seizures, *NCSE* nonconvulsive status epilepticus, *AED* antiepileptic drug
[a]*EDs* Epileptiform discharges consisting of generalized or focal spikes, sharp waves, spike-and-wave complexes, or sharp-and-slow-wave complexes
[b]Unequivocal evolution in frequency (gradually increasing or decreasing by at least 1 Hz), morphology, or location (gradual spread into or out of a region involving at least two electrodes). Evolution in amplitude alone is not sufficient

### Refractory Status Epilepticus

Refractory status epilepticus (RSE) is defined as an ongoing seizure activity despite treatment with a first-line agent (benzodiazepines) and a second-line AED (phenytoin, valproic acid, levetiracetam, or phenobarbital) [12]. RSE has also been defined as "status epilepticus requiring general anesthesia" [13]. RSE can be diagnosed clinically if obvious clinical seizure activity is evident. If, however, this is not the case and the patient has altered awareness, electrographic confirmation becomes necessary.

### Super Refractory Status Epilepticus

Super refractory status epilepticus (SRSE) is defined as ongoing electrographic seizure activity despite treatment with first-, second-, and third-line AEDs. Clinical activity, if present, is subtle. SRSE has also been defined as "status epilepticus that continues 24 h or more after the onset of anesthesia, including those cases in which the status epilepticus recurs on the reduction or withdrawal of anesthesia" [13].

## Differentiating Nonconvulsive Status (NCS) Versus Nonconvulsive Seizures (NCSE)

NCS and NCSE are often discussed together without any differentiation in their treatment paradigms. It is impossible to separate these two clinically, given that the diagnosis is based primarily on EEG findings. One of the principal components of the SE definition is the lack of complete clinical recovery to baseline in between seizures. This criterion cannot be used to differentiate NCS from NCSE due to the

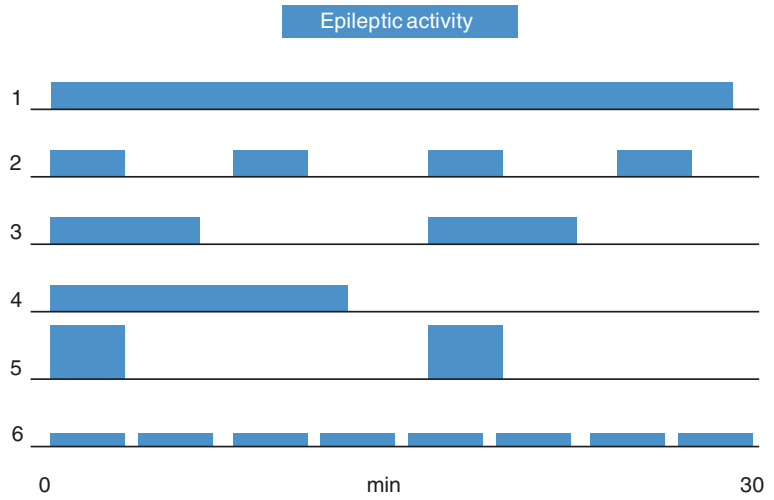


**Fig. 1** SE has traditionally been described as a continuous seizure lasting more than 30 min or two or more seizures between which there is no return to normal mental state lasting more than 30 min. In the era of cEEG monitoring, these two states can be remarkably different. The first row depicts a seizure that is 30 min long and has electrographic seizure activity during the entire time. Subsequent rows depict 30 min episodes of 2 or more seizures without return of normal mentation between the episodes. As is evident, the degree of ongoing electrographic seizure activity is different in these subsequent rows

lack of clinical features except depressed mental status. Continuous EEG (cEEG) monitoring, however, can be used to differentiate these two conditions. In NCSE electrographic seizure activity is continuous or near continuous, while in NCS, there are discrete electrographic seizures separated slowing and interictal activity noted on EEG (Fig. 1). The distinction between NCS and NCSE is important as it may have implications on treatment.

## Appropriately Aggressive Therapy

The aggressiveness of treatment depends on the degree of neuronal injury that is ongoing. It is well understood that GCSE causes neuronal injury and should be aggressively treated. Conversely, single seizures are unlikely to cause brain damage and generally do not require an immediate change in treatment. NCS and NCSE fall in between these two extremes, and the degree of aggressiveness in treating these conditions is unclear (Fig. 2).

Several animal studies have led to further understanding of mechanisms underlying neuronal injury in SE although much of the pathophysiology remains poorly understood. The basic principle underlying the development of SE involves failure of endogenous mechanisms to terminate a seizure. This can be due to excessive excitation or from loss of endogenous inhibitory mechanisms. Injury during SE is

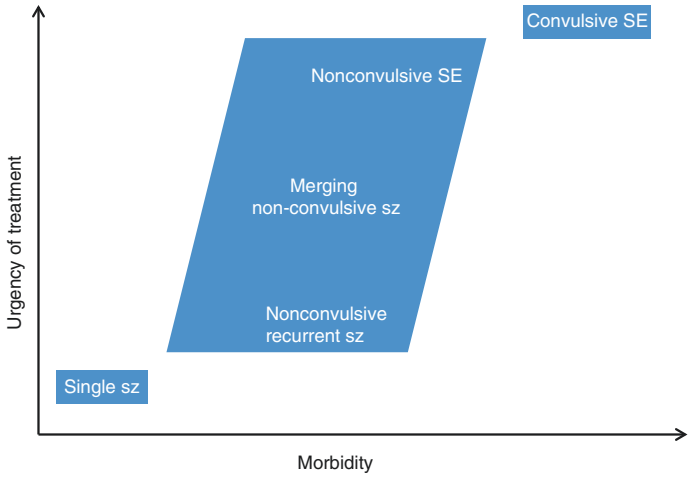


**Fig. 2** There is general agreement in how aggressive treatment must be for a single seizure (not very) and GCSE (very). However, how aggressive treatment should be for NCS and NCSE is unclear and likely on a spectrum depending on the clinical scenario, including etiology of the condition

postulated to occur in several proposed stages. In the initial milliseconds to seconds of seizure onset, neurotransmitter release, ion channel opening and closing, and protein phosphorylation may lead to a prolonged seizure. This is followed in the next seconds to min by alteration in receptor trafficking where there is a decrease in inhibitory gamma-aminobutyric acid (GABA) subunits and an increase in excitatory N-methyl-D-aspartate (NMDA) and α-amino-3-hydroxy-5-methylisoxazole-4-proprionic acid (AMPA) receptors. In the subsequent min to hours, there are changes in neuropeptide expression leading to increase in excitatory substance P and decrease in inhibitory neuropeptide Y. Days to weeks of continued seizure activity leads to genetic and epigenetic changes causing further neuronal damage [14]. Injury at neuronal level occurs concomitantly with changes in brain metabolism and systemic pathology. Initially, the sympathetic overdrive leads to a compensatory phase where cardiac output, blood pressure, and blood glucose increase. Continued seizure activity > 30 min leads to systemic decompensation with decrease in cerebral blood flow, glucose, and oxygen [1].

Although most of the animal models included GCSE, there is some evidence of neuronal injury in NCSE as well. In a series of experiments done in baboons where convulsive seizures were induced, only partial protection against neuronal injury was observed after paralysis of baboons, implying continued neuronal damage despite cessation of convulsive activity [15]. However, there is also data suggesting NCSE does not cause neuronal injury. NCSE tends to have lower-frequency discharges, which, if reproduced in animal models, cause much less neuronal damage than higher-frequency discharges. Also, animals that were previously on AEDs or had history of epilepsy are resistant to chemoconvulsant-induced damage conferring potential neuroprotection [9].

Despite conflicting evidence on molecular level, NCSE clinically has been associated with increased metabolic demand and blood flow which may cause injury to the brain. NCSE is most often secondary to an acute precipitant, which may be the underlying etiology for neuronal damage and additional injury due to NCSE may be negligible. Although human data of NCSE causing neuronal damage have been confounded by etiology, concomitant illness, and treatment, there is some evidence to suggest that there is ongoing neuronal injury secondary to NCSE [11]. For example, patients with NCSE have been found to have elevated serum levels of neuron-specific enolase, which is a marker of acute neurological injury. Patients with traumatic brain injury and subsequent NCS were noted to have delayed, prolonged increase in intracranial pressure and lactate/pyruvate ratios indicating compensatory mechanisms for increased metabolic demand [16].

The treatment of NCS and NCSE has been extrapolated from treatment of GCSE; however, the appropriateness of this practice is unclear. GCSE is a life-threatening emergency and is usually treated with high doses of sedating medications, and patients often require intubation. This aggressive approach has also been used in NCS and NCSE but adverse outcomes have been noted. Aggressive treatment of NCSE in elderly has been associated with an increased risk of death [17]. Aggressive ICU management of patients with NCSE has also been shown to prolong hospitalization without improving outcome [18]. Recent studies suggest that the use of anesthetic agents to treat NCSE may lead to higher morbidity and mortality [19, 20, 21]. In children, NCSE, but not NCS, appears to increase mortality and worsen cognitive status [22, 23].

Based on the likely differences in the pathophysiology of NCS, NCSE, and GCSE and the realization that aggressive therapy is not without potential complications, treatment of these conditions should be differentiated. Because of its recognized morbidity and mortality, GCSE should be treated aggressively. However, NCSE may not require the same degree of aggressive treatment, and NCS treatment should be even further tempered. A recent survey of neurologists noted such an approach to treating NCSE and NCS [21]. This study noted that most neurologists used nonsedating AEDs more often and were less willing to intubate for NCS as compared to NCSE.

Recognizing that the principle electrographic difference between NCS and NCSE is the amount of epileptic activity, a clinical tool, the seizure burden score (SBS), is being investigated [24]. The SBS is a composite score taking into account the amount of epileptic (ictal) time per hour weighted by the spatial extent of the seizures and EEG frequencies involved. A higher SBS score implies a more severe burden of epileptic activity. Initial reports suggest that there is a trend toward higher odds for poor outcome for patients with scores above the median compared to those with scores below the median [24].

Another way to approach treatment of comatose patients noted to have NCS and NCSE is to consider the etiology of their comatose state. If the coma is primarily due to NCSE, it is referred to as “NCSE proper,” whereas if there is another underlying etiology accounting for the coma (and possibly the subsequent seizures), it is called “comatose NCSE.” NCSE proper may be accompanied by

subtle clinical symptoms suggestive of SE and mild impairment of consciousness as seen in TASE or CPSE. Comatose NCSE does not exhibit any clinical signs of SE but has characteristic epileptiform EEG patterns. The distinction between NCSE proper and comatose NCSE may be of value in determining the aggressiveness of treatment since comatose NCSE has reasons other than the SE for neuronal injury. Even aggressive treatment of the NCSE may not result in meaningful improvement and may not be indicated [20]. However, in NCSE proper, the mental status impairment and neuronal injury (if any) are due to the NCSE itself. Treating this more aggressively may result in a favorable outcome. As noted previously, a recent study provides class III evidence that therapeutic coma may be associated with poorer outcome after SE and portends higher infection rates and longer hospitalizations [25].

## Medications

The treatment options discussed here have been used in NCS and NCSE. The absolute or comparative efficacy of these AEDs in NCS and NCSE is not clear as most studies are retrospective and often in patients with GCSE. Prospective studies are underway but results of these are not yet available. The discussion below pertains to the use of these AEDs in NCS and NCSE. Treatment of GCSE is likely to be different. A summary of the typical dosing, adverse effects, and limitations is presented in Table 2.

### Benzodiazepines

Benzodiazepines (BDZ) are used as first-line therapy for treatment of GCSE since they are potent, fast-acting AEDs. They are frequently used in prehospital settings as well as in the emergency department (ED) and inpatient units for the termination of seizures. BDZs enhance the effect of the neurotransmitter GABA at the $GABA_A$ receptor by increasing the frequency of opening of the chloride ion channel on the $GABA_A$ receptors. BZDs are most effective in terminating seizures when given in early SE. They are less effective in ongoing SE due to internalization of the BDZ receptors [25]. For emergent initial therapy for SE, benzodiazepines are the agent of choice. Lorazepam (LZP) is preferred for IV therapy, midazolam (MDZ) for IM therapy, and diazepam (DZP) for rectal administration [2]. The data for BDZs presented below is for GCSE, not NCSE or NCS.

#### Lorazepam

Lorazepam is a high-potency, intermediate-acting benzodiazepine. The half-life of LZP is 10–20 h. This is due to its pharmacokinetic properties of poor lipid solubility and high degree of protein binding, which leads to restriction of LZP to the vascular compartment allowing for the relatively prolonged peak effect. Available formulations include PO, IM, or IV. Since LZP is absorbed relatively slowly by the mouth due to its poor lipid solubility, the IV formulation is most commonly used for treatment of seizures and SE.

**Table 2** Common medications used in NCSE and NCS

| Medications | | Level of evidence[a] | Mechanism of action | Loading or initial dose | Pharmacokinetics | Metabolism[b] | Adverse effects | Comments |
|---|---|---|---|---|---|---|---|---|
| Benzodiazepines | Lorazepam | Class I Level A | GABA agonist, increase the frequency of $Cl^-$ channel opening at $GABA_A$ receptor | 0.1 mg/kg up to 4 mg IV at 2 mg/min; may repeat in 5–10 min | $T_{1/2}$ = 10–20 h | Hepatic; high protein binding; poor lipid solubility | Sedation, respiratory depression, arrhythmia, hypotension | |
| | Diazepam | Class IIa Level A | | 0.2 mg/kg up to 20 mg rectally or 0.1 mg/kg up to 10 mg IV; may repeat in 5 min | $T_{1/2}$ = 20–100 h Onset of action, 1–5 min after IV and 15–30 min after IM administration | Hepatic; high lipid solubility | Sedation, respiratory depression, hypotension | Dose modified for children ages 2–5 years[c] |
| | Midazolam | Class I Level A | | 0.2 mg/kg IM up to 10 mg IM | $T_{1/2}$ = 1–4 h | Hepatic | Sedation, respiratory depression, hypotension | Dose modified for children per weight and also for different formulations[c] |
| | Clonazepam | N/A | | 0.015 mg/kg[d] | $T_{1/2}$ = 18–50 h | Hepatic; high lipid solubility | Sedation, respiratory depression, hypotension | Limited use in SE due to paucity of evidence and availability in oral form only |
| | Clobazam | N/A | | 15.8 mg/day[d] | $T_{1/2}$ = 36–42 h Peak plasma levels= 1–4 hours | Hepatic; one active metabolite | Sedation | 1,5-benzodiazepine with selective affinity for $\omega_2$ site of the $GABA_A$ receptor |

(continued)

**Table 2** (continued)

| Medications | Level of evidence[a] | Mechanism of action | Loading or initial dose | Pharmacokinetics | Metabolism[b] | Adverse effects | Comments |
|---|---|---|---|---|---|---|---|
| Phenytoin/fosphenytoin | Class IIa Level B | Use-dependent inhibition of sodium channels | PHT: 15–20 mg/kg IV once, may give additional 10 mg/lg IV after 20 min fPHT: 18–20 mgPE/kg, max infusion rate of 150 mgPE/min IV | PHT $T_{1/2}$ = 6–24 h | Hepatic; CYPP450 inducer; high protein binding | Cardiotoxicity, respiratory depression, hypotension, hepatotoxicity, pancytopenia, and hepatic enzyme induction PHT: purple glove syndrome | Contraindicated in patients with sinus bradycardia, sinoatrial block, second- or third-degree AV block Drug interactions with CYP450 inducers and CNS depressants |
| Phenobarbital | Class IIb Level C | GABA agonist; increase the duration of $Cl^-$ channel opening at $GABA_A$ receptor | 20 mg/kg IV up to 60 mg/min | $T_{1/2}$ = 2–7 days | Hepatic; CYPP450 inducer | Sedation, respiratory depression, hypotension | May aggravate VPA-induced hyperammonemia |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Valproic acid | Class IIa Level A | Precise mechanism unknown; proposed GABA-related actions, NMDA receptor antagonism, histone deacetylase inhibition | 20–40 mg/kg IV *at an infusion rate of 6 mg/kg/min; may give additional 20 mg/kg dose after 10 min* | $T_{1/2}$ = 9–16 h | Hepatic | Hyperammonemia, hepatic and pancreatic toxicity, valproate encephalopathy, bleeding risk due to effects on platelets | No cardiopulmonary side effects Contraindicated in patients with hepatic disease, urea cycle disorders, mitochondrial disorders, pregnancy |
| Levetiracetam | Class IIb Level C | Exact mechanism unknown; potential effect via SV2A binding | 20 mg/kg at an *infusion rate of 1.5 mg/kg/min* | $T_{1/2}$ = 6–8 h | Renal | No major adverse reaction | No known drug interactions |
| Pregabalin | N/A | Exact mechanism unknown; potential effect via calcium channel modulation | 150–300 mg/day given in 2–3 doses | $T_{1/2}$ = 5–6.5 h | Renal | Sedation | No known drug interactions |

(continued)

**Table 2** (continued)

| Medications | Level of evidence[a] | Mechanism of action | Loading or initial dose | Pharmacokinetics | Metabolism[b] | Adverse effects | Comments |
|---|---|---|---|---|---|---|---|
| Topiramate | Class IIb Level C[e] | Multiple; GABA potentiation, sodium channel modulation, AMPA inhibition | 100 mg q12h | $T_{1/2}$ = 19–25 h | Renal | Metabolic acidosis, renal calculi | May potentiate GABA agonists May aggravate VPA-induced hyperammonemia |
| Lacosamide | Class IIb Level C[e] | selectively enhancing the slow inactivation of voltage-gated sodium channels | 200–400 mg | $T_{1/2}$ = 13 h | Hepatic | Nausea, headache, PR interval prolongation | May interact with drugs metabolized via CYP450 system |
| Lidocaine | N/A | Sodium channel modulation | 2 mg/kg | $T_{1/2}$ = 1.5–2 h | Hepatic | Arrhythmia | May interact with drugs metabolized via CYP450 system |

[a]Level of evidence as per 2012 Neurocritical Care Society guidelines for initial treatment of GCSE and NCSE
[b]Only the predominant site of metabolism is listed
[c]Please see text for details
[d]Dosage as per study referenced in text. Please see text for details
[e]Recommendation by Neurocritical Care Society for treatment of RSE
$T_{1/2}$ = half-life

A Veterans Affairs Cooperative Study (VACS) studied patients presenting in GCSE and treated with one of the four IV treatment regimens: LZP alone, phenobarbital (PHB), phenytoin (PHT) alone, and diazepam (DZP) followed by PHT. LZP resulted in control of overt GCSE in 65 % of patients, which was the highest percentage of the entire group and significantly better than the PHT alone group (37 %) [26]. A survey of neurologists also showed that LZP was the first choice of 44 % of respondents in treatment of NCSE and 26 % of respondents in treatment of NCS [21].

In a comparison of LZP, DZP, and placebo for the treatment of out-of-hospital SE, LZP was the most effective at terminating SE (59.1 %), followed by diazepam (42.6 %) and placebo (21.1 %). Interestingly, the rates of respiratory or circulatory complications were lower in the benzodiazepines (LZP 10.6 %; DZP 10.1 %) compared to the placebo group (22.5 %) [27]. This may have been due to the administration of lower than recommended dose of BDZ, pointing to a dose-dependent risk of side effects with BDZ use.

It is important to note that both of the above studies were in patients presenting in GCSE, not in patients with NCS and NCSE. As discussed above, other studies have noted complications of using BZP, especially high doses, in the NCS and NCSE population. One of these studies noted BDZ overtreatment of patient with NCSE was associated with higher need of intubation, leading to prolonged hospitalization [18].

LZP has Class I, level A recommendation from the Neurocritical Care Society for use in initial management of NCSE [1, 3]. Standard dosage used is 0.1 mg/kg up to 4 mg IV per dose and 2 mg/min per IV push which may be repeated in 5–10 min. Adverse effects include sedation, respiratory depression, arrhythmia, and hypotension [28]. Hypotension and arrhythmia side effects are secondary to the propylene glycol component of the IV formulation which is also found in IV forms of MDZ, PHB, and PHT. The sedation side effect is related to the prolonged peak effect of LZP as mentioned above.

### Diazepam

Diazepam is a long-acting benzodiazepine with a half-life of 20–100 h. DZP is highly lipid soluble and is widely distributed throughout the body soon after administration. It is available in PO, IV, IM, and PR formulations. It is rapidly absorbed orally and has a fast onset of action. After IV administration, onset of action is 1–5 min, and after IM administration, it is 15–30 min. The duration of diazepam's peak pharmacological effects is 15 min to one hour for IV and IM administration. The duration of DZP effect is relatively short due to its high lipid solubility and rapid redistribution to other body tissues.

The VACS study showed that LZP was more likely to be successful as a first-line AED for GCSE; however, it was not more efficacious than PHB or DZP and PHT [26]. A direct comparison of lorazepam and diazepam found no statistically significant difference between the administration of IV LZP and DZP for prehospital treatment of SE [29]. However, SE was more often terminated in LZP-treated patients (59.1 %) than DZP (42.6 %)- and placebo (21.1 %)-treated patients. DZP is available in suppository form and can be administered rectally when IV or IM administration

is not possible. This formulation is readily used in children with epilepsy due to its ease of use at home.

Rectal DZP has class IIa, level A recommendation from the Neurocritical Care Society for use in initial management of NCSE [1, 3]. The standard dosage is 0.2 mg/kg up to 20 mg rectally or 0.1 mg/kg up to 10 mg IV, which can be repeated in 5 min. For children age 2–5 years, the recommended dose is 0.5 mg/kg PR; for 6–11 years, 0.3 mg/kg PR; and for greater than 12 years, 0.2 mg/kg PR. Adverse effects include sedation, hypotension, and respiratory depression [28]. DZP rapidly redistributes and also has an active metabolite that has a longer half-life, and this may lead to accumulation of the drug during repeated administration.

### Midazolam

Midazolam is a short-acting benzodiazepine with a half-life of 1–4 h. However, the half-life in children, adolescents, and elderly is longer. It is available in IV, IM, and transmucosal (nasal, buccal, rectal) formulations. The latter are not yet commercially available in the USA. MDZ has an active metabolite that only contributes to 10 % of its biological activity. It is metabolized via the cytochrome P450 (CYP450) system; therefore, concurrent use of other medicines that are metabolized via CYP450 may prolong the metabolism of MDZ. It is water-soluble and unlikely to cause thrombophlebitis.

The value of MDZ was established in the Rapid Anticonvulsant Medication Prior to Arrival Trial (RAMPART). This trial was a double-blind randomized clinical trial that studied the efficacy of IM MDZ versus IV LZP in prehospital treatment of SE by paramedics. IM MDZ was statistically superior to IV LZP in stopping seizures before arrival to ED. Seizures were absent on presentation to ED in 73.4 % of subjects in IM MDZ group versus in 63.4 % of subjects in IV LZP group. The frequency of endotracheal intubation and recurrent seizures was similar in both groups. The IM route delivers the medication more rapidly; however, the onset of action is more rapid after IV administration. Nevertheless, the time saved by rapid administration of IM MDZ appeared to offset the delay in drug's onset of action [30]. A study comparing buccal MDZ and rectal DZP found MDZ to be at least as effective as DZP for cessation of serial seizures or SE [31]. The buccal administration was also felt to be easier to administer and socially more acceptable than the rectal route.

IM MDZ has class I, level A recommendation from the Neurocritical Care Society for use in initial management of NCSE [1, 28]. Standard dosage is 0.2 mg/kg IM up to 10 mg IM that can be repeated once if needed. For children weighing > 40 kg, the recommended dose is 10 mg IM; for children weighing 13–40 kg, 5 mg IM is recommended. Intranasal dose is 0.2 mg/kg and buccal dose is 0.5 mg/kg. Adverse effects include sedation, respiratory depression, and hypotension [28].

### Clonazepam

Clonazepam (CZP) is a potent benzodiazepine with a high affinity for the $GABA_A$ receptor. CZP also has high lipid solubility allowing for rapid central nervous system (CNS) effects. CZP has a much longer half-life of 18–50 h when compared to LZP (10–20 h). It is available in oral form only in the USA limiting its use in SE. However, it is widely used for treatment of SE in Europe and Asia despite the

relatively limited evidence supporting its use. A recent prospective observational cohort study compared the efficacy of LZP, CZP, and MDZ in status epilepticus. The results show that LZP, although insufficiently dosed, after adjustment for relative variables was associated with increased risk of refractoriness of SE as compared to CZP and required an increased number of AEDs to control SE. All of the patients in study who received IV CZP as first-line therapy for SE were treated in Switzerland. A loading dose of 0.015 mg/kg of CZP was used. The study did not collect data of adverse effects and therefore is unable to compare the safety of the three drugs. The efficacy of CZP as first-line treatment of SE is attributed to its favorable pharmacologic profile. Although the results for this study appear promising, randomized controlled trials are warranted to confirm these findings [32].

### Clobazam

Clobazam is a unique 1,5-benzodiazepine which was recently FDA approved for the adjunctive treatment of seizures in Lennox-Gastaut syndrome. It is also used for drug-resistant anxiety disorders and was initially used as an anxiolytic prior to being used for seizures. Clobazam has selective affinity for the $\omega_2$ site of the $GABA_A$ receptor which is thought to be responsible for its anticonvulsant properties. It has lower affinity for the allosteric $\omega_1$ site leading to lower sedation side effects as compared to 1,4-benzodiazepines. Clobazam has rapid oral absorption and reaches peak plasma levels within 1–4 h of administration. It is available only in PO form since it is water insoluble. Clobazam is metabolized in the liver by CYP3A4 and CYCP2C19 and has one active metabolite, *N*-desmethylclobazam, with a half-life of 71–82 h. The mean half-life of clobazam is 36–42 h.

The efficacy of clobazam in treatment of refractory epilepsy is well reported. Small case series have also demonstrated benefit with the use of clobazam in SE. A recent retrospective case series demonstrated the efficacy of clobazam as add-on therapy in RSE. Successful termination of RSE was seen in 76.5 % (13/17) of patients who had failed two or more AEDs in adequate dosing with or without anesthetics with mean duration of SE of 4 days. Dose-related side sedation required tapering and discontinuation of CBZ after successful RSE treatment in 37.5 % of patients. The mean initial dose was 15.8 mg/day and the mean maintenance dose was 22.3 mg/day. Although this is a limited study due to its sample size and confounding due to concurrent administration of other AEDs, its findings are interesting given the relatively late introduction of clobazam in the treatment of SE and demonstration of efficacy despite a primarily GABA-mediated mechanism of action [33]. Prospective, randomized controlled trials are warranted to confirm these findings and establish a role for the use of clobazam in SE. The Neurocritical Care Society does not include clobazam among the AEDs recommended for treatment of NCS/NCSE or SE.

## Phenytoin

PHT has been used in the treatment of GCSE for decades. It exerts its effects via use-dependent inhibition of sodium channels. It is available in PO and IV formulations. The IV formulation contains propylene glycol to maintain solubility.

Extravasation of the IV form can cause phlebitis and "purple glove syndrome" due to the propylene glycol component [34]. Fosphenytoin (fPHT), a water-soluble prodrug of PHT, does not require propylene glycol to maintain solubility. A USA Food and Drug Administration (FDA) white paper noted the risk of purple glove syndrome with fPHT is lower than PHT; however, fPHT has the same cardiotoxicity and hypotension risk as PHT [35]. fPHT can be used IV or IM. The half-life of PHT is 6–24 h. Advantages for PHT include its long duration of action and fast CNS entry.

The VACS study confirmed the utility of PHT when combined with a benzodiazepine. However, PHT alone was only successful in 36.8 % of patients [26]. A recent meta-analysis evaluated the relative effectiveness of AEDs in benzodiazepine-resistant SE and found the estimated mean efficacy for phenytoin was 50.2 %. However, given its side effects, it was not recommended as first-line therapy in BDZ-resistant SE [36]. A survey of neurologists noted that 40 % of respondents use PHT/fPHT as first-line for NCS and 32 % use these for NCSE [21].

PHT/fPHT has class IIa, level B recommendation from Neurocritical Care Society for use in initial management of NCSE after BDZ administration [1]. The standard bolus "loading" dosage is 15–20 mg/kg IV given once, which can be followed by an additional 10 mg/kg IV after 20 min if there is no response to the initial dose. The rate of infusion should not exceed 50 mg/min. The loading dose of fPHT in SE is 18–20 mg PE/kg with a maximum infusion rate of 150 mg PE/min IV [28]. Dose of fPHT is reported as milligrams of PHT equivalents (mg PE) since the molecular weight of fPHT is different than PHT. This helps avoid confusion as no dose adjustment is required when using mg PE. Slower rates are often preferred in less urgent situations to reduce toxicity [37]. Maintenance dosing should begin 12 h after the loading dose. For PHT, maintenance dose is 100 mg PO/IV q6–8 h [adjusted based on treatment response or serum concentration]. The maintenance dose of fPHT is 5 mg PE/kg/day IM/IV in three divided doses.

There is a black box warning for cardiovascular risk with rapid infusion; therefore, IV infusion should not exceed the maximum recommended doses noted above for PHT and fPHT. Adverse effects include cardiotoxicity, hypotension, hepatotoxicity, leukopenia, thrombocytopenia, pancytopenia, and hepatic enzyme induction [34]. Contraindications to the use of PHT/fPHT include hypersensitivity to class, sinus bradycardia, sinoatrial block, second- or third-degree atrioventricular block, and Adam-Stokes syndrome. The main drug interactions occur with CYP450 inducers and CNS depressants.

## Phenobarbital

PHB is a long-acting barbiturate that has been available for more than a century. It was initially used as a sedative and hypnotic before its anticonvulsant properties were discovered. It acts as a GABA agonist by increasing the duration of opening of the chloride ion channel on the $GABA_A$ receptors. PHB is available in PO and IV formulations. It has a very long half-life of 2–7 days.

A meta-analysis studied the relative effectiveness of AEDs including levetiracetam (LEV), PHB, PHT, valproic acid (VPA), and lacosamide (LCM) in the treatment of BDZ-resistant GCSE. The study found a mean efficacy of 73.6 % in patients receiving PHB; however, the confidence interval was very wide, making the clinical relevance of the result unclear [36]. Most neurologists rarely chose PHB as first-line therapy for SE and chose it less frequently than PHT, LEV, and VPA as second- or third-line treatments [21].

PHB has class IIb, level C recommendation from the Neurocritical Care Society for use in initial management of NCSE after BDZ administration [28]. The standard loading dose is 20 mg/kg IV up to 60 mg/min. The maintenance dose is 1–4 mg/kg/day PO or IV, divided in 3–4 doses. Maintenance dosing can be adjusted by monitoring serum concentrations. Adverse effects include sedation, hypotension, and respiratory depression. PHB is metabolized by the liver and is an inducer of the CYP450 system (CYP1A2, CYP2C9, and CYP3A4). It may aggravate VPA-induced hyperammonemia [28].

## Valproic Acid

VPA has been an extensively used AED over the last several decades. The precise mechanism of action of VPA is unknown; however, there are multiple proposed mechanisms including GABA-related actions, NMDA receptor antagonism, and histone deacetylase inhibition. VPA has a half-life of 9–16 h. It is available in IV and PO formulations.

The AED meta-analysis comparing relative effectiveness of various AEDs in controlling SE discussed above found the mean efficacy of VPA to be 75.7 % [36]. The efficacy lasted beyond the acute treatment period, and more patients were seizure-free on follow-up. VPA is also efficacious for different subtypes of SE, such as generalized tonic-clonic, focal, absence, and myoclonic with about 70 % response rate [35]. VPA is well tolerated even at large doses (~100 mg/kg) and does not appear to have significant cardiorespiratory side effects. In susceptible patients, there is a risk of hyperammonemia, hepatic and pancreatic toxicity, and valproate encephalopathy with high doses of IV VPA. There is also a theoretical risk of bleeding due to effects on platelets and platelet function, but this side effect has not been reported in SE [35].

VPA has class IIa, level A recommendation from the Neurocritical Care Society for use in initial management of NCSE after BDZ administration [1]. The standard bolus loading dosage in SE is 20–40 mg/kg IV at an infusion rate of 6 mg/kg/min. An additional 20 mg/kg dose may be administered 10 min after loading infusion if necessary. Pediatrics dosing is 1.5–3 mg/kg/min. The maintenance dose of VPA is 10–15 mg/kg/day in 2–3 divided doses. The dose can be adjusted based on response to therapy and serum concentration monitoring. Serum VPA levels can be obtained immediately after the loading dose infusion [6]. Adverse effects of VPA include dose-related nausea, vomiting, hepatotoxicity, acute hemorrhagic pancreatitis, thrombocytopenia, and hyperammonemia. The main drug interactions are with

drugs that are metabolized via CYP pathway, are CNS depressants, have antiplatelet effects, or can cause hyperammonemia or hyponatremia. Contraindications include hypersensitivity to drug class, hepatic disease, urea cycle disorders, mitochondrial disorders, and pregnancy. It is important to note that VPA is not approved for use in SE by the FDA. Unlike other AEDs discussed so far, VPA does not have cardiopulmonary side effects. Other considerations include the use with caution in patients with traumatic brain injury.

## Levetiracetam

LEV is a commonly used AED. The exact mechanism of action is unknown; however, it has been shown to bind to synaptic vesicle glycoprotein 2A (SV2A). It is not clear how this binding exerts antiepileptic effects. One possible mechanism is that LEV binding to SV2A inhibits presynaptic calcium channels resulting in decreased neurotransmitter release. LEV is available in IV and PO formulations. The half-life of LEV is 6–8 h.

The effectiveness of LEV in NCSE and NCS is uncertain. Some studies have noted utility of LEV, while others have shown LEV to be worse than other AEDs. In one study LEV was shown to be a useful alternative in SE if administered early (<4 days since SE onset) even when given to intubated patients [38]. However, dosages exceeding 3000 mg/day did not provide additional benefit. A retrospective study showed LEV failed more often than VPA and PHT in controlling SE as a second-line agent (48.3 % vs 25.4 % and 41.4 %, respectively) [39]. A meta-analysis of the efficacy of AEDs in the treatment of SE estimated that the mean efficacy of LEV is 68.5 % when given in infusions of 1000–3000 mg in young adults (20 mg/kg) [36].

LEV is not approved for use in SE by the FDA; however, it carries a class IIb, level C recommendation from the Neurocritical Care Society for use in initial management of NCSE after BDZ administration [1]. The recommended loading dose in SE is 20 mg/kg at an infusion rate of 1.5 mg/kg/min [28]. Main adverse effects include dizziness, somnolence, headache, irritability, behavioral problems, depression, and psychosis. Of course, the psychiatric problems are not of significant concern in the treatment of SE. There are no reported drug-drug interactions with LEV. It is renally cleared and requires dose adjustment in patients with renal impairment.

## Pregabalin

In addition to epilepsy, pregabalin (PGB) has been used to treat various diseases including neuropathic pain and generalized anxiety disorder. The precise mechanism of action is unknown; however, it is thought to bind to the $\alpha_{2\delta}$ modulatory subunit of voltage-sensitive calcium channels potentially leading to decreased release of neurotransmitters including glutamate, norepinephrine, substance P, and calcitonin gene-related peptide. PGB is available only in PO form, but it can also be

given via nasogastric tube (NGT) in comatose patients unable to swallow the capsules. The half-life of PGB is about 5–6.5 h.

A retrospective study of patients with NCS and NCSE demonstrated that PGB was effective in stopping seizures in 52 % of patients within 24 h of initiation. Of note, PGB was significantly more efficacious in aborting NCS (82 %) than NCSE (18 %). There was also a higher response rate noted in patients with brain tumors (67 % vs 42 % of patients without a brain tumor), and the responders were also noted to have a better outcome (64 % vs 9 % discharged home) [40].

PGB is not approved for use in SE by the FDA. Standard dosage is 150–300 mg/day given in 2–3 doses. In critically ill patients, the dose is typically approximately 300 mg/day [38]. The main side effects include dizziness and somnolence. PGB has no known drug interactions, but it may worsen sedation in patients on CNS depressants. PGB is cleared renally and requires dose adjustment in patients with renal impairment [28]. The Neurocritical Care Society does not include PGB among the AEDs recommended for treatment of NCS/NCSE.

## Topiramate

Topiramate (TPM) is approved for treatment of epilepsy and migraines. TPM has multiple mechanisms of action, including blockade of the kainate and AMPA glutamate receptor subtype, blockade of voltage-activated sodium channels, enhancement of GABA-mediated chloride flux at $GABA_A$ receptors, reduction in amplitude of high-voltage-activated calcium currents, and activation of potassium conduction. It is available in a PO formulation that can also be administered via NGT in patients unable to swallow the tablets. The half-life of TPM is 19–25 h.

TPM was noted to be efficacious in treating patients in refractory SE in one case series [41]. TPM was administered via NGT and was effective in controlling the SE in all 6 patients. These patients had previously not responded to treatment with fPHT, LZP, PHB, and VPA. TPM was effective in aborting multiple seizure types including GCSE and NCSE. The only side effect attributed to TPM in that study was lethargy [41].

TPM is not approved for use in SE by the FDA. Starting dose is 100 mg q12h with subsequent dosing of 400–800 mg/day orally administered in 2–3 doses. Adverse effects include drowsiness, paresthesias, metabolic acidosis, and renal calculi. TPM may potentiate GABA agonists. It is also a weak CYP2C19 and CYP3A4 inhibitor. TPM, like PHB, may aggravate VPA-induced hyperammonemia [1]. Topamax has class IIb, level C recommendation from the Neurocritical Care Society for the treatment of refractory SE [2].

## Lacosamide

Lacosamide (LCM) is a relatively new AED that is available in both IV and PO formulation. Though its exact antiepileptic drug action is unknown, it is thought to exert its anticonvulsant effects via selectively enhancing the slow inactivation of voltage-gated sodium channels. The half-life of LCM is 13 h.

LCM was used "off label" for treatment of NCS and NCSE soon after being approved by FDA as adjunctive therapy for partial-onset seizures. One retrospective study showed that 60 % of patients receiving LCM for NCS or NCSE achieved control of their seizures [42]. Patients with NCS responded more frequently than patients with NCSE. A case compilation study that evaluated all published reports of the use of LCM in the treatment of NCS and NCSE reported very similar efficacy (56 %) [43].

LCM is not approved for use in SE by the FDA. Though the loading dose for NCSE and NCS is not currently known, many investigators report giving a bolus of 200–400 mg, sometimes up to 600 mg over 15–30 min. Maintenance dose is 400–600 mg/day administered in 2 doses. Adverse effects include dizziness, headache, nausea, diplopia, and PR interval prolongation. Potential drug interactions may occur with drugs that are metabolized via CYP19. The clinical significance of this interaction is unclear. One of the advantages of LCM is that the IV formulation has the same bioavailability as the PO formulation, allowing for simple IV to PO conversion. Lacosamide carries class IIb, level C recommendation from the Neurocritical Care Society for the treatment of refractory SE [3].

## Lidocaine

Lidocaine is not commonly used for treatment of SE but several case reports and series support its use [44, 45]. It is a local anesthetic agent and class 1b antiarrhythmic. It acts on voltage-gated sodium channels in neurons to inhibit ionic currents during abnormal membrane depolarization. Its exact mechanism of action as an AED is unclear. Lidocaine has rapid onset of action and a short half-life of 1.5–2 h.

A retrospective study in pediatric patients with GCSE found the efficacy of lidocaine to be 44.4 % when given to patients who had failed to respond to first-line AEDs (DZP, PHT, and PHB) [44]. Interestingly, patients who had seizures secondary to infections responded more favorably than patients with epilepsy (37.9 % vs 6.8 %, $p < 0.05$). Adverse reactions occurred in 10.3 % of patients and consisted of ventricular arrhythmia and progression of focal seizure to a generalized seizure. Another retrospective multi-institutional study found lidocaine to be useful or extremely useful in 56.7 % of pediatric patients with SE [45]. It appeared to be more useful in patients with seizure clusters and SE due to gastroenteritis. In this study, however, the efficacy was poor when SE was caused by CNS infections. Dosages used in both of the above studies were 2 mg/kg as a bolus with a 2–4 mg/kg/h continuous infusion. The Neurocritical Care Society does not include lidocaine as a treatment option for SE [1].

**Conclusion**

NCS and NCSE are often only detectable with cEEG monitoring. Both need to be treated, but how urgently and with which medication are uncertain. Sedative medications used to treat GCSE may not necessarily be appropriate. Though many nonsedating AEDs have been tried in NCS and NCSE, prospective,

randomized trials demonstrating their efficacy and adverse events have not been available. Exciting new trials promise to shed more light on how best to treat this condition.

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# Treatment of Status Epilepticus with Anesthetic Drugs

28

Nicolas Gaspard

## Contents



## Introduction

Refractory status epilepticus (RSE) is defined as status epilepticus (SE) that fails to respond to an appropriate dose of a first-line and a second-line antiepileptic drugs. At this point, treatment options include additional trials of nonsedating antiseizure medications and general anesthesia. Guidelines for the treatment of SE and RSE have been published by the European Federation of Neurological Societies (EFNS) [1] and the Neurocritical Care Society (NCS) [2]. Both have focused mostly on the treatment of generalized convulsive SE (GCSE), but they also offer some recommendations for the treatment of nonconvulsive SE (NCSE) (Table 1).

N. Gaspard, MD, PhD
Neurology Department and Comprehensive Epilepsy Center,
Université Libre de Bruxelles – Hôpital Erasme, Route de Lennik, 808, 1070
Bruxelles, Belgium

Department of Neurology and Comprehensive Epilepsy Center, Yale University,
New Haven, CT, USA
e-mail: ngaspard@ulb.ac.be



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**Table 1** Available guidelines and expert opinion for the treatment of refractory NCSE

| | EFNS guidelines (Meierkord et al. 2010) [1] | NCS guidelines (Brophy et al. 2012) [2] | Survey of experts (Riviello et al. 2013) [12] |
|---|---|---|---|
| Post-convulsive subtle SE | Treat as GCSE and proceed to anesthetic treatment<br>No recommendation on the type of agent | GCSE<br>Subtle SE | N/A |
| Complex partial SE/ NCSE | Postpone anesthetic treatment and try additional antiseizure medications | Try additional antiseizure medications in patients who are hemodynamically stable and have not required intubation | N/A |
| Environment of treatment | N/A | ICU with expertise in RSE<br>cEEG available | N/A |
| Initial anesthetics | Midazolam, propofol, or pentobarbital/ thiopental | Midazolam, propofol, or pentobarbital/ thiopental | Midazolam, propofol or, pentobarbital/ thiopental in adults<br>Propofol avoided in children |
| Intensity and duration of treatment | At least 24 h<br>Titrate to burst suppression if propofol or barbiturates<br>Titrate to seizure suppression if midazolam | 24–48 h<br>Titrate to seizure suppression or burst suppression | 24 h |
| Taper | N/A | Gradual<br>Phenobarbital helpful during pentobarbital withdrawal | N/A |
| Intensity and duration of treatment if SE recurs after the anesthetic is tapered | N/A | Return to prior or higher doses of anesthetic<br>± Addition of the second anesthetic<br>Duration not discussed | 24–48 h |

*Abbreviations*: *SE* status epilepticus, *NCSE* nonconvulsive status epilepticus, *GCSE* generalized convulsive status epilepticus, *ICU* intensive care unit, *cEEG* continuous electroencephalographic monitoring

The decision to resort to general anesthesia is based on the careful assessment of the need for urgent control of SE and of the risks associated with treatment. The uninterrupted and intense motor activity of refractory GCSE poses a serious life threat as it rapidly leads to shock, multiple organ failure, and malignant cerebral edema. The potential risks associated with an aggressive treatment are thus usually considered justified, and both the NCS and EFNS guidelines recommend the urgent administration of an anesthetic agent for refractory GCSE and post-convulsive subtle SE, a form of NCSE [1, 2].

Although this systemic stress does not occur with the same urgency in refractory NCSE, there is increasing evidence that NCSz and NCSE are harmful for the brain [3–5]: the occurrence of NCSz and NCSE after GCSE is associated with higher mortality; failure to rapidly diagnose and treat NCSE is also associated with poorer outcome; seizure burden is directly related to functional outcome in critically ill children, especially in the absence of an acute brain injury; in patients with acute brain injury, the occurrence of NCSz is associated with adverse hemodynamic and metabolic effects and ICP crisis. Altogether, this suggests that aggressive treatment of NCSE might be justified, although the risks of a prolonged and deep sedation need to be carefully weighted before deciding to resort to anesthetic agents. This is reflected in the EFNS guidelines, which recommend postponing general anesthesia and trying additional nonsedating anticonvulsants in refractory complex partial SE [1]. The NCS guidelines also recommend postponing anesthesia in patients who are hemodynamically stable and have not required intubation yet [2]. However, if NCSE fails to respond to these additional trials of nonsedating agents, anesthesia becomes unavoidable.

When deciding to use an anesthetic treatment, the following questions arise:

1. Which anesthetic drug should be used?
2. How long should the patient be treated with anesthetics?
3. What should the EEG target be?
4. How should the treatment be initiated, maintained, and tapered?
5. What should be done if treatment fails?

By answering these questions, an institutional protocol for anesthetic treatment of RSE can be developed and will avoid unnecessary delay in treatment and will make local practices more uniform. Such a protocol is shown in Fig. 1.

## Available Drugs

Barbiturates have been prescribed at sub-anesthetic doses to treat SE for over 60 years. The development of intensive care and the widespread availability of mechanical ventilation have allowed the use of anesthetics at deeply sedating doses for

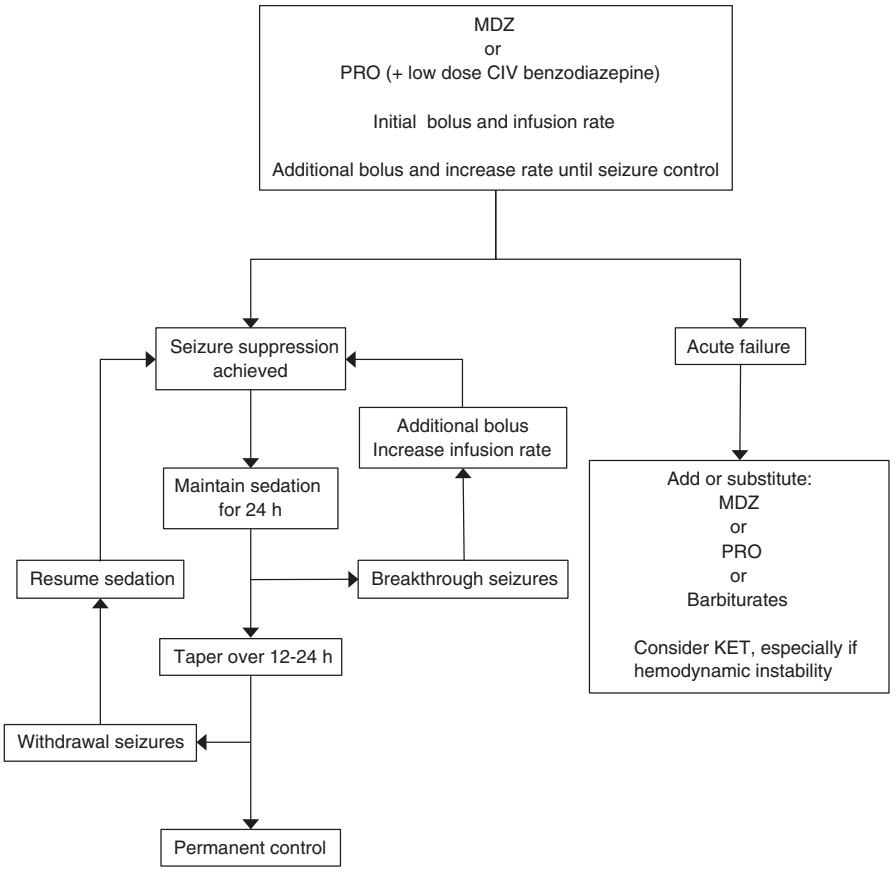


**Fig. 1** Suggested protocol for anesthetic treatment of refractory SE

RSE, initially with barbiturates (pentobarbital in the USA and thiopental in Europe and other regions of the world), followed by midazolam and propofol. More recently, ketamine has gained some interest, due to its unique mechanism of action and safety profile. More limited anecdotal evidence is also available with etomidate and inhalational compounds. The pharmacologic properties and suggested doses of the available anesthetics are summarized in Table 2.

## Mechanisms of Action

With the exception of ketamine, anesthetics used to treat RSE act mostly as allosteric modulators of the gamma-aminobutyric acid type A ($GABA_A$) receptor. Upon binding, they facilitate the action of GABA. This in turn increases the frequency of the opening of the associated chloride channel, consequently amplifying the inhibitory effect of GABA.

**Table 2** Pharmacological properties of available anesthetic drugs

| | Midazolam | Propofol | Pentobarbital | Thiopental | Phenobarbital | Ketamine | Etomidate | Inhaled (Desflurane/ isoflurane) |
|---|---|---|---|---|---|---|---|---|
| Use | CIV | CIV | CIV | CIV | IV or CIV, including very high doses | CIV | CIV | Continuous inhalation |
| Mechanism of action | *GABA(A)* | *GABA(A)*<br>NMDA<br>$Na^+$, $Ca^{2+}$ | *GABA(A)*<br>NMDA,<br>AMPA<br>nACh | *GABA(A)*<br>NMDA,<br>AMPA<br>nACh | *GABA(A)*<br>NMDA,<br>AMPA<br>nACh | *NMDA*<br>DA, NA,<br>5HTA<br>Opioid (μ, δ, k)<br>mACh<br>Substance P | *GABA(A)*<br>A | *GABA(A)*<br>NMDA<br>Glycine<br>$K^+$ |
| Vd (l/kg) | 3 | 60 | 64 | 160 | 0.55 | 4 | 4.5 | 0.7/4 |
| Lipid/ plasma distribution | 3.1 | 3.8 | 2.1 | 2.9 | 1.4 | 2.9 | 3.1 | 2.1 |
| Protein binding | 95–97 % | 95–99 % | 35–50 % | 50–80 % | 20–50 % | 45 % | 75 % | N/A |
| Metabolism | >99 %<br>Oxidation and glucuronidation | >95 %<br>(Oxidation and glucuronidation) | >99 %<br>(Oxidation and glucuronidation) | >99 % | 50–75 % | >99 % | >99 %<br>(ester hydrolysis) | Minimal |

(continued)

**Table 2** (continued)

| | Midazolam | Propofol | Pentobarbital | Thiopental | Phenobarbital | Ketamine | Etomidate | Inhaled (Desflurane/ isoflurane) |
|---|---|---|---|---|---|---|---|---|
| Interactions | CYP3A4 substrate | CYP2B6 substrate CYP2C9 substrate | CYP3A4 inducer CYP2A6 inducer CYP2C19 substrate | CYP3A4 inducer CYP2C19 substrate | CYP3A4 inducer CYP2C19 substrate | CYP2B6 substrate CYP3A4 substrate | CYP3A4 inhibitor CYP1A2 inhibitor CYP2C19 inhibitor | None |
| Active metabolites (relative activity) | 1-Hydroxy-midazolam (20 %) 4-Hydroxy-midazolam (7 %) | 4-Hydroxy propofol (30 %) | None | Pentobarbital | None | Norketamine (25 %) | None | None |
| Elimination | Renal | Renal | Renal | Renal | Renal | Renal | Renal | Respiratory Renal |
| Half-life | 2–6 h | 0.5–30 h | 15–50 h | 3–22 h | 53–118 h | 2.5–3 h | 1–5 h | Dependent on minute ventilation |
| Preparation | Solution Hydrochloride | Emulsion | Powder Sodium salt | Powder Sodium salt | Solution | Solution Hydrochloride | Solution | Vaporizable liquid |
| Solubility | Hydrophilic | Lipophilic (no PG) | Lipophilic (PG) | Hydrophilic | Lipophilic (PG) | Hydrophilic | Lipophilic (PG) | N/A |

| Adverse effects | Respiratory depression<br>Hypotension | Respiratory depression<br>Myocardial depression<br>Hypotension<br>PRIS | Respiratory depression<br>Myocardial depression<br>Hypotension<br>Propylene glycol toxicity<br>Paralytic ileus<br>Bowel ischemia<br>Immune paresis<br>Cutaneous fibrosis<br>Shivering<br>Bronchospasm<br>Laryngospasm | Respiratory depression<br>Hypotension<br>Myocardial depression<br>Paralytic ileus<br>Bowel ischemia<br>Immune paresis<br>Cutaneous fibrosis<br>Shivering<br>Bronchospasm<br>Laryngospasm | Respiratory depression<br>Hypotension<br>Propylene glycol toxicity | Cardiovascular stimulation<br>Respiratory stimulation | Respiratory depression<br>Hypotension<br>Propylene glycol toxicity<br>Non-epileptic myoclonus<br>Adrenocortical suppression | Hypotension<br>Fluoride nephrotoxicity (isoflurane)<br>Airway irritation (isoflurane) |
|---|---|---|---|---|---|---|---|---|
| Induction bolus | 0.2 mg/kg | 1–2 mg/kg | 5 mg/kg<br>50 mg/min | 1–2 mg/kg<br>50 mg/min | 20 mg/kg | 1.5 mg/kg | 0.3 mg/kg | N/A |
| Initial rate | 0.2 mg/kg/h | 1 mg/kg/h | 1 mg/kg/h | 1 mg/kg/h | 1 mg/kg/h | 1 mg/kg/h | 1 mg/kg/h | 1.5–3 % |
| Maximal rate | 3 mg/kg/h | 15 mg/kg/h<br>(5 mg/kg/h if more than 48 h) | 5 mg/kg/h | 5 mg/kg/h | 3 mg/kg/h | 10 mg/kg/h | 7.2 mg/kg/h | 1.5–4 % |
| Comments | Tachyphylaxis | Administer together with low dose of CIV benzodiazepine | | | | | | |

*Abbreviations*: *CIV* continuous intravenous, *IV* intravenous, *GABA* gamma-aminobutyric acid, *NMDA* N-methyl-D-aspartate, *Na+* sodium, *Ca2+* calcium, *AMPA* alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid, *nACh* nicotinic acetylcholine, *mACh* muscarinic acetylcholine, *DA* dopamine, *NA* noradrenaline, *5HTA* serotonin, *A* adrenaline, *Vd* distribution volume, *PG* propylene glycol

The binding sites of benzodiazepines, barbiturates, and propofol occupy different locations of the receptor, explaining their synergistic effect when applied simultaneously. Etomidate binds at the barbiturate-binding site, while inhalational agents bind at the propofol-binding site. In addition to their main mechanism of action, barbiturates and propofol also exhibit secondary activity on various receptors (N-methyl-D-aspartate [NMDA], alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid [AMPA], neuronal acetylcholine [nACh]) and channels (voltage-gated sodium and calcium channels), but the implication of these activities is unclear.

Compared to pentobarbital and thiopental, phenobarbital has a higher antiseizure/sedative ratio: a similar antiseizure effect can be achieved at relatively lower doses with phenobarbital than with other barbiturates. Non-anesthetic doses of phenobarbital are usually administered to decrease the risk of recurrence of SE during pentobarbital taper. It can also be administered at very high doses, either continuously or intermittently, as the main anesthetic treatment. There are some pharmacokinetic and pharmacodynamic differences between pentobarbital and thiopental, but they appear inconsequential in clinical practice.

In experimental models of SE, prolonged ictal activity leads to the internalization of synaptic GABA receptors and the externalization of glutamate (both NMDA and AMPA) receptors. This receptor trafficking is associated with a progressive loss of efficacy of GABAergic drugs and the increasing efficacy of NMDA antagonists. In similar experimental models, NMDA antagonists were also found to be protective against SE-induced neuronal injury and later development of epilepsy. As an antagonist and allosteric modulator of the NMDA receptor, ketamine has thus recently received increased attention as a potentially useful treatment of RSE [6].

## Safety

The most common adverse effects attributable to all GABAergic drugs are sedation and respiratory and cardiovascular depression. At doses required to treat RSE, intubation and mechanical ventilation are unavoidable. Patients treated with high doses of anesthetics also often require fluid resuscitation and vasopressors; refractory hypotension and myocardial depression are often a limiting factor with barbiturates and propofol. Prolonged sedation, immobilization, and mechanical ventilation in an intensive care environment expose patients to several nonspecific complications, such as ventilator-associated pneumonia, urinary tract infections, central line-associated bloodstream infection, pressure ulcers, deep vein thrombosis, and pulmonary embolism, regardless of the agent used. Prolonged use of high doses of vasopressors may cause visceral and peripheral vasoconstriction and ischemia. These severe and potentially lethal complications have been observed mostly with barbiturates.

Due to its different mechanism of action, ketamine does not exhibit any cardiorespiratory depressant effect and in fact can even raise blood pressure. This safety profile makes it particularly interesting in patients with hemodynamic instability,

including those where this instability is the consequence of concomitant treatment with another anesthetic. There has been some concern that ketamine might raise intracranial pressure, which could be detrimental in patients with an acute brain injury. However, this was shown not to occur in ventilated patients [7]. One case of possible neurotoxicity has been attributed to ketamine, although it is not clear if the cerebellar atrophy that was observed was due to ketamine, the underlying illness, and/or the concurrent administration of phenytoin [8].

Due to their hydrophobic nature, pentobarbital, phenobarbital, and etomidate cannot be diluted in water-based solvents and are formulated as solution containing propylene glycol. Although it is usually safe at low doses, continuous intravenous administration of propylene glycol over a short period of time can lead to toxic effects (Table 3), which include lactic acidosis, hyperosmolality, hemolysis, acute kidney injury, and shock. Underlying renal insufficiency and hepatic dysfunction increase the risk for toxicity. Serum osmolarity should be monitored daily in patients receiving medications that contained propylene glycol as a solvent as an elevated osmolar gap appears to be a good indicator of its concentration. Treatment includes hemodialysis to remove propylene glycol and supportive measures.

Propofol is another highly hydrophobic compound. It is formulated as a lipid-water emulsion that does not contain propylene glycol. However, propofol is associated with the risk of propofol infusion syndrome (PRIS) (Table 3). This syndrome is caused by mitochondrial toxicity in patients who receive high doses of propofol for a long period of time (>5 mg/kg/h for more than 24 h). It is characterized by hypertriglyceridemia, liver injury and hepatomegaly, cardiac failure and arrhythmia, rhabdomyolysis, metabolic acidosis, and renal failure. Children, critically ill patients receiving catecholamines and steroids, and patients with traumatic brain injury are at higher risk. Incidence is <10 %, although one series found an incidence of 45 %, including nonfatal and fatal cases. Mortality is approximately 30 %. Daily

**Table 3** PRIS and propylene glycol toxicity

| | Propofol infusion syndrome | Propylene glycol toxicity |
|---|---|---|
| Mechanisms | Impairment of mitochondrial respiratory chain and fatty acid metabolism | Direct cytotoxicity?<br>Proximal tubular necrosis |
| Manifestations | Myocardial failure with dysrhythmia<br>Hyperlipidemia<br>Hepatomegaly<br>Metabolic acidosis<br>Rhabdomyolysis, myoglobinuria<br>Acute kidney injury | Lactic acidosis<br>Hyperosmolarity<br>Acute kidney injury<br>Sepsis-like/SIRS-like syndrome |
| Monitoring | pH<br>Lactate<br>Triglyceride<br>Creatine kinase<br>Liver enzymes | Serum osmolarity (osmolar gap) |
| Treatment | Stop infusion<br>Supportive | Stop infusion<br>Hemodialysis<br>Supportive |

monitoring of lactate, creatine kinase, and triglyceride levels is indicated when using propofol. Treatment is supportive.

Etomidate reversibly inhibits the 11-beta-hydroxylase, a key enzyme of adrenal steroid production, and leads to primary adrenal insufficiency. Using a continuous infusion for sedation of critically ill trauma patients has been associated with increased mortality. It can also induce non-epileptic myoclonus that should not be confused for seizures. Modern inhalational anesthetics cause deep sedation and hypotension but are otherwise relatively well tolerated. The main limitation to their use is the need for an appropriate delivery system that can be used in an ICU environment.

All the discussed intravenous medications tend to accumulate in tissues, including the brain. This is particularly the case for thiopental and pentobarbital, whose activity can persist for days after the infusion has been discontinued, resulting in longer time to awakening and longer duration of mechanical ventilation and ICU stay. This is also true for short-acting agents like midazolam and propofol, whose half-life increases significantly upon continuous infusion.

## Efficacy

Only one prospective randomized trial has compared the efficacy of two anesthetic drugs in RSE, and it was interrupted after only 23 patients had been enrolled (14 with propofol and 9 with thiopental or pentobarbital) [9]. No difference was observed in the efficacy, but the study was under sampled. With the exception of this randomized control trial, the treatment of RSE has not been systematically studied. In the absence of more conclusive evidence, the choice of anesthetic drug relies mostly on observational studies, which have included variable proportions of CSE and NCSE and are subject to various biases.

A systematic review of all case series of RSE treated with midazolam, propofol, or pentobarbital between 1970 and 2001 was published in 2002 [10]. It compared patients treated with pentobarbital ($n=106$), midazolam ($n=54$), or propofol ($n=33$). Most of the patients treated with midazolam came from a single center. The majority of patients had GCSE at onset, but approximately half of them developed subtle SE at some point prior to treatment with CIV anesthetics, especially in the midazolam group. Midazolam was associated with a higher rate of acute treatment failure, breakthrough, and withdrawal seizures compared to pentobarbital and, to a lesser extent, propofol. However, midazolam was used at a relatively low dose (<0.4 mg/kg/h) and with a goal of seizure suppression, whereas pentobarbital was titrated to a more aggressive goal of burst suppression or background suppression. Accordingly, symptomatic hypotension requiring vasopressors was more common with pentobarbital. Mortality was similar with all three drugs (40 %).

Recently, a study compared a group of patients who received high doses of midazolam ($n$ = 100; median maximal dose [interquartile range, IQR], 0.4 [0.2–1.0] mg/kg/h) to a control group of patients treated with low doses (median maximal dose [IQR], 0.2 [0.1–0.3] mg/kg/h) [11]. High doses were associated with fewer withdrawal seizures (15 % vs. 64 %; OR, 0.10) and a lower mortality rate (40 % vs.

62 %; OR, 0.41). Symptomatic hypotension requiring vasopressors tended to be more frequent in the high-dose group (53 % vs. 32 %; OR, 2.40).

Overall, midazolam seems to present the most favorable combined safety and efficacy profile, and it is the agent most commonly chosen by experts, especially in the USA [12]. Propofol is less popular, especially in children, perhaps because of the risk of PRIS, but is still used by some groups. The longer duration of sedation and perhaps an overall higher toxicity are likely reasons for the current unpopularity of barbiturates, at least as a first choice.

## Goal and Duration of Treatment

It is currently unclear what the optimal EEG target is. Possible goals include seizure suppression, burst suppression, and complete background suppression. With seizure suppression, the aim is to suppress all ictal activities while avoiding deep stage of sedation characterized by the appearance of a burst-suppression pattern. It is important to recognize that even with the aim of simply suppressing seizures, the required doses of anesthetics will at times lead to burst suppression, at least intermittently and especially when using barbiturates or a combination of anesthetics. On the other hand, it is usually difficult to achieve and maintain a burst-suppression pattern or complete suppression with midazolam or propofol only.

Animal data indicates that iatrogenic burst suppression represents a state of cortical disinhibition and thus might not completely prevent the occurrence of seizures [13]. Indeed, seizures can still arise from a burst-suppression background and even from a suppressed background, further stressing the necessity of continuous EEG monitoring for the treatment of RSE, as advocated by the NCS guidelines, regardless of the EEG target.

In a small series of patients treated with pentobarbital, treating to complete suppression showed a trend toward better outcome than burst suppression (17/20 [85 %] vs. 6/12 [50 %] SE control and 12/20 [60 %] vs. 3/12 [25 %] survival), although this was not statistically significant [14]. In the same series, three patients were treated to seizure suppression; all responded and survived. More recent studies have yielded somewhat conflicting evidence, with one showing that achieving burst suppression ($n = 20$) or not ($n = 11$) did not change the outcome (74 % survival and 26 % return to baseline, overall) [15], while another indicated that complete suppression or burst suppression was associated with poorer outcome than seizure suppression (modified Rankin score $\geq 4$; 25/31 [84 %] vs. 8/16 [50 %]) [16].

In the systematic review discussed above, a goal of seizure suppression was more commonly chosen with midazolam therapy, and breakthrough and withdrawal seizures were more common in this group. This might suggest that seizure suppression is associated with a higher rate of treatment failure. However, patients who received barbiturates were not continuously monitored, likely leading to underestimating the incidence of breakthrough and withdrawal seizures in this group. Also, patients received low doses of midazolam, and in a subsequent study with higher doses of midazolam, the rate of withdrawal seizures was much lower.

Overall, since achieving burst suppression or complete suppression does not seem to offer a clear advantage, aiming for seizure suppression is a reasonable approach. Complete seizure suppression is the ideal goal to achieve, but brief intermittent seizures can probably be tolerated in order to limit escalation of doses and toxicity. There is no evidence to support a specific duration of treatment. Guidelines recommend a period of at least 24 h before the anesthetic drug is tapered [1, 2]. The duration of treatment is usually mostly dictated by the occurrence of breakthrough seizures.

## Treatment Initiation and Maintenance

Anesthetic treatment usually begins with sequential boluses of the chosen drug until seizure controlled is achieved. In parallel, a continuous infusion is started. The number of boluses required to achieve the initial control should guide the initial infusion rate, but there is no rule. If breakthrough seizures occur after control is initially achieved, then additional boluses of the drug can be administered. In parallel, the infusion rate is increased, usually by 25–50 %. There is no theoretical upper limit to the dose of anesthetics that can be given. Tissue redistribution, increased metabolism, and tachyphylaxis can lead to the administration of large doses. For most anesthetics, there seems to be no maximal dose above which no further efficacy can be expected. Similarly, there is no clear correlation between circulating levels and efficacy. With the possible exception of propofol, whose prolonged infusion of high doses (>5 mg/kg/h for >48 h) is associated with a significant risk of PRIS and should be avoided, the infusion rate is thus mostly adjusted to the EEG target and in practice will usually be limited by the occurrence of unmanageable complications, especially hypotension.

## Taper and Treatment Failure

Once SE has been controlled for at least 24 h, the anesthetic can be gradually withdrawn. There is no proven strategy, but experts usually recommend progressively tapering the infusion rate over 12–24 h [2]. If withdrawal seizures occur during or after taper, new boluses of anesthetics are given, and the continuous infusion is resumed at the rate that previously controlled seizures. Most experts would continue this second trial for longer than 24 h after control is again achieved and would subsequently attempt to taper more gradually (over 48 h, for instance). While tapering the anesthetic, patients should be receiving at least one well-dosed nonsedating antiseizure medication. In a couple of small series, IV phenobarbital (20 mg/kg; level >15 μg/ml) proved to be efficacious in preventing recurrence of SE during pentobarbital taper [15, 17].

There is no theoretical limit to the number of trials and the total duration of anesthetic trials since patients with RSE can be placed in therapeutic coma for months and yet make a full functional recovery. This is especially the case for young patients

with cryptogenic RSE. Younger age, normal neuroimaging, and reactive EEG background at onset predict a satisfactory, if not full, recovery [18]. If the initial anesthetic trial fails to permanently control SE, either because of acute failure or relapse during taper, a second anesthetic drug may be added or substituted. This situation has been referred to as malignant SE [19] or superrefractory SE [20] and occurs mostly in patients with a cryptogenic encephalitis-like illness, sometimes referred to as new-onset refractory SE (NORSE).

Theoretically, since available anesthetics have different molecular targets, either acting through different receptors ($GABA_A$ or NMDA) or binding to different sites of the same receptor ($GABA_A$), synergism can be expected from a combined therapy. Although there is some experimental and human evidence in favor of a synergistic interaction between ketamine and benzodiazepines, between benzodiazepines and barbiturates, and between benzodiazepines and propofol, this has never been clearly demonstrated for the treatment of RSE. Importantly, combined administration of anesthetics is likely to result in additive toxicity, especially severe cardiovascular depression and hypotension. In this regard, the addition of ketamine to a GABAergic anesthetic may prove potentially useful, since it is expected to raise blood pressure and cardiac output. In practice and in published series, some, but not all, patients do indeed benefit from this effect, and vasopressors can be lowered or even interrupted upon the initiation of ketamine [6, 21]. While initially used as a first choice of anesthetic for the treatment of RSE, the use of barbiturates is now mostly restricted to cases of superrefractory SE, with some efficacy but also some toxicity, especially hypotension and infections [22]. Other alternative treatments can also be considered for superrefractory SE. They are discussed elsewhere in this book.

**Conclusion**

There is very little evidence available to decide when and how to treat NCSE with anesthetics. The decision should be based on a careful assessment of the risks of ongoing SE and of the toxicity of treatment. The choice of an agent is mostly based on anecdotal evidence. Midazolam seems to be favored by most experts, due to its seemingly better safety profile, including at higher doses (>0.4 mg/kg/h) that are more efficacious. Propofol is another acceptable option, but prolonged infusion of high doses (5 mg/kg/h for >48 h) and administration in children should be avoided. Barbiturates tend now to be used for superrefractory cases that fail to respond to a first trial of anesthetics. Etomidate and inhalational anesthetics have also been used but evidence is scarce. Sedation is initially obtained by administering a bolus and, at the same time, starting a continuous infusion. Initial SE control is achieved by repeating boluses and progressively increasing the infusion rate. There is little evidence to suggest which EEG target is best. Seizure suppression can be obtained with any of the available drugs with relatively low toxicity, whereas prolonged burst suppression and complete suppression usually require barbiturates or a combination of anesthetics and might be associated with increased morbidity and mortality. Most experts recommend inducing coma for an initial period of 24 h. Continuous EEG monitoring is mandatory while treating

refractory NCSE, including during and after tapering the anesthetics, to monitor for breakthrough and withdrawal seizures. It is important to remember that burst suppression and complete suppression do not entirely prevent the occurrence of breakthrough seizures. When control of SE is achieved, the anesthetic can be progressively weaned over a 12–24 h period. If withdrawal seizures recur during or after taper, boluses of anesthetics are given, and the continuous infusion is resumed at the rate that previously controlled seizures and usually for more than 24 h. A second anesthetic drug may be added or substituted. Ketamine should be considered at this point because of its action on NMDA receptors and its cardiovascular stimulant properties. Some patients can remain in pharmacological coma for weeks and yet make a satisfactory recovery.

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# Nonpharmacologic and Nontraditional Treatments for Status Epilepticus

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Elizabeth A. Felton and Mackenzie C. Cervenka

**Contents**



## Introduction

If first- and second-line antiepileptic drugs (AEDs) fail to control status epilepticus (SE), it is termed refractory status epilepticus (RSE), and the likelihood of additional interventions stopping seizures diminishes dramatically. Both morbidity and mortality increase with longer duration of status epilepticus. One retrospective study of 47 RSE patients reported 23 % mortality and only 31 % returning to baseline [1, 2]. When RSE persists despite aggressive intervention with an anesthetic agent for 24 h or more, it is termed super-refractory status epilepticus (SRSE), and mortality rates

E.A. Felton, MD, PhD
Department of Neurology, University of Wisconsin-Madison,
1685 Highland Ave., MFCB 7170, Madison, WI 53705, USA
e-mail: felton@neurology.wisc.edu

M.C. Cervenka, MD (✉)
Department of Neurology, The Johns Hopkins Hospital, 600 N. Wolfe Street, Meyer 2-147,
Baltimore, MD 21287, USA
e-mail: mcerven1@jhmi.edu



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are reported to be 30–50 % [1]. No prospective, double-blinded studies exist to direct management of RSE or SRSE. Nonpharmacologic and nontraditional treatments for status epilepticus are typically reserved for these types of cases, perhaps following several days of failed attempts at controlling seizures using a combination of antiepileptic drugs and general anesthetics. These treatment options can include hypothermia, neurostimulation, ketogenic dietary treatment, immunomodulation, and resective surgery (also see Chap. 32 on investigational treatments of RSE).

Determining the role of nontraditional and nonpharmacologic therapies in the algorithm for treating RSE and SRSE is challenging for several reasons. Since none of these treatment options are considered first- or second-line and are typically not started for several hours to days after the initial onset of status epilepticus, determining the efficacy of a given treatment is almost universally confounded by multiple other concomitant interventions. In addition, patients with RSE and SRSE are heterogeneous with regard to the underlying etiology, which can determine prognosis. For instance, RSE is more likely to develop in patients with acute brain injury (e.g., trauma, infection, or stroke) than in patients with epilepsy. When patients with epilepsy do present with RSE (typically because of subtherapeutic antiepileptic drug levels or other precipitants), they tend to respond more favorably than patients with other etiologies, regardless of the treatment used. Therefore, it is often difficult to discern whether morbidity/mortality associated with these treatments is actually due to the intervention or to the underlying disease process in combination with multiple concurrent therapies. Finally, the numbers of patients developing SRSE is relatively small (approximately 10–15 % of patients presenting to the hospital in status epilepticus), often requiring a multicenter study design [3]. Efforts are being made to design and conduct prospective clinical trials directed at the treatment of RSE and SRSE.

This chapter will review each major nontraditional treatment option, proposed mechanism(s) of action, evidence for its use in RSE, and advantages and disadvantages of the treatment including potential side effects and contraindications. A summary of the treatments can be found in Table 1.

## Nonpharmacologic and Nontraditional Treatments

### Hypothermia

Hypothermia for seizure suppression in humans was first reported in 1963 by Dr. Ayub Ommaya who described open neurosurgical techniques for applying focal hypothermia to the human cortex [4]. One of the patients had RSE which responded to focal cooling of the brain to 20–24 °C. In 1984, moderate hypothermia (30–31 °C) in combination with thiopental was successfully used in status epilepticus in three children [1]. Evidence for the use and safety of hypothermia in humans comes mainly from literature describing post-cardiac arrest patients and neonates with hypoxic-ischemic encephalopathy. There are also extensive animal studies of hypothermia used to treat these conditions. For seizures and status epilepticus in particular, as of a 2012 review, there were four case reports on nine patients (four

**Table 1** Summary table of nonpharmacologic and nontraditional treatments for refractory and super-refractory status epilepticus

| Treatment | Typical regimen | Administration | Cautions/contraindications | Advantages | Disadvantages |
|---|---|---|---|---|---|
| Hypothermia | Mild hypothermia to 32–35 °C for 1–3 days | Endovascular or external temperature management system | Concurrent use with thiopental | Relatively low risk<br>Can also reduce brain edema<br>Safe to use with most other treatments | Side effects (all less likely with mild hypothermia): Shivering, electrolyte imbalance, acid-base disturbances, hyperglycemia, impaired drug clearance, mild coagulopathy, infections, cardiovascular depression, arrhythmias |
| Electroconvulsive therapy (ECT) | Multiple days (range 3–15), charge applied range 64–3379 mC | Electrical stimulation via electrodes typically placed bifrontotemporal | No absolute contraindications | Well tolerated<br>Safe to use with most other treatments | AEDs should be weaned prior to starting<br>Multiple sessions required<br>Side effect: Memory impairment |
| Corticosteroids | Methylprednisolone 1 g per day for 5 days | Peripheral IV catheter | Uncontrolled diabetes mellitus<br>Active infection | Well tolerated<br>Safe to use with most other treatments | Side effects: Hyperglycemia, infection, adrenal insufficiency, Cushing syndrome, hypertension, and psychosis |

(continued)

**Table 1** (continued)

| Treatment | Typical regimen | Administration | Cautions/contraindications | Advantages | Disadvantages |
|---|---|---|---|---|---|
| Intravenous immune globulin (IVIG) | 2 g/kg over 5 days | Peripheral IV catheter | Allergy<br>Congestive heart failure<br>Renal failure | Well tolerated<br>Safe to use with most other treatments | Side effects:<br>Allergy (serum IgA levels need to be checked prior to administration), aseptic meningitis |
| Plasma exchange or plasmapheresis (PLEX) | Five courses | Pheresis catheter | Infection | Relatively well tolerated<br>Safe to use with most other treatments | Requires a trained technician to administer<br>Side effects:<br>Increased risk of infection, hypotension |
| Ketogenic diet | Formula with a 3:1 or 4:1 ketogenic ratio of grams of fat: protein and carbohydrates combined | Enteral feeding tube | Certain rare metabolic disorders<br>Concurrent use of propofol | Works rapidly<br>Safe to use with most other treatments | Side effects:<br>Hypoglycemia, constipation, hyperlipidemia, kidney stones, pancreatitis |

pediatric) with RSE treated with hypothermia [3]. Of these, 100 % had initial cessation of status, and 78 % recovered from status epilepticus.

For seizure suppression, hypothermia refers to cooling of the body, typically to 32–35 °C (mild hypothermia). Either an endovascular or external temperature management system is used. The endovascular system circulates cool saline around a catheter in the inferior vena cava. The external system consists of gel pads and circulating sterile water. There can be an induction phase of 8 h followed by a maintenance phase of 24–48 h. Temperature is typically monitored with rectal and urinary bladder probes. Hypothermia is thought to be antiepileptic and neuroprotective, the latter of which occurs by slowing nerve conduction velocity [4]. There are proposed effects on sodium channels, postsynaptic voltage-gated channels, disturbances of membrane properties and ion pumps, and changes in presynaptic mechanisms which cause a marked reduction of excitatory neurotransmission [4]. There is typically a reduction in cerebral metabolic rate, oxygen utilization, and ATP consumption. Due to these effects, hypothermia may also reduce brain edema [1]. Advantages of hypothermia are that it is a relatively low-risk procedure that can be used in adults and children. There are few interactions with other drugs the patient may be receiving for the treatment of status epilepticus or underlying causes. Potential side effects include shivering (can use neuromuscular blockade to prevent or treat this), electrolyte imbalances, acid-base disturbances, hyperglycemia, impaired drug clearance, mild coagulopathy, infections, decubitus ulcers, cardiovascular depression, arrhythmias, and hypotension. Although the above side effects have been reported with hypothermia, they are less likely to occur with mild hypothermia, which is typically used for status epilepticus. There is one case of bowel ischemia and sepsis in the setting of the concurrent use of mild hypothermia and thiopental; therefore, some recommend avoiding the use of barbiturates and hypothermia due to risk of increased immune suppression [4].

## Electroconvulsive Therapy [5, 6]

Electroconvulsive therapy (ECT) is the form of neurostimulation most studied in the treatment of status epilepticus. It was developed in 1938 by Italian scientists Dr. Ugo Cerletti and Dr. Lucio Bini for patients with psychiatric illness, but was also first used for epilepsy in the same year [1]. The underlying rationale for this treatment is based on the observation that nonconvulsive status epilepticus (NCSE) is often spontaneously terminated by a convulsion. Therefore, ECT can be used to induce convulsive activity with the desired outcome being termination of status epilepticus. Because the goal is to induce a convulsion, ideally ECT should be administered when anesthetic effects are reversed and antiepileptic drugs are discontinued; otherwise, cortical excitability may be too inhibited to provoke a convulsive seizure [1]. The exact mechanism for how ECT can abort RSE is not fully understood. One proposal is that by inducing a generalized seizure, ECT can activate inhibitory mechanisms needed to abort seizures. ECT is thought to increase the presynaptic release of gamma-aminobutyric acid (GABA) and prolong the refractory period after a seizure [6].

A 2012 review of 8 case studies on 11 patients (4 pediatric) with RSE reported that status epilepticus resolved in 9 patients (82 %). Although comprehensive data were not

available for all of the individual case studies reporting outcomes, of the patients with resolution of RSE, three patients (33%) were reported to have full functional recovery, and four patients (44%) continued to have some seizures [6]. Two of the patients with occasional seizures (50%) were also reported to have minor cognitive impairment. The ECT parameters and protocols were heterogeneous. For example, the number of days of ECT sessions ranged from 3 to 15, location of electrode placement on the head varied (although typically either bifrontotemporal or frontocentral), and charge applied ranged from 64 to 3379 mC (millicoulombs). The number of days from onset of status epilepticus to ECT treatment ranged from 26 to 103, when reported [6].

The main advantages of ECT are that it is well tolerated and can be used safely in combination with other treatments. However, a major disadvantage is that anesthetics and AEDs may need to be weaned for ECT to have maximal effectiveness, so there is the question regarding the optimal titration of antiepileptic medications between treatment sessions. Often multiple ECT sessions are required. A known side effect of ECT is memory impairment, but this is typically reversible. However, in patients in status epilepticus, it would be difficult to determine whether residual memory impairment is due to ECT, prolonged seizures, or the underlying process causing the seizures.

## Immunomodulation

Of all of the therapies discussed in this chapter, immune modulating treatments are likely used more often and earlier in the course of status epilepticus compared to the other treatments. Many cases of RSE of previously unknown etiology have recently been found to be caused by autoantibody production resulting in status epilepticus. There are a number of syndromes describing patients with suspected but undiscovered autoimmune status epilepticus, including new-onset refractory status epilepticus (NORSE) and febrile infection-related epilepsy syndrome (FIRES). NORSE was first described in 2005 and typically refers to RSE of unknown etiology in adults. FIRES was first described in 2010 and typically refers to RSE of unknown cause in children [7, 8]. Patients with NORSE and FIRES have no prior history of epilepsy and tend to be young and healthy prior to the onset of SRSE other than an occasional febrile prodrome. While no underlying etiology is identified, an autoimmune process is often presumed. Although patients with RSE of unknown etiology typically have immunologic testing including a paraneoplastic panel sent to evaluate for autoantibodies, this testing is often negative. However, even in cases where there is no definitive evidence of an underlying autoimmune or neuroinflammatory process, immunomodulators are sometimes used because there are suspected undiscovered autoantibodies.

Antibodies discovered in patients with SRSE can be related to a paraneoplastic syndrome or neuronal surface antibody syndrome [9]. Examples of antibodies commonly associated with seizures and encephalitis are anti-Hu and NMDA-receptor antibodies. Other well-known examples of autoimmune status epilepticus are Rasmussen's encephalitis and Hashimoto's encephalitis. When an antibody is identified, this often helps guide further investigations and/or treatment (e.g., a search for malignancy is undertaken in patients with NMDA-receptor antibodies). See Table 2 for a summary of autoantigens known to be associated with RSE.

**Table 2** Autoantigens of encephalitis associated with seizures and status epilepticus [10]

| | Syndrome | Clinical significance | Location of epitopes | Frequency of systemic tumor | Response to immunotherapy |
|---|---|---|---|---|---|
| Intracellular paraneoplastic antigens | | | | | |
| Hu | Limbic, cortical encephalitis | High | Intracellular | >90 % | Infrequent |
| CV2/CRMPS | Limbic encephalitis | High | Intracellular | >90 % | Infrequent |
| Ma2 | Limbic, diencephalon, upper brainstem encephalitis | High | Intracellular | >90 % | Moderate |
| Amphiphysin | Limbic encephalitis, stiff-person syndrome | High | Intracellular | >90 % | Poor |
| Cell-surface or synaptic antigens | | | | | |
| NMDAR (NRI) | Psychosis, dyskinesias, autonomic instability, hypoventilation | High | Extracellular | Varies with age, gender, and ethnicity | Frequent |
| LGII | Limbic encephalitis, tonic seizures (faciobrachial dystonic seizures) | High | Extracellular | <10 % | Frequent |
| Caspr2 | Encephalitits, Morvan's syndrome, neuromyotonica | High | Extracellular | ~40 % | Frequent |
| GABA (B) receptor | Limbic encephalitis, early and prominent seizures | High | Extracellular | 70 % | Frequent |
| AMPAR (GluR1/2) | Limbic encephalitis (frequent relapses) | High | Extracellular | 70 % | Frequent |
| mGluR5 | Limbic encephalitis | High | Extracellular | >90 % | Frequent |
| DPPX (subunit of Kv4.2 K+ channel) | Encephalitis, frequent relapses | N/A | Extracellular | N/A | Frequent |

(continued)

**Table 2** (continued)

| | Syndrome | Clinical significance | Location of epitopes | Frequency of systemic tumor | Response to immunotherapy |
|---|---|---|---|---|---|
| GAD | Limbic encephalitis, refractory epilepsy, stiff-person syndrome, cerebellar dysfunction | High (may occur with cell-surface antibodies) | Intracellular | <5 % | Moderate |
| Antigens of unclear clinical significance | | | | | |
| AMPAR (GluR3) | Rasmussen's encephalitis | Unclear | Extracellular? | No tumor association | Infrequent |
| VGKC-protein complex antibodies different from LGII/Caspr2 | Multiple neurological symptoms, from neuropathy to encephalitis with seizures | Low | ? | ? | Variable |
| Thyroid peroxidase | Hashimoto's encephalitis | Low | Intracellular | No tumor association | Frequent |

*CRMPS* collapsin response mediator protein-5, *GAD* glutamic acid decarboxylase, *NMDAR* N-methyl-o-aspartate receptor, *LGII* leucine rich glioma inactivated protein I, *Caspr2* contactin-associated protein-like 2, *GABA (B) receptor* γ-aminobutyric acid-B receptor, *AMPAR* alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor, *mGluR5* metabotropic glutamate receptor 5, *DPPX* dipeptidyl-peptidase-like protein-6, *N/A* not available, too early to assess significance. (Permission from Davis et al. [10])

Immune modulators include corticosteroids, intravenous immune globulin (IVIg), plasma exchange or plasmapheresis (PLEX), cyclophosphamide, and rituximab. Typically, corticosteroids are used first (methylprednisolone 1 g per day for 5 days) followed by IVIg (2 g/kg over 5 days) or PLEX (five courses). Cyclophosphamide and rituximab are often used if these measures fail or as continued immunotherapy once SRSE ceases. Corticosteroids, in addition to immune modulation, can reduce blood-brain barrier permeability (which has a crucial influence on the persistence of seizure activity and which may reverse GABAergic inhibition) and can also lower intracranial pressure. Therapeutic PLEX separates and removes plasma from the cellular components of blood, and removing plasma is thought to also remove circulating immunoglobulins and immune complexes. IVIg consists of purified immunoglobulins and is made from pooled plasma from multiple (over 1000) blood donors.

Evidence for the use of immune therapies when the diagnosis of autoimmune encephalitis is not confirmed (i.e., in cases of FIRES or NORSE) is mostly limited to case reports, and outcomes reported are generally poor. As of a 2012 review, there were 8 case reports or case series with outcomes reported for 21 patients with RSE without an identified immunological condition treated with immunotherapy [3]. Of these, only one patient (5 %) had initial seizure control following administration of immune therapy and ultimately recovered from status epilepticus. Of note, many of the publications included were not specifically focused on patients who received immune therapy, but rather patients who received a variety of nontraditional treatment modalities, including immune therapy. Since 2012, there have been several more case reports and case series specifically focusing on immune therapy, as NORSE and FIRES are increasingly recognized as clinical entities that may have an underlying immunologic etiology. For example, there are reports of three patients with NORSE who improved from high-dose steroids ± IVIg and three patients who improved with PLEX [11, 12]. In one large retrospective multicenter study of 77 children with FIRES, 30 were treated with IVIg and 29 with steroids [13]. Of the patients treated with steroids and/or IVIg, only two patients (3 %) had a seizure reduction of >75 % and after IVIg treatment.

Each immune modulator has unique advantages and disadvantages or side effects. All can be administered easily via an intravenous catheter except for PLEX which requires placement of a pheresis catheter. PLEX also requires a trained technician to administer the treatment, increasing the overall cost. Steroids can cause hyperglycemia, infection, adrenal insufficiency, Cushing syndrome, hypertension, and psychosis. Contraindications for steroids include uncontrolled diabetes mellitus (relative contraindication) and active infection. IVIg can cause allergy (serum IgA levels need to be checked prior to administration) and aseptic meningitis. Contraindications for IVIg include IgA deficiency, congestive heart failure, and renal failure. Due to the need for a pheresis catheter, PLEX has an increased risk of infection and can also cause hypotension. PLEX is contraindicated in the setting of infection. Serum antibody tests should be obtained prior to starting therapy with IVIg or PLEX.

## Ketogenic Diets

The ketogenic diet is a high fat, low carbohydrate diet designed to mimic the fasting state. The term "ketogenic" refers to ketone bodies that are the products of fat metabolism and can be measured in blood and urine in patients treated with the ketogenic diet or fasting. In intensive care units, it can be administered via a gastrostomy tube and has also has been shown to be effective with parenteral administration. There are commercially available enteral formulas with a 4:1 ketogenic ratio of grams of fat: protein and carbohydrates combined.

The ketogenic diet has been used for epilepsy since the 1920s. However, the first reports for its use in status epilepticus were in the mid- to late 2000s. Evidence for its use in RSE consists mostly of case reports and case series. As of a 2012 review, there were 4 case reports with outcomes reported on 14 patients (3 adult, 11 pediatric) with RSE treated with a ketogenic diet (12 with a 4:1 ketogenic diet and two cases of the modified Atkins diet) [3]. Of these, 86 % achieved initial control of seizures and 79 % had resolution of seizures. A more recent case series of ten adult patients with SRSE started on a ketogenic diet resulted in resolution of status epilepticus in 90 % (all of the patients who achieved ketosis) in a median of 3 days [14]. In another study of four pediatric patients with SRSE (age ranging from 9 weeks to 13 years old, three of which had prior diagnoses of epilepsy) started on the ketogenic diet, status epilepticus resolved in all patients although all continued to have seizures [15]. Of note, the 9 week old in this series is the youngest patient reportedly treated with the ketogenic diet for treatment of status epilepticus.

Advantages of the ketogenic diet are that it can be used in children and adults and is easily administered via nasogastric tube, gastrostomy tube, and even parenterally. It can work rapidly resulting in a reduction in seizures in some cases even before the patient becomes ketotic (measured by concentration of blood or urinary ketones). The ketogenic diet does not produce hemodynamic instability that is a common side effect of anesthetic agents used for refractory status epilepticus. Once status epilepticus resolves, patients can be transitioned to an oral ketogenic diet or a less restrictive modified Atkins diet or other ketogenic dietary therapy.

The major disadvantage of using the ketogenic diet to treat status is the need for a trained multidisciplinary team to administer the diet. A dietitian or nutritionist familiar with the ketogenic diet is a critical member of this multidisciplinary team. In addition, the entire intensive care unit team (including the pharmacist) needs to be aware of the treatment and basic management principles so as to avoid bringing the patient out of ketosis (e.g., by inadvertently administering glucose containing fluids, over aggressively treating mild hypoglycemia, etc.). Another disadvantage is that it may not be safe when combined with intravenous propofol. In one case report, the ketogenic diet in combination with intravenous propofol was thought to provoke a fatal propofol infusion syndrome [16]. In addition, several contraindications limit the use of the diet in some patients including certain rare metabolic disorders, such as primary carnitine deficiency, carnitine palmitoyltransferase I or II deficiency, carnitine translocase deficiency, β-oxidation defects, pyruvate carboxylase deficiency, porphyria, and other disorders of fatty acid transport and oxidation [17]. Other

**Table 3** Considerations for implementing a ketogenic diet

| |
|---|
| *Ketogenic diet initiation* |
| Fasting lipid profile, CMP, CBC, amylase, lipase, vitamin D levels |
| Baseline weight and height |
| Continuous video EEG |
| Dietitian/nutrition consult |
| Remove dextrose from IV fluids |
| Discontinue current enteral formula |
| Minimize carbohydrates in medications and parenteral fluids with pharmacy assistance |
| Begin ketogenic formula |
| Begin multivitamin and calcium via gastronomy tube/nasogastric tube |
| *Ketogenic diet contraindications* |
| Unstable metabolic condition (persistent hyponatremia, hypernatremia, hypoglycemia, hypocalcemia, acidosis) |
| Hemodynamic or cardiorespiratory instability |
| Coagulopathy |
| Pancreatitis |
| Liver failure |
| Severe hyperlipidemia |
| Inability to tolerate enteral feeds, including ileus |
| Pregnancy |
| Received any propofol infusions within 24 h |
| Known fatty acid oxidation disorder or pyruvate carboxylase deficiency |

Included with permission from Thakur et al. [14]
*Abbreviations*: *CBC* complete blood count, *CMP* comprehensive metabolic panel

potential side effects include hypoglycemia, constipation (which can be compounded by the fact that critically ill patients may already have gastroparesis), hyperlipidemia, kidney stones, and pancreatitis. Table 3 provides an overview of the steps for initiating the ketogenic diet and several contraindications that may be relevant to intensive care unit patients in RSE.

## Surgical Resection

A variety of surgical approaches/techniques have been described for the treatment of refractory and super-refractory status epilepticus, including focal cortical resection, lobar resection, anatomic or functional hemispherectomy, corpus callosotomy, and multiple subpial transection (MST). Cortical and lobar resections involve removal of the tissue suspected to contain the underlying seizure focus based on neuroimaging and EEG findings. Anatomic hemispherectomy involves removal of an entire hemisphere, while functional hemispherectomy involves preservation of some brain tissue within the hemisphere with disruption of connecting fibers between regions of retained tissue. These procedures are used when the underlying process causing seizure activity is

suspected to affect an entire hemisphere, in cases such as Rasmussen's encephalitis and hemimegalencephaly. A corpus callosotomy is performed by severing all or portions of the corpus callosum that connects the two hemispheres, preventing seizure activity from spreading from one hemisphere to the other. The MST procedure involves sectioning the intracortical transverse fibers while sparing the vertical pathways, which can spare eloquent cortex (tissue critical for language, motor activity, or other functions). Sometimes MST is combined with cortical resection if the seizure focus is over both eloquent and non-eloquent cortex. Focal resections, hemispherectomies, and MST are typically considered when there is a clear electrographic seizure focus on routine and continuous EEG monitoring, although sometimes surgery is pursued even in nonfocal SRSE in the setting of a structural abnormality.

The decision to proceed to resection is often guided by neuroimaging data including preoperative MRI, fluorodeoxyglucose positron emission tomography (FDG-PET), and ictal single positron emission computed tomography (SPECT). In addition, intraoperative or extraoperative electrophysiological studies including electrocorticography (recording from cortical tissue using intracranial depth, strip, and/or grid electrodes) and somatosensory-evoked potentials can be performed to map out functional areas and the extent of the epileptogenic focus.

As of a 2012 review, there were 15 case reports or series with outcomes reported on 36 patients with RSE treated with resective neurosurgery [1]. Of these, 33 patients (92%) achieved seizure control as a result of the surgery and 27 (75%) had a good long-term outcome. A retrospective review of 15 children who underwent surgery a mean of 8 weeks after the start of RSE showed that RSE resolved in all patients. Four (27%) continued to have frequent seizures and required additional surgical intervention, 7 (47%) had postoperative hemiparesis (three improved), and 1 (7%) had postoperative expressive dysphasia. Nine (60%) of the patients had focal cortical dysplasia on histopathology [18]. Another literature review of 32 children who had resective surgery for RSE showed that 31 (97%) had immediate resolution of RSE and of those 24 (77%) were seizure free at long-term follow-up (6 months–5 years) [19].

The major advantage of surgery is that it has been shown to have the greatest likelihood of resulting in seizure freedom of all treatments for focal epilepsy when a single seizure focus is identified and resected. Patients who go on to surgery are typically carefully selected, so outcomes are overall better than those seen with other treatments described in this chapter. In addition, tissue samples can often be obtained to help make a pathological diagnosis of the underlying etiology of the RSE. Risks of surgery include general neurosurgical risks such as bleeding, stroke, and death. There is also risk of damage to functional (e.g., motor or language) regions of the brain.

## Other

The majority of the treatments described in this chapter are often considered third or fourth line for RSE and SRSE. Two treatments used that do not fall into other categories previously discussed include lidocaine and cerebrospinal fluid drainage. Cerebrospinal fluid (CSF) drainage, at times in combination with the infusion of air, bromide, or other fluids, has been reported since the nineteenth century in the

treatment of seizures and status epilepticus and was used for much of the first half of the twentieth century with most recent reports in the late 1970s. At the time, physicians observed that performing a diagnostic pneumoencephalogram could terminate RSE. The exact mechanism is not understood, but one thought is that it may reduce inflammation. One consideration for future use that is under investigation in animal models of status epilepticus is to coadminister intrathecal antiepileptic drugs, but this has not yet been attempted in humans [1]. The only recent publication of this method was a 2006 single case report of CSF-air-exchange for a patient in RSE [20]. In this report, 25 mL of CSF was removed and 70 mL of air was administered. Before the procedure was completed, RSE terminated and the patient became alert. However, after a week, seizures recurred and repeating the procedure was ineffective.

Lidocaine is typically used as a local anesthetic or antiarrhythmic drug, but there also have been reports since 1955 of its use for status epilepticus. Lidocaine decreases neuronal excitability by blocking voltage-dependent sodium channels, which is thought to contribute to its antiseizure effects. However, the exact mechanism for termination of seizures by lidocaine is not fully understood. Although standardized methods for its dosing and use have not been published, typically an initial loading dose of lidocaine is given followed by a continuous maintenance infusion. In some instances, the maintenance infusion is only given if the initial load or boluses terminate status. A retrospective study of 261 occurrences of status epilepticus in children that were treated with lidocaine showed providers considered it to be "extremely useful or useful" in 148 cases (56.7 %) [21]. Of the 211 cases in which a bolus infusion was given, seizures were stopped in 116 cases (55 %), and 40 cases (19 %) had a 50 % decrease in seizures. A risk of using lidocaine, especially when giving infusions, is that at higher doses, it can worsen seizures (typically with serum levels >10 μg/mL).

**Conclusion**

There is a growing interest in nontraditional and nonpharmacologic treatments for status epilepticus. An increasing number of case reports and series are being published; however, the majority of these studies highlight patients who have improved from the therapies leading to potential publication bias in favor of good outcomes. There is a critical need for more prospective trials in this population, recognizing the challenges faced when there are a large number of treatment options with no "standard of care" for comparison, relatively small number of patients with RSE and SRSE, and that these patients are a heterogeneous group, often with no definite underlying etiology identified.

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# Treatment of Status Epilepticus in Pediatrics

# 30

Arnold J. Sansevere and Tobias Loddenkemper

## Contents



A.J. Sansevere, MD (✉) • T. Loddenkemper, MD
Department of Neurology/Division of Epilepsy, Harvard Medical School, Boston Children' Hospital, 300 Longwood Ave, Boston, MA 02115, USA
e-mail: arnold.sansevere@childrens.harvard.edu; tobias.loddenkemper@childrens.harvard.edu



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## Introduction

Nonconvulsive seizures (NCS) and nonconvulsive status epilepticus (NCSE) are commonly seen in neonates and children undergoing continuous electroencephalography (cEEG) in the pediatric, neonatal, cardiac, and surgical intensive care units. Nonconvulsive seizures and nonconvulsive status epilepticus have been estimated to occur in 7–46 % of children who undergo a clinically indicated EEG in the intensive care unit (ICU) [1–4]. The neonatal population is also at high risk as 14–43 % of neonates monitored meet the criteria for status epilepticus (SE), while as many as 80–90 % of neonatal seizures are electrographic only [5, 17].

An increasing number of studies suggest that the degree of seizure burden impacts neurologic outcome and, in instances of status epilepticus, mortality [3, 4, 6]. Controversy continues to exist in both neonates and children regarding the true effect of seizures on outcome independent of the impact of the underlying etiology. Many view seizures in the critically ill as simply epiphenomena of underlying injury. Studies have, however, suggested worsening of acute brain injury as well as increasing intracranial pressure in certain subpopulations. This chapter will focus on the approach to treatment of nonconvulsive seizures and nonconvulsive status epilepticus in both the pediatric and neonatal population [21].

## Nonconvulsive Seizures and Nonconvulsive Status Epilepticus in Children

Since the identification of nonconvulsive seizure and nonconvulsive status epilepticus, there have been several approaches toward definition, classification, electrographic features, and treatment. While many studies were focused initially on adults, the increased use of continuous EEG in the pediatric ICU has allowed for an opportunity to look at this entity in pediatrics. Nonconvulsive status epilepticus is defined as nearly continuous electrographic seizure lasting greater than 30 min or recurrent, briefer seizures comprising at least 50 % of a 1-h epoch, without convulsive activity, manifesting primarily as altered mental status or coma [1]. Subtle clinical signs may be present such as eyelid myoclonia, facial twitching, and autonomic features. The consensus definition proposed in 2004 by a group of physicians with an interest in nonconvulsive status epilepticus sponsored by the Epilepsy Research Foundation suggests that NCSE be a term used to denote a range of conditions in which electrographic seizure activity is prolonged and results in nonconvulsive clinical symptoms [7].

In the pediatric population, nonconvulsive status epilepticus can be classified into two categories based on the clinical state of the patient. The first category focuses on patients who are admitted to the ICU and are critically ill, while the second focuses on patients who present in the ambulatory setting with altered mental status [8–10]. The approach to treatment of NCS and NCSE is determined by the clinical status of the patient as well as the underlying etiology. The presence or absence of an underlying diagnosis of epilepsy or epileptic encephalopathy, the baseline developmental state, and typical ictal and interictal pattern should also be taken into account when

deciding on how aggressively to treat, with options ranging from mere observation to continuous medication application and pharmacological coma induction.

The diagnosis of NCSE in children can be challenging, both in the ambulatory setting and ICU. Clinical signs can be subtle and may include eyelid fluttering, facial twitching, and eye opening. There are also many clinical features surrounding the presentation that make the diagnosis difficult. Patients are often intubated, sedated, or paralyzed. The diagnosis requires a high clinical index of suspicion and continuous EEG monitoring. It is of utmost importance that clinicians are familiar with features placing children at high risk for NCS/NCSE. Continuous EEG monitoring is often the only means of making a diagnosis in critically ill children. Familiarity with EEG patterns consistent with NCS/NCSE is important. The diagnosis on the basis of EEG can be challenging as there are many patterns seen in critically ill children that are controversial and do not have the typical features associated with clinical seizures. Uncertainty also remains regarding the impact and significance of periodic patterns and the role of these patterns on the ictal-interictal continuum.

## Nonconvulsive Status Epilepticus and Nonconvulsive Seizures in Critically Ill Patients

The first step to treatment of critically ill children with NCS/NCSE is to have a high clinical suspicion specifically in subpopulations at highest risk of NCS and NCSE (Table 1). A high proportion of children with acute encephalopathy in the pediatric intensive care unit are at risk of NCS and NCSE and may benefit from continuous EEG monitoring [2]. There are several characteristics that may lead to concern for NCS and NCSE. These include a prolonged state of postictal unawareness lasting more than 15–30 min after a seizure; reduced alertness after any surgery in which cerebral function is at risk (e.g., cardiac surgery, including extracorporeal membrane oxygenation, and brain surgery); unexplained onset of impaired consciousness; impaired consciousness with subtle motor movements or nystagmoid eye movements; episodic blank staring; aphasia, automatisms, or perseveration; and fluctuating aphasia without a related structural brain lesion [8]. These criteria are thought to be effective for the recognition of NCS/NCSE in adults with acute brain injury. Criteria for the diagnosis of NCSE include clear and persistent behavioral or mental status change, confirmation by clinical or neurophysiologic examination, EEG findings showing continuous or virtually continuous paroxysmal activity, and

**Table 1** Critically ill children at high risk of NCS/NCSE

| |
|---|
| Patients presenting with CSE |
| Acute encephalopathy (especially if s/p neurosurgery, or currently septic) |
| Acute brain injury |
| History of epilepsy |
| Younger children (<3 years) |
| Other high-risk groups (CHD s/p surgery, ECMO, cardiac arrest) |

*CHD* congenital heart disease, *ECMO* extracorporeal membrane oxygenation, *s/p* status post

**Table 2** Clinical signs suggesting NCS/NCSE [8]

| |
|---|
| Prolonged postictal state |
| Degree of encephalopathy greater than expected given underlying etiology |
| Subtle motor findings (blinking, staring, nystagmus) |

absence of major seizures [7]. The epilepsy foundation workshop subsequently proposed six categories in which to assess mental status to identify subtleties. These include motor coordination, eye contact and social smile, arousal, cognition, memory, and visual function [7]. These clinical signs may be quite difficult to assess in critically ill children. EEG patterns for nonconvulsive status epilepticus have recently been further defined and will be discussed in greater detail in later sections [12] (Table 2).

Convulsive seizures and convulsive status epilepticus (CSE) are common neurologic emergencies in pediatrics. The incidence of convulsive status epilepticus is 18–23/100,000 children per year [13]. Retrospective studies suggest that 20–26 % of NCSE is preceded by CSE and 60 % is preceded by convulsive seizures alone [9, 10, 14]. Patients frequently require intubation due to complications of medications, aspiration, or dysregulation of breathing. It is often difficult to determine whether status epilepticus has resolved due to factors such as the postictal state, effects of medication, or need for rapid sequence intubation. Therefore, these patients remain at extremely high risk for continued nonconvulsive seizures often detected solely by EEG as well as continued convulsive seizures masked by paralytics.

Acute structural brain injury is the most common etiology for patients with NCS and NCSE who present with coma and acute encephalopathy. Studies suggest this etiology in up to 48 %, with hypoxia frequently being the most common etiology [1, 14]. Traumatic brain injury, intracranial hemorrhage, CNS infection, and stroke are the other common etiologies placing children at high risk for NCS and NCSE. Patients with a documented acute structural lesion, as well as those at risk of acute brain injury, should be evaluated thoroughly with cEEG given the risk of NCS/NCSE. Pediatric patients with traumatic brain injury have been documented to have subclinical seizures in 16.1 % of patients [15]. A higher rate of electrographic seizures, up to 57 %, has been reported, with 67 % of these being electrographic only without any clinical symptoms [16].

Another high-risk group includes children that are status post cardiac surgery as well as those requiring extracorporeal membrane oxygenation. Patients with congenital heart disease requiring bypass during surgery have been found to be at risk for NCS in addition to pediatric patients that are status post cardiac arrest requiring hypothermia [17]. The process of transitioning to extracorporeal membrane oxygenation (ECMO) also puts patients at high risk, as ECMO is often applied in the setting of cardiac or respiratory arrest leading to hypoxic-ischemic brain injury [17]. Patients with recent neurosurgical procedures also warrant a high index of suspicion for EEG only seizures, especially in the setting of changes of consciousness and when patients present with more prominent encephalopathy than expected.

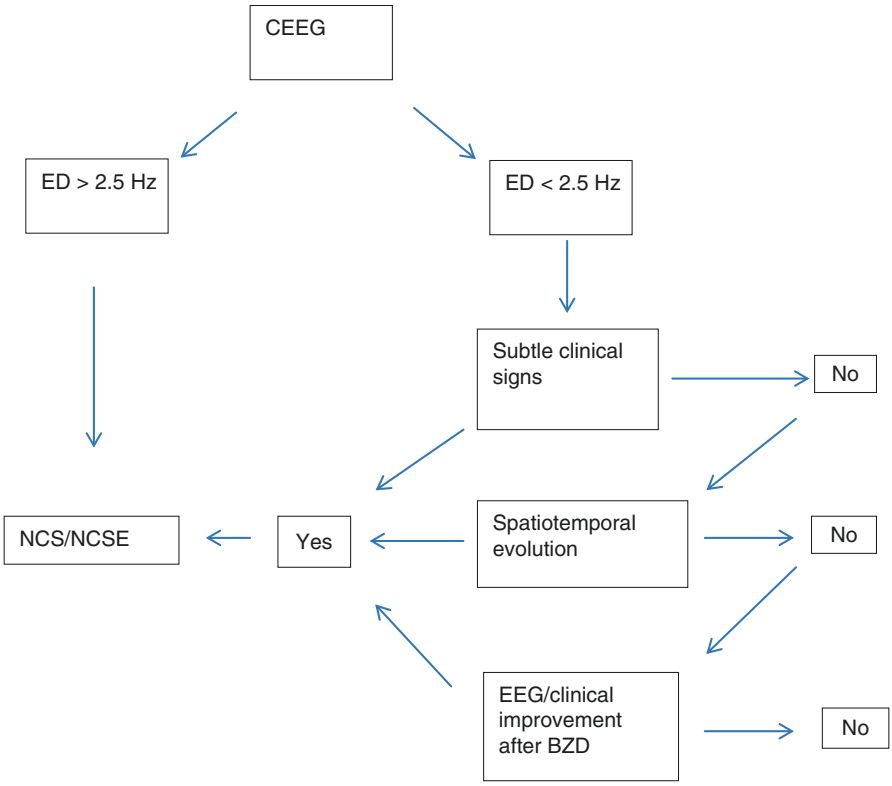


**Fig. 1** EEG criteria for NCS in critically ill children without epilepsy

A multitude of systemic illnesses ranging from underlying infection to metabolic abnormalities have been documented primarily in adults as a risk factor for NCS and NCSE [18]. While children with systemic illness may present with a nonspecific encephalopathy, they may also have coexisting nonconvulsive seizures and periodic EEG patterns. Periodic patterns such as triphasic waves (generalized periodic discharges with triphasic morphology in the new terminology) may be present. Other high-risk populations include those with underlying metabolic encephalopathies [18].

Children with the diagnosis of epilepsy and epileptic encephalopathies often require intensive care admissions due to exacerbations of seizures that may meet criteria for convulsive or nonconvulsive status epilepticus. The approach to treatment in this population may differ greatly based on factors such as typical seizure frequency, typical EEG background features, and baseline developmental status. The treating clinician needs to be aware of the patient's typical interictal background so as not to be misinterpreting the EEG and subsequently offering overly aggressive treatment.

## EEG Features of Nonconvulsive Seizures and Nonconvulsive Status Epilepticus

Nonconvulsive seizures can be categorized electrographically as generalized or focal. Focal seizures are subdivided to include simple partial status epilepticus and complex partial status epilepticus. Seizures continue to be defined as a paroxysmal event with acute onset and offset that evolves in frequency and location. One of the challenges of making the diagnosis of NCSE is that the principles that define a seizure do not necessarily apply. The electrographic definition of nonconvulsive status epilepticus can be made in absence of electrographic evolution and often relies on the response to treatment. Given these features, the diagnosis of NCSE may not be straight forward. Current criteria state that the electrographic diagnosis of NCS or NCSE can be made if there are epileptiform discharges >3 Hz lasting for 10 s or longer, if there are epileptiform discharges <3 Hz with evolution in frequency or location, or if there are epileptiform discharges <3 Hz with an accompanying clinical or electrographic response to treatment (Fig. 1) [12].

The significance of periodic patterns that do not meet the criteria for nonconvulsive seizures remains controversial in both the adult and pediatric literature. Some patterns such as lateralized periodic discharges (LPDs) and specifically lateralized periodic discharges plus (LPDs with superimposed fast or rhythmic activity), as described by the new classification, may put patients at higher risk for seizures. The role of periodic patterns and their place on the ictal-interictal continuum remains a subject for debate. Much of the knowledge we have of periodic patterns is from the adult literature with regard to risk of seizure and prognosis [19], and there may be differences between periodic patterns identified in adults versus children [20]. For instance, while LPDs are frequently associated with acute lesions and altered mental status in adults, they can also be seen in children with chronic lesions in the absence of altered mental status [20]. Recent data on generalized periodic discharges (GPDs) in children suggest that they may carry a lower mortality rate compared to adults. EEG findings need to be considered in appropriate clinical context, history, and evolution, and it should be recognized that etiologies differ in pediatrics and adults [8]. For example, a child with known Lennox-Gastaut syndrome, who had slow spike-and-wave at baseline, may be approached differently than a child without EEG abnormalities at baseline. Due to uncertainty regarding their significance, there management also remains controversial. While some physicians would recommend treatment, few would treat aggressively. Moreover, treatment may be varied based on concomitant clinical symptoms and presentation.

## Approach to Treatment (Fig. 2)

The approach to seizures in critically ill children should take several factors into consideration. The most important factor is the prognosis based on the underlying etiology. Other factors to consider include the degree of encephalopathy, probability of seizures worsening preexisting acute injury, as well as systemic side effects of

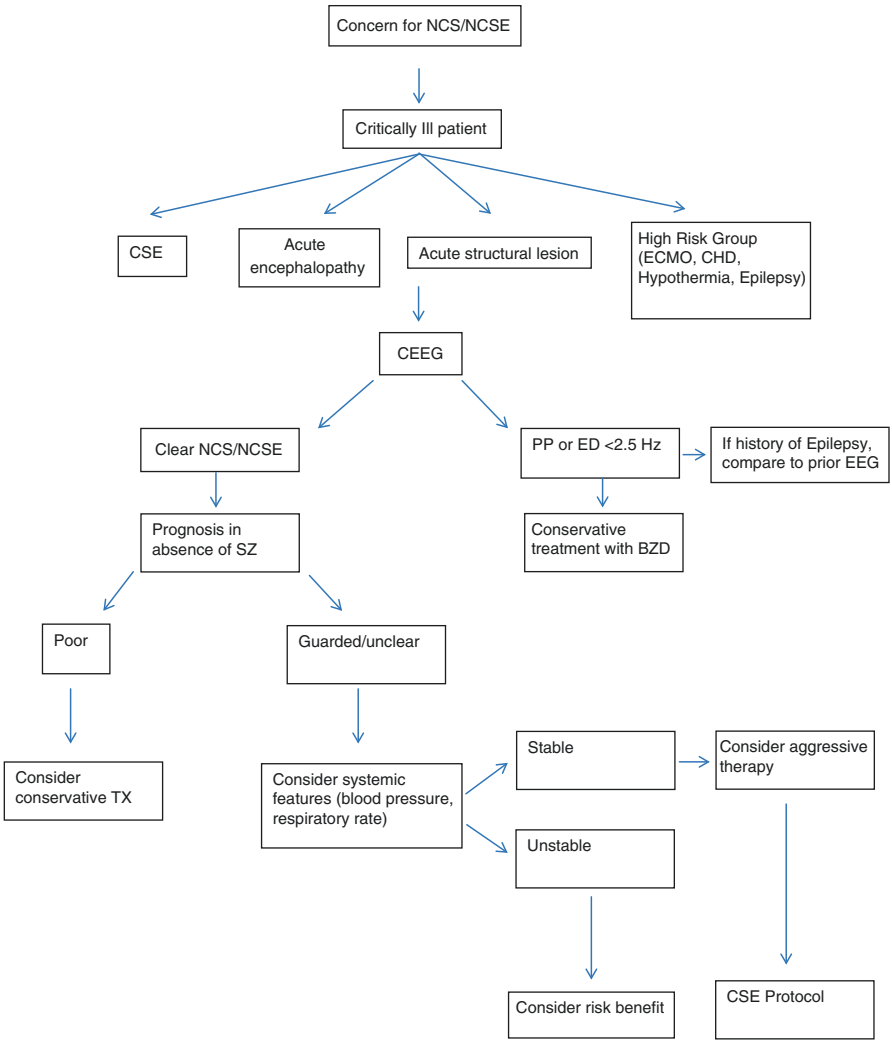


**Fig. 2** Approach to NCSE

intravenous antiepileptic medications and the impact that they may have in already unstable patients [8, 10, 18]. Overall, NCS/NCSE in the critically ill, comatose patient should be treated aggressively given the impact of seizure burden on neurologic outcome, and in some instances mortality, independent of the underlying etiology [1, 4]. Among pediatric patients with encephalopathy, the degree of encephalopathy should also be taken into consideration when deciding on approach to treatment. The patient that is mildly obtunded or lethargic may not benefit from aggressive therapy. In encephalopathic patients with acute structural injury, seizures can impact the degree of injury and level of increased intracranial pressure. Adult studies suggest that patients presenting with traumatic brain injury are at risk of

worsening increased intracranial pressure and worsening ratios of lactate to pyruvate [21].

Patients presenting with NCSE after CSE may or may not be treated aggressively, as NCSE patterns may be seen in transition for CSE to more normal brain patterns. However, NCSE after CSE has been shown to increase morbidity and mortality independent of etiology [22]. The uncertainty of the impact of NCS and NCSE should also be considered in the population that is paralyzed, sedated, and unable to show the outward manifestation of clinical seizures, including many patients in the intensive care unit and including patients presenting with convulsive status epilepticus that require intubation, patients after cardiac and neurosurgery and anesthesia, as well as those requiring extracorporeal membrane oxygenation.

Antiseizure medications also carry a degree of morbidity. Many medications have the potential to worsen preexisting systemic instability such as worsening cardiac function in a child status post cardiac arrest, worsening hypotension in a patient with sepsis, and decreasing respiratory drive in a patient with respiratory arrest. The underlying etiology and overall prognosis, in conjunction with background EEG findings, also need to be considered. In situations where the outcome is grim, such as severe hypoxic injury after cardiac arrest or near drowning, aggressive treatment may not be in the best interest of the patient, and risks of treatment versus benefits of seizure and NCS control need to be weighed against each other. To date, there is no clear evidence that treatment of NCS and NCSE improves outcome. However, there is a growing body of literature suggesting that even interictal epileptiform discharges may have an effect on cognition.

As discussed previously, the significance of many periodic patterns remains uncertain. Periodic patterns should be addressed within the context of the clinical presentation. Based on criteria for electrographic nonconvulsive status epilepticus, certain periodic patterns that respond to treatment are consistent with NCS/NCSE. Therefore, the acute onset and recognition of a periodic pattern in an encephalopathic patient may warrant a treatment trial, e.g., with benzodiazepines, to assess clinical change. In some instances, physicians suggest prophylaxis given the high probability of seizures in populations with certain periodic patterns, specifically LPDs and bilateral independent periodic discharges (BiPDs). Treatment with pharmacological coma and continuous infusions in patterns without clinical signs is usually not warranted.

## Nonconvulsive Status Epilepticus in the Ambulatory Patient

The diagnosis of NCSE is not a diagnosis unique to the ICU. Patients frequently present for an outpatient appointment or to the emergency room. Patients presenting with lethargy or altered mental status, with intermittent or continuous impairment of cognition and cognitive function, may be at risk. These signs are often clear in developmentally normal children, but can be challenging in patients with underlying developmental delay due to a preexisting epileptic encephalopathy. The approach set forth by the Epilepsy Research Workshop focusing on the mental status examination may be helpful when assessing patients in the ambulatory clinic for NCSE where the

diagnosis is not clear [7]. In these instances, the systematic assessment of several features may be helpful. Close attention needs to be paid to subtle motor phenomena such as brief behavioral arrest, subtle eye findings (e.g., brief nystagmoid movements or eye lid fluttering), and motor incoordination in the form of ataxia or negative myoclonus. Other subtle signs such as drooling and a delayed motor response may be apparent [7]. Other domains to assess include overall affect as it may relate to degree of eye contact, visual fixation, and social interactions, keeping in mind the need to have a strong understanding of baseline function. Cognition and memory decline may also be present. Children may present with regression or loss of speech. There may also be a change in school performance, overall behavior, and the ability to learn. Populations that are particularly at risk include patients with a preexisting diagnosis of epilepsy or epileptic encephalopathy and patients with genetic conditions that have the potential for comorbid epilepsy and in some instances NCS/NCSE [8]. Patients with juvenile myoclonic epilepsy are at risk for absence status epilepticus as well as subtle myoclonic status epilepticus; however, this is rare [8]. Studies have documented NCSE in up to 40 % of children diagnosed with SCN1a mutations that meet criteria for Dravet Syndrome [8]. In some cases, NCSE may be the initial presentation of epilepsy.

Despite deficits in some of these domains, the diagnosis of NCS/NCSE in the ambulatory setting is nearly impos sible without the aid of EEG, especially in children with baseline cognitive dysfunction. While in some instances a routine study may be enough to make the diagnosis, prolonged monitoring is often necessary. In instances in which there is a concern for electrical status epilepticus of sleep (ESES), sleep should be assessed.

NCSE in the ambulatory setting can be classified as either generalized or focal. The most common generalized form is typical and atypical absence status epilepticus. Absence status epileptics (ASE) may be seen in up to 3 % of children with childhood absence epilepsy [8]. The symptoms may be subtle and some children continue to function cognitively with only minor deficits. The typical presentation is drowsiness and stupor; however, motor manifestations such as rhythmic blinking, clonic twitching, myoclonic jerks, or automatisms may be present. The ictal EEG pattern consists of 3–4 Hz generalized spike-and-wave discharges. The prognosis of children with typical absence status in the presence of an underlying idiopathic generalized epilepsy is good. Aggressive treatment is usually not necessary. ASE is often responsive to benzodiazepines as well as other medications such as valproic acid and ethosuximide. Atypical forms of absence status epilepticus are also seen in children with symptomatic etiologies or idiopathic/genetic epilepsy syndromes, such as Lennox-Gastaut syndrome. In these cases, the interictal EEG pattern shows 2–2.5 Hz slow spike-and-wave.

Electrical status epilepticus of sleep (ESES) is a distinct EEG pattern in slow wave sleep that accompanies two well-defined childhood epileptic encephalopathies. The EEG pattern classically shows 1–3 Hz generalized sharp waves that produce a spike wave index of greater than 85 % during slow wave sleep [8]. The clinical presentation that accompanies the EEG pattern helps further define the clinical syndrome. In continuous spike wave in sleep (CSWS), children typically first present with seizures. The initial seizure can vary in semiology and may

range from atonic, myoclonic, absence, to focal seizures. This is followed by either an acute or subacute behavioral concerns and/or regression. This is in contrast to patients who present with Landau-Kleffner syndrome (LKS) in which language regression is the main feature. Seizures are initially apparent in greater than 50 % of patients, and the semiology can vary from atypical absence, atonic, tonic, and to complex partial seizures [8]. Even when treatment is successful, greater than 50 % of children are thought to have continued language and cognitive deficits. Treatment of ESES consists of benzodiazepines as first line with a trial of high-dose diazepam being warranted. Other medications thought to be effective include corticosteroids, valproic acid, and clobazam, and intravenous immunoglobulin (IVIg).

Complex-partial status epilepticus is extremely difficult to differentiate from absence status epilepticus without the aid of continuous EEG. While a prior diagnosis of epilepsy is typically present, this is not always the case. In cases where epilepsy is not known, systemic, metabolic, structural, and autoimmune etiologies should be ruled out. The clinical presentation may be that of confusion or drowsiness. However, other symptoms can include bizarre behaviors, as well as amnesia and aphasia. Semiology can vary depending on the location of the seizures. Patients may be able to follow commands during the interictal and ictal phases, further complicating the diagnosis. Ictal patterns often resemble focal epileptiform discharges or rhythmic focal slowing, with or without evolution. The prognosis is generally good; however, the underlying etiology needs to be taken into consideration. The diagnosis should be made quickly, and treatment with benzodiazepines is first line, followed by epilepsy medications that treat focal seizures. Depending on the acuity of presentation and symptoms, intravenous or, if parenteral formulations are not available, oral/nasogastric tube application of AEDs may be chosen. If the patient remains clinically stable, aggressive treatment is not warranted given the overall good prognosis in most cases.

## Nonconvulsive Seizures and Nonconvulsive Status Epilepticus in Neonates

Neonatal seizures are a common, affecting approximately 1:5000 newborns. Continuous EEG monitoring is of extreme importance in this population given that it has been estimated that approximately 80–90 % of neonatal seizures have subtle or no clinical correlate. This is thought to be due to electroclinical dissociation which is well-documented phenomena thought to be specific to neonates due to differences in cortical versus subcortical GABAergic signaling. The incidence of electrographic status epilepticus has been reported as 14–43 % of neonates with electrographic seizures [5, 17].

As in the pediatric ICU, the question of the impact of seizures on outcome remains controversial. Many view neonatal seizures as simply epiphenomena of underling brain injury. Several animal studies suggest that seizures may not just be a marker of underlying injury but also may act to worsen injury and impair

neurogenesis. Clinical seizures in neonates show an association between severity of seizures and elevation of lactate using spectroscopy [23]. A recent study suggested that, even after correcting for MRI injury, clinical neonatal seizures had an impact on neurodevelopmental outcome at 4 years of age [24]. While quantification of seizure burden and the definition of neonatal status epilepticus remain debatable, available literature suggests a correlation with neonatal status epilepticus as well as degree of seizure burden with worse neurodevelopmental outcome as well as the subsequent development of epilepsy [4, 6].

Neonatal status epilepticus has long been defined based on definitions accepted for adults and children: a seizure lasting greater than 30 min or seizures totaling greater than 50 % of a 1-h epoch. Clinicians are revisiting seizure burden as a biomarker of outcome in neonates, not only in children. Seizure quantification provides important prognostic information in young children: with seizure burden encompassing greater than 20 % of a 1-h epoch impacting outcome [4]. Research groups are currently working to find ways to further quantify seizure burden in neonates [5].

## High-Risk Subpopulations

Neonates with concern for hypoxic-ischemic injury remain one of the highest risk populations for electrographic seizures. It is estimated that 33–65 % of the population receiving therapeutic hypothermia for hypoxic-ischemic injury have seizures [5, 17]. This etiology should be considered in neonates with clinical concern for seizures or a presentation consistent with encephalopathy within the first 24 h, and often within the first 12 h, of life. Patients identified within 6 h of the perinatal period should be considered for hypothermia as this has been shown to decrease seizures in this population; however, clinicians should be wary as seizures have been documented during the rewarming period. This has been documented in hypoxic injury and hypothermia in both cardiac patients after cardiac arrest and hypoxic injury in the setting of a perinatal insult [17].

Seizures are the typical presentation of stroke in the newborn. The semiology is typically focal clonic; however, subtle oral movements and, in some cases, apnea have been described. This should be considered in any neonate presenting with seizures, and seizures most often present within 24 h after birth. These patients may not show signs of encephalopathy or focal feature on examination. Electrographic seizures have been estimated in up to 90% of patients with stroke [17].

Patients with congenital heart disease are also at high risk for nonconvulsive seizures. A recent prospective study looking at all patients with congenital heart disease status post cardiac surgery showed the frequency of electrographic seizures to be 11.5 % with mean onset of seizure being 21 h after surgery [23]. Other studies suggest that 5–19.8 % of patient's have electrographic seizures in the post operative period. A high index of suspicion is necessary in this patient population given the fact that they are often sedated and paralyzed.

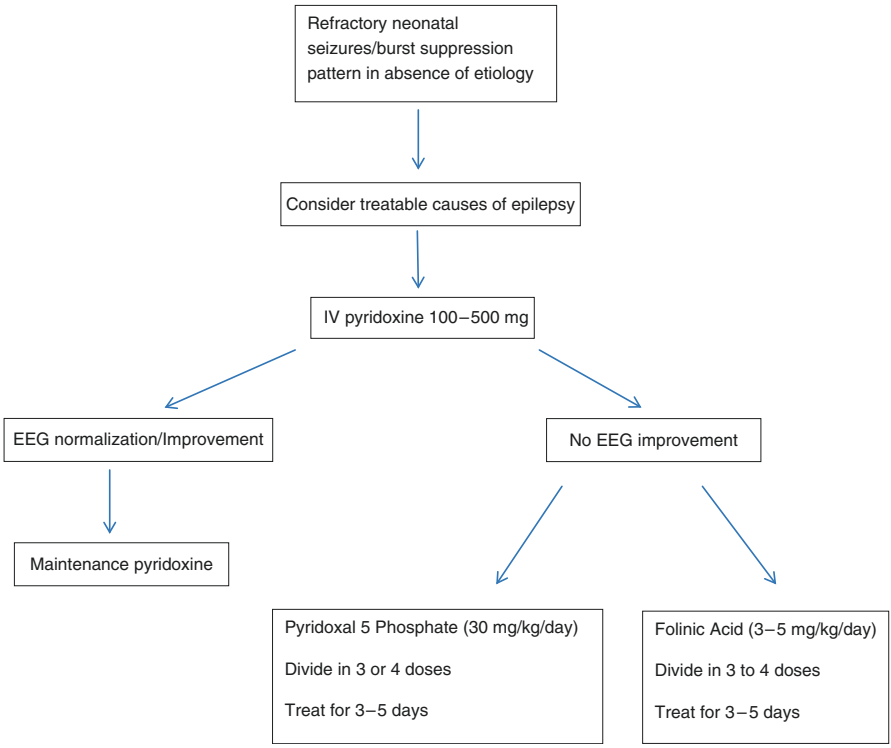


**Fig. 3** Treatment approach to refractory idiopathic neonatal seizures/burst-suppression pattern

## Treatment Approach to Nonconvulsive Seizures and Nonconvulsive Status Epilepticus in Neonates

Nonconvulsive seizures and nonconvulsive status epilepticus should be treated aggressively given that available data suggests that neurologic outcome and mortality are impacted. Recent studies also suggest that early detection and treatment of both clinical and nonconvulsive seizures may decrease seizure burden [25]. The treatment approach should also take into account the clinical state of the patient as well as the overall prognosis. This is most important in neonates with severe hypoxic injury and systemic instability. Treatment should also be focused not only on seizures but also the underling etiology, as well as potential neuroprotective strategies, such as therapeutic hypothermia, in certain high-risk subpopulations. In instances where there is not a clear etiology, treatable causes of neonatal seizures should be considered. An abnormal background that at times can be consistent with burst suppression supports this. In these cases, a pyridoxine trial is warranted. If this is ineffective, pyridoxal 5-phosphate as well as folinic acid may also be tried. These treatment trials should be attempted in addition to an ongoing metabolic and genetic workup (Fig. 3).

There are no trials assessing efficacy of specific treatments for seizures in this population, and limited parenteral options are available. First-line treatment for neonatal seizure remains to be phenobarbital and fosphenytoin. This is based on data suggesting 43 % of seizures controlled with phenobarbital alone and 45 % percent with fosphenytoin alone [26]. When phenytoin was added to phenobarbital, seizures were controlled in 57 %; seizures were controlled in 62 % when phenobarbital was added to phenytoin [26]. Both medications are not without side effects, and medication interactions often require frequent levels to guide therapy. There are also concerns for short- and long-term side effects.

Recent attention has been drawn to the use of levetiracetam for neonatal seizures. Small trials suggest that levetiracetam may be efficacious. One retrospective study suggested a greater than 50 % reduction in seizures when levetiracetam was used as first, second or third line after phenobarbital [27]. The dosing and frequency of dosing in neonates differs among institutions: a common approach is an initial bolus of 40 mg/kg, with subsequent doses of 30–60 mg/kg/day divided TID. The benign side effect profile coupled with availability of the parenteral formulation makes levetiracetam a good option for neonates.

Based mainly on small, retrospective studies, both midazolam and lidocaine have gained some popularity in the treatment of neonatal seizures. In a study assessing midazolam as a second-line agent after phenobarbital, there was a 100 % response rate noted [29]. Midazolam is thought to be well tolerated with side effects being sedation and hypotension. Two studies investigating lidocaine as second- and third-line agent suggested response primarily when initially bolused [28]. The side effect profile was that of blood pressure and heart rate change seen in up to 51 % in one study, but these side effects were not considered life threatening [28]. Cardiac arrhythmias have also been observed and at high doses there is concern for worsening of seizures.

The mechanisms that allow the neonatal brain to promote excitability and decrease inhibition may make treatment more difficult but also provides additional potential targets for treatment. One of the important physiologic differences between mature and immature neurons is the reversal of the chloride gradient. While mature neurons have a higher extracellular chloride concentration, the chloride gradient is reversed in immature neurons. This is due to a higher level of NKCC1 chloride transporter in the newborn brain. The reversed gradient theoretically renders GABAergic medications less effective. There are ongoing studies assessing the tolerability and efficacy of bumetanide, which acts to inhibit the NKCC1 channels in hopes of enhancing the effect of phenobarbital.

## Treatment Approach to Brief Rhythmic Discharges

For decades, the definition of neonatal seizures has relied on evolution as well as time. The “10 s rule of thumb” requiring an epileptiform discharge to last at least 10 s to qualify as a seizure if there are no clinical signs is used by many, but this cutoff may be arbitrary. As continuous monitoring has gained popularity, abrupt

evolving patterns have emerged with the typical qualities of a seizure, however shorter than 10 s. These discharges, first described in 1990 by Shewmon, are referred to as brief electroencephalopgraphic rhythmic discharges (BERD) or brief intermittent ictal-interictal rhythmic discharges. While the data assessing the role of B (i) RDs on outcome is small, the current literature suggests that they are not a benign entity and the presence of BRDs was associated with abnormal neurodevelopment at follow-up [30]. Other studies also suggest that BRDs are more commonly seen after anticonvulsant treatment for seizures. The significance of this phenomenon is uncertain at this time; therefore, aggressive treatment is not warranted. Further study of the impact of these discharges on outcome is necessary.

**Conclusions**

Seizures and status epilepticus are common in the pediatric and neonatal ICU, especially in certain high-risk populations. These include patients with hypoxic-ischemic injury, stroke, traumatic brain injury, recent cardiac or brain surgery, and patients with a history of epilepsy or conditions predisposing to seizures. Diagnosis requires a high degree of suspicion. Treatment should take into account the severity of the seizures, etiology, and prognosis. In many situations, the seizures, especially status epilepticus, impact outcome and warrant aggressive treatment. However, in other situations, treatment may add to morbidity without significantly altering outcome. The treatment approach must be individualized to the patient.

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# Investigational Treatments for Status Epileptics

# 31

Asim Haque, Stephen A. VanHaerents, and Frank W. Drislane

**Contents**



## Introduction

The armamentarium for treatment of seizures in the intensive care unit is extensive, but some seizures and status epilepticus (SE) remain refractory to many standard treatments, and often, an individual patient will respond more or less well than other patients do to a given treatment. Also, each treatment, whether pharmacologic or invasive, carries its own particular side effects or complications. New additional treatments are necessary in many cases. This chapter reviews some of those new treatments, particularly those currently under formal

A. Haque, MD, PhD, MPH, MSE • F.W. Drislane, MD (✉)
Comprehensive Epilepsy Center, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA, USA
e-mail: fdrislan@bidmc.harvard.edu

S.A. VanHaerents, MD
Department of Neurology, Northwestern University Feinberg School of Medicine, Chicago, IL, USA



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investigation. Immunosuppression for autoimmune encephalopathy causes of status epilepticus and focal resection for refractory cases of focal status epilepticus are becoming relatively common practices and are covered elsewhere in this book. This chapter focuses on antiseizure medications (ASDs) in clinical trials, the somewhat more remote prospect of gene therapy, transcranial magnetic stimulation.

## Neurosteroids

Steroid hormones have been recognized for decades as having potential anticonvulsant effects at the $GABA_A$ receptor [1, 2]. Studies in rodents [3] have shown that within 60 min of the onset of status epilepticus (SE), there is significant internalization of $GABA_A$ receptors, leading to a deficiency in GABA-ergic synaptic inhibition, in turn contributing to refractoriness to benzodiazepine (BDZ) treatment during prolonged seizures [4–6]. Correspondingly, NMDA-type glutamate receptors appear to increase in numbers at the cell surface [7] and subsequently at synapses after 60 min of lithium-pilocarpine-induced SE in rodents [8].

Neuroactive steroids appear to modulate neuronal excitability by enhancing GABA-mediated tonic inhibition [9], thus ameliorating SE that has proven refractory to BDZ treatment. Instead of acting on nuclear hormonal targets and exerting conventional hormonal activity as traditional steroids do, neurosteroids such as allopregnanolone (3a-hydroxy-5a-pregnan-20-one) are thought to interact at low concentrations with neurotransmitter-gated ion channels such as the $GABA_A$ receptor [10, 11], potentiating $GABA_A$ receptor currents [12]. In addition, neurosteroids, along with $GABA_A$ receptor modulators such as BDZs, are effective in attenuating withdrawal seizures from agents such as cocaine and ethanol [13–15], while not appearing to lead to anticonvulsant tolerance [16, 17].

Allopregnanolone is a derivative of progesterone, synthesized in endocrine tissue, including the adrenal gland and ovary, and in the brain [18]. It has been shown to impart seizure protection in pentylenetetrazole (PTZ) [1, 19], bicuculline [19], pilocarpine [2], kainate [2, 20, 21], kindling [22–24], and maximal electroshock seizure (MES) [25] animal models (see [26] for review), including for SE [21]. A synthetic analog of allopregnanolone, ganaxolone, has been investigated successfully in open-label pediatric studies including for refractory partial or generalized epilepsies [27] and for infantile spasms [28], and there has been a double-blind randomized controlled trial for infantile spasms and another for partial-onset seizures in adults [29, 30].

A few recent case reports have shown good results with allopregnanolone itself. In the only available adult study, one man presented with myoclonic SE in the setting of new-onset refractory status epilepticus (NORSE) syndrome. His seizures had been refractory to over 20 different anticonvulsants, required over 90 days of pentobarbital-induced burst suppression, and failed multiple attempts to taper intravenous barbiturates [31]. Ultimately, the addition of allopregnanolone over a 5-day period, to serum levels of 150 mg/L, resulted in successful discontinuation of

pentobarbital and eventual seizure freedom. Allopregnanolone was also used successfully in two children [32]. The first was an 11-year-old girl with autoimmune antibodies (antimicrosomal, anti-Gad65, and antithyroglobulin) who had both convulsive and nonconvulsive seizures throughout her hospital course. She was treated with many anticonvulsants, including pentobarbital and propofol, to achieve a burst-suppression record on the EEG, along with magnesium, ketamine, initiation of a ketogenic diet, mild hypothermia, courses of intravenous steroids (methylprednisolone), plasmapheresis, intravenous immunoglobulin, and immunomodulatory therapy with rituximab and cyclophosphamide. After nearly 2 months of treatment-refractory seizures, allopregnanolone was utilized over a 5-day course, and the patient was ultimately discharged to home [32]. The second patient was a 2-year-old toddler with a history of epilepsy and cognitive delay who presented in SE associated with a febrile illness of unknown etiology. Multiple anticonvulsants, leading to a burst-suppression pattern on EEG, and intravenous steroids were used to control convulsive and nonconvulsive seizures; the patient developed complications, including hypotension, ileus, and urinary retention. Allopregnanolone was approved for use over a 5-day course, and the patient was ultimately able to talk, walk, and regain milestones [32].

A randomized double-blind placebo-controlled clinical trial (NCT02052739) utilizing allopregnanolone (SGE-102 or SAGE-547, SAGE Therapeutics, personal communication) for refractory SE is currently underway [33]. The study will enroll adult patients intubated for refractory SE for less than 24 h, who have failed first-line (BDZ) and second-line (fosphenytoin, levetiracetam, valproate, etc.) agents. All patients will receive midazolam and either placebo or SGE-102. Midazolam will be tapered between 24 and 48 h after study initiation, and the remaining agent administered until hour 120. The study's primary end point will be the proportion of individuals with no seizures lasting more than 1 min (either clinical or electrographic) starting from 60 min after initiation of SGE-102 or placebo until treatment cessation (days 1–5).

## Clinical Trials: ESETT, TRENdS, and Brivaracetam

There are relatively few published randomized controlled trials of anticonvulsant use for SE [34, 35] and none for nonconvulsive SE [36] – which Shorvon has aptly referred to as a "wholly unsatisfactory situation" [37]. One recent phase II, prospective multicenter, single-blinded, randomized clinical trial of NS1209 [38], a new drug candidate which acts as an AMPA antagonist at ionotropic glutamate receptors [39] for the treatment of refractory convulsive and nonconvulsive SE was halted early due to insufficient patient recruitment in 2004–2006. Also, the protocol for the convulsive SE study arm was not approved due to the inability of patients to consent to treatment, and the nonconvulsive SE arm had only 14 patients who received NS1209, leaving it underpowered to allow any conclusions [38]. Another prospective multicenter, single-blinded, randomized trial comparing propofol to barbiturates for refractory SE was stopped early after 3 years, having enrolled only 24 of

the 150 patients required to satisfy primary and secondary end points [40]. The authors cited a "low frequency of eligible patients," with a significant number of patients being "missed" even after considerable training of center personnel regarding enrollment eligibility.

The Established Status Epilepticus Treatment Trial (ESETT, NCT01960075) is a phase III, multicenter, allocation-concealed clinical trial involving three arms which will use response-adaptive randomization to assign patients to fosphenytoin, levetiracetam, or valproate in the emergency department [41]. With an enrollment goal of 795 patients over 4 years, two national networks involving adult and pediatric patients will be utilized. Criteria for inclusion include age greater than 2 years and witnessed clinical seizures lasting at least 5 min after the patient has received an appropriate BDZ. Unlike the NS1209 trial, the ESETT trial has an Exception from Informed Consent agreement.

The Treatment of Recurrent Electrographic Nonconvulsive Seizures (TRENdS) study (NCT01458522) was a phase II, prospective multicenter, open-label randomized trial comparing the efficacy of lacosamide with that of fosphenytoin [36]. Eligibility criteria included at least one electrographic seizure (with or without a clinical correlate), lasting at least 10 s but less than 30 min in duration, i.e., not qualifying as generalized convulsive or nonconvulsive SE. The primary end point compared the two drugs with regard to seizure freedom for 24 h after an initial bolus followed by maintenance dosing, with a rebolus and higher maintenance dosage if a breakthrough seizure occurred. Secondary end points included the proportion of patients requiring a second ASD to control nonconvulsive seizures, comparison of safety and tolerability between the two agents, and a comparison of functional outcome at various time points. With regard to study design, the treating physician would not be blinded to treatment, but the in-house epileptologist reviewing the continuous video EEG (cEEG) and a central reviewer interpreting the cEEG for study purposes were both to be blinded to treatment assignment. Each arm was designed to have 100 patients, with the study projected to last 12–18 months [36]. Enrollment in this study was stopped due to insufficient recruitment, but data analysis is ongoing.

Finally, a phase II, open-label randomized trial sponsored by UCB Pharma (NCT02088957) was started in March 2014, assigning individuals to receive either intravenous phenytoin or intravenous brivaracetam – a new anticonvulsant which, like levetiracetam, binds synaptic vesicle protein 2A (SV2A), but with an up to 20-fold higher affinity than levetiracetam's [42]. Unlike levetiracetam [43], brivaracetam also inhibits voltage-gated sodium channels [44], extending its anticonvulsant properties. In rodents, brivaracetam (also unlike levetiracetam) provided protection in MES and PTZ seizure models [45] and possible disease-modifying effects against refractory SE [30, 46]. In the clinical trial, the primary outcome was the proportion of subjects with seizure freedom for 12 h (based on cEEG monitoring) starting 1 h after the last intravenous administration of study drug. This study, however, was also terminated due to insufficient enrollment (UCB Pharma, personal communication).

## Gene Therapy

Research in the delivery and expression of gene therapy has made significant progress in the last two decades, with over 1800 approved clinical trials [47]. Within Neurology, most efforts have been directed at neurodegenerative diseases and neuro-oncology [48], with several phase II clinical trials either completed or underway [49–52]. With regard to epilepsy, and especially SE, however, there are at least two important problems with gene therapy. First, "time is of the essence" and viral vectors can take days to weeks to induce gene expression – not rapid enough for the treatment of SE [53]. Also, while many genetic disorders are caused by a specific gene defect, many cases of refractory epilepsy are cryptogenic, so the leading therapeutic strategy has been to diminish seizures by alteration of global CNS function via excitatory or inhibitory mechanisms [54]. In the case of refractory SE, unless a genetic abnormality is known a priori, there would not be enough time with current technology to do gene testing and develop a focused plan based on those results.

Some targets of gene therapy specifically related to SE include various neurotransmitter receptors, neuropeptides, and neurotrophic factors. Adeno-associated viruses (AAV) targeting the GABA α1 receptor by an AAV-GABR α4 transgene were utilized in one investigation in a pilocarpine-induced model of SE [55]. With the α4 promoter driving the AAV-α1 expression, pilocarpine-treated rats had a nearly threefold increase in the average latency to a subsequent seizure after SE and a 60 % decrease in the number of subjects developing subsequent epilepsy after SE [55]. Similarly, neuropeptide Y (NPY) and NPY receptor expression are significantly altered in both human and rodent epileptic tissue when compared to that in normal controls. NPY is thought to have anticonvulsant properties, including considerable inhibition of seizure activity in kainic acid seizure models [56]. Overexpression of Y2 receptors in rodents undergoing kainate-induced seizures via an AAV vector showed an increased time to, and reduced duration of, the first motor seizure as well as an increased latency to the development of SE [57].

In addition, neurotrophic factors and their receptors are thought to play significant roles in synaptic plasticity and neural reorganization after seizures and cell death [58] and facilitate repair mechanisms after neuronal and glial injury [59]. Glial-derived neurotrophic factor (GDNF) is thought to promote survival in dopaminergic neurons [60] and in other neuronal populations [61, 62], provide protection from ischemic injury [63], and ameliorate seizures [64]. In AAV-GDNF-treated rodents, the frequency of generalized seizures during the self-sustained phase of SE in kindling models was significantly decreased, and the post-SE animal survival rate was improved [64]. Similarly promising results were seen in studies involving brain-derived neurotrophic factor (BDNF) and fibroblast growth factor 2 (FGF-2) in rodents subjected to pilocarpine-induced SE. One group reported that a herpes simplex viral (HSV) vector expressing both FGF-2 and BDNF injected into rat hippocampus after SE yielded antiepileptogenic effects, with reduced seizure frequency and severity, along with disease-modifying effects including decreased neuronal loss and neuroinflammation, and with increased neurogenesis [65–67].

Another method of exerting neuronal control is via visible light or optogenetics [68, 69]. This method has the advantage that instead of exerting effects throughout the entire neuraxis with potential associated side effects (similar to those with traditional anticonvulsants), optical stimulation can be utilized to convert inactive pharmacotherapeutic agents into active forms exerting their effects within localized brain regions or with specific neuronal populations. One recent study used a novel light-based caged (inactive form) GABA compound which, when activated via a blue light-emitting diode (LED), terminated seizures within seconds in rodent tissue exposed to the proconvulsant 4-aminopyridine, both in vitro and in vivo [70]. Direct infusion of GABA had a much slower onset of activity (on the order of minutes) before seizure termination. Another investigation utilized lentivirus-expressing halorhodopsin, a chloride pump, injected into motor cortices of focal neocortical epilepsy rat models induced by tetanus toxin injections [71]. After laser-induced photoactivation, halorhodopsin ultimately reduced epileptic activity and stopped acute seizures within this targeted area, without any behavioral abnormalities observed in the rats. Both of these studies involved models of focal seizures, with potential implications for the future treatment of complex partial SE.

Currently, there are major limitations to these techniques. Because once a gene therapy vector is introduced, rendering the process inherently irreversible, there remain concerns that alteration of single gene might spawn an unwanted cascade of downstream changes. Some have suggested utilizing these gene therapies first in individuals with focal seizures with known resectable lesions, so that if gene therapy failed to control the seizures, surgical ablation could be done, limiting the spread of any adverse effects [72, 73]. Significant work also remains to be done in the choice and packaging of vectors, as some viruses are well tolerated without eliciting a notable immunogenic response but are limited in their gene payload capacity, while others can carry larger gene constructs but are limited in their delivery area, thus requiring direct injection and possibly eliciting a greater immune response [73].

## Repetitive Transcranial Magnetic Stimulation

Neurostimulation for the interruption of status epilepticus is not a new idea. Penfield and Jasper reported applying electrical stimulation to the brain to treat seizures in humans over 60 years ago [74, 75]. They observed that in some cases, electrical stimulation of the cortex resulted in a flattening of the local electrocorticogram rhythms, both for normal rhythms and for epileptiform discharges [74, 75]. While the mechanism for this suppression has not been understood thoroughly, delivering an excitatory stimulation during a seizure can not only disrupt the seizure but prevent its spread. There have been numerous studies evaluating the safety and efficacy of brain stimulation to treat epilepsy [76].

There are two invasive neurostimulation therapies approved by the US FDA for treatment of epilepsy: open-loop (stimulation according to preprogrammed setting) vagus nerve stimulation (VNS) and closed-loop (modulated or adaptive therapy in response to physiologic change) responsive cortical stimulation, “responsive

neurostimulation" (RNS) [75]. Both have shown efficacy in treating epilepsy, but they require surgical intervention. Without that disadvantage, noninvasive neurostimulation is emerging as a practical therapeutic option for both seizure suppression and seizure prevention. Numerous animal studies and limited work in humans have shown epileptogenesis to involve increases in excitatory synaptic activity in a manner similar to long-term potentiation [77]. Similarly, seizure foci have a pathologic reduction of inhibitory gamma-aminobutyric acid (GABA) receptors at synapses and an increase in excitatory (glutamatergic) receptors [78, 79].

Transcranial magnetic stimulation (TMS) is a noninvasive technique that utilizes electromagnetic principles to stimulate neural tissue and thereby modulate brain activity. When applied in a continuous low-frequency (less than 1 Hz) train, repetitive TMS (rTMS) can produce a suppression of cortical excitability that outlasts the period of stimulation [80, 81]. The mechanism underlying this decrease in excitability may be similar to that of long-term depression (LTD) [82]. Thus, directly targeting a seizure focus with stimulation settings that induce long-term depression-like phenomena may either reverse or counteract the hyperexcitable state of the epileptic focus [79].

There have been four published, randomized, sham-controlled studies of rTMS in focal epilepsy (Table 1). While most studies showed only a trend toward seizure reduction, they did demonstrate a marked reduction in the occurrence of epileptiform discharges [79]. In 2002, Theodore and colleagues [83] found only a trend toward seizure reduction after active rTMS, but subsequently, Fregni and colleagues [84] and Sun and colleagues [85] showed a significant seizure reduction after active rTMS. The differences among these studies may be the result of patient selection or stimulation settings. The first (2002) study included patients with deep mesial temporal epileptic foci, which may not be affected by rTMS due to the depth of the focus [79]. A fourth, sham-controlled, study by Cantello and colleagues [86] performed rTMS targeted to the vertex, rather than toward the epileptogenic focus. Although seizure reduction was slightly superior in their actively stimulated group, the difference was not statistically significant. There was, however, a significant decrease in interictal epileptiform discharges in the actively stimulated group in that and one other study [79, 86]. In summary, only two of these four small randomized trials found that rTMS had a definitely beneficial effect in medication-refractory focal epilepsy, with a decrease in seizures of 72–81 % in selected patients [84, 85].

Case reports have suggested that rTMS may be beneficial in epilepsia partialis continua [87] and, more recently, in status epilepticus [88–90]. The magnitude of the antiseizure effect of rTMS is often reported as greater than that in some drug trials; the putative benefit could be related to the previously noted concept that low-frequency rTMS is believed to induce synaptic plasticity via a long-term depression-type mechanism, different from the mechanisms involved in ASD function [90]. Nevertheless, the relative benefit of rTMS versus pharmacotherapy has never been subjected to a careful clinical trial.

One recent case report described a patient with a worsening epilepsy syndrome, with medically refractory focal-onset seizures leading to several weeks of ICU management, requiring high doses of many ASDs [90]. Eventually, low-frequency

**Table 1** Repetitive transcranial magnetic stimulation sham-controlled studies

| Investigator (reference) | Site of stimulation | Stimulation parameters | Study design | Number of patients | Outcome measures | Conclusions |
|---|---|---|---|---|---|---|
| Theodore (2002) [83] | Epileptogenic focus, as determined by EEG | 1 Hz, 900 pulses; at 120 % motor threshold; twice daily for 1 week | Parallel | 24 | Number of seizures | No significant difference between test groups as measured at 2 and 8 weeks poststimulation |
| Fregni (2006, 2007) [79, 84] | Malformations of cortical development | 1 Hz, 1200 pulses; 70 % maximum stimulator output, five sessions | Parallel | 21 | Number of seizures; epileptiform discharges on EEG; cognitive evaluation | Significant decrease of seizures in the active stimulation group; benefit duration greater than 2 months |
| Cantello (2007) [86] | Round coil at the vertex | 0.3 Hz, 1000 pulses, 100 % motor threshold; five sessions | Crossover | 43 | Number of seizures; interictal epileptiform discharges on EEG | No significant difference in seizure reduction between groups. Significant decrease in interictal epileptiform discharges in the active, stimulated rTMS group |
| Sun (2012) [85] | Epileptogenic focus, as determined by EEG | 0.5 Hz, 1500 pulses (in 500 pulse runs); 90 % motor threshold, daily for 2 weeks | Parallel | 58 | Number of seizures; epileptiform discharges on EEG | Low frequency and high intensity had suppressive effects on seizures and epileptiform discharges. Also indicated that rTMS may improve psychologic condition |

Modified from Fregni and colleagues [79]

rTMS applied over the active occipital epileptogenic focus led to a rapid and marked improvement in seizure control, stabilization of the progressively worsening epilepsy syndrome, and substantial improvement in cognitive and overall clinical status. {In this case, the authors also demonstrated a very favorable benefit/cost ratio, with the 6 months of earlier intensive treatment, including several admissions to a major medical center, generating bills of $938,800, while the 11 rTMS sessions were charged at a total of $4400 – under 0.5 % of the inpatient billing.} Subsequently, this patient remained seizure-free for over 9 months, with "maintenance" rTMS sessions roughly every 3 months [91].

These reports and trials suggest that rTMS may be a clinically effective (and possibly, cost-effective) treatment for (highly) selected patients with refractory focal status epilepticus or possibly multifocal epilepsy with a single primary active focus. rTMS represents a potential new therapeutic option for patients with refractory focal epilepsy and without the side effects of ASDs. To confirm and extend these findings, larger, well-controlled, randomized clinical trials will be necessary.

**Conclusions**

In spite of an increase in the number of antiepileptic medications and other treatments for seizures, many patients with seizures, including those who are critically ill with status epilepticus or frequent nonconvulsive seizures, remain difficult to control. Thus, there is still a need for new and novel treatments. Development of new treatments is often hampered by the difficult logistics of such trials, although some medications, such as allopregnanolone and others, are being actively investigated. Other potential treatments, like gene therapy, are in the early stages of development. Others, like rTMS, are potentially easier to implement but are awaiting more convincing demonstrations of their efficacy.

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# Part IV

# Technical and Administrative Considerations

# EEG Equipment

# 32

Saurabh R. Sinha

## Contents



## Introduction

The technical parameters of EEG equipment required for ICU EEG monitoring are similar to those for scalp EEG recording in other situations (such as routine EEG and video EEG monitoring in an epilepsy monitoring unit) (Fig. 1). However, there are several additional considerations [1], including the need for remote access and physical configuration of the equipment. It is assumed that the equipment is digital, not analog – this is based both on current practice and the importance of features like the ability to record and review large volumes of data with video/audio and the ability to review data remotely.

S.R. Sinha, MD, PhD
Department of Neurology, Duke University Medical Center, DUMC Box 102350, Durham, NC 27710, USA
e-mail: Saurabh.sinha@duke.edu



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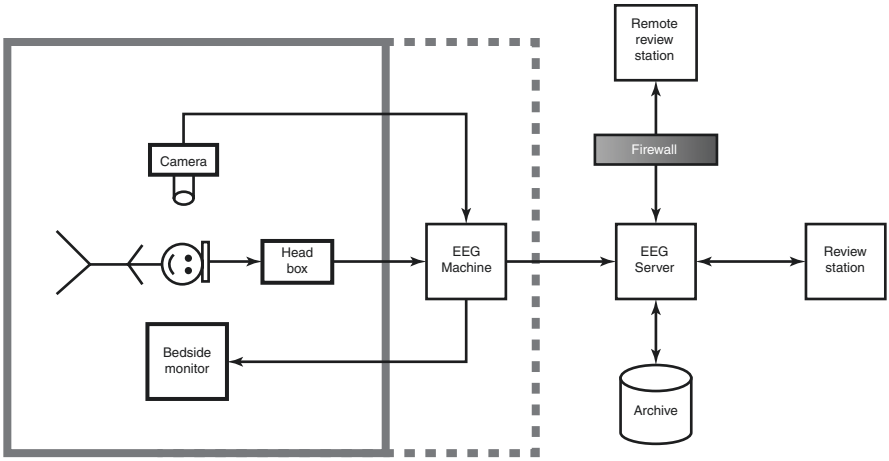


**Fig. 1** Schematic of typical setup for ICU EEG monitoring. The headbox and camera/audio recording equipment are located in the patient room. A bedside monitor is also located in the room. The actual EEG machine may be located in the room (*dashed lines*) or at a networked location. Data is stored on an EEG server which allows for local and remote review of data as well as archiving

## Technical Requirements of Amplifiers

The technical specifications of the individual amplifiers are the same as that for routine EEG/scalp recording: full-scale input range of ±2 mV. Filters available (as a combination of analog/hardware filters and digital/software filters) should include high-pass (low frequency) filters of 0.1–0.3 Hz and low-pass (high-frequency) filters of 35–100 Hz and notch filters (60 Hz). The input impedance of the amplifier should be at least 10 MΩ with a common-mode rejection ratio (CMRR) of at least 100 dB. The analog-to-digital converters should have an input range ±1–2 V with a sampling rate of at least 200 Hz per channel and a resolution of at least 12 bits (>16 bits preferred). Commercially available systems on the market today will typically exceed these requirements.

In order to record a full EEG, a minimum of 16 channels with system reference is needed. Most systems on the market currently will have 32 or more channels; additional channels are often useful for recording from other electrode locations on the scalp as well as cardiac rhythm and electromyographic (EMG) activity from selected muscle groups (to help correlate with artifact or subtle clinical activity). In addition, DC-coupled input channels may be useful for recording other physiological parameters such as oxygen saturation, respirations, intracranial pressure, and blood pressure. Such parameters may be useful in interpreting changes in EEG, especially those associated with changes in cerebral perfusion or medication effects. Most equipment today has eight or more DC-coupled input channels, including some that are specifically configured for oxygen saturation or end-tidal $CO_2$ measurement.

The capability to simultaneously record video and audio that is synchronized with the EEG data is extremely useful in ICU EEG monitoring. It can be useful for correlating subtle clinical activity with EEG patterns. For example, recognition of subtle twitching of the face/arm in combination with a periodic pattern on the EEG may suggest an ictal event, whereas without the clinical activity it may not be possible to comment whether the EEG activity is ictal or not. Another role for video is in the recognition of artifacts. For example, artifacts due to ventilators, suctioning, bed percussion, and others can be much more easily recognized with video. Lastly, changes in the background EEG or events may be related to stimulation (e.g., stimulus-induced rhythmic, periodic or ictal discharges, SIRPIDs [2]); review of associated video is the only way to distinguish these from spontaneous activity.

ICU patients should be considered as high risk for potential injury from electrical equipment due to the common presence of indwelling catheters/lines and connection to multiple pieces of equipment. Thus, it is essential that a common ground be used for all equipment attached to a patient. Also, the equipment must be routinely inspected by clinical engineering to ensure that leakage currents are low, ideally below 10 μA [3].

## Hardware Requirements

### Physical Configuration of Equipment

The actual physical configuration of the EEG equipment is another consideration. In the past, most equipment was portable, mounted on carts, and wheeled into the desired location. Cameras and microphones were typically mounted on poles in the cart. The main advantage to such equipment is flexibility; it can be taken essentially anywhere in the hospital and used for multiple purposes, including for routine EEG and long-term video monitoring. The main disadvantages include suboptimal and variable placement of equipment in the room, especially with respect to video and audio recording. Another is the physical demand put on both technologists and the equipment itself. Lastly, extra network connections are often not available, especially in older ICUs, making the study offline and requiring repeated downloads of data for review or physically going to the bedside to review data.

Fixed-/wall-mounted units have the main disadvantage of a lack of flexibility/availability – they can only be used in the room where they are located. However, their location can be optimized for higher quality video/audio and EEG recording. Also, the placement is typically sturdier, with less danger of damage to the equipment or accidental disconnection. A hybrid approach involving permanently mounted cameras and microphones in each ICU room with portable amplifiers brought in for the recordings may be ideal. In this approach, software/networking is used to select the specific camera to associate with a given amplifier. While a dedicated camera/microphone is still needed for each ICU room, the number of amplifiers needed is reduced.

Regardless of whether the equipment in the room is wall mounted or portable, the physical footprint needs to be small. ICU rooms tend to be crowded and space

for additional equipment is limited. Similar to other video EEG systems, the equipment that must be in the patient room includes the camera/microphone and EEG amplifier (up to the A/D converter). A monitor that is continuously displaying EEG (and quantitative EEG trends, if used) is also necessary at bedside. In theory, the actual acquisition machine need not be located in the room and could instead be at a networked location; however, the EEG technologist and others must be able to access the machine from the patient room, especially during setup and troubleshooting of a study.

### Computers

The EEG acquisition computer, as discussed above, should have a small physical footprint. However, the monitor size should be adequate to allow easy setup and troubleshooting of studies in the patient room. It must also allow for adequate in-room review of the raw EEG and qEEG trends. Some newer systems have computers with touch screen capabilities; this allows for easy manipulation during setup and bedside review.

The EEG review station needs to have a fairly large screen, in order to allow for display of EEG, qEEG trends, and video. Dual monitor systems are common for reviewing data. The computer and its network connections must be adequate to process, retrieve, and display the large amounts of data collected.

For any institution with more than a couple of EEG machines, an EEG server is essential as well. This serves as a central point for both immediate and long-term storage of EEG data. Data from the actual EEG collection machines can be transferred to the server soon after collection, often in real time. Storage on the server is more secure (physically removed from the patient environment), more robust (backed up routinely), continuously available (even when the recording equipment is offline), and available remotely. The storage capacity of such a server needs to be fairly large, depending on the volume of data being collected at the institution.

## Software Requirements

In addition to the basic software required for EEG acquisition and display, the equipment should have database management tools. This is especially important if the institution has a large number of acquisition machines. These tools allow for management of data acquired on different machines from a single location (generally only true for machines from a single vendor). Other features that are desirable but not essential include report generation capabilities using templates and integration with the electronic medical record (EMR) using HL7 (Health Level Seven) or other standards. EMR integration allows for passage of information between the EMR and the EEG equipment. This can include getting demographic and other data from the EMR and sending EEG reports or EEG samples back into the EMR.

Quantitative EEG software is also desirable for ICU EEG monitoring. Most vendors offer both their own tools and integrated third-party solutions (e.g., Persyst). The tools offered vary by vendor, but typically include at least density spectral

arrays. For integrated third-party solutions, it is usually necessary to purchase licenses for each acquisition machine as well as review machines. Without a license on the acquisition machine, real-time processing and display of qEEG trends is not possible. Post hoc analysis is available but can be time consuming.

The need to access ICU EEG equipment from patient rooms makes security a significant concern. Password protection including automatic time-outs is essential to prevent disruption of data collection and to keep the data secure.

## Networking Requirements

Computer networking is an essential component of ICU EEG for purposes of data collection, storage/archiving, and review. For collection, while it is certainly feasible to have all components connected to a single stand-alone computer, there are significant advantages in flexibility and security to having the amplifier and cameras connected to the computer through a network. Similarly storing the data on central server allows for more flexibility in data storage and review. It also permits review of data more easily from remote locations within the hospital or even outside the hospital. Reviewing data in patient rooms can be both inconvenient and disruptive to the clinical team.

Unlike routine EEGs or even video EEG in epilepsy monitoring units, access to live EEG data is a requisite for ICU EEG monitoring. This is due to a combination of the relatively common occurrence of status epilepticus in these patients, frequent changes in clinical status, and their relatively high acuity. These factors result in the need to frequently review data as well as requests from ICU staff to determine if a clinical change or event had a correlate on EEG. Without remote access to live data, immediate review would either require manual download of data by a technologist or the presence of the neurophysiologist at bedside. Due to the large volumes of EEG data and, in most cases, associated video/audio data, a fast network is essential.

## Data Management/Storage

Twenty-four hours of scalp EEG with video generates approximately 8–10 gigabytes of data (~90 % of which is video). In addition to the factors related to collection and review of such a large volume of data, storage is another concern. For the short term, all of the data should be stored and immediately available for review. At a minimum, this should be until the report is finalized; however, in most instances, it is reasonable to store all data for at least the period that the patient is still on EEG or still in the hospital. After short term, how much data to keep is largely determined by availability of storage space. At a minimum, samples of EEG totaling at least a few hours/day should be stored along with samples of relevant findings/changes and video along with EEG for any clinical events/seizures. This can easily add up to 0.5–1 GB of data/patient/day, although usually much less, depending on the amount

of video. If space is available, all of the EEG data with video only for clinical events/seizures can be stored, requiring about 1–2 GB/patient/day. Long-term storage can be in removable media (e.g., DVDs) or servers with large, online storage capacity (on the order of terabytes).

**Conclusions**

The basic technical requirements for EEG equipment for ICU EEG monitoring are similar to other types of EEG recording. Although in many cases, the same equipment can be used for multiple purposes, consideration should be given to constraints placed by physical location, data/study volume, and requirements for remote access to review data. Maintaining the equipment involved requires a close working relationship between the neurodiagnostic technologists and clinical engineering. Furthermore, the requirements for networking and storage also require a significant commitment from the information technology department. For larger/higher volume laboratories, routine meetings between these groups are desirable.

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# Electrodes and Montages

# 33

Michael Pietak and Saurabh R. Sinha

## Contents



## Introduction

Many issues related to electrodes and montages are the same with for cEEG as for routine EEG and long-term video EEG monitoring. Electrodes must be applied in a safe, reliable/reproducible, and standardized way to provide adequate spatial and temporal representation of cerebral activity. The montages used should allow for adequate visualization of activities of interest. However, there are several unique considerations for cEEG with respect to both.

Because cEEG is often performed for urgent indications and because the volume of studies is often high, ease of application and removal of electrodes is an issue. Studies often need to be started and stopped quickly and unpredictably, for example, for emergent procedures like imaging. Additionally, since many patients will require other diagnostic procedures, such as computed tomography (CT) and magnetic resonance imaging (MRI), compatibility with these procedures is desirable. Although not unique

M. Pietak, MD • S.R. Sinha, MD, PhD (✉)
Department of Neurology, Duke University Medical Center, DUMC Box 102350, Durham, NC, 27710, USA
e-mail: saurabh.sinha@duke.edu



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to the ICU setting, concerns about infection control make disposable electrodes a potentially attractive option. The prolonged duration of monitoring produces other issues, such as skin breakdown. Logistical issues may delay diagnosis depending on availability of skilled technicians and equipment. Rapid electrode application techniques may be useful, such as using reduced number of electrodes and electrode templates, which may permit application by less specialized personnel. In this chapter, we will review options for electrodes, application techniques, and montages.

## Electrodes

### Types of Electrodes

The quality of the data obtained during cEEG recording depends significantly on the electrodes used, how they are applied, and the stability of the placement (Fig. 1). The ideal electrode would have low impedance (although this is less

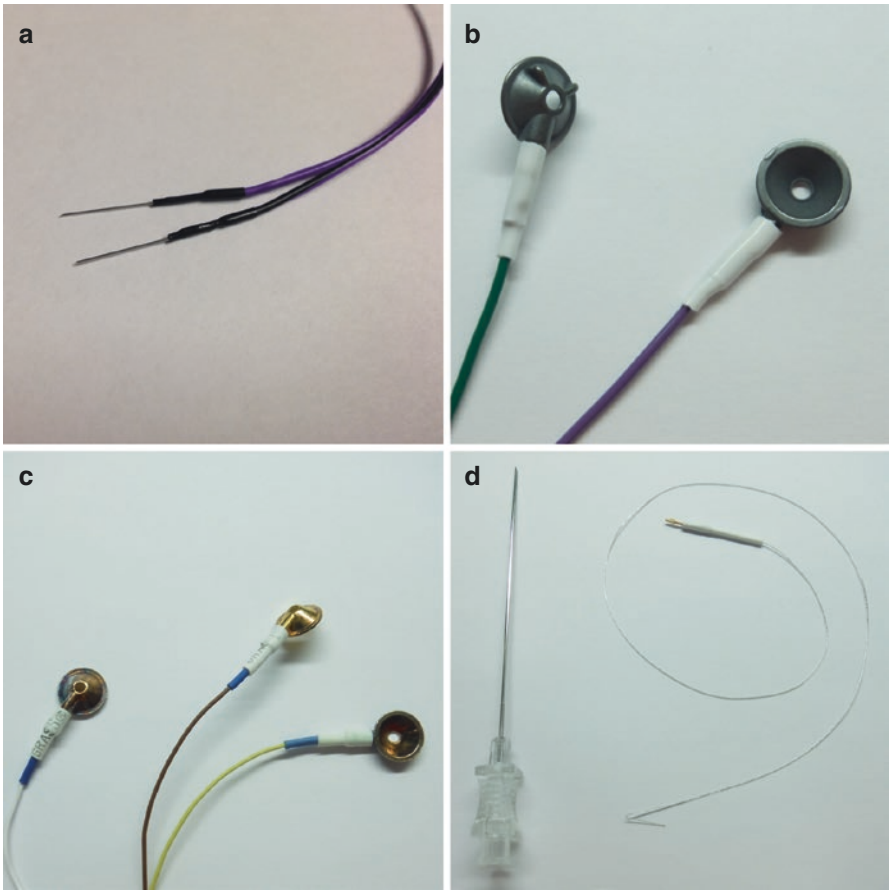


**Fig. 1** Example of different electrodes. (**a**) Subdermal needles. (**b**) Plastic cup electrodes with metal coating. (**c**) Gold cup electrodes, reusable. (**d**) Subdermal wire electrode and needle used for insertion

important with modern amplifiers that have high input impedance), be nonpolarizable/reversible (low capacitance, to provide a better frequency response), and be highly resistant to removal. The most commonly used electrodes for EEG recording are traditional metal cup electrodes. The shape of these allows for a conductive gel or paste to be applied and help with lowering impedance. Silver electrodes coated with silver chloride were commonly used in the past as they have near ideal properties, especially with respect to being non-polarizing. However, most electrodes today are made from ferrous or noble metals (gold, silver, or platinum).

Metal cup electrodes are available in both reusable and disposable varieties. The disposable type offers good-quality recording and eliminates any concern for cross infection between patients. Although the cost can be quite variable, a set of ten disposable Ag/AgCl electrodes costs approximately $5–10, compared to ten reusable gold electrodes at a cost of approximately $100. The reusable electrodes can be used repeatedly for at least 6 months and usually longer. However, they do require additional time for cleaning. In our experience, the overall cost ends up being similar, and patient safety and technician satisfaction favor the disposable electrodes.

Subdermal needle electrodes are another option for ICU EEG recording. These consist of metal (stainless steel, platinum, or others) needles that are thin, 27 gauge or thinner, and typically about 1 cm long. Patient discomfort and potential for injury to the patient and/or technologist are major concerns with their use. Another concern is that in spite of being subdermal, their impedances are actually higher than cup electrodes due to the low surface area of the needles. However, impedances are often closely matched and very stable, allowing for prolonged recording. The other main advantage is ease of application with minimal requirements for skin preparation.

Subdermal wire electrodes consist of a thin (25 gauge), Teflon-coated silver wire whose tip is exposed and coated with AgCl [1]. These are inserted under the skin using a hypodermic needle. The concerns are similar to subdermal needles; however, subdermal wires have the additional advantages of being more compatible with MRI and CT (see below) and likely safer for long-term recordings [2].

## Imaging Compatibility

In the routine management of patients in the ICU, imaging studies may be frequent and many times urgent. Metal cup electrodes cause a streak artifact on CT that may obscure vital findings (Fig. 2). Additionally, most are not MRI compatible because the metal can produce heating and displacement as well as artifacts. As a result, traditional metal cup electrodes require removal and reapplication for imaging studies, which can result in scalp abrasions and discomfort. This also places an additional workload on the EEG technologist. Fortunately, there are other electrode options that are safe for use with MRI and/or CT imaging (Table 1). These include plastic electrodes with a conductive coating. They have been proven safe for

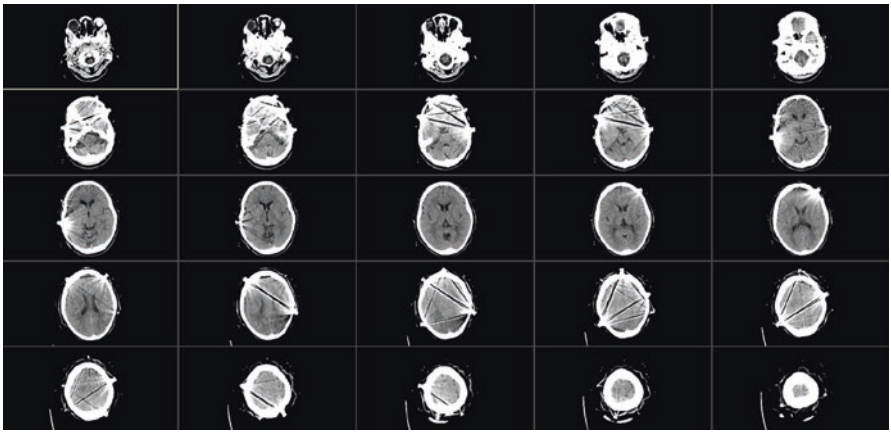

**Fig. 2** Artifact produced on head CT by standard metal electrodes

**Table 1** Imaging compatibility for different types of electrodes

| | CT | MRI | Comments |
|---|---|---|---|
| Metal cup electrodes<br>Ferrous/magnetic<br>Noble metals | Artifact | Artifact, heating<br>Compatible | Length of leads can be an issue for MRI |
| Plastic cup/disk electrode with metal coating | Compatible | Compatible | |
| Subdermal needle electrodes | Compatible | Depends on needle length | |
| Subdermal wire electrodes | Compatible | Compatible | Long-term recordings |

use in MRI and do not produce the streak artifact on CT scans (Figs. 3 and 4) [3, 4]. Like metal cup electrodes, they require the use of a conductive gel and for long-term monitoring are typically applied with collodion. Benefits to their use include continuous recording during imaging procedures, minimizing downtime, and decreased need for repeated removal and reapplication. While allowing for minimal interruption in recording, conductive plastic electrodes still require routine maintenance to maintain high-quality signal. This includes reapplication after accidental removal and refreshing with conductive gel that may dry over the course of a 24-h recording. Subdermal needle and subdermal wire electrodes are another option to consider for imaging compatibility. Subdermal needles are thin enough to not cause artifact on most CTs; compatibility with MRI depends on needle length, with longer needles having greater concern for injury. Subdermal wires cause minimal to no artifact on CT and are compatible with MRI as well. For all types of electrodes, the length of the leads connecting the electrodes must be kept in mind; longer leads or lead that are coiled to make loops are a potential source of induced currents that could place the patient at risk while in the MRI scanner.

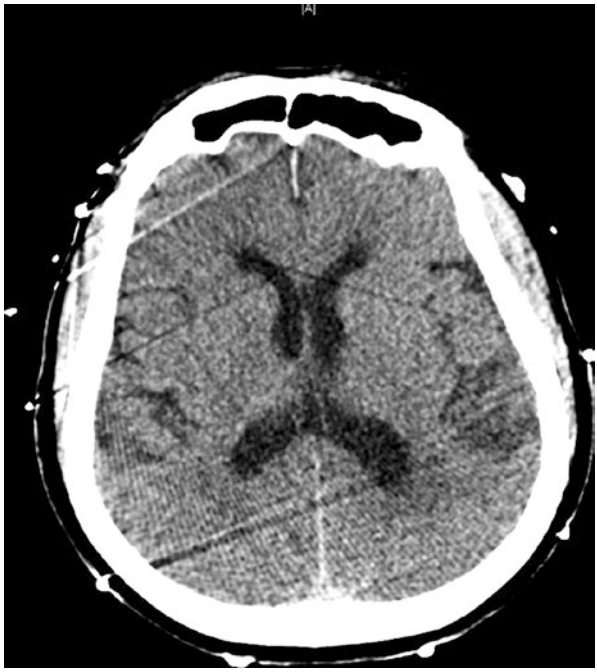

**Fig. 3** Artifact produced on head CT by conductive plastic electrodes

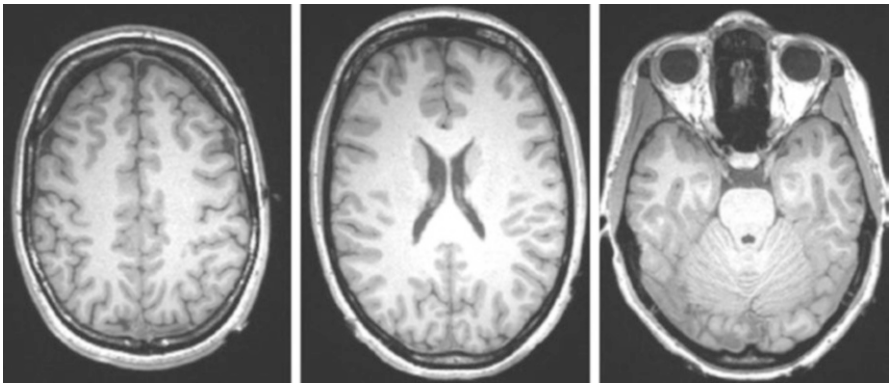

**Fig. 4** Appearance of different electrode types on MRI

## Electrode Application Techniques

As previously stated, good-quality EEG recording requires low impedance at the electrode junction. When using cup electrodes, regardless of material, technicians rub an abrasive paste to remove dirt, oils, and the outer layer of the skin, all of which contribute to skin impedance. Cup-style electrodes also typically require that a conductive paste or gel be used to facilitate transduction of ionic currents. Skin preparation and electrode application should lead to electrode impedances that meet the

same standards as for routine EEG, impedances below 5–10 kΩ. Although modern EEG amplifiers can record from higher impedance electrodes, there will be some degradation in quality. Beyond the absolute value, the impedances of all the electrodes used should be similar to each other – mismatched impedances will also compromise signal quality. Impedances should be rechecked periodically as drying out of the conductive paste or loss of electrode contact with the skin can occur.

In a routine EEG study, electrodes can be held in place by the adhesive nature of the conductive gels and pastes. Traditionally, collodion has been used to provide a more permanent attachment in longer studies, such as those typically done in the ICU setting. Collodion is a type of glue composed of nitrated cellulose that is dissolved in ether and alcohol. It is applied as a liquid and, as the ether and alcohol dry, becomes strong glue. As collodion is not a good conductive agent, gel is typically injected into the top of the cup electrodes. As the gel dries, the quality of the recording degrades over time, requiring reapplication approximately every 24 h. Acetone is used to remove electrodes. During application, collodion is both toxic and flammable, and acetone is a respiratory irritant. A well-ventilated room is required for the use of both. In lieu of collodion, other options include adhesive pastes and wrapping the head in gauze after electrode placement. Adhesive paste may be less time consuming to apply and provides equivalent recording quality to collodion [5]. At a minimum, these techniques still require daily maintenance by a qualified technician. As previously mentioned, the use of subdermal needle and wire electrodes circumvents some of these issues.

Because ICU EEG is often performed for very prolonged periods of time, sometimes weeks, skin breakdown around electrodes can be a major concern. Preparation of the skin by applying abrasives followed by prolonged contact with a hard object (the electrode) can lead to tissue injury in any patient. Patients who are critically ill are likely to be even more prone to injury due to their compromised health. At a minimum, daily inspection of the skin is necessary. Furthermore, for patients who will be monitored for an extended period of time, consideration should be given for moving the electrodes every few days, for example, by moving them to a nearby location, with care being taken to move homologous electrodes so that they remain in corresponding location (e.g., if F3 is moved 1 cm laterally, F4 should be moved 1 cm laterally as well).

### Electrode Placement/Location

For most ICU EEG recordings, electrodes are placed according to the International 10–20 system (Fig. 5). This method insures reproducible placement of electrodes during multiple studies on the same patient and across multiple patients, allowing for comparison of studies. It also insures that homologous electrodes over the left and right hemisphere are in corresponding locations, allowing for comparison between the two sides. In the ICU, it is not uncommon for patients to have cranial abnormalities such as surgical scars, traumatic lesions, drains, or pressure monitors which impair the ability to place some electrodes in their appropriate location. Leaving these electrodes off should be avoided. Reducing the number of electrodes will reduce the sensitivity for detecting seizures and other abnormalities (see

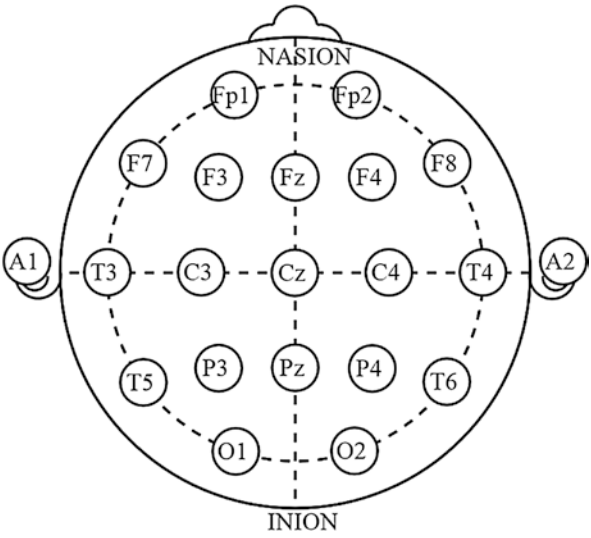


**Fig. 5** International 10–20 system for electrode placement. Not alternate names for T3 (T7), T4 (T8), T5 (P7), and T6 (P8)

discussion below) and can also interfere with quantitative EEG algorithms, requiring modification of parameters. Rather than skipping placement of these electrodes, moving them to a nearby available location is preferred. Since symmetric electrode application between the right and left hemispheres is important for detecting asymmetries, it is necessary to displace the corresponding electrode over the contralateral hemisphere to an equivalent location.

Even though placement of electrodes at measured locations by trained technologists is ideal, demands placed by ICU EEG have led many to consider alternatives that are potentially easier (allowing for placement by non-technologists) and faster. These include placement of a reduced number of electrodes using physical landmarks rather than measurement. In a retrospective analysis using a subset of 10–20 electrodes that approximate the hairline (Fp1, Fp2, F7, F8, T3, T4, T5, and T6), the sensitivity for detecting seizures was only 72 % and the 54 % for detecting periodic discharges [6]. Specificity was significantly higher ranging from 87 to 99 %. In a prospective study, using four channels to record a subhairline montage from the anterior scalp, the sensitivity compared to simultaneously recorded conventional EEG was 68 % for seizures (specificity of 98 %) and 39 % for epileptiform discharges or periodic patterns (specificity of 92 %) [7]. In a prospective study using a hairline (or subhairline) montage, sensitivity for seizures was low (54 %) with nearly perfect specificity [8]; sensitivity and specificity for detecting interictal epileptiform activity were 60 % and 94 %, respectively. Low sensitivity for seizure detection was confirmed in another recent study using a template that provided predominantly frontal coverage [9]. One potential reason for the poor sensitivity in these studies was that the limited montages only covered the frontal and anterior temporal regions. In another retrospective study, using electrodes Fp1, Fp2, T3, T4, O1, O2, and Cz (which can all be approximated by anatomical landmarks without the need for measuring), sensitivity for seizure detection was reported as 92.5 %,

with a specificity of 93.5 % [10]. Based on these studies, it is clear that the greatest limitation is the limited spatial coverage of subhairline and hairline montages, with addition of central and posterior leads providing improved sensitivities.

EEG templates are an alternative means of applying a broader set of electrodes without the expertise needed for a traditional 10–20 placement. Templates typically consist of an adjustable harness that is placed using standard bony landmarks (e.g., nasion and inion). The template then approximates typical locations with color-coded electrodes to help expedite placement and connection to the EEG amplifier headbox. Cup electrodes or needle electrodes can then be placed. In a blinded review, a neurophysiologist could not distinguish between the quality of recordings produced using a commercially available template system and traditionally applied electrodes [11]. Moreover, the speed of starting a study was reduced by 3.25 hours, with 87 % of template recordings initiated within 60 min of the request. It is also noteworthy to mention that needle electrodes were preferred by the users due to their ease of use, shorter time to apply, and generally lower impedances. Due to concerns about safety and patient discomfort, however, default use of needle electrodes should be avoided. The sensitivity of template systems in clinical practice has not been evaluated, although there is no reason to expect a significant difference in seizure detection sensitivity/specificity. Taking into account the savings in technologist time, template systems are likely to be cost effective [12].

## Issues in Neonates and Young Children

A special mention should be made when performing continuous EEG monitoring in neonates. Fewer electrodes are typically used compared to older children and adults due to their smaller head size. At a minimum, Fp1, Fp2, C3, Cz, T3, T4, O1, O2, A1, and A2 are used. Special care must be used during skin preparation and electrode placement to reduce the risk of skin breakdown. Also, the skin should be checked more frequently and either location of electrodes rotated or electrodes taken off for a period of time to give the skin a break.

## Montages for Review of Data

EEG data is arranged in montages in order to assist the interpreter in localization. Typically, a single montage is used to review large amounts of cEEG due to time constraints, making appropriate selection essential in EEG review. The most commonly used montage is longitudinal bipolar, including midline electrodes which are helpful. A referential montage may be used as well, although widespread activity (such as generalized periodic discharges or diffuse slowing) will likely contaminate any reference (single electrode or average). Referential montages may be particularly useful when dealing with missing electrodes (Fig. 6). For example, missing electrode T4 will make both Fp2-T4 and T4–T6 unavailable for interpretation. With average reference, Fp2-Avg and T6-Avg are still interpretable, while only T4-Avg is affected.

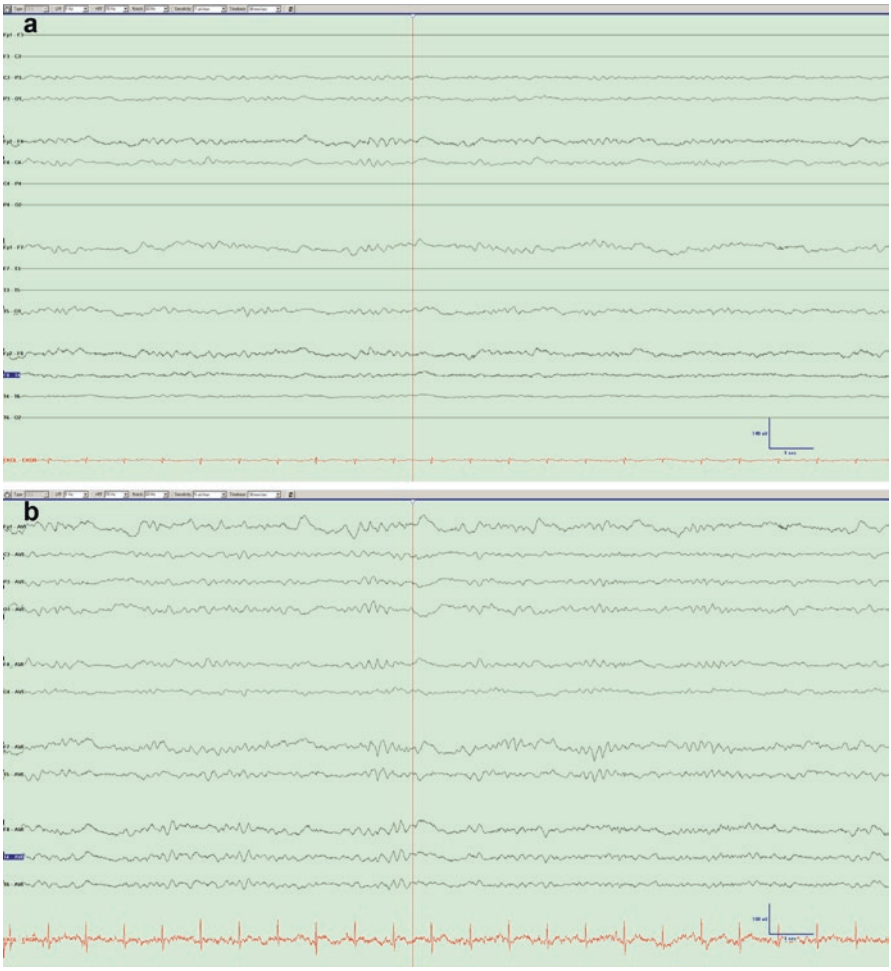


**Fig. 6** Impact of missing electrodes on montages. (**a**) Double-banana montage in a patient with missing electrodes at F3, T3, P4, and O2. (**b**) Same page with average reference allowing for better interpretation around missing electrodes (note the missing electrodes have been excluded from the calculation of the average reference)

## Conclusion

The equipment needs of continuous EEG are similar to other types of EEG recording; however, many technical factors must be considered. Selection of electrodes is influenced by the ease of application, imaging compatibility, and potential risks to the patients. Reduced electrode montages or templates may provide added benefit when there are limitations in the availability of qualified technicians or to expedite studies. However, care must be taken as sensitivity and specificity of the test may be impacted.

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# Technical Considerations

# 34

Crystal M. Keller

## Contents



C.M. Keller, BA, R EEG T, CLTM
Neurodiagnostic Lab, Duke University Hospital,
2301 Erwin Road, Box 100404, Durham, NC 27710, USA
e-mail: crystal.keller@duke.edu



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## Introduction

There are many issues for the EEG technologist to consider for continuous electroencephalography monitoring (cEEG) in a critical care setting. Most of the technologist's effort is concentrated on the cEEG hookup. However, preparation before and after going to the patient's room can be the key to a successful and efficient hookup. In addition to selecting the supplies and equipment, the locations of these things in the room and during the hookup should also be assessed. Many critical care patients are not straightforward hookups due to external ventricular drains (EVD), incisions, bandages, and wounds. These factors will affect the hookup and must be taken into account on the electroencephalography (EEG) recording. After the electrodes have been applied and the patient is being monitored, daily observation of the electrodes and the recording is necessary to maintain the integrity of the cEEG and protect the patient from skin breakdown. Removal of electrodes can occur at various stages of cEEG monitoring. Thus, it is important for the technologist to understand why the electrodes are being removed and if there is any need for reapplication before determining what method to use for removal. All of these technical considerations collectively result in optimal cEEG monitoring of the critical care patient.

## Preparation

### Initial Contact with Critical Care Nurse

Before beginning, it is important to make sure the patient is ready to be hooked up to cEEG monitoring. Once you have an order for cEEG, it is best to call the patient's care nurse to see if the patient is currently undergoing or expected to undergo any procedures. Often a patient who has orders for cEEG monitoring will also need other testing such as a computed tomography (CT) scan or magnetic resonance imaging (MRI). Both of these scans usually require the patient to leave the room and travel to another area of the hospital. It is not ideal for the patient to need this in the middle of the hookup. Furthermore, depending on the type of exam and type of electrodes used, the electrodes may need to be removed to ensure a safe and high-quality scan. Often, the patient can wait to be hooked up to cEEG monitoring after the scans have been completed to prevent the need to remove electrodes. In other cases, the need for cEEG monitoring may be most urgent and other procedures may be delayed. Some patients may need sterile procedures at bedside such as inserting arterial lines. While the technologist could wear a gown, hat, mask, and gloves during the sterile procedure, the care nurse may prefer to finish a sterile procedure before allowing the hookup to begin. During this initial contact, it is also a good time to inquire on the condition of the patient's scalp, specifically whether there are any obstacles on the patient's head that may prevent or complicate hookup. The patient's behavioral state (alert, comatose, agitated) is also a useful piece of information in preparing for a hookup.


**Fig. 1** Photograph of various supplies that may be used for cEEG electrode hookup. Pictured here: reusable pouch, disposable telemetry pouch, large roll of gauze, twist tie, scissors, tub of electrode paste, disposable tongue depressor, alcohol wipes, plastic retractable tape measure, China markers, nonpermanent markers, bottle of collodion, curve-tipped syringes with labels, abrasive prepping gel, electrocardiogram (ECG) snap cables, cotton-tipped applicators, ECG adhesive patches, electrode gel, clear adhesive film, large tightly woven gauze squares, 1 in. paper tape, 2 in. paper tape, small cut loosely woven gauze squares, and roll of loosely woven gauze

## Selecting Supplies

After it has been determined that the patient is ready for cEEG monitoring hookup, the technologist will want to gather all supplies needed to apply the electrodes (Fig. 1). Several different types of supplies will be needed for different stages of the application. First, you will need supplies to measure and mark the patient's head to know where all the electrodes should be applied. For measuring, a retractable plastic measuring tape works well, because it is easy to control and durable enough to be sterilized after each patient use. However, another option is a disposable paper measuring paper tape that increases infection control, because it is not used on multiple patients [1]. Paper measuring tapes can be harder to control especially in the setting of a bloody scalp and often tear easy. Calipers may also be helpful for patients in obstructing devices such as a neck collar or halo, patients with little head mobility, or patients who possess many obstacles on the head such as EVDs, incisions, bandages, wounds, and very tangled or matted hair. To make the marks, a nonpermanent marker or a wax China marker can be used. It is also helpful to have more than one color available in case a mistake needs to be corrected, or it is difficult to see a particular color on a patient's scalp.

Next, the technologist will need supplies to prepare the skin where the electrodes will be applied. Often an abrasive prepping gel is used to clean the scalp and improve the electrical impedances of the electrodes. The technologist may want to use cotton-tipped applicators or gauze to apply the prepping gel. Cotton-tipped applicators have the ability to prep small areas of the skin and may be best for getting through matted hair. Gauze preps a larger skin area and is best used on delicate skin, because the technologist can better assess and control the exact pressure being applied. Select thicker woven gauze to prevent the prepping gel from soaking through the gauze. Alcohol wipes may also be helpful for cleaning or improving electrode impedances. Alcohol has a drying effect on the skin and effectively removes sweat, oils, and greases from the scalp.

The technologist will also need supplies for securing the electrodes to the patient. One method is using a conductive paste and loose woven gauze squares or tape. This is suggested in situations where the patient is not moving around and not sweating, as well as, when other care staff is not moving or working around the head. If there is risk that the electrodes may fall or get knocked off, consider using glue such as collodion or a hardening cream to secure electrodes. Paste can be inserted into the electrodes before being secured, or conductive gel can be squirted into a hole in the top of an electrode cup with a syringe. After assessing which method to use, collect all supplies needed for that particular method of securing electrodes. If gluing with collodion, the technologist will need a device to dry glue such as a medical air regulator or an electric air pump along with tubing, pedal, and stylist (Fig. 2).

**Fig. 2** Example of devices that are used to dry glue. (*Left*) An air regulator, tubing, pedal, and stylist connect to medical air in the room. (*Right*) An electric air pump with tubing, pedal, and stylist eliminate the need for medical air to be present in the room

Other supplies will be needed to secure the electrode wires, protect the breakout (jack) box, and protect the electrodes on the head. Items for securing the wires could include twist ties, tape, gauze, or a plastic spiral cable covering. The breakout box could be wrapped in gauze, placed in a disposable telemetry pouch, or inserted into a bag provided by the EEG machine manufacturer. Wrapping the head with gauze, making a hat fashioned from tubular dressing retainer, or tying on a bandana protects the electrodes on the head.

## Electrodes

Lastly, the technologist will need electrodes. The technologist will need at least enough electrodes for an international 10–20 system or a modified neonatal hookup as well as for any additional locations that should be monitored on the cEEG [2]. It is also a good idea to have a few extra electrodes in case any artifacts need to be monitored or an electrode is defective. It is helpful if the technologist plugs the minimal required number of electrodes into the breakout box before heading to the patient's room. While doing this, the technologist should inspect the electrodes to ensure that they are in good condition and do not have any breaks along the wires, cup, or hub. In addition to EEG electrodes, the technologist should also select any other types of electrodes or devices to be used such as electrocardiogram (ECG) cables and patches, pneumograph, or respiratory belt.

There are several different types of electrodes that can be used for cEEG monitoring. In the event that several types are available to the technologist, deciding which type to use should be patient dependent. Reusable electrodes seem to remain in place better than disposable electrodes when gluing with collodion or using conductive paste and tape. Reusable electrodes have also been shown to be less conductive to heat, which minimizes the drying of electrode paste or gel and reduces the risk of skin breakdown. On the other hand, in hospitals that need to maintain a large supply of available electrodes to accommodate hookup requests, the use of disposable electrodes is highly effective. These populations are usually more acute and need frequent CT or MRI scans requiring electrode removal and reapplication. Also, technologists do not have to wait for electrodes to be cleaned or sterilized for the reapplication. Time is also saved at removal because electrodes are simply disposed. Some disposable electrodes are compatible with CT and MRI and do not need to be removed for these scans, thus extremely desirable by technologists for eliminating electrode removal and reapplication as well as by physicians for reducing the amount of time EEG is not recorded [2]. Needle electrodes can be very time efficient when used on a comatose patient, because they eliminate the need for prepping the skin before application [3]. However, needle electrodes could increase the risk of infection for the patient and increase risk of a needle stick for the technologist.

## EEG Machine

The technologist will also need an EEG machine for the hookup. Many neurointensive care units have EEG equipment mounted in the patient's room on a wall or boom behind the head of the bed and permanently connected to a network because

of the frequent need for cEEG monitoring. However, cEEG monitoring is also ordered on patients admitted to non-neurointensive care units for other medical problems. In this situation, a portable EEG machine will need to be taken to the patient's room. Whether mounted in the patient's room or on a portable cart, most EEG machines need the same basic parts for recording: a computer with the EEG acquiring software and storage drives, a computer monitor, a keyboard and mouse, and an amplifier for the electrodes. Most amplifiers or headboxes are connected by a cable to a smaller jack box or breakout box into which the electrodes plug. The breakout box can be easily disconnected if necessary and is small enough to be in the patient's bed. Most EEG machines used for cEEG monitoring also have a camera for acquiring video of the patient to aid the physicians with interpreting the EEG and distinguishing abnormalities from artifact.

## Preparation in the Patient's Room

### Setting Up the EEG Machine

When arriving at the patient's room, the technologist should let the care nurse know that the patient is about to be hooked up to electrodes for cEEG monitoring, verifying that the patient is still available. The technologist should use at least two patient identifiers such as name, date of birth, and medical record number to confirm that it is the correct patient. The technologist should partner with the care nurse for the best place to set up a portable EEG machine if the room is not hardwired with EEG equipment. Because many other care staff will need access to the patient, the machine should not obstruct the patient. If using a video camera, the technologist should position the machine to view the patient's whole body including a good image of the patient's face, if possible [2]. Thus, the best place for the portable machine is at the foot of the bed if the patient's room allows or on either side of the foot of the bed, being mindful to not obstruct any traffic that needs to get by the machine. If possible, the power cable, network cable, or any other cables should not run along the floor in areas of heavy traffic. This is often achieved by running the cable under the bed to outlets on the wall behind the head of the bed. If a cable must be in a walkway, it is a good idea to secure it to the floor with tape or cover it with a cable organizer or other method to minimize trip hazards (Fig. 3). When plugging the power cable into an outlet, choose one that receives power from a backup generator in case of a power outage. Some EEG machines are also connected to a backup battery that will supply power to maintain the recording even if the machine becomes unplugged or there is a power outage. The cable from the headbox to the breakout box should be kept out of the way of walking traffic. Often patients on cEEG monitoring are on several other monitors and have intravenous lines (IV). Therefore, the breakout box and cable are more likely to remain untangled from any other monitoring cables or IVs if kept near the patient's head. This location is also best for stress relief on the electrodes to

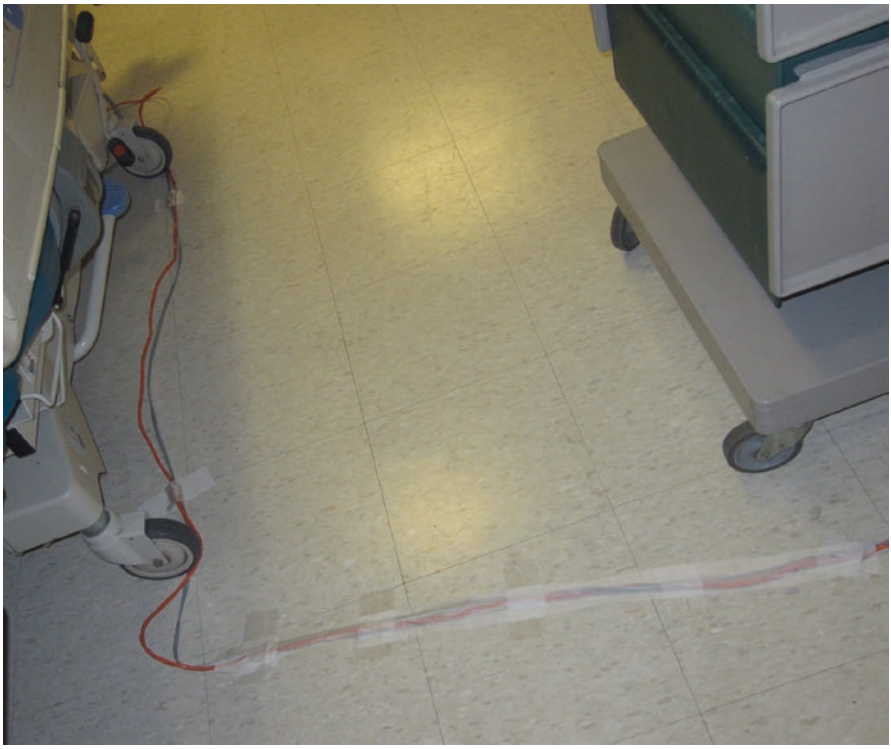

**Fig. 3** Cables are run along a hospital bed out of the walkway. Where the walkway is crossed, the cables are completely covered and taped to the floor

prevent accidental removal from the head or breakout box. Once the machine, cables, and breakout box are in position, the technologist can boot up the machine, enter the patient's information, and start the acquisition. If available, turning on the electrode impedance check at this point helps keep the technologist from having to come back to the machine before the application is complete.

## Setting Up the Supplies

Before beginning the hookup, the technologist should ensure that all the needed supplies are available. If brought by the technologist in a basket, supply box, or cart, the needed supplies should be removed with clean hands or gloves so as not contaminate any unused supplies [1]. If using a device to dry glue, it should be plugged in near the head of the bed. Often the technologist has to step over or go under cables to get to the head of the bed to reach the patient's scalp. Thus, it is helpful if all supplies are set up within reach, and the technologist does not have to come out from behind the bed to obtain anything during the hookup.

## Preparing the Patient

The next step is preparing the patient for electrode hookup. With the help of the care nurse, the technologist should position the patient to make the hookup as ergonomic as feasible. Bending and reaching should be avoided whenever possible. This includes partnering with the care nurse to raise the bed or lower the head of the bed, if necessary. Some patients have EVDs that require the patient's head is not raised or lowered while the EVD is open for draining. The care nurse would need to close the drain before moving or changing the patient's position. Other medical conditions may affect the ability to position a patient such as recent incision requiring an incline of 30° or breathing issues. Also, any hookup options for obstacles such as EVDs, incisions, bandages, and wounds on the head should be discussed with the care nurse. Removal of bandages or applying electrodes close to any incision or wounds should only be done with the approval and participation of the care nurse. For infection control purposes, it is best to stay at least 1 cm away from the open skin [1].

## Application Procedure

### Measuring and Marking

The first step in the application of the electrodes is measuring and marking the patient's head using the international 10–20 system to know where the electrodes should be applied [2]. This system uses percentages based on the measurement of the individual's head to make a grid of intersecting points where the electrodes will be placed. Once the entire process is finished, 19 locations will be identified (Fig. 4). While the international 10–20 system is used to measure for neonatal applications, electrodes are only applied to nine locations [4] (Fig. 5). If there are bandages that

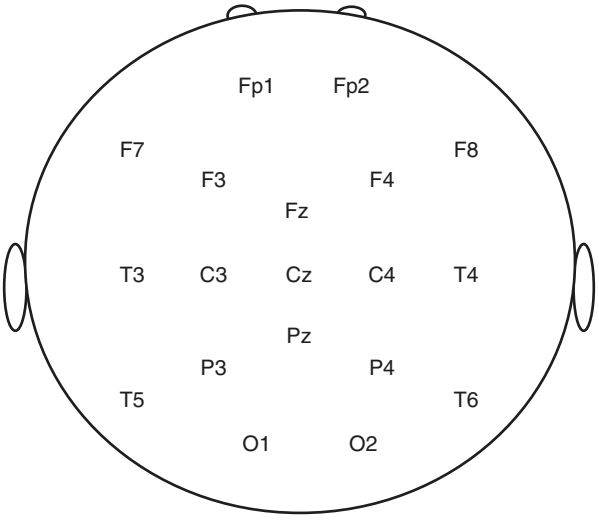


**Fig. 4** International 10–20 system electrode locations

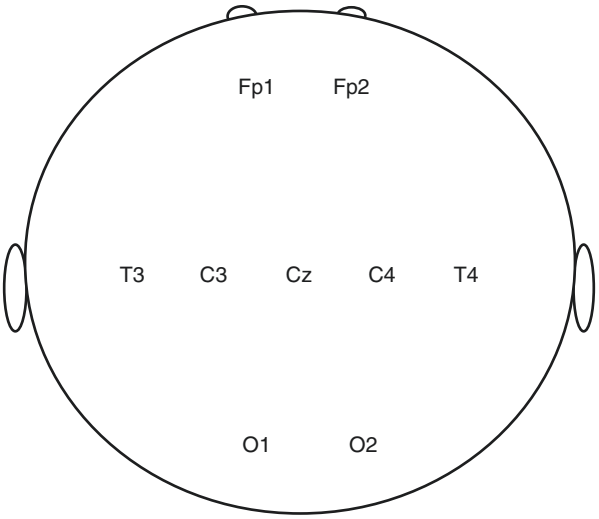


**Fig. 5** Neonatal electrode locations

cannot be removed or incisions and wounds at these locations, it will be necessary to select nearby locations to displace the electrodes. In order to create a montage that displays waveforms that can be compared accurately, whenever an electrode is displaced on one side of the head, the corresponding electrode on the other side of the head should also be displaced [2]. In extreme cases, it may be necessary to not apply an electrode. At times, the hair may be very matted or contain large amounts of dried blood making it hard to part the hair for measuring. In these cases, some of the hair may need to be cleaned before measuring and marking.

Depending on the brand of EEG equipment being used, one or two additional locations will need to be selected by the technologist for reference and/or ground electrodes. The technologist should select these spots based on where the least amount of artifact is expected, for example, between CZ and PZ on either side of midline [3]. This location is least likely to be contaminated by eye artifact, muscle artifact, and sleep architecture. Locations where abnormal activity is expected, such as near an incision or injury site, should be avoided. Many institutions also add a few additional electrodes to the application for more information and to aid with distinguishing artifact from EEG abnormalities. A1 and A2 electrodes located on the earlobes are very effective uncontaminated electrodes for a referential montage. Because it can be difficult to keep these electrodes on the earlobes, they are commonly moved to the mastoid bone behind the ear. T1 and T2, located 1 cm above the point located 1/3 the distance between the preauricular and the outer canthus of the eye, are used to record additional information from the anterior temporal lobe.

The most commonly used electrodes for monitoring physiological activity that could also be artifact on the EEG recording are the ECG electrodes. These electrodes may be the same type of electrodes as used on the head and are secured to the patient's chest with conductive paste and tape. Snap electrodes that connect to adhesive patches applied to the patient's chest could also be used to monitor ECG activity. Having an ECG channel is also helpful in determining if there are cardiac

rhythm changes during seizures or if particular behaviors mimicking seizures are actually caused by cardiac abnormalities. Other types of additional electrodes that may be used during cEEG monitoring include electrodes to monitor eye movements, muscle activity (EMG), and IV drips. A respiratory belt to monitor breathing and chin electrodes for monitoring mouth movements are often added to neonatal applications.

## Prepping the Skin

Once the locations for electrodes have been marked and selected, the next step is to prepare the skin for electrode application. If the scalp is covered with blood, dirt, or other solutions, it may be necessary to clean the scalp with soap and water before prepping. Alcohol is also an effective cleaner for blood, sweat, oils, or other greasy solutions. After removing substances that could interfere with recording quality EEG, the locations should be prepped to achieve electrode impedances at or below 5000 ohms (Ω) or 5 kΩ (kohms) for an adult or 10 kΩ (10,000 Ω) for a pediatric [5]. The technologist should prep the scalp in quick swiping motions only applying very light pressure. It is important not to over prep the scalp as this can cause skin breakdown such as scabs, ulcers, or open wounds that put the patient at risk for infection. Different types of the skin may need less or more prepping than others. The scalp is usually more durable than the skin of the face and chest. Duration and pressure of prepping should be adjusted when preparing locations on the forehead and around the eyes. Special care should also be taken with patients who have poor skin profusion or delicate skin. Some blood-thinning medications also put critical care patients at higher risk of developing skin breakdown. The elderly, newborns, and those on hyperthermia protocol are also very susceptible to skin breakdown. Applying excessive amounts of prepping gel, which is left behind on the skin, can also prevent the glue or tape from adhering securely to the patient's scalp.

## Securing the Electrodes

Once the electrode location is prepped, the electrode should be applied securely. Often the type of materials and method used depends on the patient's hair; for example, electrodes may stay on better with gauze squares in thick coarse hair and hair cut shorter than 1 cm in comparison to tape. It is frequently beneficial to use tape over glue for patients with bald heads. The combination of glue and tape can also be considered for combative or restless patients. Ultimately, electrodes should not fall off during seizures, profuse sweating, or as care staff move about the patient. While gluing electrodes tends to maintain the electrode application better over time, it may be a more time-consuming application [3]. On the other hand, if using conductive paste and tape or gauze squares, the technologist should wrap or cover the head to prevent the electrodes from slipping or falling off. Aiming the electrode hubs in a single direction provides stress relief preventing electrodes from being


**Fig. 6** The electrode wires are wrapped in gauze from the head to the breakout box. The remaining gauze is wrapped around the breakout box to ensure the electrodes do not become unplugged. The box is then inserted into a disposable telemetry pouch to protect it from any liquids in which it may come into contact. To provide stress relief on the connector, the breakout box cable is looped around the box

ripped off and allows the wires to be easily gathered. Once all the electrodes have been applied and the wires have been gathered, it is important to keep electrode wires from getting tangled about the patient and with other cables or IVs in the bed. Options include spacing tape down the length of the wires, wrapping them with gauze, or using some other covering to maintain the bundle. The wires should also be secured in the breakout box so that they do not come unplugged. Common methods include wrapping the breakout box with gauze or putting the breakout box in a pouch (Fig. 6).

## Post-application Procedure

### Starting the EEG Recording

Once the electrodes are applied and have been verified to have acceptable impedances, it is important to observe a portion of the EEG to determine if the electrodes are recording properly. A calibration should be run to ensure the machine is working properly. If calibration is unavailable, the technologist should observe 30 seconds of the recording in a montage using the primary system reference [5]. Then, any

alterations to the hookup such as missing or displaced electrodes should be annotated into the recording [2]. The technologist should also annotate if unable to get electrode impedances at or below 5 kΩ (10 kΩ for pediatrics).

## Troubleshooting Artifacts

It is also important to observe a portion of the EEG to determine if an artifact needs to be eliminated or monitored. Electrical artifact, more commonly referred to as 60 Hz, is frequently seen on EEG in ICUs because critical care patients are connected to other medical devices [6]. When troubleshooting 60 Hz artifact, the source of the artifact should be identified by unplugging other devices or monitors one by one, if possible and with the approval and participation of the care nurse. If a machine is unable to be unplugged, any cables from the machine could be repositioned away from the EEG cable or wires to test for electrical interference. Once the source of the 60 Hz artifact is identified, that machine or device should be removed from the room, replaced, or repositioned in the room away from the EEG machine, patient's head, and electrodes.

Other artifacts that may need to be resolved or identified are EMG artifact and movement artifact [6]. Most often these artifacts can be identified and monitored throughout the cEEG monitoring by placing additional electrodes on the muscle area or part of the body thought to be causing artifact such as a trembling hand or arm. Even IVs can cause a "drip" artifact on the EEG which may be identified by simply annotating on the EEG recording when the IV drips [6]. It can also be monitored with electrodes for the duration of the EEG recording. The IV drip artifact can often be reduced by moving the IV pole to the other side of the bed or a little further away from the patient. Another common artifact on the EEG is "electrode pops" which are usually caused by a small break in the electrode wire. The first step should be to re-prep under the electrode to eliminate any debris or substance that may be preventing the electrode from making consistent contact with the patient's skin. If the "electrode pops" continue, the electrode should be replaced. If the "popping" does not occur after the electrode is replaced, then the original electrode was likely defective and should be removed from service. Sweat can also cause an artifact on the EEG recording [6]. Re-prepping with alcohol can help dry the area. If available, using a fan to keep the patient cool and dry and to prevent sweating can help with sweat artifact.

## Montage

Once application is finished and all efforts have been made to troubleshoot artifacts on the EEG recording, the technologist should ensure that the correct montage has been selected or created to reflect the information being recorded from the patient. Many institutions have predetermined what montage should be set for the EEG recording for the duration of the monitoring. If additional electrodes have been

added or electrodes have been not applied, the technologist should modify or create a montage to reflect these changes [2].

### Post-procedure Communication with Care Nurse

After the EEG is recording, all supplies have been gathered or disposed of, and the technologist is ready to leave the patient's room; it is important to make sure the care nurse knows how to communicate with the lab for any EEG issues or questions [2]. Because the care nurses change from shift to shift, it is also a good idea to leave a pager number or phone number for the lab posted on the machine for quick access should the need arise. Depending on protocols and expectations, it may be reasonable to teach the care nurses how to disconnect the breakout box in the event of an emergency [2].

## cEEG Maintenance and Skin Breakdown

### cEEG Maintenance

cEEG monitoring often lasts more than 24 hours. Thus, daily maintenance is required to maintain the integrity of the EEG recording and prevent skin breakdown. Inserting more conductive gel into the electrode cup or removing the electrode, re-prepping, and re-pasting the electrode may be necessary to keep electrode impedances at or below 5 kΩ (10 kΩ for pediatrics) [3]. Observing the EEG recording and the patient's head daily also allows the technologist to screen for any new artifacts or resecure any electrodes that may be coming loose [7].

### Skin Breakdown

Skin breakdown is another concern for patients who need to have the electrodes on their head for several days. This is especially important for patients who have poor skin profusion, who are on drugs that affect the ability of the skin to heal, or who have delicate skin. Depending on the condition of the skin, several electrodes should be removed, and the skin underneath should be inspected periodically during daily maintenance [7]. The more dedicate or unhealthy the skin, the more often the skin should be inspected for skin breakdown. When skin breakdown has been identified, it should be shown to the care nurse and noted on the EEG recording as well as in the patient's chart [2]. The electrode(s) should also be moved to a new location to allow the area of skin breakdown to heal [7]. The new location should also be annotated in the recording. After skin breakdown has been found, it may be necessary to check under more electrodes and to increase the frequency that electrodes are checked for skin breakdown. The technologist should rotate which electrodes are checked from one round of maintenance to another in an effort to identify skin

breakdown as early as possible. In addition, it is often best to check more frequently electrodes around the face or electrodes that receive constant pressure from a bandage or from laying on them. To prevent skin breakdown, some institutions remove electrodes after a set period of time and give the patient a break before re-hooking up to cEEG monitoring.

## Electrode Removal

At some point, the electrodes will need to be removed from the patient's head. Regardless of why the electrodes need to be removed, it is helpful to completely clean the conductive paste, conductive gel, gauze, tape, or glue from the patient's hair, scalp, and skin. Not only is this a courtesy to the patient, it can also be helpful to other care staff including another technologist who may need to reapply the electrodes. There are several solutions that can be used for electrode removal. If electrodes were applied using paste and tape or gauze, alcohol or soap and water may be sufficient to remove the tape and dissolve the paste. For applications that were glued, a stronger dissolving agent will be needed, such as acetone or collodion remover. Collodion remover is milder on the skin and works best for patients that will not need the electrodes applied again. Because of its oil-like consistency, it remains in the hair until washed away by soap and water. As it remains, it continues to dissolve anything left in the hair, causing the hair to be cleaner in the end. However, patients and care staff should be warned of its ability to breakdown certain low-density plastics. It should not be used on patients with medical devices on or near the head and face. A disposable comb should be used to comb the solution through the hair and to help remove tangles before washing.

If electrodes are being removed only temporarily to go to a scan or to give the patient a break, acetone would be a better choice. Acetone is more appropriate for ICUs where patients tend to be connected to other medical devices near or on the head. Acetone is faster for dissolving glue and can be used for quick removal. Once acetone dries, it loses its dissolving properties allowing new glue or tape for reapplication to adhere to the hair and scalp. Likewise, acetone is not as effective in cleaning leftover glue from the hair, because any remaining glue will re-harden in the hair when the acetone dries. When removing the electrodes, the technologist should assess whether it is likely that the patient will need electrodes again or if the patient is going home. Special care should also be taken not to cause the patient pain by excessively pulling on the hair or rubbing too vigorously during removal. Excessive rubbing of already weakened skin can also lead to skin breakdown. If skin breakdown is identified at removal, it should be shown to the care nurse and entered into the patient's chart.

### Conclusion

There are many things for the EEG technologist to consider for continuous electroencephalography monitoring (cEEG) in a critical care setting. Most of the technologist's effort is concentrated on the cEEG hookup. Preparation before

going to the patient's room can be the key to a successful and efficient hookup. Once initial contact has been made with the care nurse to ensure the patient is available and to communicate any needs for the electrode application, the technologist should select the equipment and all supplies needed. Some preparation also continues once the technologist arrives to the patient's room. Determining the location of the machine, cables, and jack box is followed by the setup of the application supplies in a way that eliminates the technologist's need to leave the patient's head during the hookup. Many critical care patients are not straightforward hookups due to external ventricular drains (EVD), incisions, bandages, and wounds. These alterations will affect the hookup and must be taken into account on the electroencephalography (EEG) recording. After the electrodes have been applied and the patient is recording, maintaining the cEEG is necessary throughout the monitoring. Daily observation and repair of the electrodes maintains the integrity of the recording over time and is vital in the technologist's responsibility to protect the critical care patient from skin breakdown that could lead to infection. Removal of electrodes can occur at various stages of the EEG monitoring. Thus, it is important for the technologist to understand why the electrodes are being removed and if there is any need for reapplication before determining what method to use for removal. All of these technical considerations collectively result in optimal cEEG monitoring of the critical care patient.

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# Staffing Considerations for ICU EEG Monitoring

# 35

J. Andrew Ehrenberg, Andres Rodriguez, and Suzette M. Laroche

## Contents



J.A. Ehrenberg, BSc, R EEG T, CNIM (✉)
Neurophysiology, Emory University School of Medicine, Atlanta, GA 30307, USA
e-mail: joshua.andrew.ehrenberg@emory.edu

A. Rodriguez, MD
Neurology, Emory University School of Medicine, Atlanta, GA 30307, USA

Neurophysiology, Emory Healthcare, Atlanta, GA, USA

S.M. Laroche, MD
Mission Health Epilepsy Center, 509 Biltmore Avenue, Asheville, NC 28801, USA
e-mail: suzette.laroche@msj.org



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## Introduction

EEG monitoring in the intensive care unit (ICU) setting has been in existence for many years. Decades ago, early paper EEG acquisition units were lumbered up to the ICU bedside for intermittent recording, averaging 10 min per hour. However, EEG monitoring was used sparingly due to limitations in equipment, data storage, and staffing resources. Fortunately, EEG technology has changed significantly since the initial recording by Hans Berger in 1929 [1]. Computers have allowed for smaller recording systems, and digital storage has grown to where a significant amount of EEG and digital video can be stored in a negligible amount of space [2]. Processing power has developed to allow for computation and display of multiple "trends" of quantitative EEG (qEEG) while data network capabilities permit real time, remote viewing of patient EEG and video data. By early 2000, panel PC-based EEG systems dedicated and designed for the ICU environment became available [3].

However, technological changes alone could not facilitate the growth that has been seen in the field of ICU continuous EEG monitoring (cEEG), staff resources had to be advanced as well. EEG clinical staffing was no longer restricted to daytime hours from Monday through Friday as EEG monitoring in the critical care setting required around the clock staffing. In addition, neurophysiology staff members were expected to identify and respond quickly to serious situations found in this new critical care world. Therefore, there was a new and unique set of knowledge and skills required.

## Types of Staff: Roles and Responsibilities

Traditionally, EEG departments are staffed with the focus on providing routine EEG needs. A typical patient load for an outpatient neurodiagnostic technologist would include performance of four to eight routine EEGs in one day. In many ways, the standard outpatient EEG mentality was translated into the hospital inpatient setting with similar expectations: technologists and interpreting physicians working during daytime hours with results available to the ordering physician by the next day. However, it became quickly evident that this traditional staffing paradigm would not be sufficient when EEG services were extended to critically ill patients.

ICU EEG monitoring has increased dramatically over the last 10 years at a rate of about 33 % per year [4]. A survey of neurologists and neurological intensivists showed that despite the growth in monitoring volume, physicians considered institutional resources inadequate as far as the number of EEG technologists, EEG acquisition units, and interpreting neurophysiologists [5]. Typically the cEEG is recorded continuously but reviewed intermittently as demonstrated in the same study which reported that 23 % of institutions review studies once per day, 35 % twice per day, 25 % three times per day, and 11 % four or more times per day. Only 13 % reported nearly continuously monitoring of the recording [5]. Since it is often not possible to review the studies continuously due to the lack of staffing, seizure

recognition may be delayed. However, experts agree that identifying seizures at any point in time is preferred to the alternative of no seizure detection at all [6].

With the growth of ICU EEG, the standard staffing model has presented many challenges. The question arises: What should the new paradigm look like? Several designs have been successfully implemented and should be considered. The four main aspects that define the optimum staffing structure for an individual institution include (1). determination of number and type of staff required to meet EEG monitoring needs and expectations, (2). recognition of current staff knowledge and additional training required, (3). identification of financial opportunities and constraints, (4). and recruitment and retention of specialty-trained staff. A consensus statement from the American Clinical Neurophysiology Society (ACNS) offers key suggestions regarding personnel, technical specifications, and clinical practice [6]. These recommendations highlight qualifications and responsibilities of various levels of EEG personnel, standards for cEEG acquisition equipment and data storage, as well as examples of standard cEEG operating procedures and protocols for EEG review and reporting.

In addition, the American Society of Electroneurodiagnostic Technologists (ASET) has defined neurodiagnostic practice levels and core competencies for EEG personnel performing continuous EEG recordings in the critical care setting which can be used for the development and implementation of institutional policies and procedures [7]. While there are slight differences between the ACNS and ASET neurodiagnostic staff titles and job descriptions, this chapter will highlight common features to assist in defining a staffing structure for implementation of an ICU EEG monitoring program.

## Neurodiagnostic Technologists

In the advancing realm of neurophysiology, especially in the ICU arena, the role of a neurodiagnostic technologist has become much more diverse. Both ACNS and ASET define basic and advanced neurodiagnostic skill levels (Table 1). The primary distinction between levels is determined by duration of clinical experience and EEG registry (R. EEG T., from ABRET Neurodiagnostic Credentialing and Accreditation). However, as credentials are not universally required, each institution should still define specific job descriptions and core competencies.

Neurodiagnostic technologists perform hands on initiation and maintenance of EEG recordings and are expected to have general EEG technical knowledge. Skills required include application of electrodes, operation of recording equipment, verification of network connectivity, identification of artifacts including electrode malfunction, and documentation of pertinent patient history and daily clinical changes. Additional skills specific to the ICU environment include understanding clinical issues that influence other testing and treatment the patient might be receiving, prioritization of the cEEG in relation to other care logistics, and communication with the ICU clinical staff. Identification of open wounds or surgical sites is critical for infection control as well as making decisions regarding electrode placement.

Organizing equipment and supplies and arranging all details before going to the patient's bedside is crucial in the ICU where time, space, and efficiency are necessary.

Daily maintenance of recordings is another area where specific knowledge applicable to the ICU environment is needed. Electrode application sites and lead wires should be checked at least daily, with focus on prevention of skin breakdown for which critically ill patients are at high risk. Positioning of equipment and supplies must take into account the entire clinical environment and equipment malfunctions must be dealt with quickly. Lastly, daily reactivity testing is extremely important and requires a keen knowledge on the technologist's part of how to perform and modify under various clinical considerations and be sensitive to family presence. Neurodiagnostic technologists typically operate at a ratio of one staff for every four to eight patients undergoing EEG monitoring. However, the complexity of the specific patient population has to be considered in order to determine optimum staff ratios.

## Neurodiagnostic/ICU cEEG Specialists

Neurodiagnostic specialists require clinical knowledge and responsibility beyond what basic technologists can be expected to provide (Table 1). It is important to emphasize that the role of neurodiagnostic specialists is not to replace the ICU EEG-trained physician neurophysiologist but rather to support and work under their direct supervision for the purpose of expanding capacity and improving efficiency. As opposed to neurodiagnostic technologists, neurodiagnostic specialists may not be located at the same physical location as the patients undergoing EEG monitoring but in a centralized location either elsewhere in the facility or remotely, particularly in programs where multiple hospitals are being monitored by one integrated staff. In addition to monitoring patients in "real time" to identify and respond to critical changes, they also might prepare descriptive EEG reports, which, the neurophysiology physician will review for final interpretation and clinical correlation. Typical staff-to-patient ratios vary but with an average maximum of six patients assigned to each specialist in order to ensure quality of care.

The neurodiagnostic specialist must possess high levels of knowledge in specific areas. While senior level EEG technologists have been serving in similar roles for many years, only recently has there been progress toward formalization of this role across the field of EEG monitoring. Knowledge expectations are not simply EEG pattern recognition but a comprehensive understanding of the impact of any significant EEG change on the patient's overall clinical care. For example, a neurodiagnostic specialist would not only be expected to recognize electrographic seizures but also identify changes in background activity and how those changes are impacted by medications and the overall clinical status of the patient. An additional skill that is vital to the neurodiagnostic specialist is the ability to communicate critical EEG changes to the appropriate team in a timely and efficient manner.

Neurodiagnostic specialists should have at least 3 years of EEG experience including exposure to ICU EEG monitoring. EEG registry is required and

**Table 1** Staffing types

| ASET Job title [11] | ACNS Job title [6] | Minimum education recommendations | Job description | Registration |
|---|---|---|---|---|
| Neurodiagnostic Technologist I (NDT I) | Neurodiagnostic Technologist I (NDT I) | Associate degree or enrolled in neurodiagnostic program | Electrode application and maintenance | No registration |
| Neurodiagnostic Technologist I (NDT I) | Neurodiagnostic Technologist II (NDT II) | Associate degree or enrolled in neurodiagnostic program<br>6 months NDT experience | Performs EEG under technical supervision | Eligible for registration in EEG by ABRET, (R. EEG T.) |
| Neurodiagnostic Technologist II (NDT II) | Neurodiagnostic Technologist III (NDT III) | Associate degree or appropriate clinical experience | Perform EEG independently | Registration in EEG by ABRET (R. EEG T.) |
| ICU/cEEG Specialist I | Neurodiagnostic Specialist I (NDS I) | 3 years of NDT experience, with 1–2 years in ICU cEEG | NDT III responsibilities<br>Identification of ictal and interictal patterns<br>Expertise in QEEG<br>Notification of findings and descriptive analysis | Meets ASET National Competency Skill Standards for CCEEG<br>ACNS: Certification in Long Term Monitoring by ABRET (CLTM) |
| ICU/cEEG Specialist II with management duties | Neurodiagnostic Specialist II (NDS II) | ASET: 2 years of ICU EEG experience<br>ACNS: 3 years of ICU EEG experience after CLTM | Development of technical policies and procedures<br>Supervision and training of NDT, nurses, and other ICU staff | Certification in Long Term Monitoring by ABRET (CLTM) |

*Abbreviations*: *ASET* American Society of Electroneurodiagnostic Technology, The Neurodiagnostic Society, *ACNS* American Clinical Neurophysiology Society, *ABRET* American Board of Registration of EEG Technologists, Neurodiagnostic Credentialing and Accreditation, *QEEG* quantitative EEG

Certification in Long Term Monitoring (CLTM; from ABRET) is recommended. Specific training programs have been employed by some centers in order to provide appropriate education to technologists wishing to pursue a career as a neurodiagnostic specialist. Specific content areas in the training should include neuroimaging, neuropharmacology, and a basic clinical understanding of the common disease entities encountered in critical care units. Competency in the use of ACNS Standard Critical Care EEG terminology is also crucial [8]. Structurally,

these programs include a combination of formal didactics, clinical teaching, and practical experience.

## Non-EEG Procedural Staff

Non-EEG procedural staff include those who typically have their primary function in some other clinical role, such as nursing care, but who have received limited, targeted training to function as ancillary staff. Some care models include use of nursing staff to initiate EEG recordings "after hours" [9]. This is usually accomplished with the aid of electrode templates or EEG caps to guide electrode placement or limited recording montages such as a hairline recording. The increased use of qEEG measures has made bedside monitoring for identification of significant EEG changes including seizures feasible for non-EEG-trained staff. Neurocritical care nursing staff are ideally suited to train in pattern recognition of qEEG trends. Studies have demonstrated that with minimal training, critical care personnel (including attendings, fellows, and critical care nurses) are able to detect seizures using qEEG. In one study there was little difference in the sensitivity of seizure detection between neurophysiology fellows, critical care nurses, and physician attendings [10].

Lab assistants, or non-EEG-trained clinical staff, can help free up more highly trained EEG staff to focus on areas where their skills and knowledge are maximized. Lab assistants can help with gathering and stocking supplies, cleaning of equipment, and removal of electrodes. A safety measure taken in some institutions is to have a non-EEG staff monitor patient video in real time. It is important to be aware that staff performing this type of cEEG "monitoring" are watching video only and therefore can only detect obvious clinical seizures and events. While such non-EEG-trained patient monitors can have great utility in settings such as the epilepsy monitoring unit, it must be clear that there are certain limitations of employing non-EEG monitoring staff in the ICU setting given the majority of electrographic seizures in this patient population are without clinical correlate, and there are a variety of involuntary, non-seizure-related movements that could be mistaken for ictal events. As long as these considerations and limitations are well understood and communicated, non-EEG video monitoring staff can be very beneficial.

## Neurophysiology Administrative Staff

Administrative support will vary depending on the size of the program. Tasks can include billing, productivity tracking, patient appointments and communication, as well as staff scheduling, although not all of these tasks are necessarily accomplished by the same person. While the same administrative staff usually supports the entire EEG and epilepsy monitoring programs, it is important to factor in the additional workload represented by initiation or growth of ICU EEG monitoring.

The neurophysiology technical director serves a key function in bridging the gap between the priorities of the clinical team and objectives of hospital administration,

which are not always congruent. The medical director provides a leadership role within the ICU EEG team and ensures that facility policies and procedures are in compliance with current medical standards. While managing day-to-day operations and logistics is essential, the neurophysiology director's most important role is ensuring long-term goals are being met including program growth and development. This includes staying up to date with the latest information within the field and incorporating new technologies.

Information technology (IT) support has become essential in ICU EEG programs. This can be accomplished by a "superuser" technologist with additional IT training and knowledge, a member of biomedical or clinical engineering with expertise in data networks and familiarity with EEG acquisition hardware, or, ideally, dedicated IT staff for all neurophysiology functions. IT support should ensure computer data security and address network management, data storage, and remote monitoring. They can also be essential in identifying the root cause of equipment malfunctions, whether vendor specific or due to facility infrastructure so that the correct resources can be assigned.

Another key administrative role is the EEG educator, especially in large programs. Recruitment and retention of valuable staff needed for an ICU EEG program can be enhanced with a well-organized educational program, of which the educator is a key component. Training internal staff to higher levels of knowledge provides a means to meet future growth requirements and improves staff retention by offering personal growth opportunities to individual EEG technologists. In some institutions, there are also needs for formal nursing education programs that include basic EEG and epilepsy knowledge for which the EEG educator plays a key role.

## Physician/Electroencephalographer

A team of physicians with specialized training in clinical neurophysiology is required for interpretation of cEEG monitoring, particularly at high volume cEEG programs. Physician neurophysiologists should have completed fellowship training in clinical neurophysiology with concentration in EEG including interpretation of continuous recordings in critically ill patients. EEG recordings in the ICU can be particularly challenging given the complexity of periodic and rhythmic patterns as well as the abundance of artifacts. Therefore, it is recommended that physicians receive supervision in the interpretation of at least 100 ICU EEG studies, which should include recognition of seizures, status epilepticus, ischemia, and other EEG changes seen in the setting of acute brain injury [4]. In addition, competence in the analysis and utility of qEEG is recommended, including knowledge of the limitations. Physicians interpreting ICU EEG recordings are also expected to maintain certification by the American Board of Clinical Neurophysiology and/or the American Board of Psychiatry and Neurology (ABPN) with subspecialty in clinical neurophysiology or epilepsy [4].

The neurophysiologist serves as the communication link between the EEG team and critical care physicians and is therefore responsible for ensuring that protocols are in place for effective and timely reporting of any significant EEG change and

possible clinical correlations. In some centers, physicians also perform the role of team leaders as well as teachers of residents, fellows, and EEG staff. Continuous EEG in the ICU poses new challenges to physicians. This patient population can require nearly continuous or at least very frequent review of the EEG. Given other physician responsibilities, this can be difficult, especially in centers with limited staffing. In larger centers, the physician neurophysiologist often works very closely in conjunction with EEG fellows, technical staff, and other physicians to make frequent EEG interpretation more manageable. However, after hours and during weekends, physician staffing is often limited and strict adherence to protocols to ensure appropriate patients are being selected for monitoring is essential as well as assistance from neurodiagnostic specialists.

## Recruitment and Retention

As there are limited numbers of centers performing high volume ICU EEG monitoring, there are obvious challenges associated with the recruitment of qualified EEG staff. One option is to recruit non-ICU-specific EEG technologists and train them to be competent in the critical care environment. Ideally this would include EEG staff with epilepsy monitoring experience as it is most easily translated to ICU EEG. Even for technologists with some ICU EEG experience, there can be challenges given the heterogeneity of patient populations in the critical care environment. For example, neonatal ICU EEG monitoring requires different skills than adult monitoring as does EEG monitoring for ischemia compared to seizure detection. The traditional method of recruiting qualified staff has been through ensuring competitive pay compensation. However, many EEG technologists have other primary factors that influence their eagerness to join a program and their willingness to stay including opportunities to learn and develop new practices, being a member of a passionate and interactive team, chance to teach others in an academic environment, and involvement with research.

### Neurodiagnostic Specialists and Clinical Research

An added benefit of incorporating neurodiagnostic specialists into EEG monitoring programs is the opportunity to involve them in clinical research projects. The increasing demand of productivity concurrent with reduced funding can limit the physician's time for involvement in clinical research. Neurodiagnostic specialists can contribute to EEG-focused research projects in a number of ways including identification of potential study subjects, review of EEG recordings, and collection and de-identification of EEG data. The opportunity to be involved in cutting edge research can also serve as a means of retaining highly experienced EEG staff.

## Staffing Models

Several staffing models and variations are currently employed by centers performing ICU EEG monitoring (Table 2).

**Table 2** Staffing models

| Model type | Hospital type | cEEG volume | Staff required | Number of acquisition units | IT requirements |
|---|---|---|---|---|---|
| Continuous | Large Academic Center<br>Large Healthcare System | >6 per day | 5+ NDT I/II/III<br>3+ NDS I/II<br>3+ clinical neurophysiologists<br>Neurointensivist or neurohospitalist support | 8+ | Cloud-based or large external server<br>Dedicated IT support |
| Hybrid | Small Academic Center<br>Midsize Hospital | 3–6 per day | 3–4 NDT I/II/III<br>1–2 NDS I/II<br>1–3 clinical neurophysiologists<br>General neurologist or neurohospitalist support | 6–7 | Medium-size local server<br>Shared IT support |
| Limited | Small Community Hospital | ≤ 2 per day | 1–2 NDT I/II/III<br>1–2 Clinical neurophysiologists<br>May elect for externalizing EEG services<br>Onsite or on-call general neurologists | 2–3 | Disk storage or small-size local server |

*NDT* neurodiagnostic technologist, *NDS* neurodiagnostic specialist

## Continuous Monitoring

From a patient care perspective, the preferred model would provide continuous, real-time EEG monitoring for all patients at all times of the day. This model requires a large investment of resources and is therefore rarely employed and is typically seen only at large high volume academic medical centers [11]. Epilepsy monitoring services are usually provided at these programs as well so that the burden of around the clock staffing can be shared. Resource requirements include in-house neurodiagnostic technologists as well as a team of neurodiagnostic specialists for real-time EEG assessment, typically operating from a centralized location. Physician neurophysiologists must be available for rapid EEG interpretation and clinical correlation at all hours and be able to communicate findings quickly to the clinical team responsible for patient care. Many large ICU EEG monitoring centers currently offer a variation of this model, which provides continuous, real-time monitoring during the majority of the day and evening but with only intermittent review throughout the night. This variation of the continuous monitoring model is commonly referred to as continuous EEG recording with frequent, intermittent review.

## Hybrid Model

A hybrid model is sometimes used where both EEG-specific staff and non-EEG-specific staff (typically critical care nurses and/or physicians) are utilized. The

EEG-specific staff usually provide coverage during weekdays, while after hours and weekends are covered by non-EEG staff, who are required to possess basic skills of electrode placement (often employing limited montages or EEG templates or caps), EEG initiation, and troubleshooting. The feasibility of employing the hybrid model has been formally assessed and found to significantly increase the availability and speed of EEG initiation, while having minimal impact on the short-term quality of EEG recording [9]. However, it is important to take into account the additional training and workload that this model requires of ICU nursing staff. Furthermore, if prolonged EEG recording is required, it should be anticipated that electrode placement would be revised using standardized methods when trained neurodiagnostic staff are available. In institutions employing a hybrid model, continuous EEG monitoring and review is often not available outside of daytime operating hours.

## Limited Staffing Model

In smaller institutions where low volume of ICU EEG is expected and neurodiagnostic technologists as well as finances are constrained, a limited staffing model can be considered. With this arrangement, new cEEG hookups and routine maintenance are only offered during daytime hours with little or no coverage after hours and on weekends. This model is often the initial step toward later developing more comprehensive monitoring services. Since this model only allows for intermittent review as opposed to continuous real-time monitoring, qEEG trending software can assist with timely identification of critical events. However, critical patients requiring more frequent EEG review in order to dictate clinical management should be considered for transfer to a center that can provide more comprehensive EEG monitoring.

## On Call Versus In-House After-Hours Staffing

Deciding on use of on call versus in-house technical staff for coverage of after-hours services is both a clinical and financial issue. Often institutions will utilize on-call neurodiagnostic technologists during initial program development and later transition to full-time in-house staffing as volume grows, while other healthcare systems use a mixture of both. On-call staffing allows for expanded night and weekend coverage without a significant increase in the number of technical staff. However, excessive overtime pay can become expensive and frequent overnight callbacks can contribute to staff burnout. In-house staff provide continuous coverage without premium on-call costs and allow for rapid initiation of EEG monitoring. However, maintaining in-house neurodiagnostic staff at all hours can be less cost-effective if volumes are not sufficient. A cost-benefit analysis should be done to compare the cost of callback pay to in-house staffing to determine the ideal model for a given institution's patient volume.

## Contract Services

Given the challenge of recruiting and retaining the highly qualified staff required to operate an ICU EEG monitoring program, smaller institutions may opt for contracting these services from either a larger institution that has the resources to cover additional volume or from a private company. There are several different ways in which contract EEG services can be utilized depending on the needs of the individual institution. Contract staff can be used to fill one particular level of experience (e.g., neurodiagnostic specialists to provide EEG screening and monitoring) or can be offered as a "full service" package including all levels of cEEG neurodiagnostic needs. Other facilities may employ contract services for night shifts or weekends when in-house technical staffing is insufficient or when patient volume rises above what in-house resources can safely manage.

While it is easy to see the potential benefits of such an arrangement, there are limitations that must also be considered. Neurodiagnostic procedural staff that initiate EEG recordings must be familiar with the inpatient environment of the individual institution which can require significant training as well as credentialing. Therefore, it is usually more time and cost effective to utilize in-house technologists. Neurodiagnostic specialists that are contracted for remote EEG monitoring can more easily adapt to working with a diversity of inpatient settings but must be familiar with each hospital's method of communication and reporting. For most efficient utilization of external services, a small group of contracted neurodiagnostic specialists could be assigned to an individual institution so that recurrent training is at a minimum. Cost must also be weighed as contract services are generally more expensive than using full-time, employed staff. Additional factors to consider include travel time and logistics of remote access and networking. One final but very important drawback of the externalization of services is that the cohesive interaction between the EEG team and the clinical ICU staff can become fragmented which can ultimately affect patient care.

### Conclusions

The field of ICU EEG monitoring has evolved significantly over the years, incorporating numerous technological advances. However, despite technical advances, experienced neurodiagnostic staff are the most valuable and limited resource needed for implementation of a successful cEEG program. Procedural neurodiagnostic technologists are the "nuts and bolts" of any program and are responsible for the majority of direct patient contact in the form of initiating and maintaining technically adequate recordings. Neurodiagnostic specialists fill a new and important role in light of rapidly expanding of cEEG services to allow for continuous monitoring and rapid detection of clinically significant EEG changes. In locations with limited staffing, non-EEG personnel with targeted training and clearly defined responsibilities are a valuable resource while larger programs require administrative support staff, dedicated information technology, oversight by a technical and medical director, and EEG educators. Physicians should have formal neurophysiology training with emphasis in EEG recording in

critically ill patients. Physicians interpreting ICU EEG studies must be able to provide appropriate clinical correlations and clear communication between multidisciplinary teams while providing education and leadership to the program as a whole.

As demands for cEEG differ across various healthcare settings, customized staffing models can be employed that range from continuous monitoring and hybrid models to limited staffing scenarios. Each of these models has both benefits and drawbacks that should be analyzed carefully as staffing decisions are made. Lastly, contracting of EEG services can clearly provide benefits, particularly in locations where staffing resources are limited, but have logistical and clinical concerns that must be taken into account. While staffing an ICU EEG monitoring program can prove challenging, when careful consideration is given toward incorporating appropriately trained neurodiagnostic personnel into the properly chosen staffing model, the result will be a successful program that benefits patient care and provides rewarding career opportunities.

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# Coding and Billing Considerations

# 36

Marc R. Nuwer

## Contents



M.R. Nuwer, MD, PhD
Department of Neurology, David Geffen School of Medicine at UCLA,
Los Angeles, CA, USA

Clinical Neurophysiology, Ronald Reagan UCLA Medical Center, Los Angeles, CA, USA

UCLA Department Neurology, Reed Neurological Research Center,
710 Westwood Plaza, Los Angeles, CA 90095, USA
e-mail: MRN36@icloud.com



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## Introduction

Our profession requires administrative procedures to ensure patient safety, maintain efficient organization, and facilitate communication. These include public policy regulations about coding, billing, reimbursement, privileging, and staffing. Physicians must work within those regulations and professional business standards. EEG has been used in intensive care unit (ICU) monitoring for many years. The modern generation of full scalp EEG continuous monitoring with trending and digital automated routines now has been used in the ICU for more than 30 years [1]. It has grown to be widespread [2] and for a variety of uses [3]. Policies are described here about critical care neurology and EEG monitoring with an emphasis on aspects that affect coding.

## Current Procedural Terminology Coding

The American Medical Association's Current Procedural Terminology (CPT®) is used in the United States to specify procedures performed [4]. It includes more than 8,000 codes for medical, surgical, and diagnostic procedures. Codes covered here are used for ICU EEG monitoring and critical care patient management. Current procedure terminology includes several choices for continuous ICU EEG monitoring. These are listed in Table 1.

### Codes 95951 and 95956

The most common codes for continuous ICU EEG monitoring are 95951 and 95956. They code for 24-h EEG recordings. Both codes require that interpretations can be made throughout the recording time, and, based upon those interpretations, some clinical and technical interventions can be made to alter or end the recording or to alter the patient care during the recordings as needed. In other words, these are true monitoring codes that can affect patient care. They are not simply prolonged EEG recordings. They allow for active influence of patient care during the recording period.

Code 95951 specifies, "monitoring for localization of cerebral seizure focus by cable or radio, 16 or more channel telemetry, combined EEG and radio recording and interpretation (e.g., for presurgical localization), each 24 h." This code typically and traditionally is used in the inpatient epilepsy monitoring unit (EMU). It requires video recording and review along with EEG. Cable-hardwired recording systems may be substituted for radio telemetry. The service describes monitoring in which a clinician can read the record during the recording as needed. The recording is continuously monitored. Note that it requires at least 16 channels.

Code 95956 specifies "monitoring for localization of cerebral seizure focus by cable or radio, 16 or more channel telemetry, EEG recording and interpretation, each 24 h, attended by a technologist or nurse." Like the EMU code above, this code

**Table 1** CPT codes used for continuous ICU EEG monitoring

| | |
|---|---|
| The EEG services include recording, interpretation, and report by a physician or other qualified health-care professional. For interpretation only, use modifier 26 | |
| Codes 95812–95822, 95951, and 95956 use recording time as a basis for code use. Recording time is when the recording is underway and data is being collected. Recording time excludes setup and take down time | |
| In addition, services and skills outlined under evaluation and management levels of service appropriate to neurologic illnesses should be reported similarly | |
| *Routine electroencephalography* (*EEG*) | |
| EEG codes 95812–95822 include hyperventilation and/or photic stimulation when appropriate. Routine EEG codes 95816–95822 include 20–40 min of recording. Extended EEG codes 95812–95813 include reporting times longer than 40 min | |
| Electroencephalogram (EEG): | |
| *95812* | Extended EEG monitoring, 41–60 min |
| *95813* | Extended EEG monitoring, greater than 1 h |
| *95816* | Recording EEG awake and drowsy |
| *95819* | Recording EEG awake and asleep |
| *95822* | Recording EEG in coma or sleep only |
| *95824* | Cerebral death EEG evaluation |
| *95827* | All night EEG recording |
| *Special EEG tests* | |
| Codes 95951 and 95956 are used per 24 h of recording. For recording more than 12 h, do not use modifier 52. For recording 12 h or less, use modifier 52. Codes 95951 and 95956 are used for recordings in which interpretations can be made throughout the recording time, with interventions to alter or end the recording or to alter the patient care during the recordings as needed | |
| *95951* | Monitoring for localization of cerebral seizure focus by cable or radio, 16 or more channel telemetry, combined electroencephalographic (EEG) and video recording and interpretation (e.g., for presurgical localization), each 24 h |
| *95956* | Monitoring for localization of cerebral seizure focus by cable or radio, 16 or more channel telemetry, electroencephalographic (EEG) recording and interpretation, each 24 h, attended by a technologist or nurse |

Taken from: Current Procedural Terminology [4] (Copyright American Medical Association)

requires a clinician who can review the record during the recording as needed and make changes in patient care during the time of the recording. This code differs from 95951 because it does not include video monitoring or review. It specifies that the recording be attended by a nurse or technologist, i.e., someone is keeping an eye on this EEG continuously, either at the patient's bedside or at a central station. This code also requires at least 16 channels.

## Codes 95813 and 95827

Two other EEG codes deserve special mention: codes 95813 and 95827. Code 95813 specifies, "extended EEG, greater than 1 h." This code has several original purposes.

One such purpose was as a bedside EEG machine in the early days of ICU EEG monitoring in which the paper recording might last for only 4–8 h during the day. It does specify more than 1 h of recording. Because it was originally defined during the paper EEG era, the original definition allowed the EEG to be turned on and off at the bedside by the nurse or technologist so as to save paper. In the digital era, an analogous procedure is that the record may be reviewed in portions instead of reviewing the entire digital record, i.e., auditing a record. Another use of this code is for neonatal EEGs that may take 90 min to record quiet and active sleep and awake state. This code allows interpretation to be made after the record is completed. The present use of 95813 is for certain insurance companies that have not yet approved the use of 95951 or 95956 but will allow for 95813 for ICU EEG monitoring. Those companies have yet to update their carrier policies to the modern era of ICU EEG monitoring.

Code 95827 specifies "overnight EEG." This code is a predecessor to polysomnography codes. It is used most commonly in sleep labs for patients receiving a full EEG during an overnight stay in order to assess for seizures as a cause of a parasomnia. It has been used for the physician interpretation of that EEG record. It is not typically used in the ICU setting but might occasionally be used when a simple overnight EEG is desired without true monitoring.

## Twenty-Four Hour Clock

Coding requires a 24-h clock for monitoring services 95951 and 95956. Modifier 52 is used if less than 12 h is recorded. There is no clear definition of the lower limit of time for use of the 52 modifier. Hospitals should decide how they code time. In very short stays, it is most convenient to use a *simple 24-h clock*. If a test started at 3 PM on Tuesday and ended at 11 AM on Wednesday, code for one unit of 95951 or 95956. However, when a service is extended for several days, many hospitals and professionals often use the *calendar day rule*. Under this rule, each calendar day is coded separately. If a test started at 3 PM on Tuesday and ended at 11 AM on the following Monday, code for Tuesday and for the next Monday using a 52 modifier and code for Wednesday through Saturday as full days without the 52 modifier.

Some professionals use other clock time rules, such as the *service day rule*. Take the example of a service that typically changes attending physicians in the morning. They may use a 24-h clock set to the time of morning change of service, e.g., 9 AM. If in the course of a 6-day monitoring 2–3 different attending physicians monitored the patient, then the coding is allocated among the attending physicians by the time of change of responsibility. Using this rule, if the patient was hooked up at 3 PM on Tuesday and Dr. Jones monitored until change of shift at 9 AM on Wednesday, then Dr. Jones will code without modifier 52 for her 18 h of monitoring service. The subsequent attending will pick up the monitoring at that point in time. Because there are at least three different ways to count monitoring, each hospital's service is highly encouraged to have a written policy in place to describe the particular rules used at their institution and to keep that written policy and procedure available in case of any internal or external audits.

## Reports

Reporting can be done by event, by day, or for the entire monitoring period. This is for the formal final written signed report of the monitoring itself. For ICU monitoring, the frequency of feedback to the critical care team varies with patient care needs. In some hospitals, critical care and clinical neurophysiology teams are integrated. In many others, these are two separate services that must maintain excellent communication.

Reports generally include several components. These are the time of monitoring, reason for monitoring, techniques used, interpretation of events individually or collectively, and overall impression and comments about clinical meaning of the results. In some hospitals, separate notes are entered daily. In others, the notes are cumulative with periodic updates added to the same note so that progression of change is more easily tracked over time. Any form of written note is acceptable. What is most important is to have a system in place that communicates well the EEG findings so as to integrate that into the care plan for the critical care patient.

## Trending

Trending is a tool used for monitoring. Monitoring of EEG over extended periods of time in an ICU is enhanced by trending some EEG features. This substantially assists with identifying EEG variability and intermittent events. It allows the reviewing physician to more quickly find particular recording times that need focused attention. It also allows a view of EEG variability over long stretches of time, changes that might be missed if one is evaluating only the visual EEG on individual pages. Trending does not change the CPT code used. There is no additional code for the use of trending as a part of monitoring. Just as for spike and seizure detection in the EMU, these digital tools are a part of the service included in codes 95951 and 95956.

## Modifiers

Modifier 52 is described above for flagging a 24-h service that was provided for less than 12 h.

Modifier 25 is used with the evaluation and management (E/M) code provided on the same day by the same physician as a procedure. For most carriers, it is not necessary to use modifier 25 when providing an EEG service, e.g., EEG monitoring. Occasionally, a carrier might insist on using modifier 25 with an E/M on the same day as an EEG. There is no disadvantage to doing so other than the slight additional work of entering the modifier itself while coding. Modifier 25 is required on the E/M code when also providing some other types of procedures. For example, when performing a spinal tap or trigger point injection on a patient, modifier 25 is required with an E/M procedure on the same day by the same physician.

Modifier 59 is used to identify when two different procedures in the same family of services are performed on the same day. This code signifies that the two different procedures are separate and both should be coded. For example, an inpatient EEG test might be performed in the morning, and it indicates that the patient is at risk for nonconvulsive seizures. That EEG leads to the patient being placed on continuous monitoring later the same day. Those are two separate procedures because they were separated in time. Modifier 59 is used with those procedures to identify that they are separate in time and separate procedures. Some carriers also use modifier XS in place of modifier 59 to specify that these are two separate services. Some carriers use modifier XP in place of modifier 59 if the two procedures were read by different physicians. It specifies that not only were the two procedures separate procedures and separate in time but also that they were interpreted by separate physicians. Not all carriers use the XS or XP modifiers.

However, when a routine EEG is performed as the baseline portion of a continuous ICU EEG monitoring, it should not be coded separately. That initial baseline recording is a bundled part of the monitoring itself, so it is not a separate procedure. These two parts of the recording generally are neither separated in time nor do they require separate application and removal of electrodes.

## Code 95957

Code 95957 specifies, "digital analysis of EEG, e.g., for epileptic spike analysis." This is used for dipole localization, i.e., source localization. It should be used only for a separately identifiable procedure. The typical use is for three-dimensional dipole modeling in presurgical epilepsy evaluations. It requires a separate report and separate work [5]. This code may not be used for spike and seizure detection. It also should not be used for simple trending. Codes 95951 and 95956 include those latter services as inherent parts of those codes themselves. In general, this would entail an extra hour's work by the technician to process the data from the digital EEG and an extra 20–30 min of physician time to review the technician's work and review the data produced.

## Integrated Total Power

Integrated total power monitoring is used for some neonatal ICU patients. It is comparable to compressed spectral array (CSA) monitoring used in adult ICU patients. It is usually recorded in two or four channels. There is no CPT code for this service. When it is performed in the neonatal ICU by neonatologist, it is included in the neonatologist's daily visit code. When it is interpreted separately by a clinical neurophysiologist, use code 95999, "unlisted neurodiagnostic procedure."

### Telemonitoring

Telemonitoring is becoming more popular. Interpreting EEG is not inherently tied to any distance. It is technologically possible to read an EEG at a long distance from the site at which the EEG was recorded. Telestroke and tele-ICU practices are increasing in popularity for clinical patient care purposes. For interpreting EEG at remote sites, the physician should be on the medical staff of the hospital in which the patient is hospitalized, privileged for EEG at that site, and licensed in that state. Communications with the critical care physician and the local hospital should be straightforward, and documentation in that hospital's medical record should be the same as if the physician were practicing in his or her own local hospital. As at any site, the EEG should be continuously monitored by a nurse or technologist and for smaller hospitals that might be done at a centralized remote site away from the local hospital itself.

## Diagnostic Coding

With the change to ICD-10, the new seven-digit alphanumeric system has changed the coding for diagnoses with which the physicians have become familiar. The new seizure codes are arranged in a family that is similar to the ICD-9 families. Status epilepticus has many ICD-10 codes which depend upon whether the seizures are focal or generalized and depend upon the type of epilepsy and whether it is intractable or not. One code commonly used for ICU EEG monitoring patients with nonconvulsive seizures may be G40.803, other epilepsy and recurrent seizures, intractable, with status epilepticus.

### Linkage Tables

Carriers create policies about which ICD diagnoses are considered medically necessary for particular CPT codes. This automates decisions about whether a procedure is "medically necessary." These paired ICD-CPT lists are called "linkage tables." They are implemented in carrier computer systems. When a CPT procedure is submitted for payment with ICDs none of which are on the carrier's linkage table for that procedure, the computer automatically returns a denial that the procedure is considered "not medically necessary." One can reinterpret the statement "not medically necessary" as meaning, "That ICD code is not on our linkage table for that CPT procedure."

The epilepsy ICD codes are generally accepted to justify providing EEG CPT codes. Other diagnoses are variably treated. As a result, it is important to consider the ICD codes used when providing EEG services. This is especially so for 24-h EEG codes 95951, which was designed initially for epilepsy monitoring unit (EMU) use. Some carriers still link 95951 solely to typical EMU diagnoses.

Medicare carriers linkage table are online [6]. Some states require all carriers to make available the linkage tables and other rules used for coverage determinations. It

can be very helpful for users to obtain the linkage tables for their main local carriers so as to understand which diagnostic codes are considered acceptable. That is true for two reasons. First, each patient often has several reasonable ICD codes that apply to their case. One should use codes that are not only correct but also on that carrier's linkage table for that procedure. That avoids the need to exchange appeals of denials in order to achieve payment. Second, it allows the physician community to point out to the carrier's medical director any missing ICD codes that ought to be on the linkage table.

Listing more than one diagnosis on a charge document can help with the automated computerized linkage tables. As noted above, denial of payment occurs if the physician codes for a procedure but the diagnosis given is not on the carrier's list of approved diagnoses. By listing several diagnoses, each of which was true for the patient and part of the considerations of the physician during the service, one decreases the chances of a denial of payment.

## Hierarchical Condition Category Codes

Hierarchical condition category (HCC) coding is a coding system not familiar to many physicians. Nevertheless, it is important to reimbursements. It is used to set the patient's acuity level. HCC may determine hospital's payment for a patient's stay. Sometimes it determines the physician's payment, especially within advanced model payment systems. ICD diagnostic codes are bundled into groups of HCCs. The HCCs are associated with acuity coefficients, often called risk adjusted factor (RAF) scores. The more severe the diagnoses, the higher is the payment. When caring for a patient in the hospital, it is important to code for all of the medical conditions that were encountered in the care of the patient. This will influence the HCC into which the payment is grouped. As medical care moves into the greater realm of value-based reimbursement schemes, these HCC codes and RAF scores will be more and more important in adjusting payment.

## Documentation

Documentation is important to support the diagnoses listed on the charge document and therefore the reason for doing the testing. Physicians should ensure that documentation supports the codes used on the charge document. Each applicable condition should be mentioned somewhere in the note. It is highly preferable to be clear and specific in the language of documentation. Physicians should recognize that auditors are not clinicians, they cannot read our minds, and they are not allowed to make deductions. They can only go by what is actually written. Therefore, actually specifying the diagnosis, severity, risk, complications, and other factors in one's note can justify the actual reason why the service was provided and allow the auditor more easily to see that when reviewing that single note. They may not have the full hospital record in hand.

## Evaluation and Management Coding

Along with continuous ICU EEG monitoring, many physicians also provide evaluation and management (E/M) services on the same day. Some notes about critical care E/M codes are helpful as reminders about the constraints for the use of those codes. The term *critically ill* means "a high probability of imminent or life-threatening deterioration in the patient's condition" [7–9]. Although the patient may not be in crisis at the moment, patient must have a threat of immanent deterioration in at least one organ system. In many EEG monitoring patients, the organ system at risk is the nervous system. While using the critical care codes, the daily note needs to document not only that the patient was at immanent risk of deterioration but also why and what was being done about it that day. If the threat of immanent deterioration has waned, the patient is not a candidate for use of the critical care E/M codes even if the patient remains in an ICU bed. In the latter case, more routine inpatient subsequent day visit codes are suitable, e.g., 99233.

The usual CPT codes for ICU E/M critical care services are 99291 and 99292. These are given in Table 2. In contrast to the EEG monitoring codes that use *recording time*, these critical care codes are based on *physician time*. If more than one neurologist from the same group (the same federal tax identification number) provides E/M time to the patient that day, the times can be consolidated in a process

**Table 2** Current Procedural Terminology (CPT) for critical care

| *The CPT section for critical care is extensive. It has been abbreviated here. The following is from the CPT code section for the critical care is codes*: | |
|---|---|
| *99291* | *Critical care*, *evaluation*, *and management* of the critically ill or critically injured patient; first 30–74 min |
| *99292* | Each additional 30 min (list separately in addition to code for primary service 99291) |
| Critical care is the direct delivery by a physician or other qualified health-care professional of medical care for a critically ill or critically injured patient. A critical illness or injury acutely impairs one or more vital organ systems such that there is a high probability of imminent or life-threatening deterioration in the patient's condition. Critical care involves high complexity decision-making to assess, manipulate, and support vital system function(s) to treat single or multiple vital organ system failure and/or to prevent further life-threatening deterioration of the patient's condition. Examples of vital organ system failure include, but are not limited to, central nervous system failure, circulatory failure, and shock, renal, hepatic, metabolic, and/or respiratory failure. Although critical care typically requires interpretation of multiple physiologic parameters and/or application of advanced technology(s), critical care may be provided in life-threatening situations when these elements are not present. Critical care may be provided on multiple days, even if no changes are made in the treatment rendered to the patient, provided that the patient's condition continues to require the level of attention described above | |
| Providing medical care to a critically ill, injured, or postoperative patient qualifies as a critical care service only if both the illness or injury and the treatment being provided meet the above requirements. Critical care is usually, but not always, given in a critical care area, such as the coronary care unit, intensive care unit, pediatric intensive care unit, respiratory care unit, or the emergency care facility… | |

(continued)

**Table 2** (continued)

| | |
|---|---|
| *The CPT section for critical care is extensive. It has been abbreviated here. The following is from the CPT code section for the critical care is codes*: | |
| Services for a patient who is not critically ill but happens to be in a critical care unit are reported using other appropriate E/M codes. Critical care and other E/M services may be provided to the same patient on the same date by the same individual | |
| Time spent with the individual patient should be recorded in the patient's record. The time that can be reported as critical care is the time spent engaged in work directly related to the individual patient's care whether that time was spent at the immediate bedside or elsewhere on the floor or unit. For example, time spent on the unit or at the nursing station on the floor reviewing test results or imaging studies, discussing the critically ill patient's care with other medical staff, or documenting critical care services in the medical record would be reported as critical care, even though it does not occur at the bedside. Also, when the patient is unable or lacks capacity to participate in discussions, time spent on the floor or unit with family members or surrogate decision-makers obtaining a medical history, reviewing the patient's condition or prognosis, or discussing treatment or limitation(s) of treatment may be reported as critical care, provided that the conversation bears directly on the management of the patient… | |
| Code 99291 is used to report the first 30–74 min of critical care on a given date. It should be used only once per date even if the time spent by the individual is not continuous on that date. Critical care of less than 30 min total duration on a given date should be reported with the appropriate E/M code | |
| Code 99292 is used to report additional block(s) of time, of up to 30 min each beyond the first 74 min (see the following table) | |
| The following examples illustrate the correct reporting of critical care services: | |
| *Total duration of critical care codes*: | |
| Less than 30 min | Appropriate E/M codes |
| 30–74 min | 99291 × 1 |
| 75–104 min | 99291 × 1 plus 99292 × 1 |
| 105–134 min | 99291 × 1 plus 99292 × 2 |
| 135–164 min | 99291 × 1 plus 99292 × 3 |
| 165–194 min | 99291 × 1 plus 99292 × 4 |
| 195 min or longer | 99291 and 99292 as appropriate |

Taken from: Current Procedural Terminology [4] (Copyright American Medical Association)

known as *aggregation*. Each part of the service is documented, the time of each part is documented, and the total daily time is used for coding. An attending physician, however, may not aggregate time with residents or nurse practitioners. In a teaching physician setting, the attending must be present for the time coded. Residents' time does not count.

Time on the patient's unit counts toward codable time when performing medically necessary services even when away from the patient's bedside. Time away from the patient's unit does not count, unless the patient was also where the physician was, e.g., with the physician in radiology.

Many individual procedures are bundled together with the critical care E/M codes. EEG monitoring is not a bundled service [10]. When provided, it may be separately coded.

Notes for critical care E/M need to identify that the patient has a threat of imminent deterioration, identify the threat, and document what was done that day to evaluate or manage the threat.

## Staffing

A licensed physician must supervise technologists. Carriers, hospitals, and some states have supervision policies. American Medical Association policy also states that allied health professionals work under physician supervision. EEG tests usually require general supervision [11]. This requires a physician to be responsible for a technologist's job duties and training. *General supervision* means the procedure is furnished under the physician's overall direction and control, but the physician's presence is not required during the performance of the procedure. Under general supervision, the training of the nonphysician personnel who actually performs the diagnostic procedure and the maintenance of the necessary equipment and supplies are the continuing responsibility of the physician.

Technologists may identify basic, easily apparent features of an EEG record. But technologists may not make diagnostic interpretations about the record, such as the presence, absence, type, location, or severity of an illness, injury, or other pathology. For example, a technologist can raise suspicion of a seizure, e.g., flag a suspicious event for review or alert others to review it, but he or she may not officially conclude that an event was a seizure.

Technologists who provide monitoring must have suitable skills, knowledge, ability, training, and experience to provide interpretations and respond to the more challenging moments of monitoring. The American Board of Registration for Electroencephalographic Technologists provides board examinations for technologists in EEG and in EEG monitoring. The EEG technologists are identified as Registered EEG Technologist (R. EEG T.), and the EEG Monitoring technologists are identified as Certified in Long-Term Monitoring (CLTM). These are ways for a technologist to demonstrate competence. A hospital medical staff office should provide a well-organized process for privileging and credentialing process for physicians for continuous ICU EEG monitoring to ensure that each physician meets appropriate standards. The privileging might be separated from routine EEG, so a physician's qualifications for continuous ICU EEG monitoring can be judged on its own merits.

Physician certification is conducted by national organizations generally known as examining boards. Boards develop written and oral examinations in a specialty or subspecialty and administer them to qualified individuals. Board qualifications usually include an extended period of training in the specialty or subspecialty as well as suitable training in all relevant background areas of medicine and technology. The validity of board organizations is based in part on their community acceptance and the reputation of their sponsoring organizations. The American Board of Clinical Neurophysiology (ABCN) examines physicians in clinical neurophysiology with an emphasis on EEG and evoked potentials. The ABCN offers subspecialty written

examinations in intraoperative monitoring, epilepsy monitoring, and ICU EEG monitoring.

**Conclusion**

Monitoring teams should be aware of professional and public policy as it pertains to EEG monitoring [12, 13]. Some policies regulate organizational issues such as procedural coding. Many others are in place to ensure patient safety and quality of services. The latter includes policies on supervision, staffing, privileging, credentialing, technologists, and physicians. These are ways that the profession passes judgment on individual's skills, knowledge, abilities, and training relevant to monitoring. Good practice also includes good record documentation, clear communications with the critical care team, and the professional conduct of the monitoring team. As we go through the steps of such processes, we must always keep in mind that the goal here is to serve the patients first, do no harm, and protect the public trust placed in us as professional caregivers. Continuous ICU EEG monitoring is a field of service in which we can offer excellence inpatient protection and enhance outcomes. We can and should carry out our mission within the boundaries of professional and public policy as they pertain to our field.



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# Reporting Results

# 37

Tadeu A. Fantaneanu and Jong Woo Lee

## Contents



## Introduction

The written EEG report has always carried a monumental task in its scope. On a fundamental level, its reading and interpretation is meant to conjure a picture of the actual recording on which it is based. Perhaps more impressive is the fact that this formed picture should remain relatively similar between different readers, assuming of course that they are knowledgeable in the tenets of electroencephalography. The EEG report must convey this information with coherence and flow: it must be

T.A. Fantaneanu, MD, CM • J.W. Lee, MD, CM, PhD (✉)
Division of Neurology, Clinical Neurophysiology and Epilepsy, Brigham and Women's Hospital, 75 Francis St., Boston, MA 02115, USA
e-mail: tfantaneanu@toh.ca; jlee38@partners.org



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complete, though succinct, but also remain objective such that its reader should arrive at the same conclusion as the interpreter regarding the analysis of the recording. Creating a stable and invariant mental picture from one reader to the next should be the primary goal in writing an EEG report.

EEG interpretation and, by extension, reporting has become increasingly complex. In the earlier days of electroencephalography, the interpretation of the analog tracings was centered on the identification of individual waveforms, at times removed from the clinical setting as video capability and mobile digital telemetry were not yet available. As the equipment improved, so too did our collective appreciation of complex semiology as it related to the EEG record; this allowed epileptologists to refine scalp EEG monitoring with the goal of epilepsy focus identification, the mainstay of an epilepsy monitoring unit admission. Once the technology migrated to the critical care setting, the focus once again shifted to pattern identification as critically ill patients were now faced with disturbed consciousness, often in the setting of multisystem dysfunction. The video EEG recordings, now carried out in the dynamic setting, that is, the intensive care unit, are likely to capture various rhythmic or periodic patterns as well as subtle clinical manifestations that the interpreter must dissect with care and caution from the surrounding, artifact-rich environment. The EEG report, once read, must still be able to conjure the same mental picture of the recording to the neurologists, intensivists, and other healthcare professionals who are taking care of the patient. In the critical care setting however, it must also remain complete in its description of the hardware, montages, and quantitative analysis tools used in the recording's interpretation. This added complexity has brought with it new challenges, such as where and how to store the mounting volume of information.

Given the large volume of critical care studies performed in academic institutions, EEG reports are now often stored in large databases. These databases are frequently capable of automatically generating the written report based on user-selected terms from predefined lists. This practice facilitates intra- and interinstitutional research studies while maintaining a permanent backup of each study's report. This chapter will review current guidelines and practices regarding the writing and reporting of EEGs with particular attention to the EEG report in the critical care setting. The authors will highlight examples of critical care EEG reporting databases and their functionality and reinforce the need to adhere to the commonly used ACNS critical care terminology when reporting studies. Finally, the authors will share their own institutional experience with the ICU EEG service.

## Guidelines on EEG Reporting

Few published articles or guidelines exist to guide the electroencephalographer in the writing of reports, perhaps even less so for the synthesis and generation of reports in critically ill patients. The ACNS guidelines on writing reports for routine EEGs and for long-term monitoring for epilepsy provide the most distilled version of what a report should contain, namely, the following sections [1, 2]:

1. *Introduction*: accompanied by a statement of the clinical problem and intent of the procedure, patient's status (sleep deprived, medications), and technical considerations of the recording and any activating procedures (hyperventilation, stimulating procedures).
2. *Description of the recording*: including identification of waking, drowsy, and sleeping patterns, results of activation procedures, epileptic and nonepileptic electrographic abnormalities, and behavioral events.
3. *Interpretation*: including an overall subjective impression of the record on whether the record is normal or abnormal and a comment on the extent of the identified abnormality (most EEG laboratories use an internal gradation system that often lacks external validity). A clinical correlation, usually as a comment on the overall significance of the findings in the larger clinical context, is also provided. The clinical correlation should refer back to the indication for monitoring, and it should be as specific as possible.

Similar considerations should apply when reporting routine or prolonged EEG monitoring in the critically ill, with modifications:

1. *Introduction*: This should be updated on a daily basis, as sedating medication as well as the patient's neurological status may change markedly. The patient's current level of arousal (awake, obtunded, comatose) should be documented.
2. *Description of recording*: Whereas precise detail regarding localization and electrographic morphology of interictal discharges and seizure onset, as well as behavioral correlation, is necessary in the epilepsy monitoring unit, such painstaking information is often superfluous in continuous EEG (cEEG) monitoring of critically ill patients, as the record is substantially more dynamic and the background usually grossly abnormal. As many patients suffer from significant gross intracranial lesions, the underlying etiology and location of the source of electrographic dysfunction are more often readily apparent. Excessive detail regarding specific rhythms is incredibly time consuming (both for the writer and reader of the reports) and rarely focuses on the most significant aspects of the recording. Greater attention, in turn, should be paid to the evolution of electrographic dysfunction, whether it is the change in seizure frequency or gradual or abrupt changes in the background. Response to intervention/medication should be carefully documented. Results from trend analysis software or automated seizure detection algorithms should be clearly and separately stated. Documentation of an activating procedure in comatose patients is critical as well.
3. *Interpretation*: A daily interpretation as well as a final interpretation at the end of a multiday recording session should be provided. If an abnormality is noted during long-term monitoring, the report's impression should include a statement as to whether there was an improvement during the course of the day's recording. Treatment recommendations have no role in the interpretation or anywhere else in the cEEG report. Any additional or ancillary tests (repeat recording, video if not obtained, other neurophysiological procedures) that would clarify the findings on the EEG may be suggested with careful phrasing (e.g., "additional testing may provide further information, if clinically indicated").

## Using the ACNS Terminology when Reporting Critical Care EEGs

For different readers to conjure the same mental picture of the recording based on a single report, all readers should be familiar with the same language and terminology. Critical care EEGs are challenging to interpret in part because the observed rhythmic and periodic patterns still lack consensus among epileptologists as to their clinical significance. Some patterns are considered more epileptogenic than others but all lie on the ictal-interictal continuum. Interpretation is further hampered by the lack of widely accepted criteria for nonconvulsive seizures or status epilepticus, though most epilepsy specialists will refer to variants of the Young criteria [3, 4]. Recently the ACNS has published a revision to critical care EEG terminology which has shown high inter-rater agreement for a number of proposed terms, including the first two main terms [5, 6]. Not only does this new terminology serve as a good way to certify research collaborators across different institutions, it also serves as a powerful clinical tool when reporting critically ill EEGs to the treating physicians and care teams. This terminology should be used when generating critical care EEG reports. A detailed review of this terminology is beyond the scope of this chapter; however, a link to the latest version of the manuscript and training module are both provided at the end of this chapter. A certification test is also available for readers that wish to be certified.

## Reporting Databases

Traditionally, EEG reports are manually entered into patients' electronic medical records and are usually typed by the interpreter, often an electroencephalographer. This often takes the form of a free text format, often in the narrative style, but can also be generated using a point-by-point short form. Unfortunately, this method reduces the interobserver agreement, as different interpreters may have varying levels of experience with electroencephalography and different institutions have their own local terminologies, thereby limiting the external validity of each study report. To circumvent this problem, software that prompts observers to choose between predefined mandatory terms, as opposed to using optional ones, should ideally be used. Research studies have shown this method to have consistently higher interobserver agreement, as compared to giving the interpreter unlimited choice [7].

Software programs capable of generating reports based on the entry of preselected terms not only improve efficiency but allow the interpreter to add more technical information to the report, as well as improve their detection of certain EEG patterns by always being focused on their identification. Since all categories must be completed, this prevents the interpreter from missing important components of the recording. Another benefit of using such programs lies in their ability to use more commonly and more widely accepted terminology, thereby improving the external validity of the reports. These programs can also collect the individual reports and store them in databases that can be accessed by other collaborating institutions, thus enhancing the number of samples collected for critical care EEG studies. Such software tools can be integrated into existing institutional electronic medical records, since the generated and

finalized EEG report can be migrated to the patients' individual records. One obvious concern when using such software programs and databases can be the time requirement to generate and maintain reports on a daily basis, particularly since certain demographic information will inevitably have to be reentered, as seamless integration into most electronic medical records (EMRs) with external databases (e.g., through HL7 standards) is not yet available [8]. In the authors' experience, this practice is actually timesaving in the long term, despite a learning curve that may initially appear time consuming. Demographic data may be entered by a technologist or support staff to save physician time. Another oft-cited concern is the "homogeneity" of the reports being generated, the stamping out of the personal touch, and the expression conveyed by each electroencephalographer in their style and wording in favor of the, "machine-generated," chain-assembly report. Subjective interpretations are not only allowed but also encouraged when using this type of software, namely, through the use of free text dialog boxes which are seamlessly incorporated into the program's interface.

Database generation and maintenance are of particular importance when institutions commit to providing a critical care EEG monitoring service, since a large volume of data needs to be collected and stored, making their adoption ideal. Several previous EEG reporting databases have been described, but have not gained widespread use outside the local institutions [9, 10]. More recently, with the advent of vast improvements in standard computer network protocols and database software systems, there are renewed efforts to introduce reporting databases that are more easily adaptable to local environments. An example of such programs includes the standardized computer-based organized reporting of EEG (SCORE) software developed by Holberg, a company established in Norway in 2009 which was among the first to pioneer EEG reporting databases [11]. SCORE is freely available for download and may in time help promote a European standard for EEG report generation as more centers adopt its use. An appealing feature of the SCORE database system lies in the ability of the reader to capture screenshots of EEG segments and append these to the report, thereby providing the reader with a visual example of the pertinent findings summarized in the report. Another perhaps more relevant example of such a program is the Critical Care EEG Monitoring Research Consortium (CCEMRC) database program, established according to the latest ICU EEG terminology and which also supports computerized EEG report generation.

None of these databases will likely suffice as a complete report-generating database without minor modifications. As there are substantial interinstitutional differences in billing and reporting regulatory guidelines, it is necessary for the EEG monitoring team to tailor the reports to comply with local guidelines. These may include details in the technical portions, attestation statements, or reporting frequency requirements, for example.

## CCEMRC EEG Reporting Database and the cEEG Report

The CCEMRC in the United States has an established critical care EEG database, shared across participating institutions and capable of generating EEG reports based on selecting from predefined terms and parameters. In this section, we will use this

database as a model to delineate the necessary components of critical care EEG reports. The following sections are routinely completed and, based on the authors' experience, should be included in any critical care EEG report.

## Patient-Identifying Data

Each entry into the database contains the basic patient-identifying data, including name, date of birth, gender, and medical record number. The start/stop dates and times of monitoring are entered (Fig. 1). Of note, pregnant patients can be identified by entering the gestational age of the pregnancy in this section.

## Clinical Data

Pull-down menus will reveal a preselected list of primary and secondary neurological diagnoses and primary indications for EEG (Fig. 2). The selections will automatically generate billing codes. Additional clinical information is entered manually when necessary and is usually obtained from the electronic medical record and preferably from a neurology/neurocritical care consultation note.

## Technical Information

In this section, the interpreter enters more technical information including the number of channels (usually predefined at 21), the electrode types (predefined as disk, and nearly always plastic, making them CT and MRI compatible), as well as which

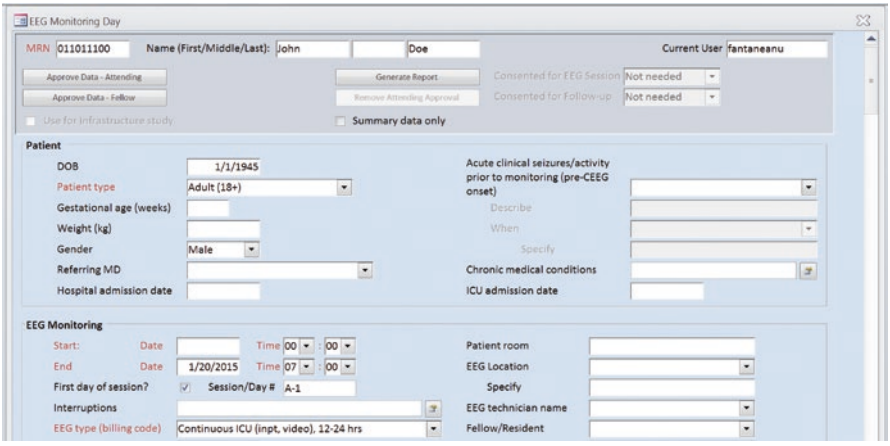


**Fig. 1** CCEMRC database entry fields for patient-identifying data

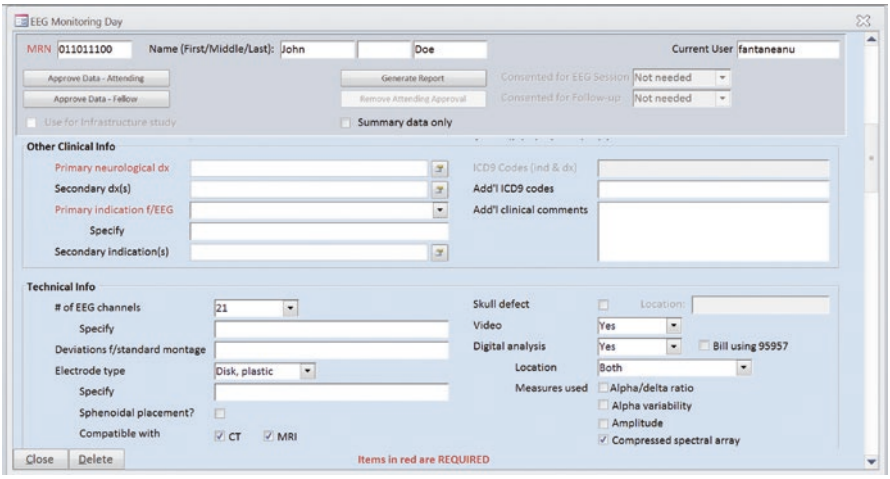


**Fig. 2** CCEMRC database entry fields for patient clinical information

adhesive types are used (for allergy purposes). Note is made of video recording capability, as well as whether digital analysis tools are used. In the latter case, one specifies which quantitative methods in particular are incorporated into the analysis algorithm such as alpha/delta ratio, rhythmicity, or compressed spectral array.

## EEG Results and Day/Epoch Reporting

Each day's recording is characterized by one or more epochs; a change in epoch signifies shifts in baseline EEG due to underlying nonphysiologic changes such as burst suppression or new disease states. Within each epoch, the following must be documented.

### Treatments and Medications

Daily antiepileptic medications are entered and daily dose changes are tracked. Note is made of sedative medications such as propofol, fentanyl, or midazolam, as well as any muscle-paralyzing agents. The patient's mental status is also documented (awake, comatose, lethargic, obtunded), as well as whether the patient is intubated and whether focal neurological deficits are observed (Fig. 3).

### Background Activity

The predominant background rhythm is documented, including the presence or absence of a posterior dominant rhythm. This is further qualified by commenting on symmetry, voltage, variability, reactivity to stimulation, and organization. Any focal slowing or attenuation is recorded by selecting elements from a predefined list of terms and specifying their location. If additional information is required, a free text box can be filled to highlight important details (Fig. 4).

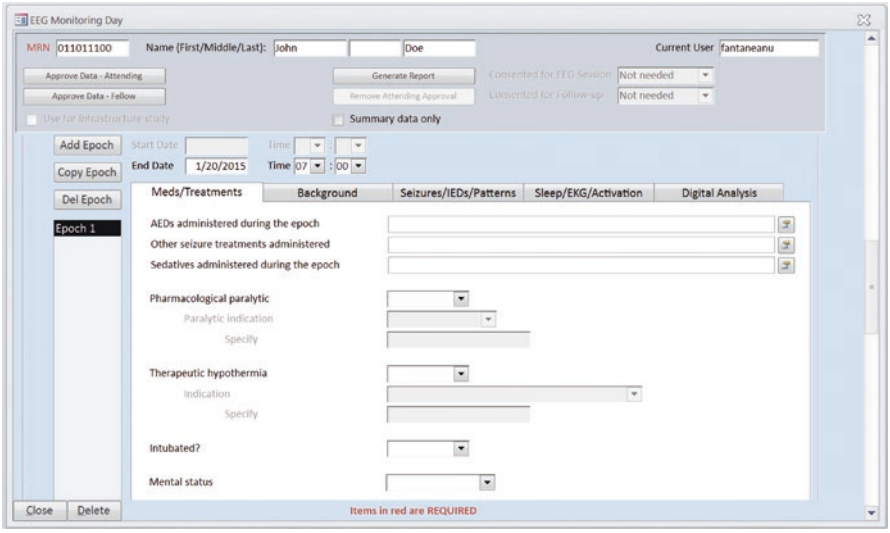


**Fig. 3** CCEMRC database entry fields for medications and clinical state of the patient

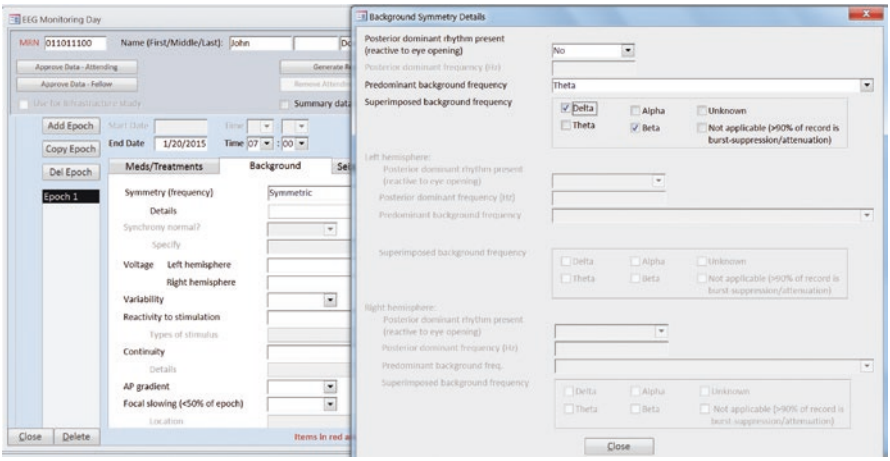


**Fig. 4** CCEMRC database entry fields for background activity

## Seizures, Interictal Activity, and Rhythmic/Periodic Patterns

If seizures are observed during the recording, the list item menu provides details on seizure length, frequency, location, morphology, as well as whether any associated clinical manifestations are observed. Documenting status epilepticus is an important feature of this section of the report. This section also includes a subsection stating whether or not nonepileptic events were captured (psychogenic or various motor manifestations in the critical care setting such as tremors, jerks, posturing, or

rigors). Finally, mention is made of the presence of brief potentially ictal rhythmic discharges (B[i]RDs), sporadic epileptiform discharges or rhythmic and periodic patterns, and whether these are stimulation induced or not (Stimulus induced rhythmic, periodic, or ictal discharges [SIRPIDs]). The description of their frequency, amplitude, location, morphology, phases, sharpness, evolution, polarity, as well as major terms and minor modifiers is meticulously documented according to the ACNS terminology (see above) (Fig. 5).

### Sleep, EKG, and Activation Procedures

Sleep stages are documented, and note is made of the presence or absence of sleep spindles, K complexes, or vertex sharp waves as well as any asymmetry or abnormality in the sleep architecture. This section provides an opportunity to document the EKG findings (normal sinus rhythm or arrhythmia) as well as whether activation procedures such as hyperventilation and photic stimulation are performed and what the relevant findings are. A brief description of any identified breach rhythm is also made under this section (Fig. 6).

### Digital Analysis

In this section, the interpreter identifies to which extent his/her interpretation was aided by quantitative analysis specifically whether seizures were detected by the software (particularly useful in patients with frequent seizures). Note is also made of quantitative analysis tools that helped identify background asymmetry, if this is present (Fig. 7).

### Impression

On a daily basis, an impression is formulated based on the totality of the data and usually serves as a summary of the major electrographic abnormalities documented

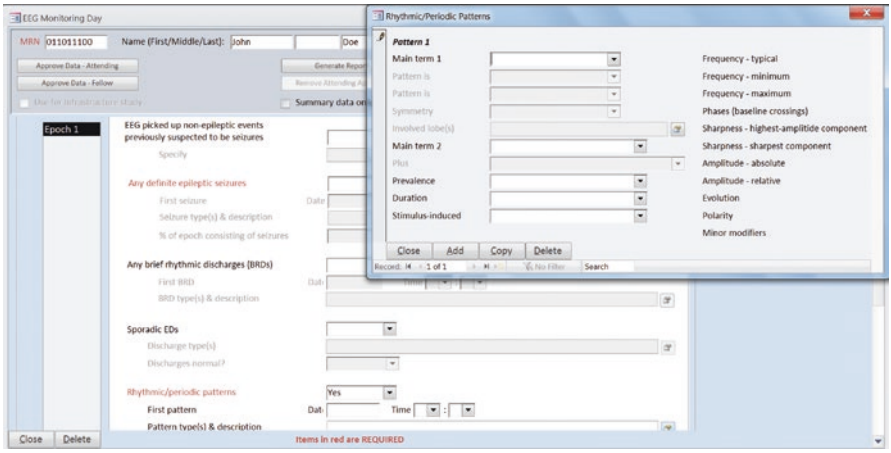


**Fig. 5** CCEMRC database entry fields for seizures, epileptiform abnormalities, and periodic patterns

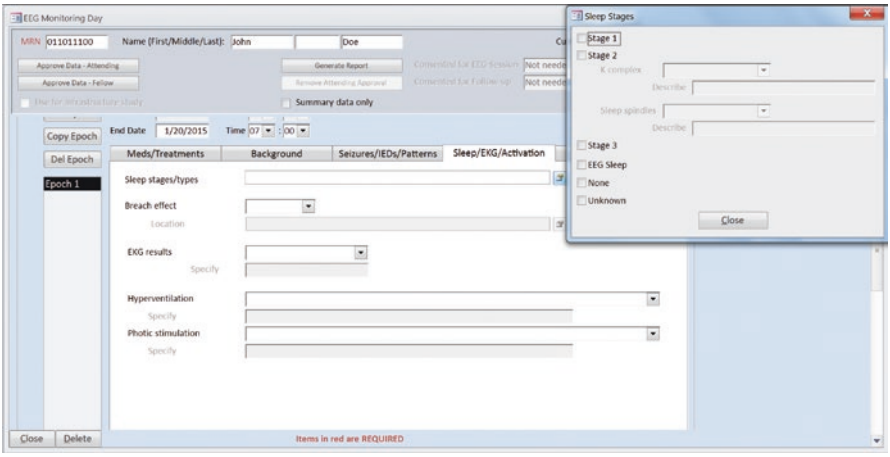


**Fig. 6** CCEMRC database entry fields for sleep, EKG, and activation procedures

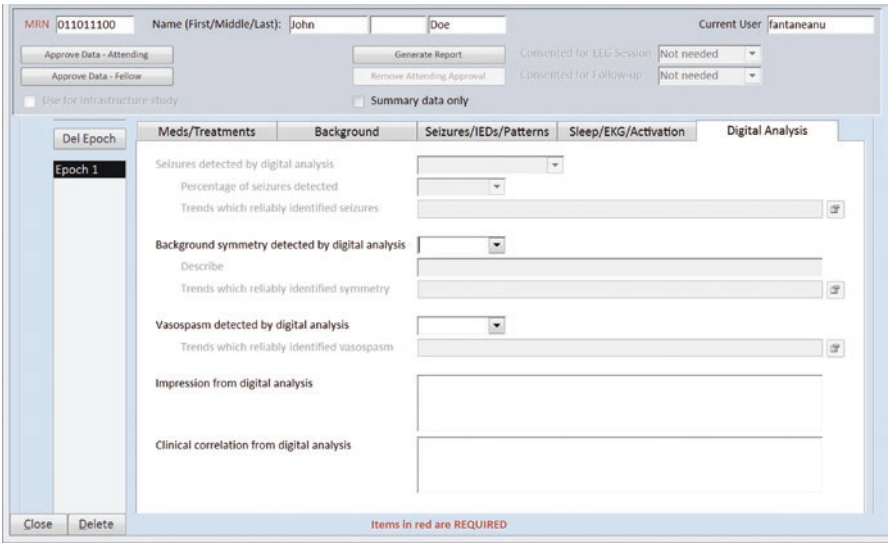


**Fig. 7** CCEMRC database entry fields for digital EEG analysis

during the entire recording. The interpreter provides an opinion as to whether the study is normal or abnormal as well as a gradation of severity in the latter case. A clinical correlation consisting of the interpretation of the results in the context of the patient's clinical status, with an explanation as to whether or not the EEG recording fits with the clinical picture, can be provided separately from the electrographic impression. This section of the report documents whether the identified findings suggest status epilepticus or cortical irritability, cerebral dysfunction, or both. A brief differential diagnosis can be provided if the EEG is more specific of a certain

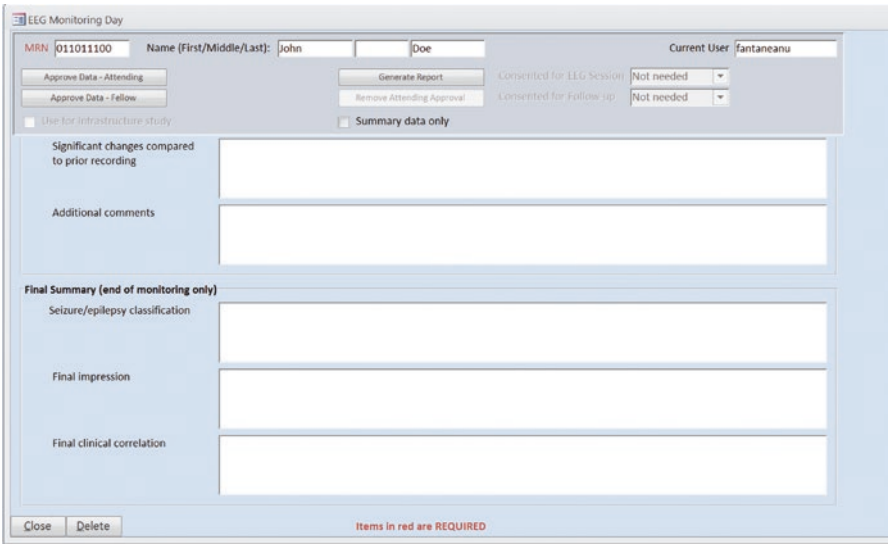


**Fig. 8** CCEMRC database entry fields for report summary and interpretation

condition such as focal polymorphic delta activity suggesting the possibility of a structural lesion in the brain. Any significant changes over the course of the day's recording, including improvements or deteriorations, should be noted, for example, if observed periodic discharges become less frequent or disappear during the course of the recording. A final impression and clinical correlation should be stated at the end of the total recording session (Fig. 8).

### Written Report Generation

The database is capable of generating a written report based on the completed sections of the patient's record on the database. The generated report is not formatted in the narrative style and follows a more sequential, point-by-point approach. This report is rich in the technical aspects of the recording and provides a day-by-day summary of the relevant clinical information and EEG findings. Each record has an assigned epilepsy fellow reading the study as well as an assigned staff physician. Once the report is reviewed, both fellow and staff must approve the study before finally generating a report based on the entered dataset.

## Reporting and Communicating Logistics

Local resources, technologists, and equipment availability will often dictate review and reporting practices within each center. In a survey of practices across different centers in Canada and the United States, it has been shown that EEGs can be

reviewed anywhere from once per day (21 %) up to almost continuously (18 %) when being used to screen for nonconvulsive status epilepticus (NCSE). Most commonly, it is reviewed twice per day (29 %) [12]. The ACNS ICU EEG guidelines suggest that recordings should be reviewed within the first 60 min and interpreted as soon as possible with the results being conveyed to the critical care team immediately. Regardless of whether the initial review is performed by clinical neurophysiology and epilepsy fellows or technologists, the attending physician is ultimately responsible for the final interpretation and report of the study. Institutions should review their studies at a minimum of twice per day as per the ACNS ICU EEG guidelines, though specific situations (e.g., patient in status epilepticus) may call for more frequent updates. Expectations regarding the frequency of reporting for particularly ill patients should be made by the EEG monitoring team and the critical care team a priori, particularly for nights and weekends. Similar expectations should be communicated if any external third-party monitoring readers are utilized.

Surveyed practices suggest that most institutions provide daily reports (72 %), with only a minority providing twice daily reports (11 %) [12]. Communication with the critical care treating team should be in person, which is our preferred method and recommended in the authors' opinion. Telephone conversations or written updates are acceptable alternatives but detract from the rich information conveyed via face-to-face interaction such as CT/MRI results or recent medication changes and clinical evolution updates. In the abovementioned survey, reports were provided through update of the electronic medical record (48 %), handwritten in the hospital chart (25 %), or verbally relayed to the treating primary physicians (27 %). Finalization of the EEG report is most often performed on a daily basis, though there may be interinstitutional differences in requirements.

Giving treatment recommendations regarding anticonvulsants may seem like a natural extension of services provided by the EEG monitoring team, who usually have substantial expertise in this field. In the authors' opinion, it is strongly advisable to avoid formal recommendations, either in written or verbal form, unless a formal epilepsy service consultation is requested by the primary clinical service. Informal advice may erroneously be interpreted as formal recommendations, particularly by more junior house staff, without realization that certain medication recommendations may be found to be inappropriate with full evaluation of the patient's clinical condition.

## Authors' Own Experience

The Brigham and Women's Hospital ICU EEG service uses the CCEMRC database to generate ICU EEG reports. Studies are read by the fellows and reviewed by the attending epileptologists twice per day for stable patients. Patients with active seizures are reviewed more frequently, up to four times per day. After each reading, the treating team will receive an update. Communication with the treating teams on the neurological and neurosurgical critical care services is achieved in person during daily morning multidisciplinary ICU EEG rounds, where the recording is reviewed

in the presence of the epilepsy fellow, the epilepsy attending, and the treating team (students, residents, and critical care fellows). For treating physicians who cannot attend rounds, the fellow informs them via telephone or text messaging of the results. Reports on the critical care reporting database are updated daily, and a final report is generated at the end of the recording period, once the patient's electrodes are disconnected; this is then appended to the patient's electronic medical record.

### Conclusion

Electroencephalography reporting in the critical care setting remains an art, one where the electroencephalographer must still be able to evoke a picture of the actual recording in the reader's mind. With the emergence of a standard terminology and guidelines available to interpreters to help them craft the EEG reports of critically ill patients, the discipline has matured into the new millennium. It is more efficient as well with software now capable of generating reports based on user selections from predefined lists; this practice will improve the interobserver reliability and external validity of reports coming from academic institutions and ultimately only serve to enhance the care provided to patients. These software packages are often part of larger databases, with ubiquitous access to patients' electronic medical records. An example of such a software package is provided in this chapter, and it is the authors' hope that future electroencephalographers will benefit from this tool when reporting EEGs in the critically ill.

## Appendix: Links to ACNS Critical Care Terminology Training Module and Manuscript

- http://www.acns.org/research/critical-care-eeg-monitoring-research--consortium-ccemrc/education
- http://www.acns.org/pdf/guidelines/Guideline-14.pdf

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# Information Technology Issues

# 38

Ronald G. Emerson

## Contents



## Introduction

Digital communication and storage are fundamental technologies for cEEG monitoring. Without them, the field would not exist. These technologies continue to improve, increasing in speed and capacity the rate of "Moore's Law" – doubling approximately every 18 months. Despite periodic proclamations that this trend will not continue forever, in fact, it has remained more or less intact since Moore's initial observation in 1965 [1]. A basic understanding is useful, therefore, not only for managing and troubleshooting current cEEG monitoring systems but also as a framework for anticipating future innovation.

R.G. Emerson, MD
Department of Neurology, Cornell University, 525 E 71 Street, New York, NY, USA
e-mail: emersonr@hss.edu



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## Background

### IP Numbers and Networks

The Internet, and digital network communication in general, began as a Cold War effort to develop a robust communication system that could withstand wartime destruction. Fundamentally different from prior telephony or telegraphy, which relied on continuous analog signals traveling over dedicated point-to-point wires and cables, data on the Internet travels of discrete, routable, packets (Fig. 1). Data originating from any point on the Internet can travel to any other point based on the "address" of the packet. No fixed pathway is required; moreover packets can arrive, at their destination, out of order and the message can still be understood.

Routing of data on the Internet depends on a system of Internet Protocol (IP) addresses. Each device has a unique IP address that specifies the location of the device on the network, much like a street address identifies the location of a building. Each device also has another unique identifier, the Media Access Control (MAC) address, which is assigned by the manufacturer. When a device joins the network, a Dynamic Host Control Protocol (DHCP) server automatically keeps track of its MAC address and assigns an appropriate IP address. IP addresses are used to route data from source to destination; the path taken is governed by a set of rules implemented by routers throughout the Internet. IP addresses are 32-bit numbers, allowing for over 4 billion unique addresses. To make them more easy for humans to read and to manipulate, they are traditionally divided into four 8-bit "octets," each separated by a "." and expressed as a decimal number from 0 to 255. For example, the address of the computer on which this text is being written is 68.173.40.88. The currently dominant IPv4 address system will be replaced by the IPv6 system, which supports $2^{128}$, or approximately $3.4 \times 10^{38}$, addresses. Notation is in the form of eight sets of four hexadecimal numbers, i.e., 2604:2000:e1a3:8400 :918b:7be6:471e:e791. Formalized in 1998 to address the anticipated exhaustion of IPv4 addresses, IPv6 adoption was initially slow, but is now accelerating [2].

The Domain Name System (DNS) provides a mechanism for substituting machine-friendly, but human-unfriendly, IP number with convenient easily remembered names or Uniform Resource Locators (URLs). When a user specifies a URL, a DNS server automatically looks up the URL and returns the corresponding IP number.

A subnet is a local division of the Internet, roughly analogous to a street on a map. Commonly, the subnet is specified by the highest order 3 octets (68.173.40 in the above example). In this case, there would be a maximum of 256 addresses on the

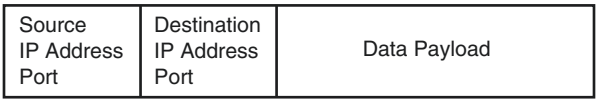


**Fig. 1** Internet data packet, showing the "data payload," along with source and destination IP addresses and ports

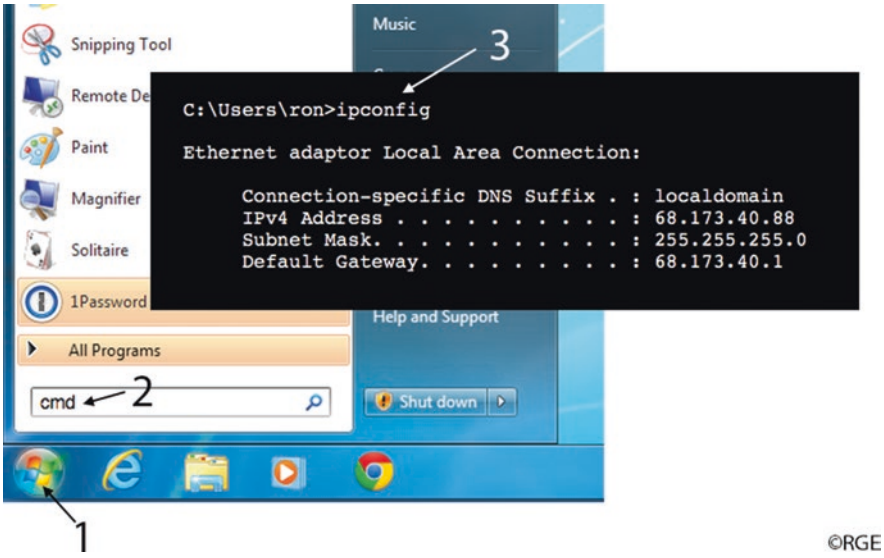


**Fig. 2** To run IPCONFIG from a Windows 7 machine, press the Windows button (*1*), enter "cmd" (*2*), and type "iconfig" in the terminal window, as shown in (*3*)

"subnet" 68.173.40.x (where x is an integer from 0 to 255), perhaps corresponding to the devices on a floor or portion of a building. A special device, a switch or router, provides a gateway between the subnet and the rest of the world; all packets not destined for devices on the subnet travel out through the gateway. On a Windows® computer, the command IPCONFIG returns various settings, including its IP address and the IP address of its gateway (Fig. 2).

The IPCONFIG command can be useful for debugging problems with network connectivity. If IPCONFIG returns an unexpected IP address for a cEEG acquisition or review system, it may indicate that the device is plugged into a wall jack intended for a different application. For example, some hospitals reserve specific wall jacks, on dedicated subnets, for specific functions, e.g. for radiology systems. Under some circumstances, the IP address assigned to a particular machine may change when the machine is disconnected for a period of time and then reconnected, even to the same wall jack; the change, however, will normally affect only the rightmost octet; the subnet will usually remain unchanged. Also, IP addresses of 0.0.0.0 and 169.254.x.x are invalid and usually indicate that, for some reason, the machine was unable to obtain a proper IP address.

On Windows 7® systems, the network icon, appearing toward the lower right-hand corner of the screen, indicates the status of the network connection (Fig. 3). A red X indicates that the physical connection has failed. A common cause for the red X (other than forgetting to plug in the network cable) is loss of stiffness of the RJ-45 network connector's plastic tab (Fig. 4). Repeated plugging and unplugging of the RJ-45 jack will cause this tab, which holds the plug securely in the wall jack, to weaken. Users of portable cEEG equipment should be encouraged to routinely

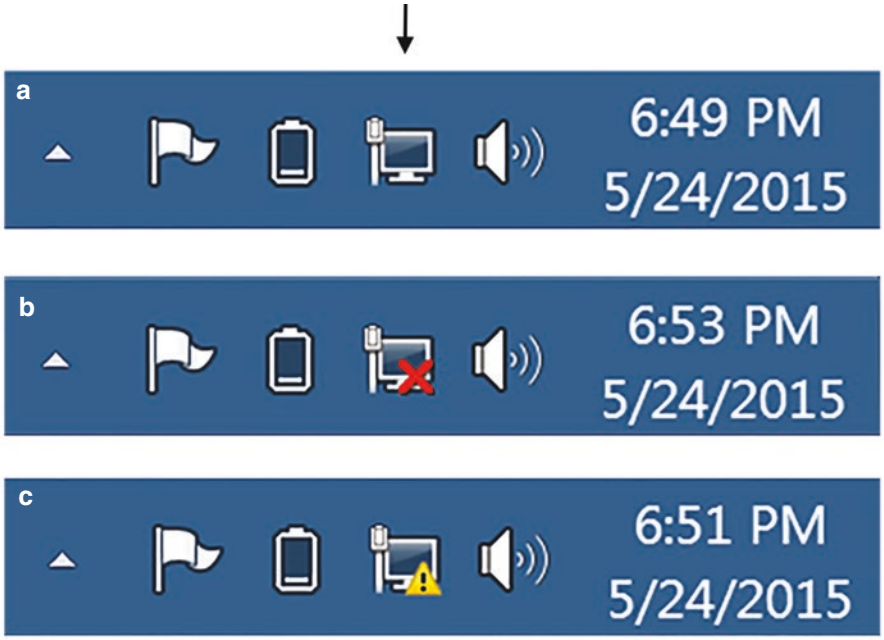


**Fig. 3** The network icon (*arrow*), located in the system tray at the lower right-hand corner of the screen in Window 7, displays the status of the network connection. Panel (**a**) shows normal status. The red "X" in Panel (**b**) indicates loss of physical connection. The "!" in the *yellow triangle* in Panel (**c**) indicates another problem with network connectivity, possibly involving the host or gateway IP address, DHCP renewal, or network interface driver software

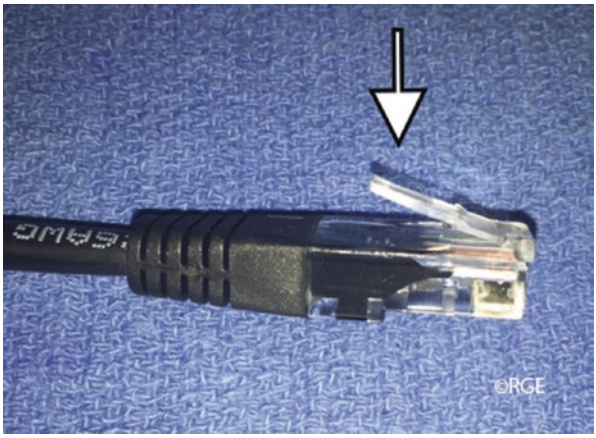


**Fig. 4** Ethernet plug. With repeated plugging and unplugging, the plastic tab (*arrow*) tends to lose its resilience, causing an unreliable electrical connection to the wall outlet. When this happens, the cable should be replaced

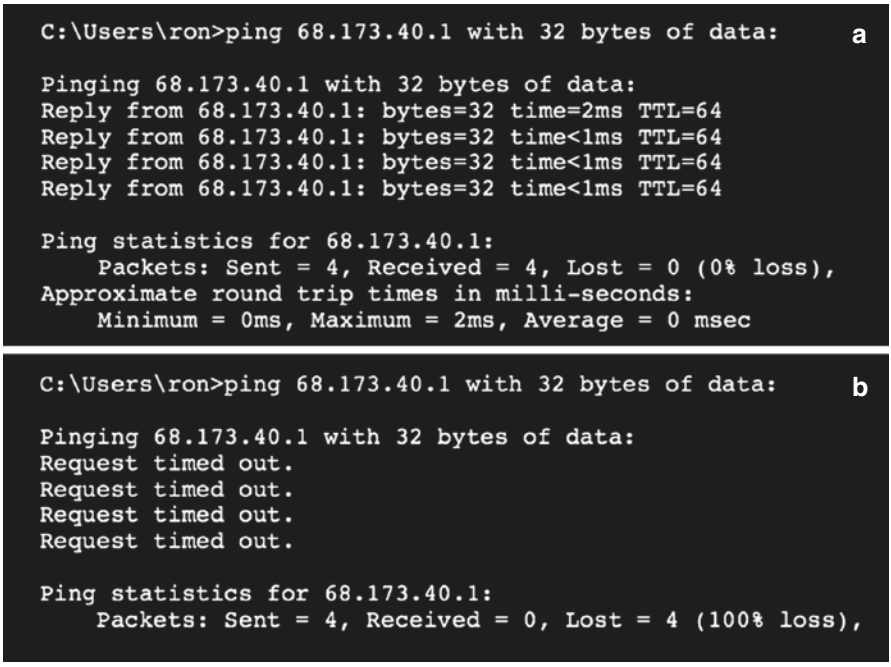


**Fig. 5** To ping another device from a Windows 7 machine, press the Windows button and enter "cmd" (see Fig. 1). In the terminal window, type "ping" followed by the address of the device that you wish to ping. (**a**) illustrates a successful ping of gateway 68.173.40.1; in (**b**), the same ping fails

examine the condition of the RJ-45 plug and to replace the cable when the tab seems soft. Wiggling or taping a defective connector to "make it work" is a bad practice and is asking for trouble. If the network cable is connected but there is another network-related problem, a yellow triangle with an exclamation point superimposed is seen. Causes include problems with DHCP IP address renewal and buggy network interface driver firmware.

The PING command (Fig. 5) is a great tool for verifying that a system is connected to the network and that the network is working. PING sends a test message to another device and displays the time it takes for the test message to be received; PING will fail if the reply is not received. In Fig. 5a, the command PING 68.173.40.1 successfully tests the connection between my computer (68.173.40.88) and its default gateway (68.173.40.1). In Fig. 5b, the same test fails ("request timed out").

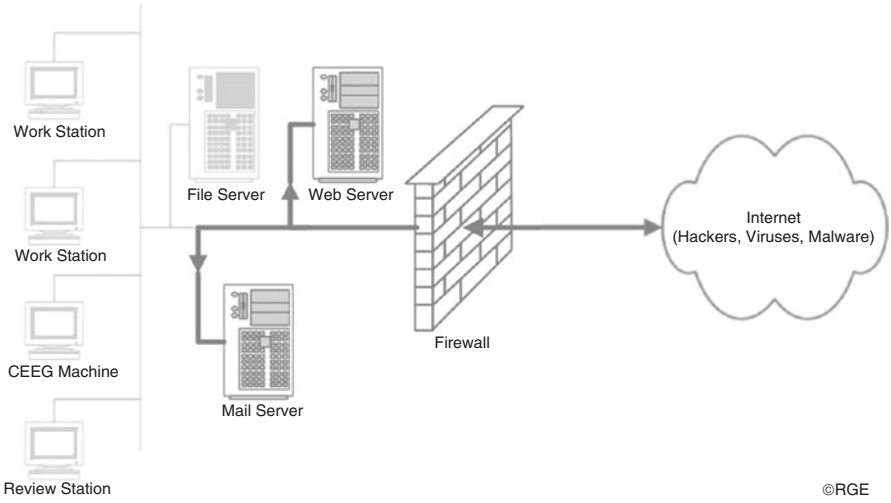


**Fig. 6** Firewall blocking all inbound traffic except messages destined for the web server and the mail server. In addition to restricting traffic to those specific hosts, the firewall would typically be configured to permit only specific types of messages by restricting ports, i.e., port 80 for the web server and port 993 for the mail server. In a typical configuration, inbound web traffic might also be permitted to reach the workstations on the network, but only if it was in response to returning in response to messages sent by those stations. In this manner, a workstation could browse the web, but it could not be a web server

## Restricting Access

In the early days of the Internet, information was generally permitted to flow freely between all connected devices. Over time, as information security becomes an important concern, institutions implemented special systems to safeguard internal communication while permitting necessary external communication. Typically, data are permitted to flow freely between devices on local networks, but at points where the local network joins a larger network or the public Internet, routers and firewalls control the flow of traffic.

Firewalls may restrict communication based on IP addresses, permitting information traffic between specific IP addresses or subnets and blocking others. Firewalls may also control communication by passing only certain *types* of data and blocking others. In addition to specifying source and destination IP addresses, data packets are also labeled with source and destination "ports," indicating the sending and intended receiving applications (Fig. 1). Institutional firewalls often impose a default "deny all" policy on inbound traffic, making exceptions only for specific data types and destinations. Figure 6 illustrates a firewall configured to allow inbound traffic only to a web server and a mail server; note that the cEEG machine, the review station,, and the file server are all inaccessible to the Internet.

In addition to institutional firewalls protecting entire networks, modern operating systems have "personal firewalls" that function in a similar manner to protect

individual computers. By default, commonly used ports are enabled. On occasion, it is necessary to "open" one or more additional ports in order for a particular application or function (e.g. remote access) to work. Rather than simply turning the personal firewall off (a very bad idea), both Windows (press the Windows button, click Control Panel, click System and Security, click Allow Program Through Firewall, click Change Settings, click Allow Another Program, and select the program from the list) and OSX make it easy to specify the programs for which need access.

By convention, IP addresses within certain ranges (192.168.0.0–192.168.255.255 [commonly used by home routers], 172.16.0.0–172.31.255.255, and 10.0.0.0–10.255.255.255) are not routed on the Internet. Institutions commonly use these non-routable IP addresses internally, providing a large number of private IP addresses. Most outbound and inbound traffic, to and from the public Internet, is remapped to routable IP address by the firewall using the Network Address Translation (NAT) protocol. Only systems that must be exposed to the Internet are assigned routable IP numbers.

## cEEG Systems: Reliability and Performance

cEEG monitoring systems commonly consist of several cEEG acquisition machines, a file server, and one or more review stations – all interconnected using the hospital network infrastructure. Acquisition systems typically write cEEG data to a server as they are recorded; for interpretation, data files are then transferred to a review station. This arrangement can present challenges, and problems at any point in the system can adversely impact both reliability and performance.

Failure of connectivity between an acquisition machine and the server is a potential cause of data loss. This risk can be mitigated by storing data locally, on the acquisition machine, in addition to writing it to the server. Alternatively, acquisition systems can have a provision to revert to local storage in the event of a failure to write the server. Ideally, all conditions that can cause such a failure should be detected, including loss of physical network connectivity (e.g. the network plug becomes disconnected), failure of network communication, and failure of the server. It is important that the cEEG team be aware of these various failure modes and test them at the time of system installation and again following system upgrades and modifications.

cEEG data (EEG and video files) are written to the server in real time during acquisition but must be transferred from the file server to the review station at much faster speeds, perhaps 20 times real time, for interpretation. The latter requirement can stress the system, a bottleneck at any of involved components can result slow review speeds. "File servers" found in cEEG systems range anywhere from systems designed specifically for high-performance real-time I/O applications to desktop computers designated to function as servers. Although it is common for users to think of servers only in terms of their storage capacity, in fact, performance is dependent on technical details of a server's hardware and software configuration. Review station hardware and software (both operating system and vendor-specific

cEEG application software) will also impact system performance. A detailed discussion is beyond the scope of this chapter. But, it is important that when a cEEG system initially purchased, and when additions are made, consideration be given to selecting a configuration that will provide adequate performance under maximum load, when all acquisition and review stations are operating concurrently.

The network is also a potential source of bottlenecks. While many modern computers have 1 Gbps (gigabit per second = 1000 Mbps or megabits per second; 1 Mbps = 1 million bits per second) network interfaces, network switches providing connection at 10 Mbps, 100 Mbps, and 1 Gbps are in use today; 10 Mbps connections are generally inadequate for cEEG applications, especially with video. Importantly, these are nominal speeds and do not reflect actual data transfer rates. A moderately loaded 100 Mbps network may only provide actual throughput of 25 Mbps/s. Network efficiency is affected by numerous factors, including the amount and type of traffic, the number of nodes on the network, and network diameter (i.e., the longest of the shortest paths from every node to all other nodes) [3]. For these reasons, it is wise to consult with your institution's IT department prior to installing a cEEG system. Remember, simply observing that a network connection works well for browsing the web does not guarantee that it will work well for reviewing cEEG.

If a wired network connection is not available, it may be possible to use Wi-Fi. However, wireless connections present challenges. Regardless of type (802.11 A, B, G, or N), data rates and stability of the connection are very dependent on distance from the wireless access point, building construction materials, physical obstructions, and other simultaneous users [4]. Provisions for local storage of data, therefore, are particularly important. Options, in addition to those already discussed, may include writing data first to a local hard drive and then copying it, automatically, to the file server using a third-party application designed for fault-tolerant data transfer. Alternatively, data could be reviewed on the acquisition system remotely over Wi-Fi using an application such as Virtual Network Computing (VNC). In the later case, only screen images (plus mouse and keyboard data) would be transmitted wirelessly, making reliable connectivity less critical.

## Data Storage and Retention Requirements

High-capacity disk storage is an important "enabling technology" that has helped to make cEEG monitoring practical. Typical cEEG data files occupy 1–2 GB (gigabyte, 1 GB = 1000 MB or megabytes, 1 MB = 1 million bytes; byte refers to an 8-bit "word") per day for EEG only and about 5–20 GB/day with video, depending on sampling rate, compression, etc. As of this writing, a 1 TB (terabyte = 1000 GB) disk drive of the type used in most desktop computers costs about $50. While high-performance and reliability drives cost several times more, and associated electronics add substantially to the real cost of data storage, online storage of many patient days of complete cEEG data is still quite feasible.

Disk drives are mechanical devices. They will eventually fail. Their substantial storage capacities magnify the potential consequences of a failure, both in terms of

data loss and disruption of monitoring. For this reason, redundant arrays of independent disks (RAIDs) should be used for cEEG data storage. RAIDs store data redundantly across multiple disk drives, so that failure of a single disk does not cause data loss. In its simplest form (a so called RAID-1), a RAID employs two disks, one "mirroring" the other. More sophisticated RAID systems, found of file servers, utilize many disks in such a manner that one or two drives can fail without data loss, with failed drives replaced by "hot" spares and data redundancy reestablished automatically. RAIDs on cEEG file servers should be selected to provide both sufficient I/O performance (i.e., speed necessary for good review speed) and online capacity in terms of patient days of cEEG data.

Separate from online RAID storage, provision for data backup and archiving is necessary. Regardless of its capacity, a RAID will ultimately become filled. Further, RAID storage does not provide a 100 % protection; various hardware and software failures, as well as human errors and environmental events, can cause irrecoverable data loss. A wide range of archival storage options is available. Some institutions elect to simply archive to removable media, such as CDs or DVDs. If this option is selected, carefully implemented policies and procedures for handling and storage of these media are necessary. Without them, media containing "interesting" cases may predictably go missing. It is strongly recommended, indeed mandatory at some institutions, that removal media be encrypted. Alternative solutions include various removable and online tape and disk storage systems. Ideally, cEEG data archives are stored on high capacity, institutionally managed systems.

Practices for selection of data to be permanently archived vary among institutions. Video data is generally not retained in its entirety. Common practices include (1) retention of only EEG and video data that correspond to background and clinical or electrographic events or (2) retention of all EEG, but only of that video that corresponds to events. The former practice mirrors that commonly employed in epilepsy monitoring units. The later may be appropriate to ICUs, where analysis of long-term trends can be important. State law governs data retention requirements, and specific requirements vary between states. It is recommended that policies regarding both data "pruning" and data retention be established in consultation with hospital health information management and legal authorities.

## Remote Connection

### Virtual Private Networks

Effective cEEG monitoring requires that the interpreting neurologist always has access to real-time information. As such, effective remote access is essential. One commonly employed solution makes use of a virtual private network (VPN) to effectively extend the hospital's internal network to the remote sites. Computers connected through a VPN appear as if they were behind the hospital's firewall; if the institution uses private IP addresses (e.g. 10.x.x.x), these are usually directly

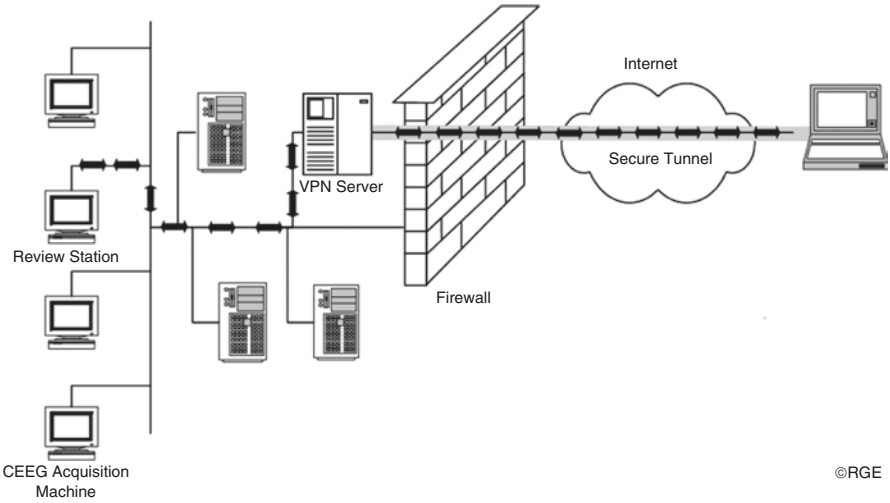


**Fig. 7** A VPN creates a secure tunnel (*gray*) through which data can travel to a remote computer allowing it to function as if it were behind the institutional firewall

| Source IP Address Port | Destination IP Address Port | Encrypted Data Payload | | |
|---|---|---|---|---|
| | | Internal Source IP and Port | Internal Destination IP and Port | Data Payload |

**Fig. 8** VPN packet. The internal network source and destination IP addresses, ports, and data payload are encrypted and form the data payload of a VPN packet, with external (Internet) IP addresses and ports

addressable when connected through the VPN. From a technical standpoint, the VPN creates a secure "tunnel" connecting the remote site and the hospital's internal network (Fig. 7). Internal data packets (including the data "payload" along with internal network source and destination IP addresses and ports) are encrypted and form the data payload of the VPN data packet, with public (Internet) IP addresses and ports corresponding to ends of the tunnel (Fig. 8). At the tunnel's destination, the payload is decrypted, revealing both the data payload and internal source and destination IP addresses and ports. Institutions providing VPN network access will generally provide the necessary "client" software for remote computers; some make it simple to connect using a web browser.

Since a VPN effectively extends the hospital's internal network to remote sites, it potentially exposes the hospital's network to viruses or other malicious software that may be present on remote computers. For this reason, institutions may require that remote computers be actively managed and kept current with the security patches and antivirus software, just like desktop systems located physically within the institution. Additionally, a special firewall may separate the VPN from the rest of the internal network, restricting traffic to particular internal subnets and data types.

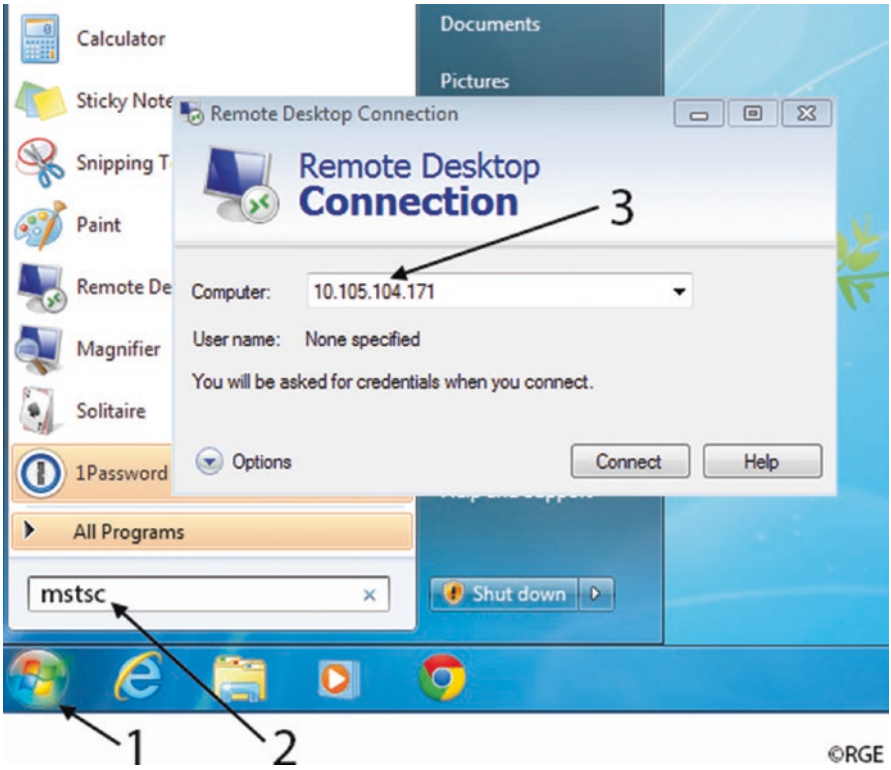


**Fig. 9** To connect remotely to a Windows® computer using RDP from another Windows® machine, simply click on the Window button (*1*), enter "mstsc" (*2*), and enter the IP address or name of the host (*3*). You will typically then be prompted to enter your user name and password. A user who is logged on to the host computer will be disconnected when you connect

Although it is possible to run review station software remotely over a VPN, a better solution may be to use a remote desktop solution, over the VPN, to view and control an on-site review station from the remote computer. The keyboard, monitor, and mouse of the remote computer effectively become the keyboard, monitor, and mouse of the host. In addition to obviating the need to specialized cEEG review software on the remote computer, this type of arrangement is often more resilient to slower Internet speeds and network interruptions that can impact performance of the VPN. Windows® includes support of the Remote Desktop Protocol (RDP); to use it, simply run MSTSC on the remote computer and enter the name or IP address of the host (Fig. 9). Before it can be used for the first time, it is necessary to enable RDP on the host (Fig. 10). Various other RDP clients are available for both Windows® and Apple® (both for OSX® on Macs® and IOS® on iPads®) and Android® remote devices. One limitation of connecting remotely to Windows® desktops with RDP is that the local user is logged out, and the local screen closed, when a remote user connects. Virtual Network Computing (VNC),

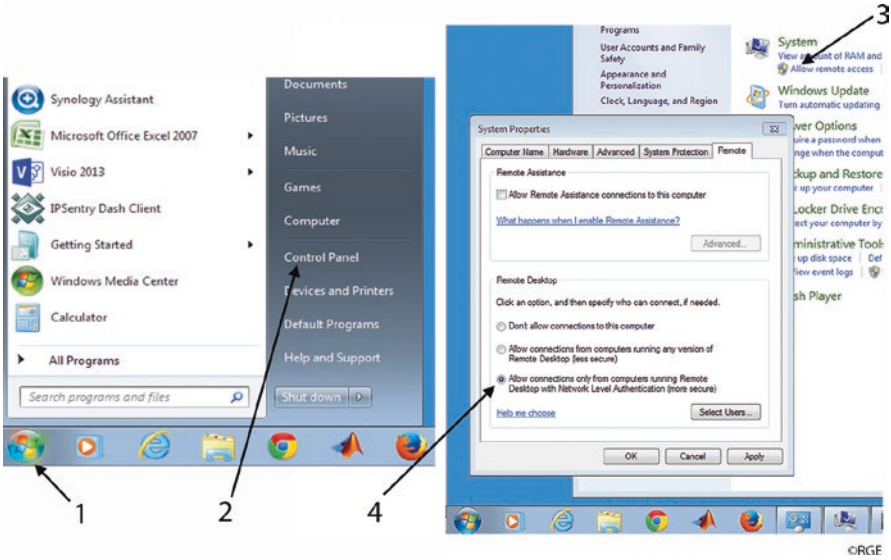


**Fig. 10** Remote desktop is not enabled by default and must be enabled on the host before a remote connection using RDP can be made. To enable RDP, simply click on the Windows® button (*1*), Control Panel (*2*), Allow Remote Access (*3*), and Allow Connections (*4*). This setting needs only to be made once, but making it requires that the user has Local Administrator permission. On institutionally managed computers, this may need to be set by IT personnel

an open-source alternative, can be configured to permit the host computer to be viewed and controlled simultaneously, both locally and remotely [5]; it is available from multiple vendors.

## Reverse Connection Remote Control Software

Programs such as GoToMyPC® and LogMeIn® provide functionality similar to that discussed above and can make connecting to and controlling a hospital computer from the Internet particularly easy and convenient. Most firewalls block initiation of communication on all but very specific inbound ports; outbound connections are usually less restricted, and once an outbound connection is initiated, related inbound traffic is generally permitted. These programs function by initiating and maintaining an outbound connection to a third-party server; when you connect to a hospital computer through one of these services, you are effectively joining a conversation already in progress, initiated from within the hospital's firewall.

These programs offer good security; for example, communication is encrypted between host and remote machines and is not decrypted by the third party [6]. Importantly, however, security is critically dependent on proper configuration by the

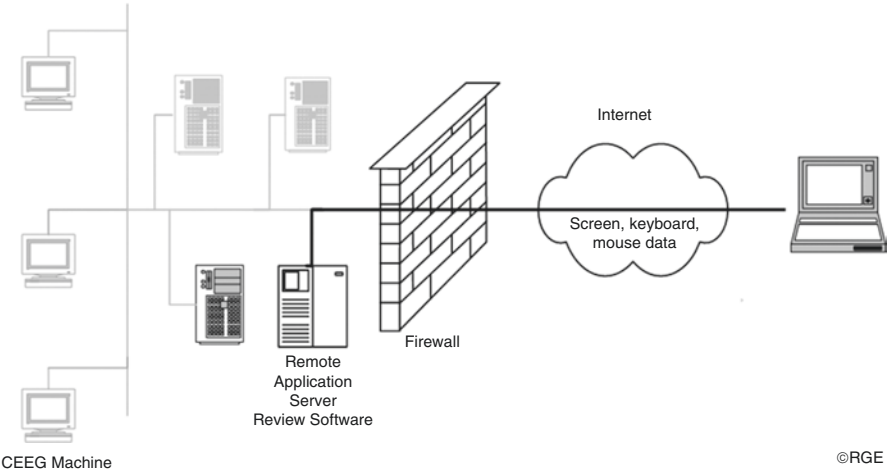


**Fig. 11** Remote application server. In this arrangement, the cEEG review software runs on the remote application server. While the server has access to assets to systems within the hospital network, only screen, keyboard, and mouse data travel beyond the firewall

user. Further, and particularly because they effectively circumvent institutional firewalls, their use may be contrary to institutional policy. It is recommended, therefore, that users consult with appropriate institutional authorities prior to using these products.

## Remote Application Servers

Alternatively, the target application, such as cEEG review software, may be hosted on a special remote application server. In contrast to a VPN, remote users do not have direct access to the hospital's internal network, but instead have direct connection only to the remote application server, which in turn has access to the necessary internal assets (Fig. 11). No other systems on the hospital's internal network need to be exposed to the Internet. As with the remote desktop arrangement described above, the remote computer merely serves as a keyboard, mouse, and monitor for the system actually running the application. The remote application server provides encryption, so a VPN is not required.

Typically a remote application server will support multiple concurrent users and may host multiple different applications. System administrators can control who has assessed to which application, whether users will see only specific applications or more complete "virtual" desktops, and whether or not files may be uploaded or downloaded. One convenience of this type of arrangement is that only a single copy of a given application (i.e., cEEG review software) needs to be installed on the remote application server. Special licenses permitting multiple concurrent users

may, however, be required. Citrix Systems Inc. offers remote application system based on Windows Terminal Services® and provides supports to Windows®, Apple® (IOS® and OSX®), and Android® client devices.

**Conclusion**

A cEEG program of almost any scale requires digital communication and storage. While it is not essential to have personal detailed knowledge of these technologies to perform and interpret cEEG, the involvement and support of people with such knowledge is necessary. A close working relationship with the clinical engineering and information technology departments of the institution is necessary to setup and maintain a cEEG system. Involving them early in the process can lead a more robust system but routine maintenance, and upkeep is equally important.

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