Orbital Cellulitis and Periorbital Infections

Michael T. Yen
Thomas E. Johnson
Editors

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Dedicated to my parents, Frank and Lie-hwa Yen, my wife Kimberly, and my children, Ashley, Christopher, and Emily, for inspiring me every day by their example.

Michael T. Yen, MD

Dedicated to my daughter Olivia, who amazes me every day with her compassion, dedication, positive outlook on life, and sense of humor.

Thomas E. Johnson, MD

Foreword

Orbital Cellulitis and Periorbital Infections

Periorbital infections are an important group of conditions that can vary from a minor infection with no sequelae after treatment to major infections that can lead to blindness, major permanent neurological disabilities, multiple organ failure, or death. The variable severities of these diseases have, however, several features in common. First, all need early recognition and urgent treatment if we are to avoid unnecessary and permanent morbidity. Secondly, many infections can be due to unusual organisms that originate from neighboring areas—such as the paranasal sinuses or oral cavity—or even from systemic infection elsewhere. Thirdly, the spectrum and presentation of disease has changed markedly over the decades, thus mandating evolving methods for diagnosis and treatment. These major changes involve periorbital imaging, medical therapy, and surgical interventions—changes over the last century resulting from many causes, such as surgical progress during World Wars, the advent of antibiotics, and more recently the antibiotic "arms race" and control of antibiotic usage required to combat antibiotic resistance.

The two editors have very successfully assembled an experienced group of ophthalmic colleagues to address these many issues for this complex group of conditions. The book comprises a series of chapters covering all aspects of orbital cellulitis and periorbital infections in a very logical sequence. While individual in style, each chapter follows a logical pattern and they are well written, clearly illustrated, and adequately referenced. There is some inevitable repetition between chapters, but this is not enough to annoy the reader and certainly allows each chapter to be a "free-standing" article that can comfortably form a single, highly readable lesson. Some chapters—such as those covering the history of treatment, mechanisms of visual loss, and orbital infections in cancer patients—are of particular interest and are often omitted from standard texts.

Michael Yen and Tom Johnson are to be heartily congratulated on producing a concise text about this serious group of conditions. The book's logical layout and readability make this a particularly good reference text that is not only easily read for enjoyment, but also should find a valuable place in the library of any physician dealing with this group of patients.

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Preface

While most infections of the eye and orbit can be successfully managed, the potential complications of these infections can include vision loss, impaired visual function, intracranial extension, and even death. Furthermore, inadequately or inappropriately managed infections often progress rapidly. With a constantly changing microbiology of infectious organisms, advances in orbital imaging techniques, and the frequent introduction of new medical and surgical therapies, it can be difficult for the practicing physician to remain up to date on the diagnosis and management of orbital infections. The management of orbital cellulitis can certainly be intimidating.

To successfully manage orbital cellulitis requires an understanding of the pathophysiology, microbiology, and clinical presentation of the disease. Selecting the proper diagnostic imaging, the appropriate medical therapies, and determining when surgical intervention is required are necessary for optimal outcomes. This text provides a consolidated yet comprehensive source for the evaluation, diagnosis, and management of orbital cellulitis and associated infections. For this text, experts in the fields of pediatric ophthalmology, oculofacial plastic surgery, neuro-ophthalmology, vitreoretinal surgery, radiology, otolaryngology, and neurosurgery have written in-depth chapters that can serve as a reference guide for the clinician. This text is an excellent resource for not only those in training but also the seasoned practitioner wanting to be updated on the newest diagnostic and treatment approaches for orbital cellulitis.

We are greatly indebted to all the authors for their contributions to the text. Special thanks to the editors and staff at Springer, especially Rebekah Amos Collins, Lizzy Raj, and Saanthi Shankhararaman, for their assistance in bringing this manuscript to completion.

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Chapter 1
The History of Treating Orbital Cellulitis

Karima S. Khimani and Kimberly G. Yen

Introduction

Orbital cellulitis is a serious infection and inflammation of the soft tissues of the orbit posterior to the orbital septum. If left untreated, orbital cellulitis can lead to vision loss and life-threatening consequences such as cavernous sinus thrombosis, meningitis, brain abscess, osteomyelitis of the orbital bones, and septicemia [1]. A frequent complication of orbital cellulitis is subperiosteal abscess (SPA) which forms when infection spreads underneath the periosteum of the frontal, ethmoid, or maxillary bones, resulting in the collection of purulent material between the periorbital and the orbital bones [2]. Over the decades, with the advancement of diagnostic tools, introduction of new broad-spectrum antibiotics, and improvement in surgical techniques, the approach to managing the complications of orbital cellulitis and SPA has evolved, although the basic principles have remained the same [3].

Diagnosis

In the early twentieth century, history and physical examination were the mainstay of the diagnosis of orbital cellulitis since this was prior to the development of antibiotics and radiographic imaging. Patients would be diagnosed with orbital cellulitis based on clinical signs such as severe pain and swelling of the eyelids, edema of

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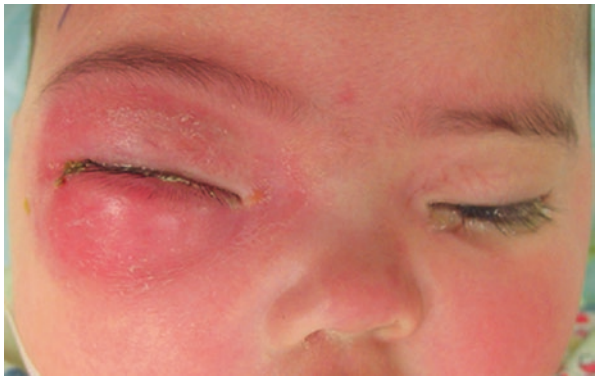

Fig. 1.1 Orbital cellulitis on the right side presenting with significant upper and lower eyelid edema (Image courtesy of Michael T. Yen, M.D.)

the eyelids and conjunctiva, and limited ocular movements with or without vision changes, generally with a concomitant or recent history of upper respiratory tract infection [4]. The diagnosis of orbital cellulitis at that time was not, however, based solely on the presence of redness and swelling of the eyelid, since these features could occur from preseptal cellulitis as well as other conditions such as a hordeolum, dacryocystitis, or cellulitis of the scalp or face [5]. The distinguishing feature of orbital cellulitis was the presence of proptosis in combination with a congested eye and inflamed eyelid (Fig. 1.1). The constellation of these clinical signs helped to establish the clinical diagnosis of orbital cellulitis prior to the advent of imaging in these early days [5].

The classification of orbital cellulitis can be traced back to 1937, when Hubert published a seminal paper describing infections around the orbit arising from sinusitis [6]. In 1970, Chandler et al. modified Hubert's classification and presented a five-level classification system for orbital cellulitis which is still used today [4]. In this classification, group I consists of patients with edema confined to the eyelids only. Group II represents true orbital cellulitis, manifested by edema of the eyelids, diffuse orbital edema, vision changes, and painful eye movements. Group III is characterized by the presence of a subperiosteal abscess (SPA), which is marked by accumulation of pus between the periosteum and the orbital bones. Group IV is distinguished by the presence of a true orbital abscess, which causes more severe proptosis and ophthalmoplegia. Group V is the end stage of orbital cellulitis with extension of the infection into the CNS, causing cavernous venous thrombosis [4, 7–9].

Perhaps the development that had the greatest impact in the evaluation and management of orbital cellulitis was the introduction of computed tomography (CT) in the late twentieth century (Fig. 1.2). Since then, imaging has played an important role in the diagnosis of orbital cellulitis and, in particular, subperiosteal abscesses [2]. Controversy among scientists regarding the use of CT as part of the initial workup of SPAs has existed since the introduction of the CT, especially since abscess formation is not visible on a CT scan when it is in the early stages [10, 11]. Some physicians maintain that, due to the aggressive nature of SPAs, CT scans

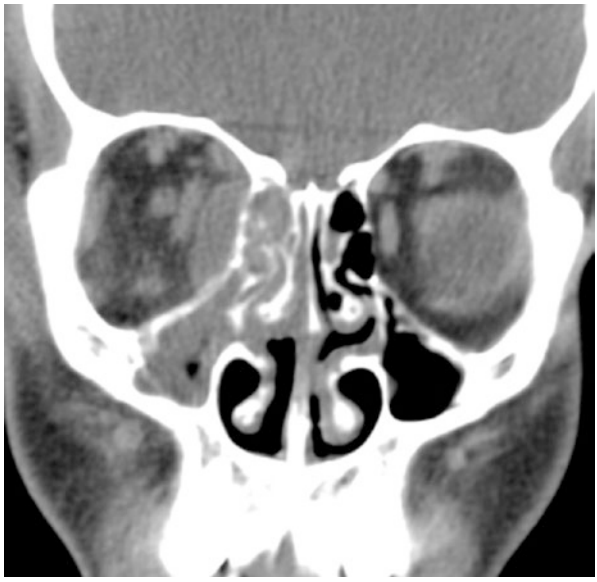

Fig. 1.2 Coronal CT scan demonstrating complete opacification of the maxillary and ethmoid sinuses associated with a subperiosteal abscess in the medial orbit on the right side (Image courtesy of Michael T. Yen, M.D.)

should be obtained in all cases even if the initial presentation is consistent with preseptal cellulitis. Other authors have reported orbital ultrasound to have a better sensitivity for orbital abscesses [10]. However, the general consensus is that ultrasound has poor resolution at the orbital apex and does not allow the simultaneous visualization of the surrounding sinuses and intracranial tissues [10].

Etiology

In the early twentieth century, the most common etiology of orbital cellulitis in adults was frontal sinusitis; these patients would often present with downward and outward displacement of the globe [1]. In children, suppuration of the ethmoid sinus was the most common cause of orbital inflammation in the early twentieth century, and these patients presented with the globe displaced outward [1]. Prior to 1985, the most common causative organism in children was *H. influenzae*, and, until a specific organism was identified in children presenting with orbital cellulitis, initial therapy was always directed against this organism [12]. After introduction of the *H. influenzae* vaccine in 1985, however, *Staphylococcus aureus* and *Streptococcus* species emerged as the most common causative organisms.

Currently, sinus infections still remain the most common cause of orbital inflammation in children. About 60% of all orbital inflammatory processes extend from sinusitis, with ethmoiditis being the most common source [4]. In adults, modern-day orbital cellulitis is usually the result of a recent illness or trauma, such as orbital fractures and intraorbital foreign bodies [13].

Epidemiology

Prior to the 1940s, when antibiotics first came into widespread use, 17% of orbital cellulitis patients died, and 20% of the patients lost vision [3, 9]. Over time, however, with increased awareness of possible complications and better techniques of diagnosis and management, these rates have declined dramatically. By the late twentieth century, the rate of blindness dropped to 3–11%, while the rate of mortality was reduced to 1–2.5% [3]. In cases where infection spreads to the cavernous sinus or to the intracranial area, however, the rate of morbidity and mortality still remains high with incidences cited between 10–20% [14]. Fortunately, intracranial complications have now become a rare occurrence, and in recent years, the incidence of these complications has decreased to less than 1% [9].

Globally, orbital cellulitis is primarily a disease of children and adolescents. In the United States, the condition is reported to be most common in patients under 15 years of age, with the median age being 7 years [15]. The high incidence of the disease in children can be explained by the underdeveloped immune system, especially the underproduction of IgGs in infants between the ages 1 and 5 years, which makes them more susceptible to infections by encapsulated organisms such as *Haemophilus influenzae* and *Streptococcus* species [13, 16, 17]. The incidence of orbital cellulitis due to *H. influenzae* has significantly decreased since the early 1990s due to widespread immunization, resulting in a decrease in the overall incidence of orbital cellulitis [15, 16].

Medical Management

The medical and surgical management of orbital cellulitis has undergone shifts over the course of time. In the early twentieth century, treatment options were limited. Since the introduction of antibiotics to the treatment of orbital cellulitis in the 1940s, the overall incidence of complications of orbital cellulitis has decreased.

In the mid-twentieth century, the most common pathogens causing orbital cellulitis in children were identified as aerobic bacteria, namely, *Haemophilus influenzae*, streptococci, and staphylococci [12]. Other less common organisms included *Klebsiella*, *Micrococcus*, and *Enterococcus* [12]. The mainstay for initial therapy at this time included empiric treatment with penicillin in combination with penicillinase-resistant antibiotics, such as methicillin, or in combination with other synergists, such as streptomycin, sulfonamides, or chloramphenicol [12, 18–21]. In some cases, high doses of ampicillin were initially administered, along with intranasal decongestants, sedatives, and analgesics [4]. Cases of orbital cellulitis that were complicated by an abscess were reported to be successfully managed with antibiotic injections, penicillin ointment, and hot fomentations, which caused the abscess to burst and allowed the pus to drain [22]. Visual changes and proptosis were seen to improve within days of this intervention [22]. In adults, anaerobic

coverage was added to the coverage against aerobic organisms [23]. In general, anaerobes were susceptible to penicillin, metronidazole, and chloramphenicol [24]. While cefoxitin and clindamycin also provided good coverage against anaerobes, they had the disadvantage of poor CNS penetration [24].

In the late twentieth century, antibiotic recommendations changed with the introduction of new generations of pharmacodynamically optimal antibiotics, such as third-generation cephalosporins [2, 25]. Ceftriaxone replaced the older combinations of antibiotics and helped avoid the bone marrow suppression previously caused by chloramphenicol [2]. In patients allergic to penicillin or cephalosporin, vancomycin was used as an alternative medication [2, 7, 15]. For anaerobic coverage, cephalosporins were used in combination with clindamycin [2].

The introduction of *H. influenzae* vaccine has been an important preventative tool in decreasing the incidence of *H. influenzae* as the most common causative organism for orbital cellulitis, as well as decreasing the incidence of orbital infection in the pediatric population as a whole [10, 26]. The *H. influenzae* vaccine, however, does not provide protection against nontypeable *H. infleunzae* [15]. Consequently, the most likely pathogens now causing orbital cellulitis are nontypeable *H. influenzae* and *Staphylococcus* and *Streptococcus* species, with *Streptococcus anginosus* emerging as a pathogenic group in the pediatric population [15, 27]. *Moraxella catarrhalis* and anaerobic bacteria have also been identified, although less commonly, as causative bacteria of orbital cellulitis [28]. In the twenty-first century, adequate antibiotic coverage for pediatric orbital cellulitis includes a combination of beta-lactamase-resistant penicillin for *Streptococcus* or *Staphylococcus* species, clindamycin for anaerobes, and a third-generation cephalosporin for *H. influenzae*, *Moraxella*, and resistant pneumococci [15].

In recent years, newer fluoroquinolones, such as gatifloxacin and moxifloxacin, have shown promising results in the treatment of orbital infections [29]. Older fluoroquinolones preferentially inhibited DNA gyrase in gram-negative organisms and DNA topoisomerase IV in gram-positive organisms. In contrast, the new generation of fluoroquinolones has a dual mechanism of action, where they are able to inhibit both enzymes involved in bacterial DNA synthesis in both gram-positive and gram-negative organisms [29].

In recent years, bacterial resistance to antibiotics has been a major concern, particularly due to the rising incidence of community-acquired methicillin-resistant *Staphylococcus aureus* (MRSA). About 20% of *S. aureus* isolates from orbital and sinus cultures are identified as MRSA [9]. A study conducted in France found 30% of *H. influenzae* and 80% of *Moraxella* resistant to beta-lactams [10, 28]. Over time, pneumococci also became increasingly resistant to macrolides and penicillin G [28]. In efforts to combat the rising resistance against antibiotics, the Centers for Disease Control and Prevention and the World Health Organization have proposed some strategies to delay the development of antibiotic resistance [29]. Current recommendations include the fact that antibiotics should be prescribed only when needed and should be selected based on the identification of causative pathogens and their sensitivity testing, eventually switching to oral therapy [27, 29].

Furthermore, the course of antibiotic therapy should be completed in its entirety, and the use of antibiotics for optimization of animal and agricultural growth should be avoided [29].

Surgical Management

Over the years, controversy over the necessity and timing of surgical intervention in the management of orbital cellulitis and SPAs has persisted. Clinical signs of developing an abscess include increasing edema of the eyelid, worsening of visual acuity, fixed displacement of the globe, and severe pain [1, 4]. As early as the 1930s, recommendations for initial therapy of orbital cellulitis with SPA were to treat with intranasal medications until localization of the abscess occurred, followed by drainage of the abscess [19, 30]. A 1935 paper by Layton suggested that acute cases of orbital cellulitis with SPA should be managed with the least amount of surgical intervention in order to prevent the seeding of adjacent structures with bacteria from orbital infections and reduce the risk of complications such as osteomyelitis and cavernous sinus thrombosis [30].

Prior to the 1980s, surgical management of SPAs involved rapid decompression of the abscess [9]. In the pre-antibiotic era, progressive orbital signs were an indication for external drainage that involved the opening up of sinuses, removing the infected bone, and draining any medially located SPAs [31]. During this time period, the surgical approach to managing SPAs secondary to sinusitis depended on the sinuses involved. Frontal sinuses were opened externally by making a Moore's incision underneath the eyebrow. Rubber tubes were then placed to drain the sinuses into the nasal fossa [32]. Ethmoid sinuses, on the other hand, were drained intranasally by performing external ethmoidectomy, which involved creating Lynch incisions between the nasal bridge and the eye to enter the sinus and then removing the middle turbinate [18, 32]. Maxillary sinuses were visualized by the Caldwell-Luc approach, where an incision was made underneath the lip along the upper gumline [3]. The sinus was then drained by performing an intranasal antrostomy, and a rubber drain was left in place before loosely closing the external incision [18]. Suction apparatus supplemented the passive flow of discharge from the nose and incision wounds [33]. Lastly, any fluctuating area in the temporomalar region, indicating the presence of a superficial abscess, was incised and drained [32]. While these procedures provided good visualization for evacuation of SPAs, they also caused significant discomfort and prolonged recovery. By the late twentieth century, surgical exploration and drainage of the sinuses were reserved for patients who did not respond to medical treatment within 24–48 h [23, 34, 35].

The advent of CT allowed visualization of the anatomical delineations of the orbit, sinuses, and intracranial structures, which proved to be valuable in localizing orbital infections and identifying orbital abscesses earlier in the course of the disease [19, 35]. Identification of the site of abscess formation was no longer dependent

on following the location of the inflammatory signs and the direction of globe displacement [19]. Consequently, CT scanning allowed timely and correct surgical approach for the drainage of abscesses and decompression of the orbit, resulting in reversal of proptosis, as well as recovery of visual acuity, visual fields, and ocular motility [19]. Furthermore, CT scanning allowed for diagnoses of cerebral complications of orbital cellulitis, such as cerebritis, brain abscess, and epidural infections, a delay in the treatment of which would prove fatal [19, 34]. In mild cases of orbital cellulitis, the use of CT imaging to rule out SPA became essential, as patients could be treated less aggressively with intravenous cephalosporin inpatient initially, followed by outpatient treatment with intramuscular third-generation cephalosporin [25].

In the twenty-first century, systemic antibiotics remain the initial treatment for orbital cellulitis with surgical drainage reserved for cases with abscess formation, visual impairment, or no response to antibiotics [15]. More recently, studies have revealed that many SPAs in children can be successfully treated with IV antibiotics alone, if the following criteria are met: (1) patient is less than 9 years of age, (2) patient has no visual impairment, (3) abscess is medially located and is of a moderate size, and 4) there is no intracranial or frontal sinus involvement [36, 37].

With recent advances in medical technology, the introduction of transnasal endoscopic sinus surgery has reduced the necessity for external incisions to drain sinuses. Caldwell-Luc procedures have now become obsolete, and external ethmoidectomy is reserved for cases where endoscopy results in poor visualization or where the orbital signs fail to resolve [31, 38]. Generally, transnasal endoscopy has been studied to be a safe and successful approach in managing SPAs [11, 39] as it causes less scarring, allows for a rapid resolution of periorbital swelling, and decreases the risk of bleeding or further spread of infection by avoiding incisions in the periorbital region [31].

Corticosteroids

Most recently, corticosteroids in the treatment of orbital cellulitis with SPA have been found to reduce the incidence of adhesions, sinus swelling, and stenosis, when used as an adjunct to systemic antibiotic therapy and to improve perioperative surgical outcomes due to their anti-inflammatory effects [40–42]. Even though antibiotics hasten the resolution of infections, the resulting bacterial lysis causes inflammation that persists postinfection [41]. Corticosteroids reduce edema and cell migration, preventing elevation of orbital pressure and compression of orbital structures. Furthermore, they inhibit fibroblast proliferation, allowing for reduced scarring. The use of corticosteroids in patients with orbital cellulitis, both with and without SPA, has been found to shorten the treatment course of parental antibiotics as well as the length of hospital stay, resulting in a decrease in the cost of care [41, 42].

Conclusion

Over the years, the approach to treating orbital cellulitis has evolved, and its prognosis has improved. The introduction of advanced diagnostic tools, in addition to the use of clinical ophthalmic findings to determine the need for surgical intervention, has prevented wasting valuable time over expectant management [37]. Consequently, the length of hospital course has decreased, and risk for hospital-associated morbidities has declined [37]. An increase in the awareness of possible complications of orbital cellulitis, along with the introduction of new broad-spectrum antibiotics and innovative surgical techniques, has contributed to improved outcomes of orbital cellulitis [3].

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Chapter 2
Clinical Evaluation of the Infected Orbit

Preeti J. Thyparampil and Michael T. Yen

Introduction

Orbital cellulitis is an acute inflammation of the orbital tissues. It is most commonly due to spread of an infectious process from the adjacent sinuses or arises, less commonly, through hematogenous spread and posterior spread of a preseptal cellulitis or through an infected globe. Orbital infection can result in the formation of orbital abscesses. Abscesses are typically subperiosteal in location and develop via spread of infection from the parinasal sinuses, through the thin orbital walls, into the subperiosteal space. Intraorbital abscess can develop through collection of infected material within the orbit or from rupture of a subperiosteal abscess into the orbital space. Orbital cellulitis can result in serious systemic complications including meningitis, cavernous sinus thrombosis, brain abscess, and death. Serious ocular and orbital complications can also occur including orbital scar tissue formation and loss of vision. Subperiosteal and orbital abscesses can further exacerbate the problem of orbital congestion, which is seen in orbital cellulitis, and increase the risk of damage to the optic nerve, retina, and other orbital components.

The Chandler criteria, established in 1970, has been the standard for describing the clinical range of infections of the orbit and periorbital region. The

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orbital septum, a fascial membrane extending from the orbital rim to the tarsus of the eyelid, was recognized as an important anatomic landmark delineating preseptal from orbital disease. In this grading system, stages of infection were characterized based on the nature of the infectious process and its location. Stage I patients had inflammation anterior to the orbital septum, limited to the eyelids, and were described as having preseptal cellulitis. Stage II patients have inflammation of the orbit posterior to the orbital septum and are described as having orbital cellulitis. Stage III patients have developed an infectious fluid collection between the bones of the orbit and the orbital contents and are described as having a subperiosteal abscess (SPA). Stage IV patients have the formation of an infectious fluid collection within the orbit itself, termed an orbital abscess. Stage V patients have developed phlebitis which has extended posteriorly to the cavernous sinus. This results in bilateral eye findings, and often with prostration, and is referred to as having a cavernous sinus thrombosis [1]. Given the potential severity of orbital cellulitis, it is important to recognize the clinical manifestations of this condition and initiate treatment in a timely fashion [2, 3].

Clinical History

Antecedent history can be useful in the initial evaluation of patients with potential preseptal or orbital cellulitis. Patients' age, concomitant medical conditions, and recent history can all aid in differentiating the two and identifying orbital infection. In pediatric cases, demographic characteristics vary between typical patients with orbital versus preseptal cellulitis. A study by Weiss examining 137 pediatric patients with preseptal cellulitis and 21 pediatric patients with orbital cellulitis found the mean age to be 2.8 years for patients with preseptal cellulitis and 8.3 years for patients with orbital cellulitis. In the same study, patients with preseptal cellulitis were more likely to have a prior history of recent nontraumatic ocular or periocular infections, periocular trauma, and upper respiratory tract infections, whereas the patients with orbital cellulitis were a more homogenous group, most (90%) having had recent sinusitis. A paper by Jones and Steinkuller summarizes preseptal cellulitis risk factors as recent trauma, skin infection, and younger age (less than 6) and risk factors for orbital cellulitis as trauma, surgery, sinusitis, diabetes mellitus, and immunosuppression [2]. Orbital infection with the rare but serious fungal infection, mucormycosis, should be considered in diabetic or immunocompromised patients.

Differential Diagnosis

The clinical manifestations of orbital infection are often nonspecific, and the initial differential diagnosis must include noninfectious processes as well such as hemorrhage, tumors, allergic or inflammatory reactions, and immune-mediated inflammatory conditions such as sarcoidosis and granulomatosis with polyangiitis [4]. Clinical findings that support an infectious process of the orbit include antecedent history of rhinorrhea, upper respiratory tract infection, or sinusitis, recent trauma or surgery to the orbit, or history of immunosuppression. Findings such as fever, leukocytosis, and nasal or sinus congestion and purulent nasal discharge can support a diagnosis of orbital cellulitis [5].

Etiologies of Orbital Cellulitis

Traumatic Orbital Cellulitis

Posttraumatic orbital cellulitis may occur as a result of any injury in which the orbital septum is violated (Fig. 2.1). Signs of orbital infection after trauma typically begin to occur 48–72 h after the injury but can be delayed, particularly in cases of retained foreign bodies. At the time of the initial injury, orbital infection may not be suspected due to a relatively minor entry wound with minimal surrounding inflammation or, alternatively, be masked by marked hemorrhage or edema on initial evaluation. The clinical suspicion for orbital infection should remain high, therefore, based on the mechanism of injury and

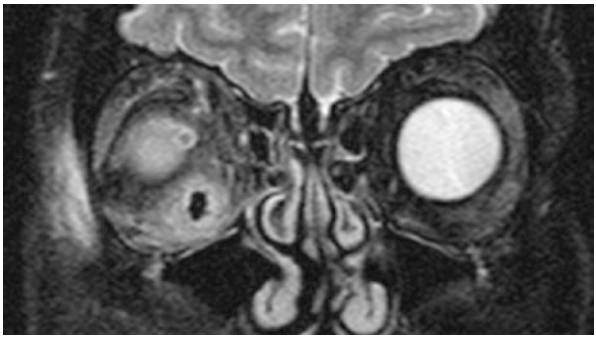

Fig. 2.1 Coronal MRI scan of the orbits showing orbital cellulitis on the right side associated with a retained wood fragment foreign body sustained after patient was struck with a tree branch

the possibility of foreign matter entry within the orbit. Infection may arise from traumatic entry of normal skin flora into the orbit or through infectious material transported into the orbit via foreign material. The most common cause of infection in posttraumatic orbital infection is *Staph. aureus*, although mixed bacterial and anaerobic infections can also occur [2].

Postsurgical Orbital Cellulitis

Orbital infection may occur after orbital surgery. Infection may also occur after treatment of endophthalmitis due to direct inoculation of the orbit by the infected globe. *Staph. aureus* is again the most likely organism, but anaerobic and mixed infections can also occur. Orbital infection typically develops within the first 2–3 days after surgery, and clinical signs of orbital infection may initially be mistaken as orbital edema and erythema secondary to expected orbital congestion after surgery. Fever, discharge, and leukocytosis point more clearly to orbital infection rather than routine healing [2].

Sinusitis-Related Orbital Cellulitis

Sinusitis is the most common cause of orbital infection and is found in 70–90% of cases of orbital cellulitis [6]. Clinical features of sinusitis-related orbital infection include headache, rhinorrhea, fever, and eyelid swelling. Purulent discharge from the nose can also be seen. The orbital infection typically progresses rapidly with acute onset of eyelid edema, proptosis, and motility restriction (Fig. 2.2). Fever and leukocytosis are also often seen. Vision changes and double vision may develop due to orbital congestion but may not be discerned initially due to eyelid swelling and pain. Sinusitis-related orbital infection is most commonly caused by sinus pathogens such as *Staph. aureus*, *Strep. pneumoniae*, or other *Streptococcus* species and anaerobes [2]. The most frequently infected sinus is the ethmoid, followed by maxillary, frontal, and sphenoid. Often two or more sinuses are involved with the most common paired infections being that of the ethmoid and maxillary sinuses [7]. There is a suggestion of increased occurrence of orbital cellulitis during the winter months due to increased rates of sinusitis at this time [8].

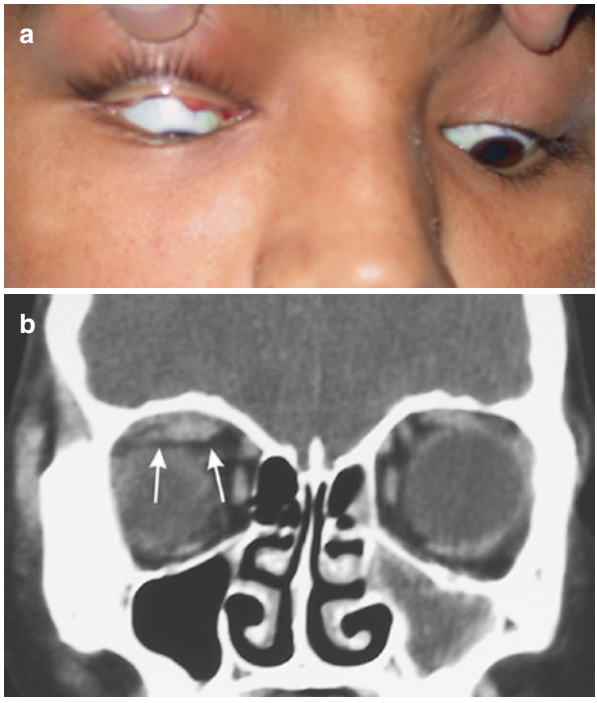

Fig. 2.2 (**a**) Superior orbital cellulitis on the right side causing downward displacement of the right globe. (**b**) Coronal CT scan demonstrating a subperiosteal abscess of the right orbital roof (*arrows*)

Orbital Fungal Infections

Mucormycosis is a rare but serious fungal infection caused by a group of molds called mucormycetes. Classic predisposing risk factors for mucormycosis include diabetic ketoacidosis or immunosuppression related to chemotherapy, immunotherapy, chronic steroid treatment, prior radiation, or immune deficiency diseases [9]. Mucormycosis has also occurred in previously undiagnosed or mild diabetics. The clinical course is characterized by aggressive progression of illness. Initial symptoms may include headache, orbital pain, and fever. Within 1–7 days, typical signs of orbital congestion, including proptosis, restricted motility, and vision changes, may be accompanied by anesthesia or paresthesia of the ophthalmic and maxillary branches of the trigeminal nerve as well as of the facial nerves. Necrosis of orbital tissue and of the adjacent nasal and oral mucosa may occur resulting in a dark,

gangrenous appearance to the tissues. Inflammation and perforation of the ipsilateral eardrum have also been reported. Physical exam should include evaluation of the nasal and oral mucosa, and an otolaryngology evaluation should be requested if mucormycosis is suspected [2].

Aspergillosis is a more indolent orbital infection which is characterized by slow progression of orbital inflation, occurring over the course of months to years [10].

Secondary Orbital Cellulitis

Rarely, orbital cellulitis occurs as a result of other infections. The orbit may become infected due to endophthalmitis or panophthalmitis that has extended through the sclera (Fig. 2.3). Acute dacryocystitis with extension of infection from the nasolacrimal sac past the orbital septum can also result in orbital cellulitis [11]. These infections are typically due to *Staph. aureus* and *Streptococcus* species. Dental infections resulting in maxillary sinusitis can rarely cause orbital cellulitis and are typically due to mixed bacteria, including anaerobes. Osteomyelitis of the orbital bones and phlebitis of facial veins are other, rare, potential causes of orbital cellulitis [12]. A careful history, including inquiring about recent surgery, trauma, infections, and systemic symptoms, and a detailed physical exam, with special attention to the orbit and facial region, should be performed as part of the clinical evaluation of patients with suspected orbital cellulitis [2].

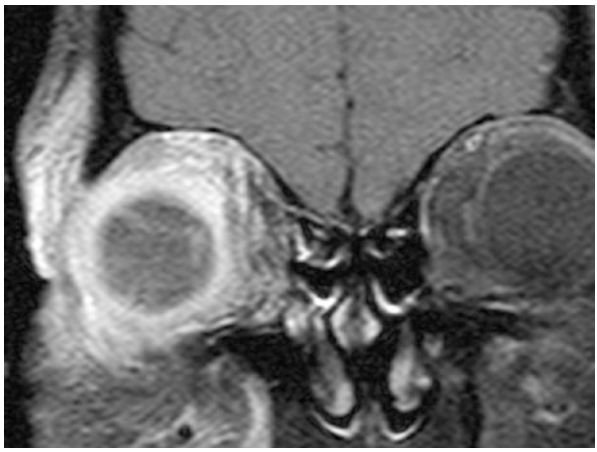

Fig. 2.3 Coronal MRI scan showing orbital cellulitis associated with panophthalmitis of the right eye. Note the loculations of the opacified posterior segment of the right globe as well as thickening of the sclera

Exam Findings

Physical examination findings are critical to making a prompt diagnosis of orbital cellulitis. Examination should begin with an assessment of vital signs and general medical condition. Patients with orbital cellulitis often show systemic signs of illness such as fever and may have fatigue and loss of appetite. In severe cases, patients may appear toxic. External examination of the face should include objective measurement of globe position. Both orbital and preseptal cellulitis can cause significant eyelid edema; however, a finding of proptosis is strongly suggestive of orbital cellulitis. A focused eye exam can show decreased vision and decreased color vision due to optic neuritis or compressive optic neuropathy. A pupil exam should also be performed to observe for abnormalities related to orbital or optic nerve inflammation or mass effect due to orbital abscess. Extraocular motility deficits and pain with eye movement are also physical exam findings which are strongly supportive of a diagnosis of orbital cellulitis. The swollen lid should be lifted for careful examination of the globe as well (Fig. 2.4). Injection of the conjunctiva and conjunctival chemosis are signs which are consistent with orbital cellulitis. A complete eye exam should be performed including evaluation of the optic nerve for optic nerve head edema, which may suggest optic nerve inflammation or compression. Significant periorbital pain, pain with eye movement, and globe injection are earlier signs which point to orbital cellulitis before the onset of later findings such as proptosis, extraocular motility restriction, optic disc swelling, and decreased vision [13]. The spectrum of periorbital and orbital infection ranges from preseptal cellulitis to orbital cellulitis, subperiosteal abscess, orbital abscess, and cavernous sinus thrombosis. There may be overlap in the signs of symptoms of these conditions, but generally more severe systemic and focal findings point to infection that is greater in severity along that spectrum.

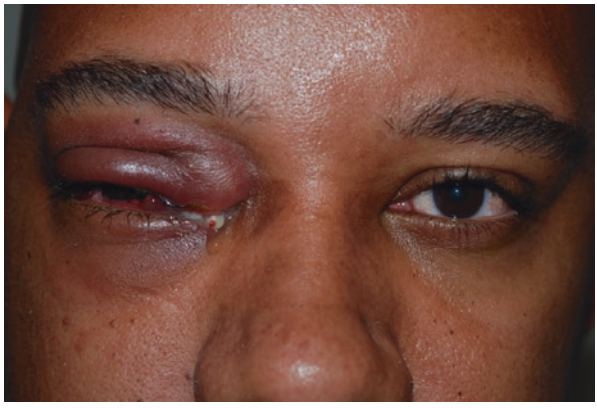

Fig. 2.4 Significant edema of the right upper eyelid with proptosis, limited ocular ductions, conjunctival injection, and discharge are suggestive of orbital cellulitis

Exam Findings with Preseptal Cellulitis

Orbital cellulitis is differentiated from preseptal, or periorbital, cellulitis based on involvement of the soft tissues of the orbit in the former. The orbital septum is the membrane extending from the orbital rim to the eyelids which behaves as the anterior border of the orbit. Preseptal cellulitis is characterized by hyperemia and edema of the eyelids without evidence of orbital congestion. There may be a history of infection of the eyelid or preseptal tissue, for example, an infected chalazion or hordeolum or acute dacryocystitis, with exam findings of acute infection or abscess formation in these locations. There may be exam findings of prior trauma to the lids.

Exam Findings with Orbital Cellulitis

Clinical signs and symptoms of orbital soft tissue involvement include blurry vision, double vision, restricted eye movement, pain with eye movement, conjunctival chemosis, proptosis, and hypesthesia along the distribution of the nasociliary branch of the trigeminal nerve [1]. The clinical findings of ophthalmoplegia and proptosis have been found to have the highest specificity and sensitivity for postseptal infection [14]. The presence of edematous, inflamed eyelids in conjunction with proptosis, motility restriction or signs, or orbital inflammation warrants treatment as presumed orbital cellulitis pending further evaluation.

Exam Findings with Subperiosteal Abscess, Orbital Abscess, and Cavernous Sinus Thrombosis

Clinical signs that are suggestive of the presence of a localized abscess within the orbit include pain with eye movement in a particular direction of gaze and displacement of the globe away from the site of the periorbital sinus with associated subperiosteal abscess [15]. Bilateral eye findings, prostration, and signs of meningeal infection should raise concern for cavernous sinus thrombosis [10].

Additional Testing

Evaluation of a patient with suspected orbital cellulitis should include detailed history taking and physical examination and may involve additional evaluations such as laboratory testing and imaging studies.

A complete blood count may be elevated in patients with preseptal or orbital cellulitis but is more likely to be abnormal in patients with orbital cellulitis [2]. Blood

cultures should be taken prior to the initiation of intravenous antibiotic treatment in orbital cellulitis; however, bacteremia is usually not found [8].

A culture may be taken from orbital abscesses if the patient undergoes surgical abscess drainage. Direct aspiration of an infected sinus is the best source of culture medium, short of open or endoscopic surgery for abscess drainage. If purulent or gangrenous material is present in the nose, a swab of the infected tissue can be taken and sent for culture. Swabbing of nonpurulent material from the nose or conjunctiva has not been found to be informative [2].

Imaging of the infected orbit and sinuses may include CT scanning or MRI which can provide valuable information regarding the intraorbital and intracranial extent of the infection. On the CT, abscess may appear as a low-density mass effect without enhancement or, more specifically, can present with an air-fluid level. Classic displacement of the periosteum away from the lamina papyracea, especially in the medial orbit, can be seen with a subperiosteal abscess. MRI may be useful to identify suspected intracranial extension and to better identify the location and extent of an orbital infection [16–18].

Monitoring Patients with Orbital Cellulitis

The treatment of orbital cellulitis involves admission to the hospital for intravenous antibiotics and close monitoring. Prior studies by Harris have shown that older children and adults with orbital cellulitis are more likely to have a severe clinical course and are more likely to be managed medically, while older patients are more likely to require surgical drainage of any abscess collections. These patients are more likely to have complex infections with multiple bacteria, including anaerobes [17].

All patients should be monitored closely after initiation of antibiotic therapy with a lower threshold to proceed with surgical drainage of abscesses in older children and adults. A failure to show clinical improvement within 24–48 h of initiation of antibiotic therapy should mandate consideration of surgical drainage, especially in older patients [18]. Patients should receive daily or twice-daily exams, and worsening of vision, proptosis, or motility restriction or development of pupil abnormalities should prompt movement toward surgical drainage. Patients without evidence of abscess formation on initial imaging should be reimaged to evaluate for new abscess formation if the clinical picture is worsening, keeping in mind that imaging findings can sometimes lag behind the clinical picture. A patient with a clinical exam that is suggestive of abscess formation may not immediately demonstrate an abscess on CT or MRI. Indications to proceed to surgical intervention as described by Younis are (a) initial presentation of 20/60 or worse visual acuity or severe orbital complaints such as diminished pupillary response and restriction of eye movements, (b) CT evidence of abscess formation, and (c) rapid progression of orbital signs and symptoms despite treatment [19].

Older patients are more likely to have more severe sinusitis and orbital cellulitis, with multiple infectious organisms, and prompt drainage of the sinuses should be

performed in these patients, whether an intraorbital or intracranial abscess has yet to develop. Drainage of abscesses in the orbit should also be performed more promptly in these patients [2, 20]. These patients should be monitored twice daily given the possibility for progression to severe disease, and worsening of vision, pupillary abnormalities, or worsening clinical signs should prompt surgical drainage or reimaging with possible repeat drainage if surgical evacuation has already been performed.

Signs of improvement can be gradual in patients with orbital cellulitis, particularly in older patients with more severe disease. Systemic and constitutional signs may begin to improve before resolution of orbital signs such as proptosis, marked lid edema, and motility restriction. Patients who are showing overall improvement should continue to be monitored closely until improvement is seen in orbital signs and symptoms.

Conclusion

Orbital cellulitis is an infection of the postseptal orbital tissues which can result in serious vision and life-threatening complications. Careful clinical evaluation is critical to the timely diagnosis and treatment of this condition. Antecedent history most often includes history of recent sinus infection and may also include recent surgery, trauma, or immunosuppression. Exam findings may include fever, proptosis, and limited extraocular motility. Globe displacement on exam may point to the presence of a subperiosteal or orbital abscess. Prostration and meningeal signs, as well as bilateral eye involvement, are suggestive of cavernous sinus thrombosis and meningitis. Additional testing may include evaluation for leukocytosis and bacteremia as well as imaging of the orbit and sinuses.

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Chapter 3
Mechanisms of Visual Loss from Orbital Cellulitis

Paul D. Chamberlain and Rod Foroozan

Abbreviations

CRAO	Central retinal artery occlusion
CRVO	Central retinal vein occlusion
CST	Cavernous sinus thrombosis
HIV	Human immunodeficiency virus
IOP	Intraocular pressure
MRI	Magnetic resonance imaging

Introduction

Orbital cellulitis has been regarded as one of the most dreaded ophthalmic conditions. This is chiefly because, while infection can be limited within the orbit, the process can spread to the intracranial compartments where it becomes life-threatening. The other fear is that of visual loss, which may be reversible, particularly with early treatment, or become fixed. But what are the mechanisms of visual loss? While most reviews of the complications of orbital cellulitis mention visual loss as a primary issue, the specific mechanisms are infrequently discussed. The major difficulty in identifying such mechanisms is the infrequency with which each of these individual events occurs. Because of this, such mechanisms are often more speculative than definitive; however, understanding the theoretical causes for visual loss may be useful for clinicians who encounter rare presentations.

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We review the mechanisms of visual loss based on an anatomic approach from the anterior visual pathways, with a particular focus on the role of optic neuropathy, extending to the occipital lobes. The four common factors involved in the mechanisms of visual loss are an increase in intraorbital pressure, extension of infection to key anatomic structures, extension of inflammation to key anatomic structures, and vascular inflammation leading to vasculitis and thrombosis. This chapter focuses on how these processes contribute to visual loss by affecting structures within the orbit and the afferent visual pathways, specifically in cases of bacterial and fungal orbital cellulitis.

Accepting that there may be multiple mechanisms causing visual deficits in a single patient, an understanding of the pathophysiology of visual loss may be helpful in the treatment of patients with orbital cellulitis. However, as most patients with orbital cellulitis are successfully treated with medical therapy, pathology which confirms the specific mechanism is often lacking. The type of infection (bacterial, fungal, viral, and parasitic) often is predictive of the mechanisms of visual loss, with fungal infections most commonly infiltrative. In addition, it is important to remember that orbital cellulitis often results as an extension of infection of nearby structures such as the paranasal sinuses. Vision loss in some instances may be due to processes involving this initial infection, with orbital cellulitis occurring before, concomitant with, and after the onset of the visual deficit.

A summary of the mechanisms of visual loss is included in Table 3.1, and a schematic of those mechanisms is shown in Fig. 3.1.

Table 3.1 Summary of most commonly cited mechanisms of visual loss based on anatomic site of involvement in patients with orbital cellulitis

Most commonly noted disease processes					
Anatomic location of visual impairment		Compression	Inflammation	Infiltration	Vasculitis/ thrombosis
	Anterior segment	Proptosis causing exposure keratopathy	Ciliary body rotation causing angle closure glaucoma	–	–
	Retina	CRAO, CRVO combined retinal artery and vein occlusion	CRAO, CRVO, exudative retinal detachment, endophthalmitis	CRAO, CRVO	CRAO, CRVO
	Choroid	–	Choroidal effusion and angle closure glaucoma	–	Choroidal infarction
	Optic nerve	Ischemic optic neuropathy, direct compression from abscess or mucocele formation, stretch optic neuropathy	Ischemic optic neuropathy, optic neuritis	Ischemic optic neuropathy, direct infiltration of optic nerve (particularly with fungal involvement)	Cavernous sinus thrombosis-related papilledema, ischemic optic neuropathy
	Optic chiasm/ tract	Compression from abscess formation	–	Fungal invasion	–
	Cerebral cortex	–	–	Fungal invasion	Stroke from cerebral venous sinus thrombosis

CRAO central retinal artery occlusion, *CRVO* central retinal vein occlusion

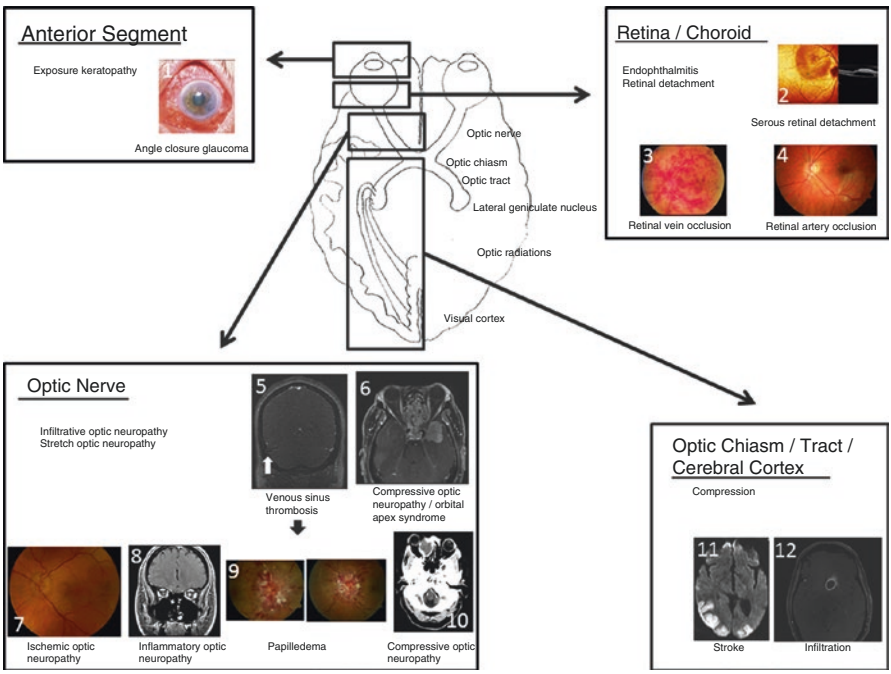

Fig. 3.1 Schematic for mechanisms of visual loss from orbital cellulitis in relation to an illustration of the visual pathways. (*1*) Angle closure glaucoma. External photograph showing conjunctival injection and corneal edema from acute angle closure glaucoma. (*2*) Serous retinal detachment. Optical coherence tomography showing elevation of the retina with hypointensity consistent with subretinal fluid. (*3*) Retinal vein occlusion. Fundus photograph of the left eye showing multiple retinal hemorrhages and optic disc edema from a central retinal vein occlusion. (*4*) Retinal artery occlusion. Fundus photograph of the left eye showing cotton wool spots with retinal whitening from an inferior branch retinal artery occlusion. (*5*) Venous sinus thrombosis. Coronal image from magnetic resonance venography showing an occluded right transverse sinus (*white arrow*) compared to the normally filled left side. (*6*) Compressive optic neuropathy/orbital apex syndrome. Magnetic resonance imaging with contrast, axial T1-weighted image, showing an inflammatory mass involving the left orbital apex and compressing the left optic nerve. (*7*) Ischemic optic neuropathy. Fundus photograph of the left eye showing hyperemic optic disc edema from anterior ischemic optic neuropathy. (*8*) Inflammatory optic neuropathy. Magnetic resonance imaging with contrast, coronal T1-weighted image, showing enhancement of the left intraorbital optic nerve from inflammation. (*9*) Papilledema. Fundus photographs showing optic disc edema with hemorrhages and cotton wool spots in each eye. (*10*) Compressive optic neuropathy. Computed tomography, axial view, showing hyperdensity in the right ethmoid paranasal sinus from a mucocele, resulting in compression of the right globe and optic nerve. (*11*) Stroke. Magnetic resonance imaging, axial diffusion-weighted sequence, showing hyperintensity within the occipital lobes on each side consistent with acute stroke. (*12*) Infiltration. Magnetic resonance imaging with contrast, axial T1-weighted image, showing enhancement in a ring pattern from an intracranial abscess

Anterior Segment

Involvement of the anterior segment is typically readily apparent. Proptosis from the underlying orbitopathy may cause exposure keratopathy and, in more severe cases, corneal ulceration [1]. Anterior extension from posterior involvement in endophthalmitis rarely may involve the ciliary body and anterior

segment. Orbital cellulitis is also a rare cause of choroidal effusion [2], which may cause anterior rotation of the ciliary body and subsequent forward lens displacement, resulting in acute angle closure glaucoma. This has been reported in a case series of three patients with idiopathic orbital inflammation (orbital pseudotumor) [3], and a similar presentation may be possible in patients with orbital cellulitis.

Retinopathy and Choroidopathy

Retinovascular occlusion has been noted in isolation or combined with optic neuropathy in relation to orbital infection. Retinal artery occlusion appears to be the most common form of retinovascular occlusion related to orbital cellulitis. Occlusion commonly results from compression of the central retinal artery due to increased orbital pressure. Four reported cases of central retinal artery occlusion (CRAO) in the setting of orbital cellulitis noted rapidly increasing intraocular pressure (IOP) prior to the onset of CRAO and in the absence of any sign of coagulopathy [4–6]. However, this does not mean that all cases of CRAO in orbital cellulitis are due to compression of the central retinal artery. Retinal artery occlusion may also occur from thrombosis. At least two cases have been reported in pregnant women with CRAO in the setting of orbital cellulitis with normal or mildly elevated IOP. The CRAO in these patients was more suggestive of a thrombotic etiology, especially considering the hypercoagulable state in pregnancy [7, 8]. Direct infiltration or inflammation (vasculitis) of the central retinal artery could also lead to CRAO, although pathologic confirmation is lacking for this mechanism. Retinal vein occlusion may likewise occur secondary to compressive, thrombotic, infiltrative, or inflammatory processes [9]. Central retinal vein occlusion (CRVO) attributed to cavernous sinus thrombosis has also been described [10] and may be possible in the setting of orbital cellulitis.

In addition to retinovascular occlusion, exudative retinal detachment secondary to orbital cellulitis may also result in visual loss. Three cases have been reported of retinal detachment in the setting of orbital cellulitis, all of which had recovery of vision following successful treatment of the orbital infection [11–13]. The mechanism by which exudative retinal detachment occurs in orbital cellulitis is not known. One possibility is that orbital cellulitis results in septicemia, which is known to cause exudative retinal detachment [14]. Whatever the cause of the retinal detachment, this is likely a rare cause of vision loss in orbital cellulitis. Orbital inflammation involving the sclera may result in exudative detachment of the choroid, and scleral abscess formation, in the setting of orbital cellulitis following ocular trauma, with vision loss has also been reported [15].

Much like the exudative retinal detachments in orbital cellulitis, a case report of choroidal detachment and associated vision loss also showed resolution of visual symptoms following successful treatment of the infection [11]. Another reported

cause of visual loss due to choroidal involvement includes choroidal infarction, which has been described in combination with retinal infarction [16].

Endophthalmitis can be a devastating complication of orbital infection and is covered thoroughly in Chap. 15.

Optic Neuropathy

Papilledema Related to Cerebral Venous Sinus Thrombosis and Meningitis

Perhaps one of the most dreaded complications of orbital cellulitis is cavernous sinus thrombosis (CST). The inferior and superior ophthalmic veins drain directly into the cavernous sinus, and infiltration of these routes by infectious organisms or propagation of clot from inflammation may lead to CST. In addition, the valveless pterygoid plexus of veins, angular veins, and nasofrontal veins connect directly to the ophthalmic veins. Infection can then spread to the cavernous sinus from the paranasal sinuses and nasofrontal region, which are often the sources of infection leading to orbital cellulitis. Vision loss may result from subsequent central retinal vein occlusion (see section on retinopathy), papilledema, optic neuritis, or ischemia to a variety of structures due to compression of the carotid artery. It can also lead to stroke or meningitis (discussed below). In part because of the extensive interconnections between the two cavernous sinuses, thrombosis on one side may affect the contralateral eye, a hallmark of CST [17]. Involvement of the intracranial cerebral venous sinus system may also result in elevated intracranial pressure.

A hallmark of papilledema in most patients is the relative parallel between the level of visual dysfunction and the optic disc appearance, and visual acuity loss is generally a sign of severe or prolonged papilledema. The mechanism of visual loss from papilledema is thought to be due to mechanical effects of elevated intracranial pressure followed by ischemia of the optic nerve head due to compression of its blood supply secondary to axoplasmic flow stasis [18]. Blood flow to the optic nerve head is highly sensitive to changes in pressure. Elevated intracranial pressure is transmitted through the optic nerve sheath and disrupts the normal gradient between the intraocular pressure and intracranial pressure. An increase in the retrolaminar pressure may cause stasis of axoplasmic flow as the nerve fibers course through the lamina cribrosa. The stasis results in a further increase in pressure and possibly intra-axonal edema. The increase in pressure may eventually occlude branches of the short posterior arteries supplying the nerve fibers resulting in ischemia [18].

Similarly, involvement of the meninges from posterior spread of an orbital infection may impair cerebrospinal fluid resorption resulting in elevated intracranial pressure and papilledema. Intracranial complications related to orbital cellulitis are discussed more thoroughly in Chap. 14.

Ischemic Optic Neuropathy

The optic nerve may be categorized into anterior and posterior segments based on the differences in their blood supplies. The anterior portion of the optic nerve, including the optic disc, is supplied by the short posterior ciliary arteries arising from the ophthalmic artery. The posterior portion of the optic nerve receives its blood supply from the pial plexus, which arises from the ophthalmic and internal carotid arteries [19]. Inflammation, infiltration, or compression of the posterior ciliary arteries or pial plexus in the setting of orbital cellulitis may cause an anterior or posterior ischemic optic neuropathy, respectively. Though such occlusion would be difficult to show in vivo, imaging studies may show findings suggestive of ischemia. In one reported case of a patient with invasive fungal orbital cellulitis, diffusion-weighted sequences of magnetic resonance imaging (MRI) with contrast showed hyperintensity of the optic nerve of the affected eye, suggestive of ischemia [20]. Follow-up MRI, several weeks later after the infection resolved, showed improvement in the optic nerve hyperintensity consistent with resolution of the ischemia. Although such imaging may demonstrate optic nerve ischemia, it cannot differentiate between inflammation, infiltration, or compression as the underlying cause. In another case of orbital cellulitis and visual loss from 1945 [21], postmortem biopsy revealed severe thromboangiitis of the optic nerve vasculature and significant optic nerve necrosis [22, 23]. These pathologic findings provide some of the best evidence for an inflammatory etiology of ischemic optic neuropathy in orbital cellulitis, though they are not likely to be confirmed because improvements in therapy generally have limited mortality.

Inflammatory Optic Neuropathy

Optic neuritis, or inflammation of the optic nerve, is typically associated with multiple sclerosis, neuromyelitis optica, and other related autoimmune disorders, where it is a sterile inflammatory process. In addition to these autoimmune disorders, several systemic infections are known to cause optic neuropathy. Such parainfectious optic neuropathies may develop secondary to infection with *Bartonella henselae*, *Mycobacterium tuberculosis*, *Brucella* species, *Borrelia burgdorferi*, *Treponema pallidum*, *Cryptococcus neoformans*, and human immunodeficiency virus (HIV) [24]. Although these infectious causes occur more commonly in the absence of orbital involvement, optic neuropathy following orbital cellulitis with *Streptococcus pyogenes* has been described [25]. In this report, MRI showed optic nerve enhancement consistent with optic neuritis without evidence of central retinal artery occlusion, central retinal vein occlusion, cavernous sinus thrombosis, or compressive optic neuropathy. In the setting of orbital cellulitis, the physiologic inflammation present to combat infection may spread to the optic nerve due to its close proximity and cause an inflammatory optic neuropathy [26–28]. Involvement

of the more posterior (ethmoid and sphenoid) paranasal sinuses by infectious organisms has been thought to predispose to an inflammatory optic neuropathy although this has been somewhat controversial [22, 27, 29–31]. One case series of children with CST found that five out of ten patients had concomitant orbital cellulitis [32]. Of these five patients, however, three suffered from visual loss from optic neuritis implied by contrast enhancement of the optic nerve on MRI, without evidence of papilledema or vascular occlusion. This suggests that despite the presence of CST, the underlying cause of vision loss was actually inflammation of the optic nerve.

Infiltration

Direct infiltration of the optic nerve may also cause visual loss. Invasive infectious disease is most common with fungal infection such as that due to aspergillosis and mucormycosis. Infection may spread intracranially from the optic nerve and may also result in an abscess at any point along its path (see sections on optic tract and cerebral involvement), and this has been histopathologically confirmed. A patient with rhinocerebral mucormycosis showed gross ulceration and pathologic confirmation of direct invasion of the optic nerve [33]. The patient was immunosuppressed following liver transplantation and chemotherapy. Immunosuppression from HIV or uncontrolled diabetes is a common feature of patients with these types of infections [34].

In patients with orbital cellulitis and sinusitis due to fungal disease, careful attention to a history of immunosuppression should be assessed by the clinician. Although this case was not actually associated with orbital cellulitis, a similar process may produce vision loss in invasive fungal orbital disease. Despite the possibility of direct infiltration with fungal disease, it is important to remember that there are likely multiple mechanisms leading to vision loss in these patients. In particular, it is well known that fungal invasion of blood vessels can lead to thrombosis and occlusion with resultant ischemia of the optic nerve [35]. Such ischemia is responsible for the necrosis found in all tissues affected by this disease.

Compressive Optic Neuropathy

Increased pressure within the orbit due to infection, inflammation, abscess, or mucocele formation can have serious compressive effects on the optic nerve resulting in visual loss. Abscess often occurs in the medial wall of the orbit because of two main predisposing factors. First, the periorbita or periostea of the bony orbital structures, while tightly adherent at the rim, apex, and suture lines of the orbit, is only loosely attached elsewhere [36]. Second, the lamina papyracea, the bony wall

separating the ethmoid sinuses from the contents of the orbit, is not only very thin but typically has small dehiscences that may allow for the spread of infection [23, 37]. Thus, spread of infection from the ethmoid sinuses through the lamina papyracea may be bound by the loosely adherent periorbita and results in a rapidly expanding abscess and a subsequent increase in intraorbital pressure [38]. This may lead to vision loss from direct compression of the optic nerve, decreased optic nerve perfusion secondary to compression of its vasculature [17, 39, 40], or stretching of the optic nerve due to proptosis [5, 23]. The increased intraorbital pressure may also cause visual loss through compromise of blood supply to other structures such as the retina in CRAO.

Stretch optic neuropathy is typically thought of as a possible mechanism of visual loss in indirect traumatic optic nerve injury. Although the mechanism is incompletely understood, it is thought that stretching of the axons of the optic nerve activates cellular messaging systems that result in the destruction of affected axons and subsequent Wallerian degeneration [41]. Optic neuropathy from a similar mechanism has been noted in other orbitopathies such as thyroid eye disease [42–44]. Mucoceles are epithelial-lined mucus-filled sacs located in the paranasal sinuses and occur secondary to obstruction of sinus drainage. While normally they are slow growing with gradual onset of symptoms from mass effect, infection can create a rapidly growing pyocele which may result in orbital cellulitis and a sudden increase in intraorbital pressure [45]. This may lead to vision loss from the compressive effects discussed previously. Mucoceles may cause visual loss long after an acute process of the paranasal sinus or orbital infection has resolved. In patients with chronic paranasal sinus disease, they may also occur in those who have been otherwise relatively asymptomatic.

Accompanying Orbital Apex Syndrome

Orbital apex syndrome may occur with compression of the nerves and vasculature as they pass through the optic foramen and the superior orbital fissure. Vision loss may occur due to any of the processes discussed previously and may be most likely due to damage to the optic nerve and ophthalmoplegia from compromise of cranial nerves III, IV, and VI [46, 47] due to the location of infection. Because the location of infection is deep within the orbit, patients may initially present with minimal accompanying inflammatory orbital signs [23, 28]. In one case series of three patients with orbital apex syndrome, all patients had monocular vision loss preceding any other sign of infection [23]. The most common source for infection causing orbital apex syndrome is direct extension of fungal infection (particularly aspergillus and mucormycosis) from the paranasal sinuses [48]. Partial or "posterior" orbital cellulitis may be thought of as a less severe form of orbital apex syndrome. The location of infection is essentially the same, but only a segment of the optic nerve or the vasculature accompanying it may be affected with sparing of the other cranial nerves [37, 47].

Optic Chiasm and Tract

Infection, especially invasive fungal disease as discussed previously, may spread posteriorly to include the optic chiasm and tract. One case report of a patient with long-standing sino-orbital aspergillosis noted sudden progression of the disease and development of perineural spread to the optic chiasm [49]. Necrotic tissue was found extending into the optic nerve, chiasm, orbit, and ethmoid sinuses. A similar report that included postmortem examination showed that infarction of the optic chiasm was associated with vascular invasion by fungal hyphae in addition to direct invasion of the optic nerve [28].

Intracranial complications are covered more thoroughly in Chap. 14.

Cortical Involvement

Visual loss due to cortical involvement anywhere along the visual pathways may occur in the setting of stroke, a complication of orbital cellulitis. Stroke is more commonly associated with mucormycosis-related orbital cellulitis [50–53]. Although the authors of this chapter were unable to find any reports of orbital cellulitis-induced stroke resulting in visual impairment, it may be considered a possibility. Most likely, in a case severe enough to cause stroke, other mechanisms of visual loss would also likely be present, and it would be difficult to determine the exact etiology of visual loss.

Cortical complications of orbital cellulitis are discussed more thoroughly in Chap. 14.

Conclusion

Visual loss is a serious, although infrequent, complication or orbital cellulitis. Although the mechanisms of visual loss remain poorly understood, we provided a framework for understanding such mechanisms based largely on case reports and case series. The first axis of this framework is the anatomic location of pathology resulting in visual loss and includes the anterior segment, retina, choroid, optic nerve, optic chiasm/tract, and cerebral cortex. The second axis of the framework includes the most common disease processes related to orbital infection, which may affect the anatomical portions of the visual pathway and lead to compressive effects, infiltration, inflammation, and thrombosis. These processes are by no means mutually exclusive and appear to frequently occur in tandem to produce visual loss in patients with orbital cellulitis. We also emphasize the difficulty in assessing such mechanisms. Nearly all published reports which focused on visual deficits in patients with orbital cellulitis had little definitive evidence of the etiology of vision loss. Despite these limitations, understanding the theoretical mechanisms may be helpful in the assessment and treatment of patients with orbital infection.

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Chapter 4
Imaging of Infected Orbits and Sinuses

Christie M. Malayil Lincoln, Tomas Uribe, Peter Fata, and Shalini V. Mukhi

Introduction

Orbital cellulitis is a disease that requires prompt diagnosis and treatment due to permanent, debilitating effects on vision and grave intracranial complications [1–3]. It is a secondary process as the primary areas of infection are from penetrating trauma and foreign body or from neighboring structures such as the paranasal sinuses, skin, teeth, nasal cavity, and nasopharynx [1, 3–5]. The more commonly affected demographic with periorbital and orbital infection are children and immune-compromised adults.

Anatomic Relationship

The orbital septum (palpebral fascia) divides the orbit into periorbital (preseptal) and orbital (postseptal) compartments and allows for the eyelid to be separated from the orbital cavity. The anatomic division is not visible on imaging. However, the orbital septum is a thin fibrous tissue that attaches superiorly to

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the orbital rim, involves the levator palpebrae and inserts into the tarsal plate inferiorly, and provides a strong barrier preventing infections of the eyelids to spread into the orbit. The tarsal plate, in turn, is contiguous with the periorbita, a strong periosteum of the orbital wall, which is loosely attached to the orbital bone except at the strong sutural attachments where it pierces the suture to fuse with the periosteum on the opposite side. For this reason, the periorbita can remain intact and raised when there is pathological destruction of the orbital bone [6–12]. The lamina papyracea is an anatomically important thin barrier between the ethmoid air cell system and orbital cavity [13]. The primary mode of spread of infection occurs via valveless veins or via tiny congenital dehiscence of the anterior and posterior ethmoidal foramina [4, 14, 15]. The periosteum lining the orbital side of the lamina prevents penetration of infection from the ethmoid air cells to the orbital cavity.

Typically, infection involves the soft tissues anterior to the septum producing cellulitis without vision loss or ophthalmoplegia. However, infection deep into the septum results in orbital or postseptal cellulitis, which can involve the optic nerve, extraocular muscles, or orbital apex and result in impaired visual acuity, proptosis, pain, or limited mobility. If there is increased pressure in the orbital cone/apex, it can induce central retinal artery or vein occlusion and nerve damage leading to vision loss. Hence, the management of orbital cellulitis differs from periorbital cellulitis [10, 13].

In about 60–80% of cases of orbital cellulitis, sinus infection is the most common cause, and this is due to the shared interface of the paranasal sinuses with the orbit and valveless venous system of the paranasal sinuses, which communicate freely with the orbits, cavernous sinus, and face [15–17]. Some studies have looked at the specific paranasal sinuses as a cause of cellulitis. Jackson et al. reported 89% of cellulitis being caused by infection of the maxillary sinuses, while Barone et al. reported that in the pediatric population, infection of the ethmoid air cells is more common.

The other causes of orbital cellulitis include skin infection, such as eczema, furuncle, and facial cellulitis, in 16% of cases, followed by a less common cause, the dentition. Though dentition is not as common, it is also underdiagnosed, and when cases of periorbital or orbital cellulitis do not adequately respond to treatment, CT imaging can assist in evaluating the teeth. The premolar and molar maxillary teeth are in close proximity to the maxillary sinus floor and when infected can result in maxillary sinus opacification, which can then propogate to the orbits. Other routes by which the infected dentition can reach orbits are the premaxillary soft tissues, infratemporal fossa and inferior orbital fissure [3]. Other causes for orbital cellulitis include surgery or trauma to the area, complication of preseptal cellulitis or acute dacryocystitis.

Organisms

In the preantibiotic era, the morbidity and mortality from orbital cellulitis were high with as much as 17% of cases resulting in death and 20% in blindness [6]. Prompt identification of the inciting organism and antibiotic use has dramatically decreased death and blindness.

For periorbital/preseptal cellulitis, the most common organisms are staphylococci, beta-hemolytic streptococci, and *Haemophilus influenzae*, which is primarily due to trauma or skin-related infection [17]. Over the years, however, the incidence of *Haemophilus*-related infection has decreased, which is due to both the widespread use of Hib vaccination and use of more potent antibiotics. Anaerobic infections are typically from soil-contaminated wounds. Other organisms implicated in cellulitis are *Pseudomonas*, *Neisseria*, *Mycobacterium*, and *Treponema pallidum*. Rarely, tuberculous and *Treponema* organisms are a cause [17].

Orbital/postseptal cellulitis most commonly afflicts children and young adults. The common organisms are *Haemophilus influenzae* in kids and *Streptococcus* and *Staphylococcus* species in adults.

Classification

Smith and Spencer introduced a classification system for orbital inflammation, which was later revised by Chandler et al. and is now a five-group classification, not necessarily reflecting the different stages of the same disease process. The groups are preseptal cellulitis, orbital cellulitis, subperiosteal abscess, diffuse orbital abscess, and cavernous sinus thrombosis [1, 6, 18].

Imaging of Periorbital and Orbital Cellulitis

In cases of periorbital cellulitis, imaging is not required with a straightforward clinical picture and physical examination. It is only when the patient's presentation is atypical and difficult to diagnose clinically or clinical course worsens with new orbital symptoms/signs or lack of response to antibiotic therapy that further imaging is warranted [7, 11]. These symptoms and signs can range from proptosis, globe displacement, ocular dysmotility, and vision changes.

Imaging is exceptionally important for accurate diagnosis, especially in search of complications related to the infection. There are a variety of ways in which this can be accomplished.

Plain Films

Plain films were a mainstay of imaging the orbits prior to the advent of CT and MRI. These are images obtained in limited planes, and, therefore, the amount of information elicited from this modality is not as valuable to diagnose and manage patients promptly or properly. The only finding of use on plain film is opacification of the ethmoid air cells or other paranasal sinus, suggesting sinusitis as a possible cause for orbital cellulitis.

Ultrasound

Ultrasound (US) is a noninvasive, inexpensive imaging technique that relies on ultrasonographic waves being emitted by the transducer at different velocities as it penetrates the variety of orbital tissue with the reflection of different echoes. The images produced are calculated and, unlike plain film, are not a still photograph. In the case of the orbit, a high frequency transducer is utilized because the orbit is anatomically small and superficially located. A nonirritant gel is placed over the closed eyelid, and the ultrasound probe glides over the gel. Pressure on the probe on the eye is light compared to other parts of the body [19–21].

US is an easily available imaging modality that can be performed at bedside without radiation or contrast exposure, or sedation. For these reasons, ultrasound is favored in the pediatric population. Many of the studies showing success in diagnoses have been performed in the pediatric population. Mair et al. showed that ultrasound imaging of periorbital soft tissue swelling can be successfully performed to exclude and diagnose orbital inflammation, including diagnosis of subperiosteal abscess and inflammation [20]. Pinzuti et al. also showed that US in the pediatric population can be useful in patient management where discrimination between medical and surgical management is necessary [19]. US is rarely used in the adult population due to the wide availability of CT and inherent limitations of US.

The limitations of ultrasonography includes operator dependency and difficulty in imaging deep into the orbit at the level of the apex. Identifying sinusitis as the etiology for the cellulitis cannot be determined by US as imaging is focused on the orbit and unable to visualize the nasal cavity or paranasal sinuses. Ultrasonography cannot be utilized to search for intracranial complications related to orbital cellulitis, which is where CT and MRI would be the most beneficial imaging modalities [4, 19, 20].

The well-established role for US is in assessing response to treatment at the bedside, principally in the pediatric population, or as a complimentary role with computed tomography (CT) in diagnosis as both are readily available [15, 20].

Computed Tomography

The arrival of CT provided a novel imaging modality to radiology and contributes a major role in patient management. The advantage of CT is its wide availability and short imaging time, unlike its complimentary counterpart, magnetic resonance imaging (MRI). Accurate clinical staging of a patient can be difficult, and CT has a critical and influential role in the Chandler classification [22]. This is primarily due to better anatomic imaging, though at the cost of radiation exposure to the patient. Givner has proposed that CT scan be performed, if bedside examination for orbital cellulitis cannot be performed or if orbital cellulitis is suspected [13, 23].

The bony detail of the orbital cavity, paranasal sinuses, and dentition and confirmation of paranasal sinusitis and/or odontogenic source are far more superior to ultrasound particularly in evaluation for subperiosteal abscess, which is readily identified on CT as a fluid collection between the periorbita and the lamina papyracea [3, 22]. CT is particularly useful in the immune-compromised and severely debilitated patients with system disorders like diabetes and those with cancer and undergoing chemotherapy. Based on the Chandler classification, a CT can help distinguish between cases requiring medical management with intravenous antibiotics and surgical drainage in stages III and IV, where there is a subperiosteal and orbital abscess, respectively [22, 24]. Anecdotally, several studies have shown that the incidence of surgical drainage was required when abscesses were larger and patients were more symptomatic as well as in young adults [2, 18, 25].

On CT, the paranasal sinuses are evaluated for inflammatory mucosal thickening, opacification, or air fluid level. The infected teeth can be sought for by looking for abnormal periapical lucency, loss in definition of the lamina dura, and widening of the periodontal ligament space [3].

The most widely agreed upon and utilized orbital CT algorithm is contrast-enhanced, thin-section axial (between 1 and 3 mm) scans. The CT technologist then performs computer-generated coronal and sagittal reconstructions, which are exceptionally useful in identifying the precise location of the fluid collections or phlegmon. Contrast enhancement is necessary to produce better distinction of inflammation and phlegmon from abscess formation and to better visualize focal intraconal or retrobulbar mass. Noncontrast imaging alone can delay diagnosis and results in unnecessary radiation exposure to the patient especially in the pediatric population. When CT imaging is performed of periorbital cellulitis, there is soft tissue thickening of the eyelid with fat stranding (Fig. 4.1). On occasion, if the patient was not seen by a health care provider in a timely manner or not treated promptly, there can be a preseptal abscess demonstrated as a rim-enhancing, centrally hypodense fluid collection. CT can also assist in distinguishing the cause of preseptal cellulitis from the variety of etiology [26].

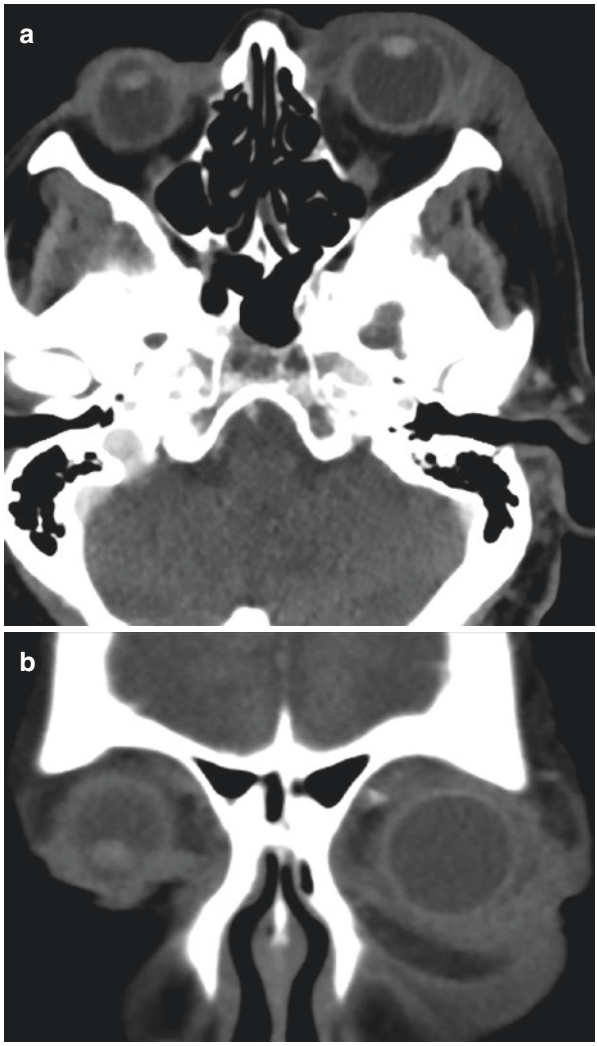


Fig. 4.1 Young adult with left eyelid swelling. Axial (**a**) and coronal (**b**) noncontrast CT scan demonstrating soft tissue of the left preseptal region and left medial canthus

Orbital cellulitis on CT demonstrates inflammation of the intraconal fat (Fig. 4.2) with possible enlargement of the extraocular muscles or osseous erosion. A phlegmon is seen as a homogenously enhancing lesion. A phlegmon can be indistinct from other pathologies such as orbital inflammatory syndrome, lymphoid lesion, and malignancy on CT, and, therefore, MRI plays an important, complimentary role. An orbital abscess has similar imaging features to a subperiosteal abscess, though location differs (Fig. 4.2). The amount of tension produced in the orbital cone by a space-occupying lesion such as an abscess can result in proptosis and tenting of the posterior globe [27].

In the assessment of periorbital or orbital cellulitis, the paranasal sinuses, nasal cavities, skin, and dentition are a part of the search process. This also includes searching for a foreign body.

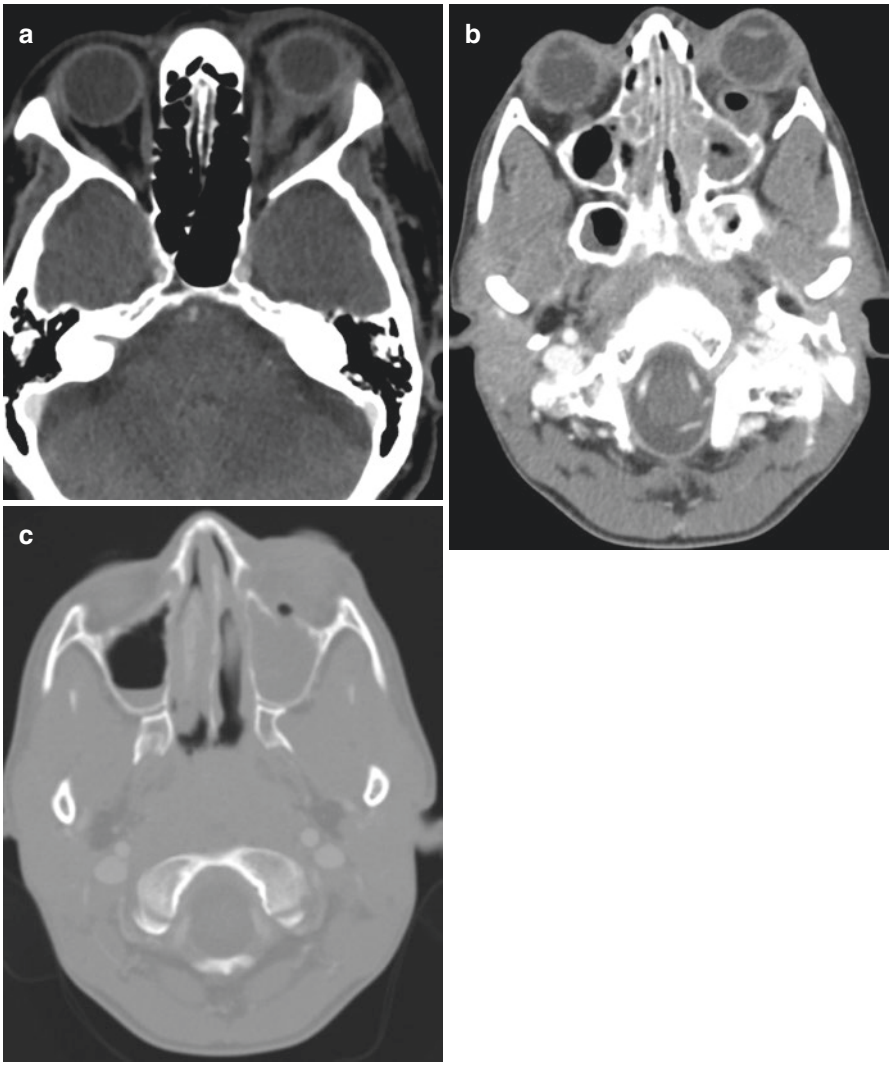


Fig. 4.2 Contrast-enhanced axial orbital CT (**a**) shows left intraconal and retrobulbar fat infiltration by a soft tissue density lesion representing orbital cellulitis and phlegmon in a patient, who has preseptal cellulitis. Axial postcontrast soft tissue images (**b**) of the orbit of a different patient exhibits a retrobulbar abscess and in bone window (**c**) reveals the cause of the abscess as left maxillary sinusitis

It is also important to image pediatric and adult patients with forehead swelling, fever, and headache as this could be a Pott's puffy tumor, also known as osteomyelitis of the frontal bone, where the bone of the frontal sinus dehisces due to the underlying sinusitis and extends to the periorbital and orbital soft tissues (Fig. 4.3). This process can also have intracranial complications like extra-axial abscess or meningitis [28].

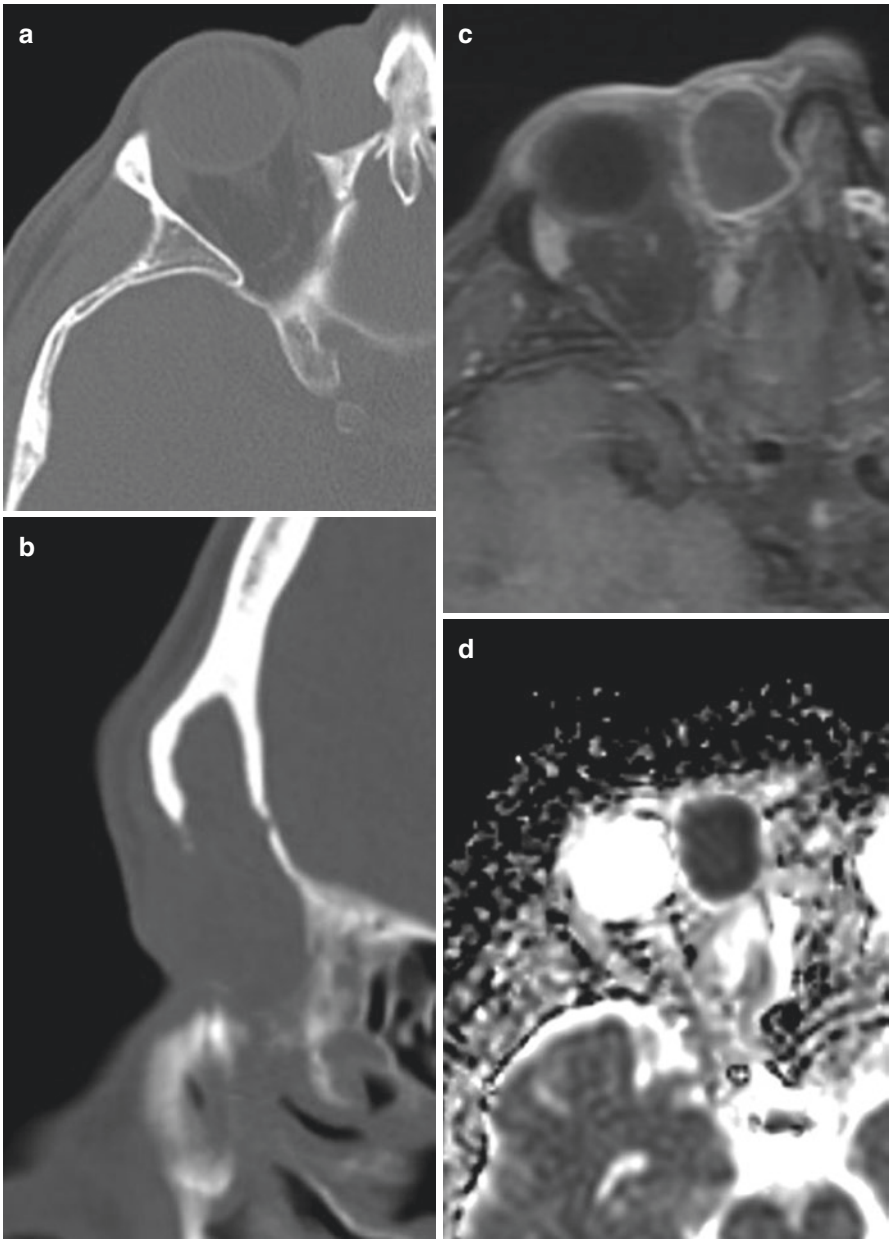
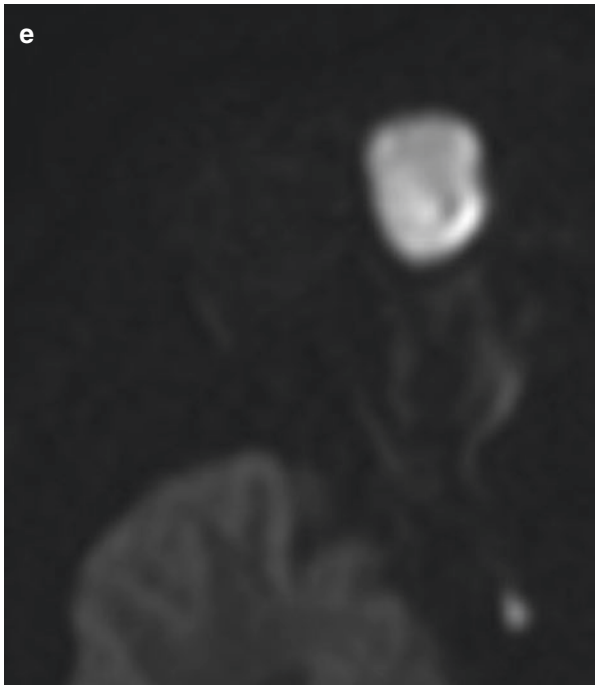


Fig. 4.3 Young child with headaches and forehead swelling. Axial (**a**) and sagittal (**b**) CT bone window images show a wide area of dehiscence of the outer table of the right frontal sinus with a rounded soft tissue in the right medial extraconal compartment. Contrast-enhanced MRI shows a rim-enhancing fluid collection (**c**), which has increased signal on diffusion-weighted images (**d**) consistent with an abscess (**e**), with corresponding dark signal on the ADC map

Fig. 4.3 (continued)



CT is best at depicting the complications of cellulitis including superior ophthalmic vein thrombosis, intracranial abscess, cavernous sinus thrombosis, cavernous internal carotid artery aneurysm, and meningitis, though in certain cases MRI can be complimentary [29]. These complications occur primarily from the extensive anastomoses among the valveless venous network that drains the orbit, skin of the periorbital tissues, and the maxillary and ethmoid sinuses [2].

The superior ophthalmic vein (SOV) begins in the medial aspect of the orbit as a confluence of the angular, supratrochlear, and supraorbital veins, for short distance follows the same course as the ophthalmic artery, passes between the two heads of the lateral rectus muscle, and exits via the superior orbital fissure to end in the cavernous sinus. When a thrombus forms in the SOV, there is enlargement and hypoenhancement of the vein, and on occasion, there can be perivenular stranding from inflammation (Fig. 4.4). Extension of the thrombus to the cavernous sinus can also be seen on contrast-enhanced CT as a filling defect in the cavernous sinus or lateral dural enhancemen (Fig. 4.4). There are instances where a CT venogram or contrast-enhanced MRI would better depict and/or compliment the contrast-enhanced CT findings.

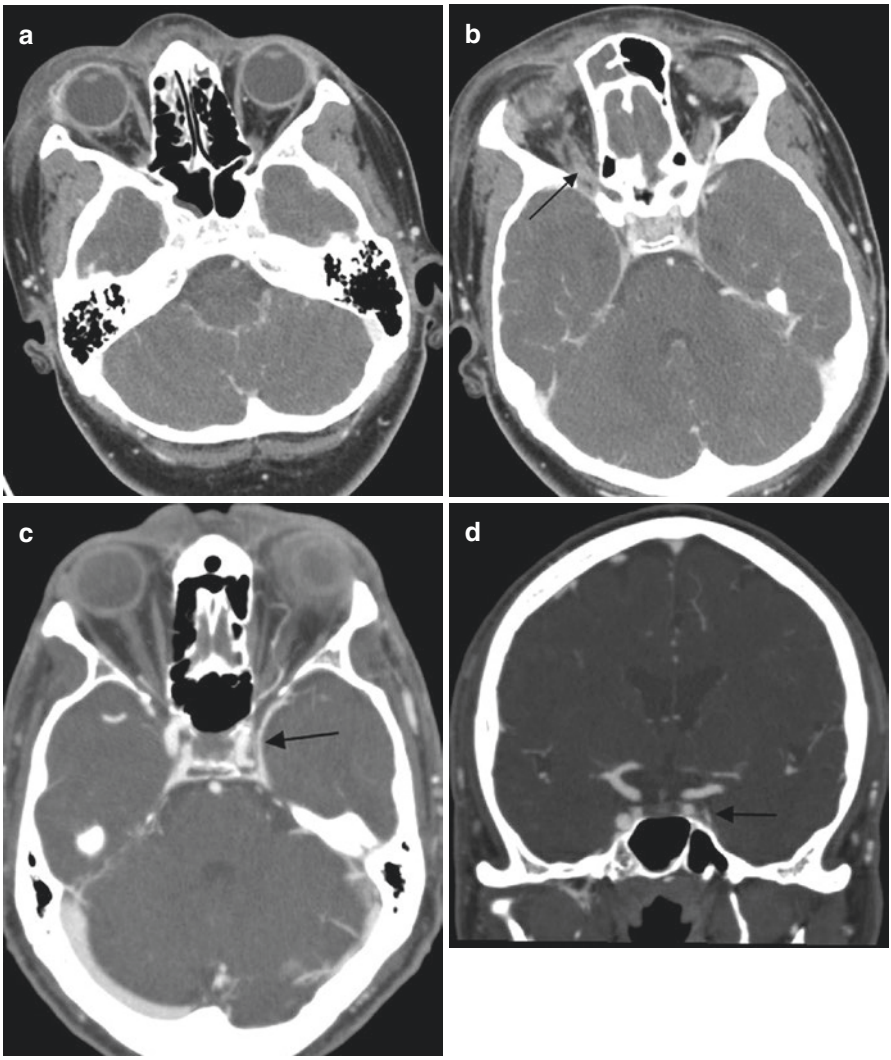


Fig. 4.4 A patient with right preseptal cellulitis (**a**) and postseptal cellulitis has increased size of the hypodense right superior ophthalmic vein with perivenular inflammatory stranding (*arrow*) on contrast-enhanced axial CT scan of the orbits (**b**). Intracranial CTA, which was performed on a different patient with multiple cranial neuropathies and left orbital cellulitis, shows left lateral dural enhancement (*arrows*) on the (**c**) and coronal (**d**) planes, consistent with cavernous sinus thrombosis

Magnetic Resonance Imaging

MRI is a more sensitive examination with better anatomic detail and contrast resolution compared to CT and is ostensibly true for the orbit. In cases of suspected orbital cellulitis, MR can be performed as a complimentary modality to CT when there is concern for intracranial complication or as a stand-alone modality to assist in diagnosis of orbital cellulitis and its complications.

In order to assist in patient management, the best possible images with patient cooperation are necessary. The MRI examination is lengthy, and therefore, to obtain quality, diagnostic images particularly in the pediatric or claustrophobic adult patient, oral or intravenous sedation under the supervision of a radiologist and radiology nurse is unavoidable.

Similar to CT, contrast material is necessary for MRI as images are performed before and after contrast administration to better elucidate pathology. Gadolinium-based contrast agents (GBCA) are used in MRI, but administration is contraindicated in certain situations, such as in patients with stage IV or stage V renal disease due to the possibility of a rare but grave nephrogenic systemic fibrosis or in those patients with anaphylaxis [15, 30–34].

The multiplanar capability and variety of pulse sequences performed allow for better visualization of pathology. There are a few sequences that are most helpful to look at the orbit and in particular, for orbital cellulitis. For better discrimination of orbital pathology localized to the lacrimal gland, extraocular muscles, and intraconal compartment including the optic nerve sheath complexes, orbital fat suppression is paramount on T2-weighted and pre- and postcontrast T1-weighted images [15, 34]. The pre- and postcontrast T1 fat suppression is also necessary for distinguishing true enhancement. Fat suppression techniques are also susceptible to metal and air-bone interface causing artifacts to be seen on images [15].

At times, the diagnosis of orbital cellulitis can be difficult as the clinical presentation and imaging appearance can be indistinguishable with considerable overlap on conventional MR imaging from orbital inflammatory syndrome and lymphoid lesion. A collaborative approach among specialties, in particular ophthalmology and radiology, would be important as a history of cutaneous infection, sinusitis, trauma with or without orbital fracture, dental procedure, strabismus surgery, or scleral banding are associated with orbital cellulitis [5]. A trial with treatment for orbital inflammatory syndrome can also be performed with follow-up imaging to assess response. Kapur et al. looked at diffusion-weighted imaging in all three pathologies and found that their small sample size produced increased signal on DWI, which is typical for lymphoid lesions due to increased cellularity as seen with lymphoid tissue elsewhere in the body.

Orbital Cellulitis Complications

Subperiosteal Abscess

The incidence of subperiosteal abscess in children as a known complication of rhinosinusitis is 9% [6, 35]. It is an infected collection that occurs between in the periorbita and the orbital bone.

On ultrasonographic examination, a subperiosteal abscess is seen as an anechoic lesion with a hyperechoic wall emanating from the lamina papyracea and resultant lateral displacement of the medial rectus muscle and optic nerve sheath complex. On the other hand, subperiosteal inflammation medial to the medial rectus muscle is seen as a hyperechoic lesion in a similar location.

Cross-sectional imaging with CT shows an extraconal hypodense fluid collection along the lamina papyracea that either homogenously or rim enhances depending on the size and cavitation of the lesion and may have perilesional fat stranding from surrounding inflammation. MR imaging demonstrates a T1 hypointense and T2 hyperintense peripherally enhancing lesion and bright signal on diffusion with reciprocal dark signal on the apparent diffusion coefficient map due to lack of water movement from dense cellular packing and increased viscosity [36, 37] (Fig. 4.5). Osteomyelitis can also be seen of the orbital wall in advanced cases.

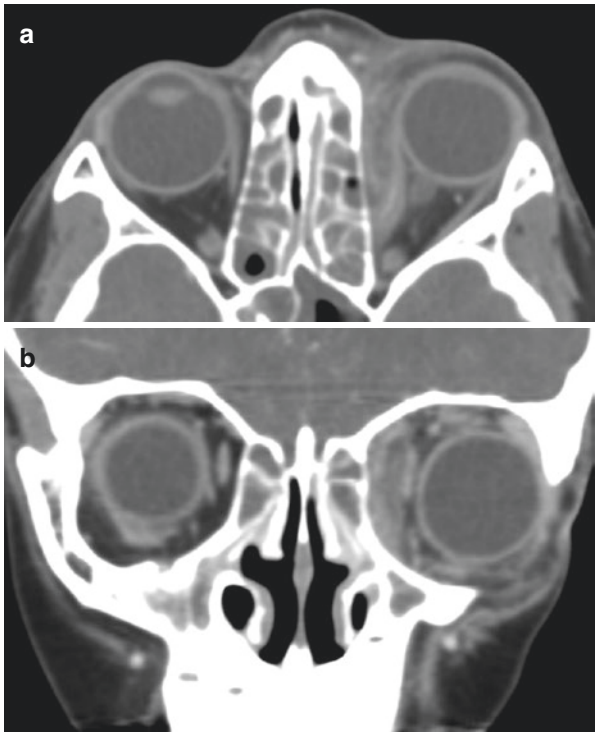


Fig. 4.5 Young child with contrast-enhanced CT in axial (**a**) and coronal planes (**b**) demonstrates a rim-enhancing fluid collection along the left lamina papyracea and with medial displacement of the left medial rectus muscle

The mainstay of treatment is primarily with a combination of antibiotic medical therapy and surgical drainage and decompression. Surgical abscess drainage is necessary to prevent mass effect on the globe and optic nerve sheath complex [10, 19]. Generally, very few practitioners solely rely on medical management though this has been more successful in young children [38].

Cavernous Sinus Thrombosis

Rarely, infection of the orbit can produce cavernous sinus thrombosis, a neurologic condition, wherein the thrombus of the cavernous sinus results in third, fourth, and sixth and first and second trigeminal division cranial neuropathies. The mechanism that allows for this stems from the absence of valves in dural venous sinuses and cerebral and emissary veins resulting in variable flow that depends solely upon pressure gradients. These intracranial sinuses and veins have extensive direct and indirect communication with the veins of the face, sinonasal cavity, and orbits [39].

Though the clinical picture with cranial neuropathies and/or meningismus points toward the diagnosis, imaging would be performed with either CT or MR venogram for validation.There are a variety of ways cavernous sinus thrombosis can manifest on imaging and includes cavernous sinus expansion, filling defect in the cavernous sinus, lateral dural enhancement or superior ophthalmic vein enlargement. Unlike CT, MRI has many more sequences that can confirm the diagnosis, such as precontrast T1, which shows acute thrombus as bright signal, or T2 imaging, which shows thrombus as intermediate to bright signal. In addition, there has been a single case report by Parmar et al. that suggests restricted diffusion of the thrombus [40].

The treatment for this condition is aggressive antibiotics with the debatable role for anticoagulation. If left untreated, the cavernous sinus thrombosis could culminate in carotid artery narrowing leading to arterial insufficiency, ischemia, and ultimately infarct [39, 41].

Intracranial Infectious Aneurysm

An even more rare complication is infectious aneurysm formation particularly of the cavernous internal carotid artery due to its close proximity to the paranasal sinuses and orbits [42, 43]. The incidence ranges from 0.7 to 6% [44] with extravascular spread of infection from adjacent orbital cellulitis, meningitis, or cavernous sinus thrombosis spurring on inflammatory-mediated destruction of the vessel wall. As this is an infectious aneurysm, prompt diagnosis is necessary because once the aneurysm occurs, it can progress rapidly and result in intracranial hemorrhage (Fig. 4.6). When compared to other intracranial aneurysms, infectious aneurysms have a higher mortality rate with a 30% rate in unruptured and 80% in ruptured aneurysms [42, 45, 46]. Imaging can be performed via either CT or MR angiogram or digital subtraction angiography. The limitation of CTA is for very small aneurysms particularly at the skull base [45].

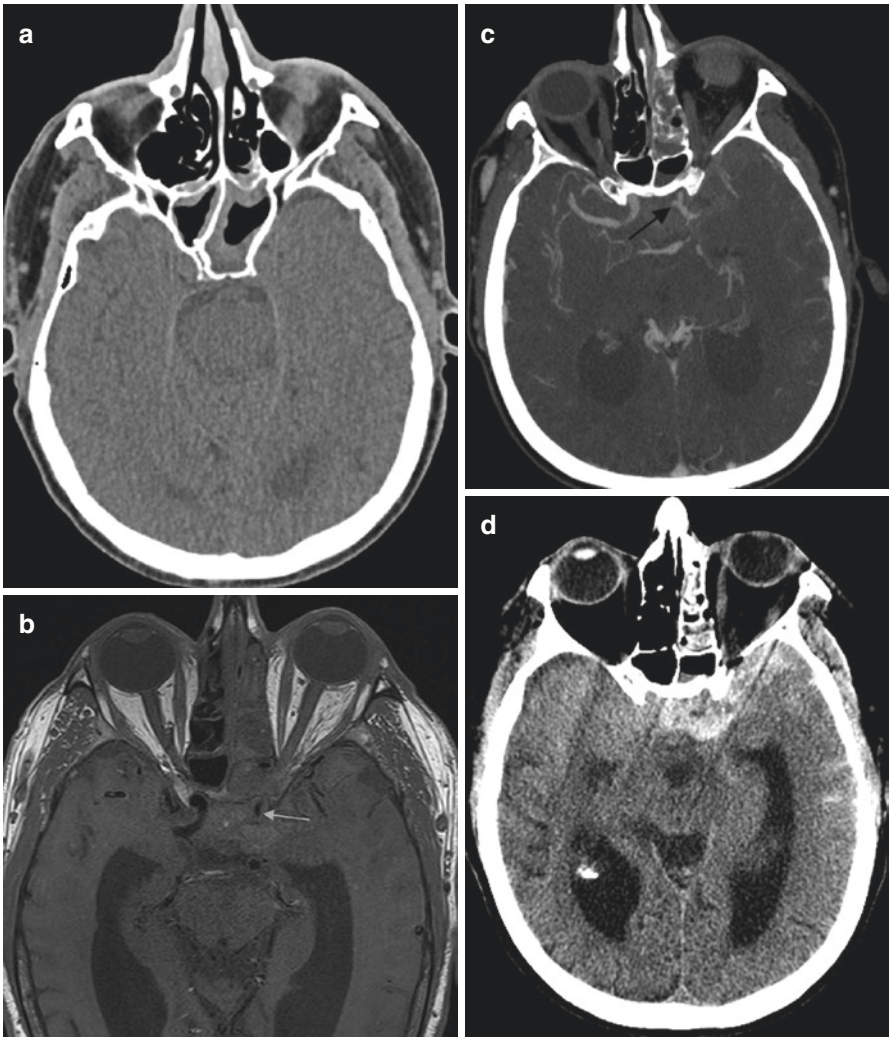


Fig. 4.6 Middle-aged male on dialysis presents with nonspecific inflammatory mucosal thickening of the left sphenoid sinus (**a**) on noncontrast CT of the face, which progressed rapidly in size on subsequent imaging (images not available). Patient develops left third and fourth cranial neuropathies and noncontrast brain MR (**b**) due to renal failure, which shows marked narrowing of the left intracranial internal carotid relative to the right (*arrow*) with biospy proven fungal sinusitis at the orbital apex (not shown). Emergent intracranial CTA was done (**c**) and showed a new clinoid left internal carotid artery aneurysm and narrowing (*arrow*) when compared to prior CTA (not shown). Patient became confused, and noncontrast head CT (**d**) shows subarachnoid hemorrhage from rupture of the infectious clinoid internal carotid artery aneurysm

Due to the increased mortality rates, prompt treatment is required and usually performed successfully with open or endovascular occlusion of the intracranial infectious aneurysm while the patient is undergoing effective antibiotic treatment [47, 48].

Intracranial Complications

Intracranial complications are rare primarily due to the advent of antibiotics. Meningitis, encephalitis, subdural empyema, epidural abscess, and dural sinus thrombosis can occur as a result of progression of septic emboli or transmission of emboli via the valveless diploic veins of the face and skull base that penetrate the dura. These complications can result from extension of orbital cellulitis or directly from rhinosinusitis. Many of the retrospective studies including from Germiller et al. showed that the vast majority of these complications occur in children with acute sinusitis, while chronic sinusitis was more prevalent in the adult population [49, 50]. The incidence is overall low in all of the retrospective studies performed. Bradley et al. demonstrated a fourfold decrease in incidence of intracranial abscess secondary to sinusitis and Gallagher et al. showing an 8.5% incidence [50, 51]. Imaging plays a significant role in evaluation and is most important when medical treatment is unresponsive or when patient is experiencing new neurological symptoms.

Meningitis can be readily seen on FLAIR and postcontrast T1 images where there are increased signal and enhancement, respectively, of the meninges (Fig. 4.7).

Cerebritis, on the other hand, on imaging is an amorphous bright signal on T2 and FLAIR imaging in the cortical and subcortical brain with associated bright signal on DWI and reciprocal dark signal on apparent diffusion coefficient map (Fig. 4.8). In cerebritis, there is no associated rim enhancement.

Epidural abscess or epidural or subdural empyema is typically hypointense on T1 with peripheral rim of enhancement and T2, FLAIR, and DWI hyperintense with dark signal on apparent diffusion coefficient map. The morphology and shape of the collections is the ultimate distinguishing feature wherein an epidural collection is lenticular and a subdural collection is crescentic. In cases where there is contraindication to GBCA, such as anaphylaxis or renal failure, DWI can play an integral role in the diagnosis of an abscess. Alternatively, CT can play a role in demonstrating the abscess or meningitis with similar enhancement pattern as seen on MRI. If the abscess causes mass effect or herniation, surgical decompression may be warranted.

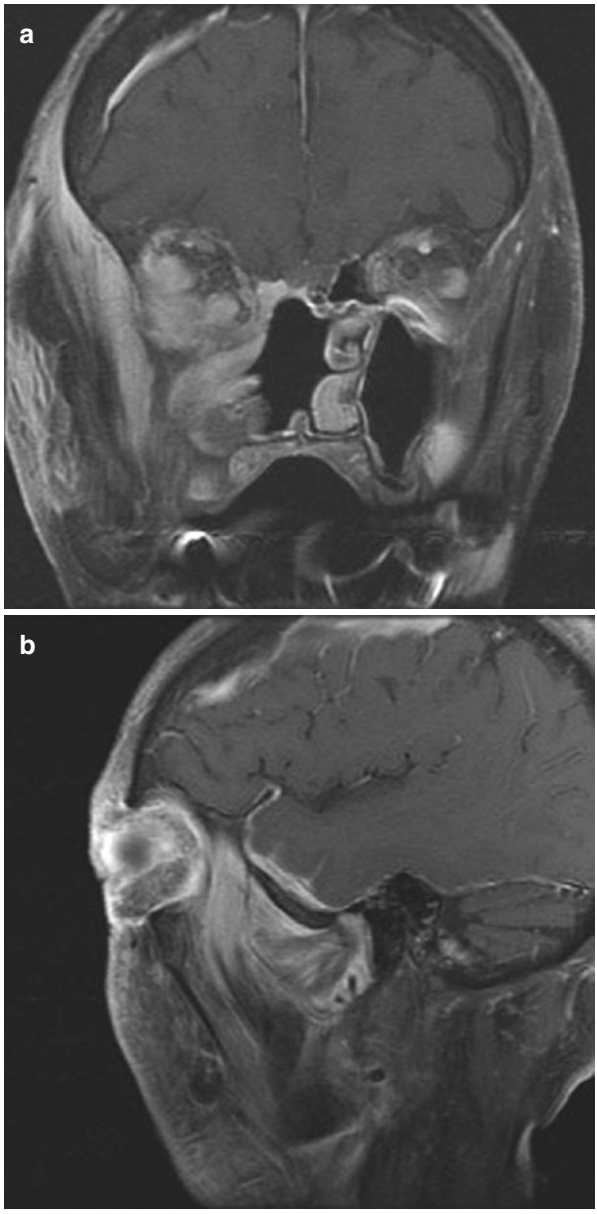


Fig. 4.7 Middle-aged female presents with orbital cellulitis and unrelenting headaches. A contrast-enhanced brain MRI was performed which showed orbital cellulitis (**a**) and meningeal enhancement (**b**)

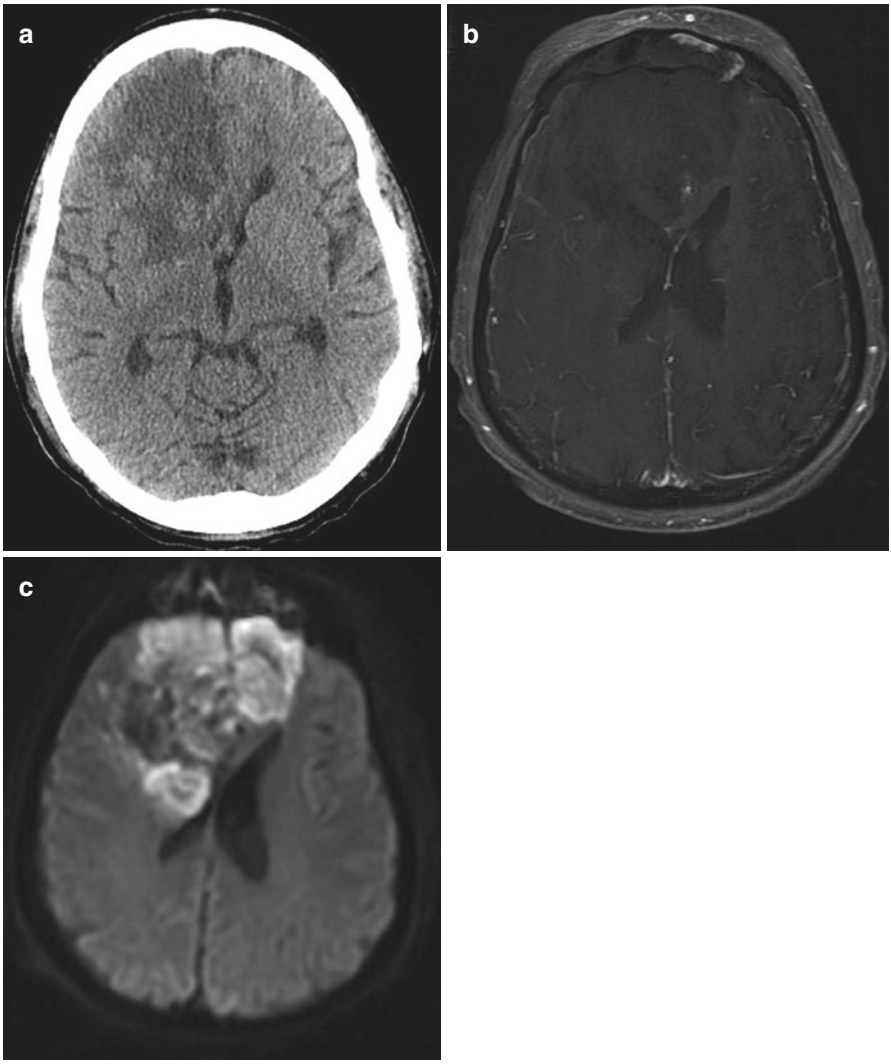


Fig. 4.8 Chronic lymphocytic leukemia patient with known sinonasal infection presents with increasing confusion, and noncontrast head CT reveals a large bilateral frontal lobe cortical-based area of hypoattenuation (**a**) presumed to represent cerebritis. Further imaging was done with contrast-enhanced brain MR, which confirmed findings of cerebritis with nonenhancing areas of edema (**b**), and restricted diffusion (**c**)

Conclusion

The variety of imaging modalities discussed reinforces the vital and integral role imaging has in diagnosing and managing cases of periorbital and orbital cellulitis and their grave and rare complications. When there is uncertainty of diagnosis, there are many options, and a collaborative, multidisciplinary approach will ultimately assist in the best possible care for the patient.

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Chapter 5
Current Guidelines for the Management of Orbital Cellulitis

Janice C. Liao and Gerald J. Harris

Abbreviations

APD Afferent pupillary defect
SPA Subperiosteal abscess

Introduction

Orbital cellulitis is a well-defined orbital infection with potential vision- and life-threatening sequelae [1]. Although there are no microbes within the normal orbit, a robust population lurks just beyond its borders—on the eyelid skin, eyelashes, and conjunctiva and in the nose and sinuses [2, 3]. Peaceful coexistence with microbes is maintained by host defenses, both anatomic and immunologic. Orbital infection occurs if normal defenses are overcome by hypervirulent organisms (e.g., skin-surface methicillin-resistant *Staphylococcus aureus* [MRSA]) or if defenses are compromised—by breach or bypass of anatomic barriers (e.g., penetrating trauma, hematogenous spread), by systemic immunocompromise (e.g., diabetic ketoacidosis, immunosuppressants), or by altered local physiology. The last mechanism underlies bacterial sinusitis, which remains the leading cause of orbital infection [4].

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Sinus obstruction by allergic or viral rhinitis leads to changes in the local pO_2, pCO_2, and pH that allow normal upper respiratory flora to proliferate to pathogenic numbers [4]. Bacteria can then easily access the orbit through thin bony partitions and neurovascular foramina.

The advent of computed tomography (CT) allowed the delineation of subperiosteal abscess (SPA) as a specific, common entity within the overarching category of "orbital cellulitis," appearing as a focal elevation of the periorbita typically adjoining an opacified paranasal sinus. The presence of SPA has dual significance. Because it occurs in an enclosed potential space, its rapid expansion within this finite area can increase orbital pressure beyond the perfusion pressure of the optic nerve and retina, threatening vision. Additionally, the subperiosteal space is relatively avascular, potentially hindering antibiotic penetrance sufficient to eradicate the bacterial agent. In turn, the infection can progress rapidly and even spread intracranially [1].

Management Protocol for Sinusitis-Related Orbital Cellulitis and Subperiosteal Abscess

All patients are treated with dual-therapy intravenous antibiotics, either amoxicillin-sulbactam or a third-generation cephalosporin to cover most aerobes and anaerobes, combined with either clindamycin or vancomycin to cover MRSA. All patients receive twice-daily oxymetazoline nasal spray.

Because of the drastic potential morbidity and mortality associated with SPA, in earlier decades, virtually all patients with this finding underwent prompt surgical drainage of the orbit and sinuses. However, in a retrospective analysis of 37 cases treated from 1977 to 1992, the authors found that the bacteriology and response to antibiotic treatment correlated with patient age [4, 5]. Among those under 9 years, 83% either cleared without drainage or had negative cultures at the time of drainage, implying adequate antibiotic penetration and relatively submissive pathogens. Patients 9–14 showed a transition toward more complex infections. Half had positive cultures when drained within the first 3 days of antibiotic treatment, but the infections then cleared rapidly (follow-up cultures from the removed drains were negative). Patients 15 or older all had refractory infections, with positive cultures after more than 3 days of antibiotics—and some went on to severe complications. In the youngest patients, with only 2 of 12 cases culture positive, a single aerobe was recovered in each case. In the 9–14-year group, pathogens became more complex, with 12 of 16 cases culture positive and multiple species isolated in single cases, including anaerobes in 3 of 12 culture-positive cases. Nine years was the youngest age at which anaerobes were recovered. Among the oldest patients, multiple pathogens were the rule, with an average of five species per case and anaerobes in every case.

Because of the demonstrated trend from simple aerobic pathogens causing responsive infections in younger children to mixed aerobic-anaerobic pathogens

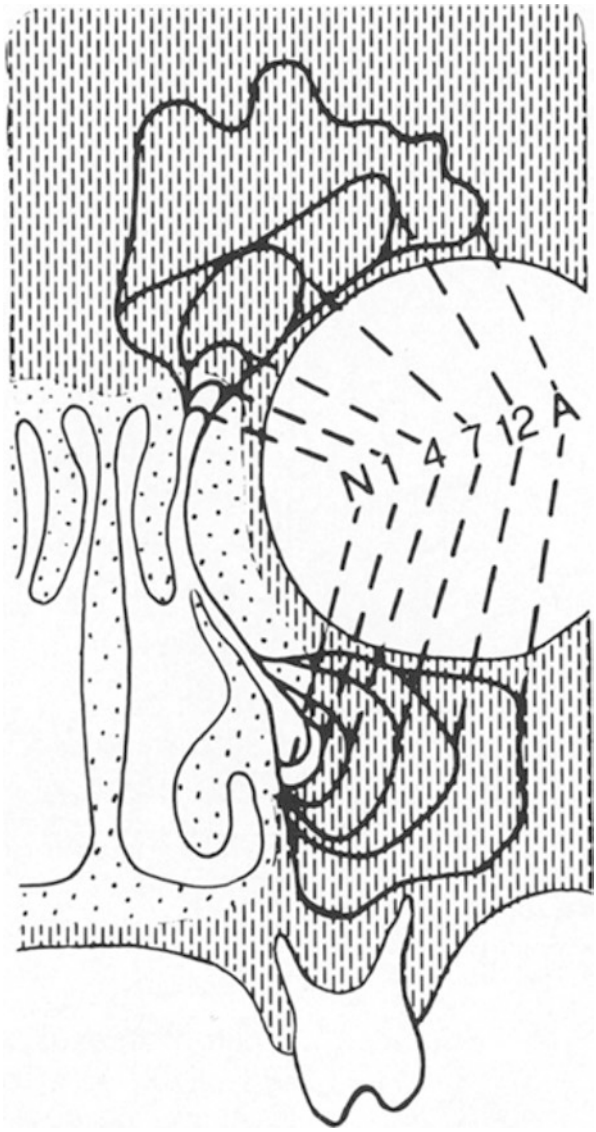

Fig. 5.1 Normal enlargement of the frontal and maxillary sinus cavities with increasing age (1–12 = age in years; *A* adult, *N* neonate)

causing refractory infections in older children and adults, the authors speculated that age-related anatomical and physiological differences in the sinuses might account for the more complex infections of older patients. From the neonate to the adult, the sinus cavities enlarge markedly, but the sinus ostia remain constant in size (Fig. 5.1) [6]. Younger children with "wide" ostia relative to the cavities drained may rarely achieve strictly anaerobic conditions, while older children and adults with relatively "narrow" ostia may be prone to more complete sequestration—and mixed aerobic and anaerobic infections [4, 5].

An anaerobic environment can compromise oxidative transport-dependent antibiotics and oxidative metabolism-dependent natural defenses. In addition, mixed infections may be synergistic: aerobes consume oxygen that would otherwise be toxic to anaerobes; certain anaerobes can deactivate antibiotics otherwise effective against aerobes. These factors cause sinusitis-induced SPAs in children beyond the first decade to be generally more refractory to treatment. It might be noted, however, that younger children with underlying *chronic* sinusitis can also harbor anaerobic pathogens (e.g., a 4-year-old who presented with SPA and nasal polyps [7]).

Early identification of patients expected to recover with medical management avoids the morbidity of unnecessary surgery. Conversely, patients with signs suggestive of poor response to medical observation alone should be triaged to emergent or urgent surgery. With this in mind, a management protocol was developed based on findings from prior studies [4, 5, 8]. As noted above, all patients are treated with dual-therapy intravenous antibiotics and oxymetazoline nasal spray.

Patients are triaged to medical therapy alone if the surgical criteria listed below are absent:

1. Acute optic nerve or retinal compromise
2. Large SPA
3. Nonmedial location of SPA
4. Presence of frontal sinusitis
5. Evidence of gas-producing organisms within the SPA
6. Infection of known dental origin
7. Evidence of chronic sinusitis (e.g., nasal polyps)
8. Age of patient 9 years or older
9. SPA after an earlier medically managed episode of orbital cellulitis or SPA

Patients of any age with optic nerve or retinal compromise are triaged to *emergency drainage* (as soon as possible) of the SPA and sinuses. Patients of any age with the remaining indications are triaged to *urgent drainage* (within 24 h). With large SPAs (Fig. 5.2), the interval to vision loss with further expansion may be

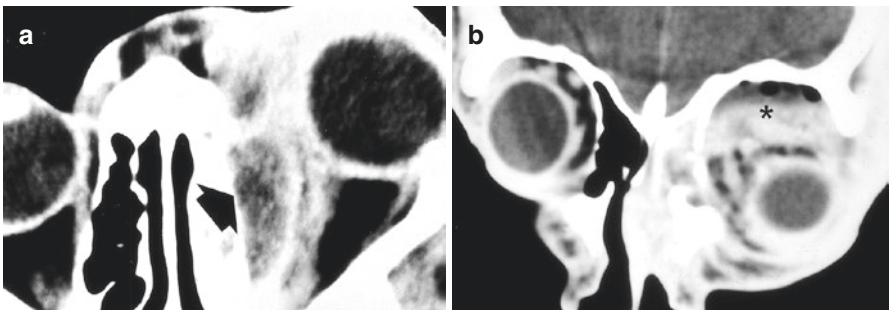

Fig. 5.2 Orbital subperiosteal abscesses meeting surgical criteria. (**a**) A *large* left medial orbital subperiosteal abscess (*wide arrow*). (**b**) A *large superior* subperiosteal abscess (*asterisk*) and sinusitis in a 26-year-old patient with a dental abscess after 2 weeks of intravenous antibiotic treatment elsewhere

shorter than the time required for medical control. SPAs that extend superiorly or inferiorly beyond the medial subperiosteal space (Fig. 5.2b) may be less likely to respond completely to medical therapy, even with resolution of sinusitis. Frontal sinus involvement carries a higher risk of intracranial extension. SPAs suspected to harbor anaerobes include those with areas of gas density, those of known dental origin, and those associated with chronic sinusitis. In such cases, early drainage and ventilation are indicated to restore the normal aerobic environment, in turn impeding bacterial proliferation and strengthening defense mechanisms. Patients ≥9 years of age—considered at risk for anaerobic infection based on the youngest age of anaerobic recovery in all series by the authors—undergo urgent drainage as well [4, 5, 8, 9].

Patients managed expectantly are monitored for an afferent pupillary defect (APD) every 2 h by nursing staff and are evaluated every 8 h by house staff. Patients may still default to surgery if an APD develops at any time, if they fail to defervesce after 36 h of appropriate intravenous antibiotics, if there is clinical deterioration despite 48 h of treatment, or if there is no clinical improvement after 72 h. In nonsurgical cases, dual-therapy inpatient intravenous antibiotics are continued for an average of 4 days [9]. An oral antibiotic (generally, amoxicillin-clavulanate) is prescribed for 3 weeks of outpatient treatment after hospital discharge. In surgical cases, inpatient and outpatient antibiotic choices and durations are dictated by culture results and clinical response.

Validity of the Subperiosteal Abscess Management Protocol

The authors have prospectively applied the guidelines for expectant observation—including possible default to surgery—for more than 25 years. Through 2008, successful outcomes in about 80 patients under 9—among a much larger number of patients of all ages—had been published as a single-institution experience [8, 9].

Despite the success of this approach, vigilance is needed to avoid undertreatment. The pathogens ultimately responsible for sinusitis-related orbital cellulitis and SPA are the normal upper respiratory flora. This distinctive pathogenesis differentiates these conditions from orbital infections that arise from other sources, such as traumatic wounds, skin lesions, dacryocystitis, or dacryoadenitis. However, evolutionary trends in the general microbiome may impact sinusitis-induced SPA as well as other types of orbital infection. Widespread antibiotic use has fostered the emergence of more robust strains, such as MRSA, and immunization against specific organisms has favored competing species.

MRSA first appeared in the United Kingdom in 1961, only 2 years after the introduction of methicillin. It has since become increasingly common, even accounting for the majority of community-acquired and nosocomial *Staphylococcus aureus* infections in some geographical areas [10–17]. Its particular pathogenicity is not due to drug resistance per se but to production of multiple virulence factors, including exotoxins, staphylococcal enterotoxins, leukocidins, and hemolysins [18].

MRSA's clinical impact is most obvious in microenvironments where staphylococcal species predominate, such as the skin, and MRSA is increasingly common in eyelid and orbital soft tissue abscesses that develop rapidly with or without minor surface trauma [19]. Less obvious, but increasing, is its role in microenvironments with diverse competing flora when the latter are suppressed by widespread immunization. This applies to the upper respiratory tract, and the introduction of vaccines directed against *Haemophilus influenzae* in 1985 and *Streptococcus pneumoniae* in 2003 has resulted in greater representation of *S. aureus* in sinus infections [15]. Accordingly, with greater antibiotic use, the prevalence of methicillin-resistant strains of *S. aureus* has increased. A recent meta-analysis reported a rise in the recovery of MRSA in acute rhinosinusitis from 0% in a 2006 study to 15.9% in a 2012 series [10].

Considering the pathogenesis of sinusitis-related orbital cellulitis and SPA, a commensurate increase in MRSA would be expected in these conditions. Indeed, multiple cases of MRSA-positive orbital cellulitis and MRSA-positive SPAs of sinus origin have been reported [13–15, 20–23].

Our recent analysis noted not only an increase in *S. aureus* strains but also an increase in *Streptococcus anginosus* group and group A β-hemolytic streptococcus over time [23]. These normal floras of the oral cavity and gastrointestinal tract are unique among streptococcal species in their ability to cause abscesses through a variety of virulence factors [24]. The pathogenicity of group A β-hemolytic streptococcus (*S. pyogenes*) is attributed to capsular elements that protect it from phagocytosis, adhesion factors that aid attachment to host cells, and enzymes that facilitate spread through host tissue layers [25].

Over the last 35 years, SPA culture results have demonstrated the emergence of more aggressive aerobic pathogens [4, 5, 23]. In a 1977–1992 cohort, the aerobes recovered from patients ≥9 years of age were more diverse and more commonly polymicrobial than those from patients <9 years of age [4, 5]. In a recent 2002–2012 cohort, both age groups had fairly similar aerobic constituencies, including *S. anginosus* as the most commonly isolated species, minority representation by MRSA, and multiple species in some individual cases [23]. Despite this, in patients <9 years of age, the proportion requiring surgery has remained a minority, and anaerobes have continued to be absent in this age group [8, 9, 23]. A review of adequately detailed published cases of MRSA-positive sinusitis-related SPA reveals that the criteria for prompt drainage were met at initial presentation [19–21, 23]. Specifically, in a recent 2002–2012 cohort, MRSA and other virulent aerobes—by their aggressive nature, presenting with more advanced degrees of infection—triggered surgical criteria that superseded age in the initial encounter. Four patients were noted to have MRSA-positive surgical cultures. Of these, three presented with an afferent pupillary defect; three presented with large SPA size; and two had inferior subperiosteal extension (Fig. 5.3). Similarly, a patient with surgical cultures positive for *Streptococcus viridans* and mixed oropharyngeal pathogens presented with a large subperiosteal abscess with superior and inferior extension and intracranial extension, prompting urgent drainage (Fig. 5.4). Although urgent intervention in such cases does not guarantee a successful

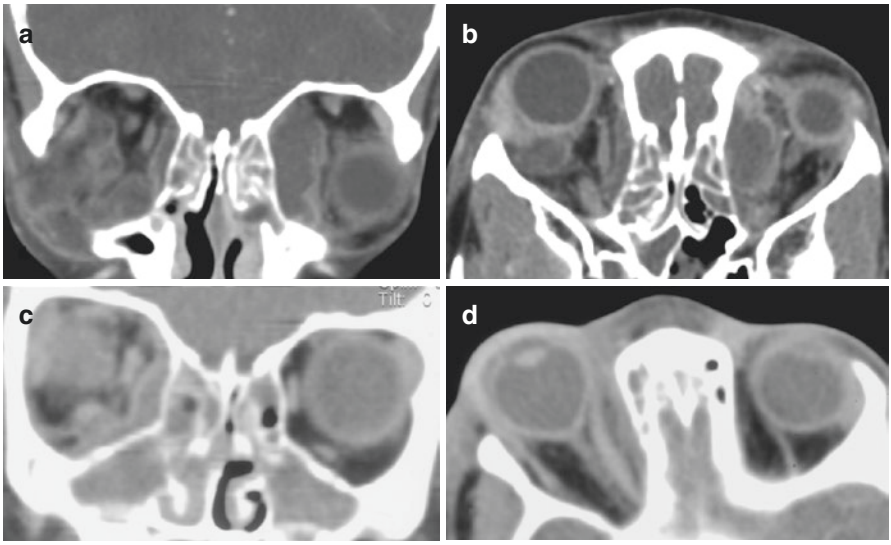

Fig. 5.3 Subperiosteal abscesses (SPAs) positive for methicillin-resistant *Staphylococcus aureus.* (**a**, **b**) Coronal and axial images of a 4-year-old girl show bilateral medial SPAs, as well as a large inferior SPA and multiple intraorbital and anterior soft tissue abscesses on the right side. Complete recovery followed emergency surgical drainage and prolonged antibiotic treatment. (**c**, **d**) Coronal and axial scans of a 3-year-old boy show a right medial SPA that extends inferiorly and posteriorly and causes tenting of the posterior pole. Severe vision impairment was not reversed, despite surgical drainage within 3 h of patient presentation

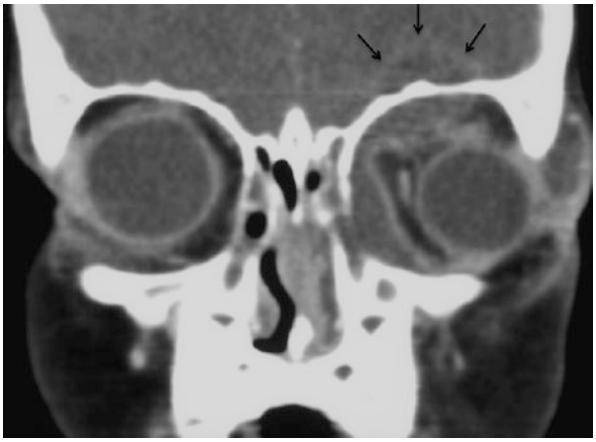

Fig. 5.4 Left orbital subperiosteal abscess requiring surgery in a 7-year-old boy. Medial, inferior, and superior subperiosteal spaces are widely expanded, and the process extends intracranially (*arrows*). The findings triggered urgent surgical drainage, including orbitofrontal craniotomy, with isolation of *Streptococcus viridans* and mixed oropharyngeal pathogens. The patient recovered fully

outcome, in this series, no patient had extraorbital sequelae, and only 1 of 94 patients had a permanent vision deficit. In that case (Figs. 5.3c, d), it is unclear that any other therapeutic approach would have been more effective. Meanwhile, almost three-fourths of patients <9 years old in this series recovered without surgical intervention. Therefore, a more aggressive "blanket" approach to all younger children would mean unnecessary surgery for many.

The pathogens in sinusitis-related SPA and orbital cellulitis have evolved over the past several decades. Additional changes, fostered by future vaccines, antibiotic resistance, and natural selection, might be anticipated. However, for now, a management algorithm that considers multiple variables, including patient age, continues to be effective and avoids surgery in a large proportion of younger children.

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Chapter 6
Medical Therapy for Bacterial Preseptal and Orbital Cellulitis Associated with Sinusitis

Adam C. Weber and Michael T. Yen

Orbital cellulitis is a common ophthalmologic complication of infectious sinusitis. At present, most cases respond well to medical management. Medical therapies have supplanted most surgical remedies as the mainstay in treating orbital cellulitis and have also led to a marked improvement in the mortality and morbidity of the disease. Medical management of orbital cellulitis has evolved with advances in antimicrobial therapies and will continue to change with the shifting dynamics of local microbiologic populations and antibiotic susceptibilities.

Background

Prior to World War II, orbital cellulitis was treated primarily by packing the nasal passages with epinephrine [1]. While many patients improved with this therapy, morbidity and mortality from orbital cellulitis were significant, with 17% of patients expiring and 20% being left blind in the affected eye. The discovery and application of antibiotics led to more effective medical management of the condition and in turn better outcomes for patients [2].

In the 1970s, empiric antibiotic treatment was aimed against the common causes of sinusitis: *Haemophilus influenzae*, *Streptococcus pneumoniae*, and gram-positive

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Staphylococcus and *Streptococcus* [3, 4]. Culture positivity rates were not high for nasal collections, and most of the microbiology was based on surgical aspirates or blood cultures from bacteremic patients, a large portion of whom were under 5 years old. *H. influenzae* and *S. pneumoniae* were the most common organisms in bacteremic patients [4, 5]. It should be noted, however, that a gross majority of patients with orbital cellulitis are not bacteremic [6].

Based on this data, the typical antibiotic regimen consisted of penicillin and chloramphenicol [7]. This protocol was effective at decreasing the need for surgical intervention, especially in younger patients [3]. Nasal vasoconstrictors continued to play a role in medical management of orbital cellulitis to decrease inflammatory edema and, presumably, facilitate normal sinus drainage [2]. Sinus lavage was also recommended [8]. Of note, some literature argued for the prophylactic use of heparin to prevent thrombophlebitis [7], but there was no evidence to support its efficacy.

Through the following decade, more investigations elucidated the microbial causes for orbital cellulitis and the role of antibiotic therapy in treating the condition. Multiple studies showed the most common offending organisms to be *H. influenzae*, *S. aureus*, *S. pneumoniae*, and other streptococci [8–10]. Furthermore, age was found to be an important factor in predicting the type of infection. Rubinstein et al. showed 25% of cultures positive for *H. influenzae* and 17% positive for *S. aureus.* 74% of the *H. influenzae* cultures were in patients under 3 years old, and 81% of the *S. aureus* cultures were in patients under 2 years old. These findings indicated that initial therapy be directed against these organisms [8].

Jones et al. illustrated the effect of disease etiology on microbiology, showing postsurgical cases were most likely due to *S. aureus* while those due to sinusitis to be secondary to *S. pneumoniae*, *H. influenzae*, *S. pneumoniae*, or anaerobes [10]. As more antibiotics came to market over the 1970s and 1980s, along with increasing antibiotic resistance, treatment guidelines shifted to penicillinase-resistant penicillins along with chloramphenicol or a broad-spectrum (second- or third-generation) cephalosporin. In cases with high suspicion of *H. influenzae*, aminoglycosides were commonly added [9, 10]. Some also argued for the use of metronidazole given the drugs good penetration of the blood-brain barrier [11].

While orbital cellulitis is a common disease process, it should be noted that most periocular complications of sinusitis are limited to the preseptal compartment. Kinis et al. showed 85–95% of orbital complications from sinus disease are preseptal cellulitis, with only 5–15% of cases manifesting as orbital cellulitis [12]. This trend was also supported by an observational study out of Jordan that showed orbital complications present in 5.8% of patients with acute bacterial sinusitis. 72.2% of those were preseptal cellulitis, 22.2% orbital cellulitis, and 5.6% abscesses [13].

Current Trends in the Microbiology of Orbital Cellulitis

Modern medical approaches developed in the wake of two sea-change events that altered the microbiology of orbital cellulitis. The first of which was the advent of the *H. influenzae* vaccine. In 1985, the vaccine was approved for use in patients 2–5 years old and in 1990 for patients over 2 months old. The result was a 99% decrease in *H. influenzae* invasive disease from 1989 to 1995 [14]. Expectedly, this drastically changed the microbiology of orbital cellulitis. After 1985, *Streptococcus* and *S. aureus* replaced *H. influenzae* as the most common cause of orbital cellulitis [15, 16]. Additionally, the vaccine effectively eliminated one of the worst causes of orbital cellulitis. Up to 80% of patients with orbital cellulitis due to *H. influenzae* were bacteremic [16]. Barone et al. reported zero out of 101 blood cultures positive for the organism in orbital cellulitis patients after July 1987 [17].

A second public health change that altered the orbital cellulitis landscape was the pneumococcal vaccine. The pneumococcal vaccine (PCV-7) was approved and recommended for use in patients younger than 24 months in June 2000. Similar to the effect of the *H. influenzae* vaccination program, the prevalence of *S. pneumoniae* orbital cellulitis markedly declined. Pena et al. demonstrated *S. pneumoniae* isolates in 22.4% of orbital cellulitis prior to widespread use of the vaccine and no isolates following the implementation of PCV-7 vaccinations. *S. aureus* prevalence expanded from 20.4% to 42.4% over this time period, effectively filling the space previously occupied by *S. pneumoniae* [18].

Pena et al. also showed an increase in methicillin-resistant *S. aureus* comparing pre- and post-pneumococcal vaccine with no positive isolates prior to the vaccine and 14 of 25 *S. aureus* being MRSA after the vaccine [18]. Concern over the increasing prevalence of community-acquired MRSA orbital cellulitis was noted by Nageswaran et al., and they suggested a change in empiric antibiotics to cover the resistant organism [19]. Brook et al. displayed a marked increase in MRSA prevalence in sinusitis through the 2000s. Between 2004 and 2006 MRSA was isolated in 69 and 61% of *S. aureus* acute and chronic sinusitis cases, respectively, compared to 30 and 27% from 2001 to 2003 [20]. McKinley showed a similar trend with 73% of *S. aureus* orbital cellulitis cases resulting from MRSA infection [15].

In some patients, orbital cellulitis can produce a subperiosteal abscess (Fig. 6.1). Garcia and Harris proposed criteria for determining which patients should undergo surgical drainage, and 93.1% of patients not meeting their criteria cleared the abscess on medical therapy alone. They established nine surgical criteria: age 9 years or older, frontal sinusitis, nonmetal subperiosteal abscess, large subperiosteal abscess, suspicion of anaerobic infection, recurrence of subperiosteal abscess after previous drainage, evidence of chronic sinusitis, acute optic nerve or retinal compromise, or infection of dental origin. In patients not satisfying any of these criteria, 93.1% had resolution of the subperiosteal abscess with medical therapy (Fig. 6.2) [21].

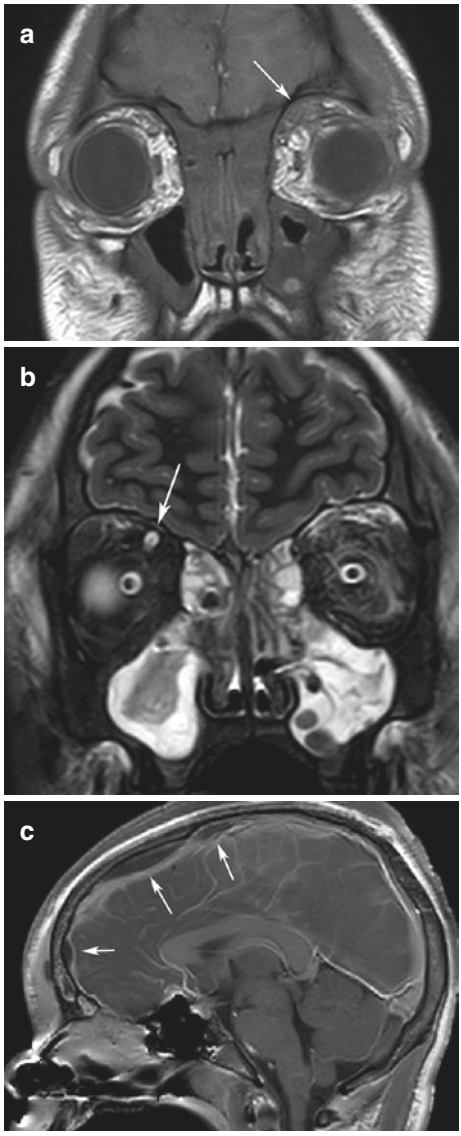

Fig. 6.1 (**a**) T1-weighted coronal MRI scan showing a large superior orbital abscess (*arrow*) on the left side associated with sinusitis. (**b**) T2-weighted coronal MRI scan showing obstruction of the superior ophthalmic vein on the left side. The patent superior ophthalmic vein on the right side is identified (*arrow*) for comparison. (**c**) Sagittal cuts of the MRI scan showing multiple intracranial empyema (*arrows*)

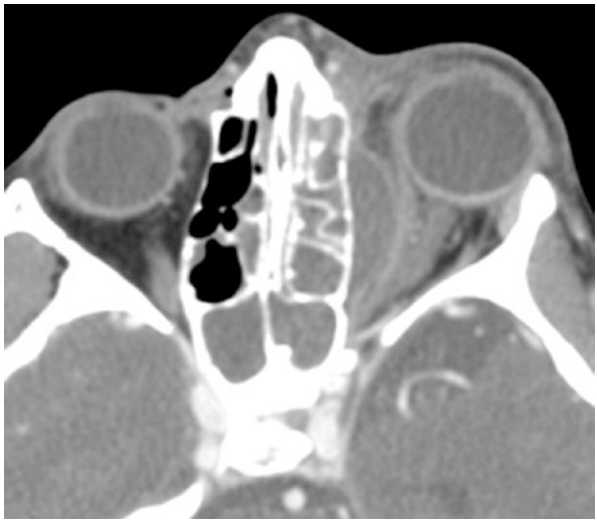

Fig. 6.2 Axial CT scan demonstrating ethmoid sinusitis associated with a subperiosteal abscess of the left medial orbit. Despite the size of the abscess, these will often respond to medical therapy alone

Medical Treatment of Orbital Cellulitis

As most cases of orbital cellulitis are related to acute sinusitis, optimal management of orbital infections requires appropriate treatment for the underlying or associated sinus infection. For most cases, management of sinusitis will entail use of saline nasal sprays, nasal decongestants, and nasal corticosteroids in addition to systemic antibiotics and anti-inflammatories. In some cases, surgical drainage of the sinuses is necessary. A more detailed discussion of sinusitis management is provided in the subsequent chapter.

This rise in community-acquired MRSA (CA-MRSA) demands physicians to differentiate between the hospital-acquired MRSA (HA-MRSA) version of the organism, which is perhaps more familiar to healthcare practitioners. The CA-MRSA is known to be more virulent than its HA-MRSA counterpart due to cytotoxin Panton-Valentine leukocidin secretion. However, the CA-MRSA is more susceptible to tetracyclines, trimethoprim-sulfamethoxazole, clindamycin, and fluoroquinolones than the nosocomial strain. For this reason, some guidelines suggest non-beta-lactam antibiotics where CA-MRSA prevalence is greater than 15% [22]. Despite this con-

sideration, a 2011 review of 94 children with orbital infections in Colorado showed two-thirds of patients were discharged on antibiotics not effective against MRSA, despite being on intravenous drug regimens covering MRSA while inpatient [23].

Antibiotic regimens differ by geography, reflecting both differences in microbiology and susceptibilities as well as economic differences that can dictate available treatment options [24–27]. Modern treatment recommendations include intravenous therapy with a variety of antibiotic combinations. Some empiric regimens include vancomycin, ampicillin-sulbactam, and/or piperacillin-tazobactam [16] and a third-generation cephalosporin with good central nervous system penetration such as ceftriaxone, clindamycin, or ampicillin-sulbactam depending on suspicion for MRSA [28, 29]. The National Health Service in the United Kingdom published guidelines in 2013 recommending intravenous co-amoxicillin, ceftriaxone, and metronidazole [30]. All treatment regimens also included nasal decongestants during treatment. Intravenous antibiotics are recommended for at least 2–3 days, followed by a course of oral antibiotics [16, 31]. Of consideration, in third-world countries where cost can be a prohibitive issue and patients must pay for medication out of pocket as well as obtain the medications themselves, the recommendations include Ampiclox, gentamicin, and metronidazole [27].

Indeed, medical therapy has become markedly more effective in treating orbital cellulitis. In a 2016 survey of the UK National Health Service database, 87.9% of the 14,149 cases of orbital cellulitis between 2002 and 2010 were managed without surgical intervention. Surgery was least likely to be needed in the youngest patients, with 5.1% of patients under 5 years of age requiring surgical intervention [32].

Corticosteroids in the Management of Bacterial Orbital Cellulitis

In the 1970s, corticosteroid therapy was discouraged in orbital cellulitis treatment, as it was associated with poorer outcomes. It was felt to delay patients' antibiotic response and failed to show improvement in edema [7]. There continued to be a thought that steroids may be beneficial in orbital cellulitis patients by decreasing edema, decreasing cell migration and inflammatory mediators, and decreasing fibroblast proliferation to limit scarring. In a 2005 retrospective study of patients with subperiosteal abscesses receiving steroid therapy on admission, Yen et al. showed steroids combined with antibiotic therapy decreased duration of hospitalization from 10 to 6.5 days. Additionally, only 2 of 12 patients receiving steroids required intravenous antibiotics after discharge compared to 7 of 11 patients not receiving steroids [33].

In a 2013 prospective study by Pushker et al., patients were placed on a standardized antibiotic regimen of intravenous vancomycin and ceftriaxone with the addition of metronidazole if no improvement was seen in 2 days or if anaerobic infection

was suspected. Following 3 days of antibiotic therapy, patients in the test group were dosed with oral prednisolone 1.5 mg/kg/day for 3 days and then 1 mg/kg/day for 3 days. Steroids were tapered over the course of 1–2 weeks. The steroid group exhibited several beneficial effects over the control group: quicker resolution of fever, less pain, faster edema and proptosis resolution, and faster return of normal ocular motility. Patients receiving steroids reached maximal vision improvement at 10 days compared to 12 weeks in the control group. No subjects in the test group had return or spread of infection. Steroid treatment was also shown to decrease hospital stay from 14.1 to 18.4 days and decrease the duration of intravenous antibiotic therapy. Of note, due to ethical concerns, no patients under 10 years of age were included in the study [34].

Building on this data, Davies et al. examined the effect of initiating steroid therapy earlier in the treatment course. Patients were started on 1 mg/kg/day prednisone treatment once C-reactive protein levels fell below 4, which was 2.9 days on average. This study also showed a significant decrease in hospital stay with patients receiving steroids hospitalized an average of 3.96 days compared to 7.17 days in the control group. All patients enjoyed a full recovery with no permanent disability [35].

Based on these results, there is a strong consideration for including steroid therapy in the medical management of orbital cellulitis.

Fungal Orbital Cellulitis

While bacteria are the most common cause for orbital infection, fungal pathogens can cause devastating disease. Fungal orbital cellulitis is most often found in immunocompromised patients. This state is commonly due to diabetes mellitus, acquired immunodeficiency syndrome, hematologic or lymphoproliferative malignancy, congenital immunodeficiency, and iatrogenic causes such as chemotherapy, antirejection medication, or treatment for autoimmune inflammatory disorders. These infections may occur secondary to hematogenous spread in fungemic patients or from adjacent spread of the fungus, either along tissue planes or through angioinvasive routes. Due to severity of underlying fungal infection and markedly reduced host response, fungal orbital infections carry a high mortality rate with case series showing 71–85% mortality [36, 37].

Orbital-cerebral phycomycosis was first clinically described in 1943 by Gregory et al. [38]. This type of infection is commonly due to spores of *Rhizopus*, *Mucor*, or other organisms entering the nose of the patient. These patients almost always have underlying acid-base imbalance, commonly due to diabetic ketoacidosis or dehydration accompanying metabolic acidosis secondary to diarrhea in the pediatric population. Patients tend to develop rapid facial swelling, proptosis, ptosis, orbital

cellulitis, and vision loss. There is commonly a necrotic ulcer on the palate. Histologic exam of affected tissue shows broad, nonseptate hyphae that stain well with hematoxylin-eosin occluding the vasculature and extending into adjacent tissue [1]. This aggressive disease has a high mortality and must be treated promptly with antifungal therapy and surgical debridement [39].

While phycomycosis can be heralded by a marked inflammatory response and proptosis, the immunocompromised nature of most patients can result in few if any symptoms in patients with rampant orbital fungal infection. This paucity of initial symptoms demands the clinician to have a heightened clinical suspicion for fungal orbital infection in immunocompromised patients with periorbital edema, headache, and facial pain. As the disease progresses, cranial neuropathies can develop resulting in extraocular motility disorders, vision loss, paresthesias, and paralysis [1].

McCarty et al. recommended MRI to evaluate the extent of infection and early multidrug antifungal therapy combined with surgical debridement and hyperbaric oxygen therapy. The underlying metabolic and/or immunologic disturbance should also be promptly rectified. Frequently, sinus washings were inadequate to make the diagnosis, and biopsy was required [37].

Aspergillus is another common fungal cause of orbital cellulitis. The disseminated, fulminant orbital aspergillosis is almost always found in severely immunocompromised patients. The fungus can invade and destroy adjacent structures as well as proliferate within vessel walls in a vaso-occlusive pattern. The initial symptoms are similar to those encountered in *Mucor* infections: proptosis and decreased vision. However, due to immune status of the patient, more severe signs of inflammation are rare until the later stages of the disease, if they manifest at all [1].

Commonly, direct biopsy or fine needle aspiration of the affected area is required to make the diagnosis. Histology of aspergillosis tends to show small branching hyphae branching at acute angles. The organism preferentially stains with methenamine silver and periodic acid-Schiff [1].

Kronish et al. described a case series of invasive aspergillosis in HIV patients in which all patients had adjacent ethmoid and maxillary sinus involvement. The patients were treated with surgical debridement and intravenous amphotericin B dosed at 0.5–0.6 mg/kg/day. In some of these chronic cases, local injection or irrigation of amphotericin B was employed and felt to be beneficial [40]. Modern treatment azole antifungal medications combined with aggressive surgical excision perhaps provide a more effective means for combating *Aspergillus* orbital cellulitis [1].

This fungal sinusitis is markedly different from the noninvasive chronic aspergillosis encountered in immunocompetent patients, as the invasive disease rarely occurs with CD4 counts above 50/mm^3 [40].

Conclusion

Orbital cellulitis remains a common disease process that must be addressed with appropriate gravity and diligence given the potentially devastating outcomes that can result. Modern antibiotics and further understanding of the microbial pathogens

and pathophysiology have made the condition amenable to medical treatment in a majority of cases. However, the clinician should be keenly aware of local flora and their antibiotic sensitivities as well as practice good antibiotic stewardship to discourage antibiotic resistance. By continuing to stay abreast of recent developments of the evolution of medical therapy for orbital cellulitis, one can help patients achieve the best outcomes and fullest recovery possible.

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Chapter 7
Management of Acute Rhinosinusitis

Andrew J. Victores and Masayoshi Takashima

Introduction

Rhinosinusitis is a significant healthcare problem that is highly prevalent, affecting approximately 16% of the adult population in the United States annually [1–3]. The costs associated with the disease are substantial, including direct costs of management and indirect costs of lost productivity [1]. Rhinosinusitis accounts for the fifth most common diagnosis for antibiotic prescription [1].

Historically, inflammation of the sinuses has been referred to as sinusitis. In recent years, the term *sinusitis* has largely been replaced by *rhinosinusitis* [4]. This change came about largely to stress the close relationship between the nose and paranasal sinuses. Most multidisciplinary societies support the concept that nasal mucosal inflammation, or rhinitis, often precedes and almost always accompanies sinus mucosal inflammation [2, 5–7]. Some limited objective data has been obtained to provide support for this concept. Gwaltney et al. used computed tomography (CT) imaging to demonstrate nasal cavity changes in patients with acute rhinosinusitis (ARS) [8]. Other studies have shown histologic evidence of inflammatory changes in the nasal mucosa in patients with rhinosinusitis [9, 10].

Sinusitis is categorized by the duration of sinonasal inflammation. Sinonasal inflammation with sudden onset of symptoms lasting up to 4 weeks is considered acute rhinosinusitis (ARS) [6]. Key diagnostic symptoms include purulent nasal drainage, nasal congestion, and facial pain or pressure. One of the challenges in the diagnosis of ARS is differentiating viral from bacterial etiologies.

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This distinction is important as viral causes of ARS will largely resolve spontaneously, whereas bacterial episodes may benefit from antibiotics. The most recent clinical practice guideline from the American Academy of Otolarynology–Head and Neck Surgery suggests a diagnosis of bacterial ARS be considered when symptoms persist longer than 10 days or worsen after a period of initial improvement [6].

Some patients have recurrent episodes of ARS. Recurrent acute rhinosinusitis (RARS) is defined by the presence of four or more episodes of acute bacterial rhinosinusitis (ABRS) without signs or symptoms of rhinosinusitis between episodes [6]. These patients do not have rhinosinusitis symptoms between episodes. Chronic rhinosinusitis (CRS) is diagnosed if symptoms are persistent for more than 12 weeks [6]. CRS is further delineated by the presence or absence of nasal polyposis.

Pathophysiology

The sinonasal tract acts to trap and expel foreign material as well as mount an immune response to these agents. Sinonasal inflammation in ARS begins as a response to foreign antigens, including viruses, bacteria, fungus, and allergens. Unfortunately, this inflammation can lead to sinus obstruction and ARS.

The primary cause of ARS is thought to be viruses. Many patients with the common cold were found to have involvement of the sinuses [8]. Inoculation with rhinovirus frequently causes symptoms associated with ARS [11]. Impaired sinonasal function from viral infection has also been thought to predispose patients to bacterial infection. However, most viral ARS episodes resolve without proceeding to bacterial rhinosinusitis with only about 0.5–2.2% becoming bacterial ARS [12].

Bacteria frequently found in patients with acute bacterial rhinosinusitis include *Streptococcus pneumonia, Haemophilus influenza*, and *Moraxella catarrhalis* [13]. Some studies have also implicated *Staphlococcus aureus* as a major pathogen [14]. In complications that arise from acute sinusitis, polymicrobial isolates are often found with respiratory pathogens or oral flora implicated as sources of the infection [15, 16].

Anatomic variations can be a predisposing factor in ARS. Variations of anatomy associated with rhinosinusitis include structural abnormalities, increased pneumatization, and supplementary sinus openings [17]. Although the evidence is limited, the anatomic abnormalities most associated with ARS include concha bullosa, large infraorbital ethmoid cells, accessory sinus ostia, and ethmoid infundibulum stenosis (Fig. 7.1) [18–20].

Environmental irritants, such as allergens and cigarette smoke, may predispose patients to ARS. Many patients with rhinosinusitis suffer from allergic rhinitis [21]. Retrospective studies found that at least half of patients presenting with rhinosinusitis also have positive allergy skin test responses [22]. Diagnosis and treatment of allergies may aid the management of sinus disease. Sinus function can also be harmed by smoke exposure. Smoking has been linked to a number of upper airway

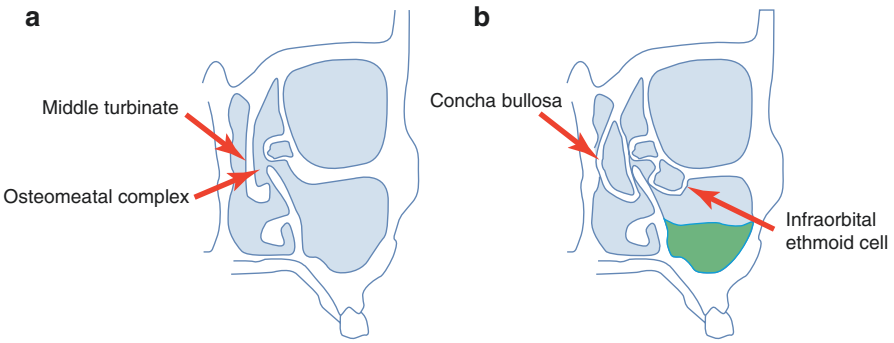

Fig. 7.1 (**a**) Figure demonstrating normal sinus anatomy. (**b**) Figure demonstrating concha bullosa and large infraorbital ethmoid cell causing obstruction of the ostiomeatal complex

diseases in both children and adults. With regard to the sinuses, studies have linked smoking with altered flora colonization of the sinuses to harbor more potential pathogens [23]. Mucociliary clearance also appears to be impaired by smoking [24].

Management of Uncomplicated ARS

Saline Irrigations

Management of sinus disease frequently includes use of saline irrigations. Studies have shown improvement in symptoms and quality of life as well as decreased medication use [6, 25, 26]. Saline irrigations appear to help patients with rhinosinusitis by improving mucociliary clearance and thinning mucus as well as providing an anti-inflammatory effect [27, 28]. Both isotonic and hypertonic saline have been used for sinusitis. Limited data suggests that hypertonic saline may be superior to isotonic saline [27, 29, 30]. Two randomized clinical trials have demonstrated significant benefit with use of hypertonic saline irrigations, including improvement in sinus-related quality of life, symptoms, and mucociliary clearance [26, 31].

Intranasal Corticosteroids

Another adjunct of sinusitis management is intranasal corticosteroids. The primary function of intranasal corticosteroids is a local anti-inflammatory effect which can in turn provide some symptomatic relief from ARS. Several randomized controlled studies have been performed evaluating the effects of intranasal corticosteroids in ARS [32, 33]. These studies have demonstrated reduced daily impact of ARS symptoms with intranasal corticosteroid use. A recent Cochrane review also

demonstrated significant improvement of ARS symptoms with intranasal corticosteroid use [34]. A modest group of patients may even have complete resolution of symptoms. A number of different formulations of intranasal corticosteroids have been used for sinus complaints. A couple of commonly used formulations include fluticasone propionate 110 μg daily or twice daily or mometasone furoate 200 μg daily or twice daily. The adverse events associated with intranasal corticosteroids are relatively limited given the negligible systemic uptake of the medication. Intranasal corticosteroids have been shown to have no significant effect on glucose levels in diabetic patients [35]. There also does not appear to be any effect of intranasal corticosteroids on the hypothalamic-pituitary-adrenal axis [36, 37]. Even in pregnant patients, many clinicians still recommend continuing to use intranasal corticosteroids [38]. This is in stark contrast to oral corticosteroids, which are better known for their potential side effects.

Oral Corticosteroids

Oral corticosteroids serve an important role in the management of nasal polyposis, which can develop in patients with chronic rhinosinusitis. The role of oral corticosteroids in acute rhinosinusitis remains less clear. Few studies have specifically addressed this therapy in acute rhinosinusitis, and there is significant variability in the dosage and length of therapy that is utilized [39]. In addition, many of these studies are confounded by antibiotic use. A Cochrane review meta-analysis failed to find significant evidence to support systemic corticosteroids as a monotherapy in ARS [40]. Although some studies did show a modest benefit with oral coritcosteroid use in combination with oral antibiotics, there was no clear consensus. In addition, short-course oral corticosteroid has been associated with adverse events, including gastrointestinal disturbances and insomnia [41]. Given the limited data demonstrating any benefit of use and potential side effect of use, oral corticosteroids are generally not used in uncomplicated ARS.

Oral Antibiotics

Antibiotics have traditionally played a role in the management of acute bacterial rhinosinusitis (ABRS). As previously discussed, the challenge can be in differentiating viral and bacterial etiologies. Current practice guidelines suggest using the time course of symptoms to make this distinction [6].

Of note, some recent studies have cast doubt on the role of antibiotics in uncomplicated ARS, even in cases of bacterial infections. Many cases of ABRS will resolve spontaneously without antibiotics. In addition, there are adverse events associated with oral antibiotic use. Several randomized controlled trials have compared antibiotic use with placebo for ABRS [42–45]. Antibiotics as a first-line treatment

for ARS was found to have limited benefit in terms of shortening the recovery period yet had considerable side effects [43]. For this reason, some have suggested a period of watchful waiting for uncomplicated ARS. Some clinicians and patients may find this period difficult due to the potential inconvenience, expense, and delay should watchful waiting fail. For this reason, recent clinical practice guidelines from the AAO-HNSF suggest providing a prescription once the diagnosis of ABRS is made but asking that the patient not fill the prescription unless symptoms worsen or persist longer than 7 days [6].

When antibiotics are deemed appropriate for use, the clinician must then select the appropriate regimen. Most research and consensus guidelines currently recommend amoxicillin with or without clavulanate for 5–10 days as first-line therapy for adults with uncomplicated ABRS [6]. With regard to dosage selection, higher-dose regimens may be more appropriate, as has been demonstrated with amoxicillin with clavulanate. Studies have found reduced nasopharyngeal carriage of pneumococcus with higher dose of amoxicillin with clavulanate [46]. Unfortunately, evidence suggests organisms are becoming increasingly resistant to penicillin-based antibiotics. In fact, penicillin-resistant pneumococcus was isolated in the middle meati of most adult and pediatric patients (72%) [47]. Clearly, antibiotic resistance is and will remain a serious concern in the treatment of acute bacterial sinus infections.

In some patients, first-line therapy will fail, and alternative antibiotics will need to be considered. Moreover, many patients are allergic to the first-line options. Consideration should be given to choosing an antibiotic with adequate coverage, particularly if a culture was obtained. Second-line drugs include trimethoprim-sulfamethoxazole, doxycycline, and a combination of clindamycin plus a third-generation oral cephalosporin [6]. Respiratory fluoroquinolones have also been used extensively, especially for patients with recalcitrant disease. Unfortunately, fluoroquinolones are associated with severe adverse events, including cardiac, musculoskeletal, and peripheral neuropathy. For this reason, they have recently fallen under the scrutiny of Food and Drug Administration (FDA) advisory committees [48]. As of 2016, a boxed warning was placed on use of fluoroquinolones for the purpose of treating sinusitis due to the risk of disabling and potentially irreversible adverse reactions. This will clearly discourage future use of these antibiotics for sinus disease. Perhaps further studies can refine the patient populations for whom the benefits of fluoroquinolones outweigh the risks. The duration of therapy for second-line therapies is typically similar to first-line regimens, with most recommending 10 days or less of therapy [2, 6]. Shorter courses are generally recommended due to less risk for side effects and greater patient compliance [2, 6].

Other Non-surgical Treatments

Various additional therapies aimed at symptomatic relief have been used for ARS. These include decongestants, antihistamines, ipratropium bromide, and mucolytics. Although these therapies are often used by clinicians, there is

relatively limited clinical data to confirm their efficacy. Decongestants act to improve nasal obstruction, one of the primary complaints associated with ARS. Unfortunately, randomized controlled studies have not been able to demonstrate a significant clinical benefit of using decongestants compared to placebo [31, 49]. Decongestants have relatively limited adverse events associated with their use over a short period of time. Prolonged use, on the other hand, can result in rebound nasal swelling and congestion when weaned from the decongestant, referred to as rhinitis medicametosa. Given the lack of clear clinical efficacy for ARS but limited side effect profile with short-course administration, consensus guidelines are unable to recommend or caution against use of decongestants for ARS [7]. Another medication proposed for use in ARS is antihistamines. Although antihistamines are thought to decrease nasal drainage, no significant benefit could be demonstrated from their use with adult ARS in several studies [2, 50]. Similarly, ipratropium and mucolytics have no definite evidence to support their use in ARS.

Management of Treatment Failure and Complications

Most episodes of ARS resolve spontaneously or with nonsurgical management. Unfortunately, treatment failure or complications of ARS do occur and can require more intensive management. Failure of ARS treatment is defined by worsening or failure of improvement of symptoms after 7 days from the initial diagnosis [6]. The complications of ARS are categorized into orbital, intracranial, and osseous [7, 51]. Orbital complications of ARS occur about twice as frequently as intracranial complications, with osseous complications the least frequent [52]. Osseous complications include osteomyelitis of the frontal or maxillary bones. The most common orbital infection is preseptal cellulitis, although an overall small portion (9%) of these infections are due to ARS compared to post-septal orbital infections (91%) [53]. Sinusitis accounts for approximately 10% of intracranial infections [7, 54, 55]. Complications of ARS are more often found in children [56, 57]. Males appear to be more frequently affected by complications of ARS than females [52, 58].

Orbital complications of sinusitis can vary in severity. The progression of sinus infection to orbital complications can be understood using the Chandler classification system [59]. This classification is composed of a progression of five stages of infection from the sinus to the orbit. The least severe and most common (70–80%) of these is periorbital cellulitis (Chandler class I). In patients with periorbital cellulitis, the inflammatory process is confined to the periorbital space by the orbital septum with lack of orbital involvement. As a result, patients typically develop swollen eyelids without pain or impairment in extraocular movement or vision. When inflammation extends past the orbital

septum to involve the orbital contents, the patient is deemed to have orbital cellulitis (Chandler class II). Coalescence of infectious fluid between the lamina papyracea and medial periorbita results in a subperiosteal abscess (Chandler class III). In rare cases, intraconal coalescence of purulence can form an orbital abscess (Chandler class IV). Cavernous sinus thrombosis has traditionally been classified as a late stage orbital infection (Chandler class V) with the hallmark of bilateral ocular symptoms. However, cavernous sinus thrombosis has more recently been thought of as an intracranial infection potentially independent of orbital infection [56].

Management of complications of ARS includes the same conservative measures typically utilized in uncomplicated ARS. These include saline irrigations, intranasal corticosteroids, and potentially decongestants. However, additional means are usually required to adequately address the complications of ARS.

Intravenous Antibiotics

Intravenous (IV) antibiotics are rarely needed for uncomplicated ARS. On the other hand, they frequently serve a role in the management of complications of ARS. Broad-spectrum coverage should be considered. Cultures taken from purulent drainage should be obtained and used to further direct antibiotics selection. Consideration of local antimicrobial susceptibilities may also need to be factored into the decision. Intravenous antibiotics along with conservative measures can treat the majority of ARS complications without the need for surgical intervention. Surgery is typically reserved for severe complications of ARS or those patients with complications who fail appropriate IV antibiotic therapy.

Surgery

During an episode of ARS, the sinonasal mucosa becomes edematous and hyperemic. The narrowed space and increased susceptibility to bleeding make surgery during this state more difficult. Moreover, nearly all cases of uncomplicated ARS resolve without surgical intervention. For this reason, there is very limited role, if any, for surgery in the management of uncomplicated ARS. Unfortunately, untreated or resistant bacterial species of ARS can develop complications which necessitate surgery. The goals of surgery are to decompress pressure on vital structures in the orbit or intracranially if present, drain any purulent fluid collection, obtain cultures to direct antibiotics, and facilitate future irrigation and drainage by expanding sinonasal access to the site of infection.

Surgery for orbital complications of ARS depends on the extent and severity of infection. As previously discussed, Chandler et al. described a classification for the severity of orbital complications from ARS [59]. Clinical and radiographic findings help to distinguish these complications. Most patients present early enough to be managed nonsurgically with antibiotics and other conservative measures. However, the formation of subperiosteal abscess or orbital abscess may require endoscopic sinus surgery to open the sinuses, drain the abscess, obtain cultures, and potentially decompress the orbit.

Subperiosteal abscesses usually result from extension of infection from the ethmoid sinuses to the periorbita adjacent to the lamina papyracea bone [60–62]. For this reason, subperiosteal abscess formation mostly occurs medial to the orbit. They account for approximately 12–17% of orbital infections [62–65]. Management of this complication is controversial, with some advocating for a more conservative approach with IV antibiotics and others encouraging rapid surgical drainage [62, 64, 66, 67]. Surgical intervention can usually be performed through a transnasal endoscopic approach with anterior ethmoidectomy and opening of the lamina papyracea bone (Fig. 7.2) [62]. This approach is preferable to an external approach due to the lower morbidity and superior cosmesis [64, 66]. Endoscopic surgery can be used even when the abscess extends partially superiorly or inferiorly to the orbit [68]. Further extension could require an external surgical approach to the orbit. Surgery is not always needed for adequate subperiosteal abscess management. In fact, medical therapy alone may be sufficient, particularly in younger patients. Patients who are younger than the age of nine appeared more likely to respond to medical therapy than older patients [62, 65, 69]. One possible reason for this difference could be that younger patients more often contain a single bacterial isolate within the subperiosteal abscess as opposed to older patients with polymicrobial isolates [69, 70].

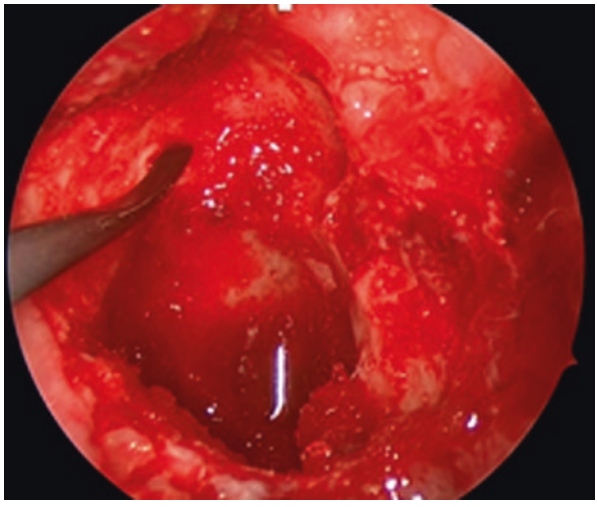

Fig. 7.2 Intraoperative photograph of an anterior ethmoidectomy and removal of lamina papyracea bone

Unlike subperiosteal abscesses, the presence of an orbital abscess usually necessitates surgical intervention. This is particularly the case if there is lack of improvement with antibiotic management or there is concurrent intracranial infection. The surgical approach required for adequate drainage of the abscess is dependent on positioning within the orbit. Purulent loculation located medially can potentially be addressed with a transnasal endoscopic approach, whereas a location farther from the lamina papyracea can be more challenging to access endoscopically and require and external approach.

Some patients who suffer from orbital complications of ARS also develop intracranial complications. One study found nearly half of patients with intracranial complications of rhinosinusitis had periorbital cellulitis or abscess [71]. Fortunately, intracranial complications are relatively rare, only identified in about 3–4% of adults and children admitted with ARS [72, 73]. Intracranial complications include meningitis and intracranial abscess. Aggressive management must be undertaken if one of these complications occurs. Intravenous antibiotic coverage should be utilized with selection of an agent that crosses the blood-brain barrier. Surgical intervention consists of drainage of the involved sinuses and evacuation of any coexistent abscess. An external approach to intracranial drainage can require a craniotomy or burr hole.

Some patients suffer from recurrent episodes of ARS. Recurrent ARS can significantly impair patient quality of life [74]. Management of this disease can be challenging with limited success using antibiotics and intranasal corticosteroids [75, 76]. Endoscopic sinus surgery has shown promising results, improving quality of life to near normal postoperatively [74, 77, 78].

Conclusions

Acute rhinosinusitis is a common disease that affects both pediatric and adult patients. Most patients will improve spontaneously or with nonsurgical measures. Unfortunately, complications from this disease still occur and can require more intensive management. Complications arise from extension of infection from the sinuses to the orbit or intracranially. Abscess formation at these sites may require surgical intervention for drainage and decompression.

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Chapter 8
Surgical Management of Subperiosteal Abscess

Catherine J. Choi and Thomas E. Johnson

Introduction

Orbital cellulitis is defined as an acute infectious inflammation of the post-septal orbital tissues, and the majority of cases result from secondary extension of a paranasal sinus infection. Other causes include trauma, insect bites, surgical procedures, foreign bodies, and endogenous spread of infections into the orbit. Bacterial orbital cellulitis can be complicated by the development of a subperiosteal abscess (SPA). The incidence of this complication has been reported to occur in between 5 and 15% of patients with orbital cellulitis. These abscesses can be vision and life-threatening and need to be evaluated and managed urgently.

Evaluation

The evaluation of patients with orbital cellulitis requires a thorough history and physical examination including a detailed ocular examination. Signs of this disease include proptosis, decreased ocular motility, chemosis, decreased vision, fever, and, in severe cases, afferent pupillary defect [1, 2]. Imaging is imperative, and computed tomography (CT) is preferred, with and without contrast and including axial and coronal views. Thin cuts are needed for adequate visualization of the

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orbits and sinuses and to assess the frontal lobes of the brain for evidence of intracranial extension [3]. Specialized CT protocols may be necessary for intraoperative image guidance, which is sometimes used in endoscopic surgeries. The presence of sinusitis is noted, and the cavernous sinuses are carefully examined to determine if cavernous sinus extension of infection and/or thrombosis is present. Magnetic resonance imaging (MRI) can also be used and does not expose the patient to ionizing radiation, which can be a consideration in very young pediatric patients.

Location of Subperiosteal Abscess

The most common location of a SPA is along the medial orbital wall, adjacent to the ethmoid sinus. Infectious material from the infected sinus can enter the orbit through natural bony foramina and small dehiscences or fractures in the thin ethmoid bone (lamina papyracea) separating the sinus from the orbit (Fig. 8.1) [1–3, 5, 6]. These abscesses can expand to involve the orbital apex, which can result in visual loss secondary to compressive or infectious optic neuropathy. Untreated, the abscesses can extend into the intracranial cavity and cause meningitis, cavernous sinus thrombosis, or even brain abscess [1–3]. Frontal sinusitis can result in a superior SPA, and maxillary sinusitis can cause an inferior SPA. Abscesses along the lateral wall are unusual but may occur from external trauma.

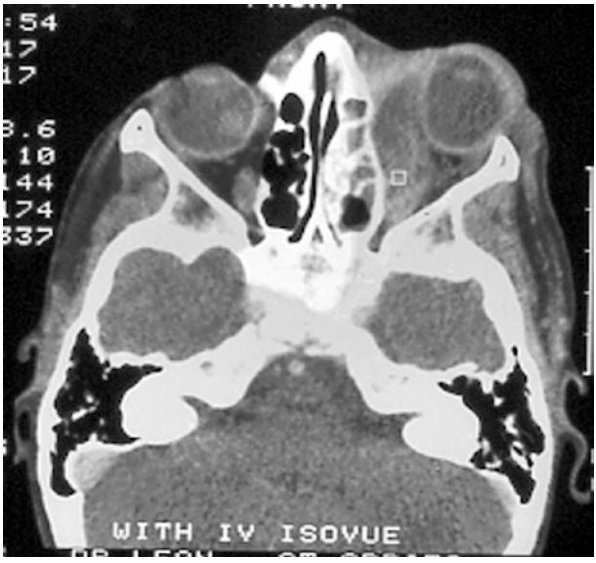

Fig. 8.1 CT scan showing a large left medial subperiosteal abscess with apical optic nerve compression requiring emergent drainage

Decision for Drainage

The decision to perform surgery on a SPA depends on multiple factors and has been thoroughly described by Harris and coauthors in several published articles [7–9]. Not all abscesses require drainage, and the urgency of surgical intervention is determined using multiple criteria. Briefly, any abscess causing visual loss, optic nerve compromise, or intracranial complications needs to be drained emergently. Age is an important factor in this decision-making process [7–9]. Garcia and Harris discussed age as it relates to the need for surgical intervention [7]. Patients younger than 9 years of age with a small medial SPA not causing visual or optic nerve compromise can often be treated with intravenous antibiotics, and these abscesses may resolve without the need for surgery [7–11]. These subperiosteal collections are often due to a single aerobic organism, and, when surgery is performed, cultures are often negative [9]. Tables 8.1 and 8.2 summarize the indications for surgical drainage of SPA according to these studies.

In patients aged 9–14 years, there is a transition to more complex infections, and patients aged 15 years and older almost always require surgical drainage of the SPA. The urgency depends on the location, optic nerve status, and condition of the patient. These patients may also be watched expectantly over the first 24–48 h while being treated with intravenous antibiotics and undergoing frequent vision checks, but the surgeons must be prepared to intervene quickly if visual or systemic deterioration appears at any point during the course of the condition. These patients usually

Table 8.1 Indications for surgical drainage of SPA

Age of patient 9 years or older
Presence of frontal sinusitis
Non-medial location of SPA
Large SPA
Suspicion of anaerobic subperiosteal infection (e.g., presence of gas within the abscess on CT)
Recurrence of SPA after previous drainage
Evidence of chronic sinusitis (e.g., nasal polyps)
Acute optic nerve or retinal compromise
Infection of dental origin (e.g., higher likelihood of anaerobes)

Table 8.2 Indications for surgical drainage of SPA in patients less than 9

Vision loss, RAPD (relative afferent pupillary defect)
Absence of defervescence within 36 h of appropriate medical therapy
Clinical deterioration after 48 h of appropriate medical therapy
Absence of clinical improvement after 72 h of appropriate medical therapy

are found to have positive cultures at the time of drainage, with polymicrobial infections containing a combination of aerobic and anaerobic bacteria [9]. This difference in bacteriology is due to the effect of sinus maturation. Young children are less likely to develop anaerobic infections due to their larger ratio of ostia size to sinus size than that in older individuals. With increasing age, the sinus cavities enlarge greatly, while the ostia remain essentially the same size, therefore creating an environment more favorable for the growth of anaerobic bacteria [3, 5, 12].

Superior subperiosteal abscesses have a worse prognosis and are more likely to result in intracranial extension. They should be drained within the first 24 h. Inferior abscesses are unlikely to clear with antibiotic therapy alone and should also be treated within the first day of presentation [1, 3, 5, 7]. Todman and Enzer noted that the volume of the SPA measured on CT scan was a determining factor in identifying which patients needed surgery, both in the under and over 9-year-old age groups. Patients with a SPA volume of less than 1250 mm^3 in their study did not require drainage. Additionally, they found that most patients with concurrent frontal sinusitis did not require surgical intervention [13].

Otolaryngology Involvement

Since most patients with orbital cellulitis and SPA have paranasal sinusitis, a decision must be made whether to drain the SPA only or to combine drainage of the SPA with sinus surgery. Dewan and coworkers studied patients with sinusitis and SPA and found that those with drainage of the SPA alone had statistically significant higher rate of reaccumulation of the SPA (5/9 patients), compared to those with combined SPA and sinus drainage (0/6 patients) [14]. Therefore, it is often beneficial to plan on both sinus and SPA drainage at the same time. One study revealed that patients with superior/medial abscesses treated with endoscopic drainage alone had a strong association with surgical failure and advocated combined internal and external drainage in those patients [15].

Drainage Approaches

The surgical approach depends on the location of the abscess and the preference of the surgeon. Abscesses can be drained externally via a skin or conjunctival incision, or intranasally using an endoscopic approach.

External skin approach to a medial SPA. This commonly used approach is a modified Lynch incision, the traditional incision for performing an external ethmoidectomy. The incision is made on the side of the nose beginning at the medial aspect of the brow and extending inferiorly about 15 mm. (Fig. 8.2a) Dissection is carried down to the periosteum, and the periosteum is sharply opened with a #15 Bard-Parker blade. Care is taken to avoid the supraorbital and supratrochlear neurovascular

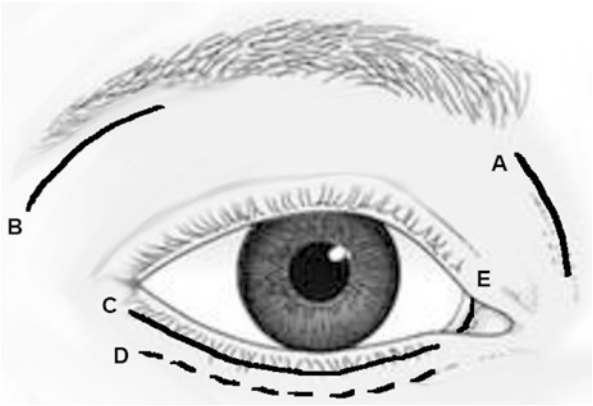

Fig. 8.2 Surgical approaches for draining SPAs (*A*) Modified Lynch incision, (*B*) superolateral brow incision, (*C*) subciliary incision, (*D*) inferior transconjunctival incision, (*E*) transcaruncular incision

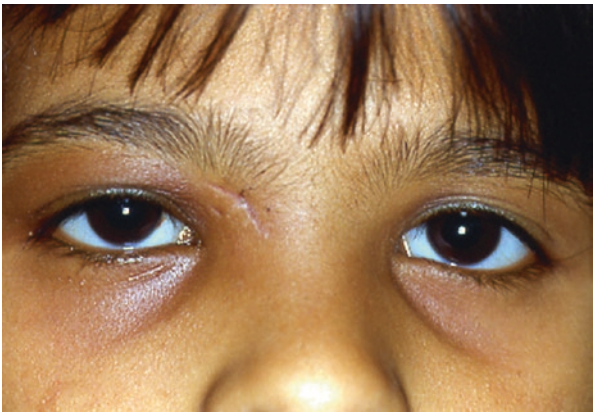

Fig. 8.3 Unsightly facial scar after modified Lynch incision for SPA drainage

bundles, the trochlea, and the medial canthal tendon. Subperiosteal dissection is carried out with a Freer elevator until the abscess cavity is entered. Cultures are taken of the abscess fluid, and the abscess cavity is suctioned to remove liquid pus and inflammatory exudate. A blunt Freer elevator can be used to gently open any loculations. The subperiosteal space is irrigated with an antibiotic solution, and a small Penrose drain is placed. The wound is closed in layers, and the drain is advanced over the next 2 days and then removed. The advantage of this technique is that it is an easy, direct approach to the SPA. The disadvantage is that it can leave an unsightly facial scar despite a meticulous closure technique. The combination of infectious material and the drain can affect the proper wound healing of the skin (Fig. 8.3).

External skin approach to a superior SPA. For a superior abscess, a sub-brow incision is made in the skin just inferior to the brow cilia laterally (Fig. 8.2b). Care is taken to avoid the supraorbital neurovascular bundle. The periosteum is identified at the orbital rim and incised either with a #15 Bard-Parker blade or the sharp side of a Freer elevator. The subperiosteal space is entered, and dissection is carried down posteriorly until the abscess cavity is identified. The pus is cultured and aspirated, and a small Penrose drain is placed and brought out through a separate stab

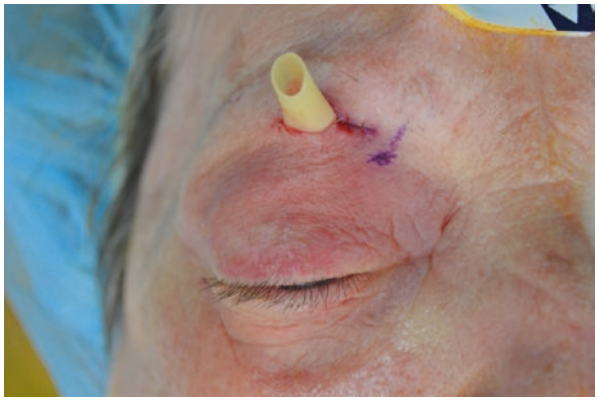

Fig. 8.4 Drain in place after draining a superior subperiosteal abscess, taking care to avoid the supraorbital neurovascular bundle

incision (Fig. 8.4). The abscess cavity is irrigated with antibiotic solution, and the wound is closed in layers. The drain is advanced over 2 days and removed.

External skin and transconjunctival approaches to an inferior abscess. Either performing a transcutaneous approach or transconjunctival approach can drain an inferior abscess. For the transcutaneous route, a subciliary incision is performed with the eyelid pulled up using a 4–0 silk Frost suture. (Fig. 8.2c) Dissection is carried inferiorly in the plane between orbicularis muscle and orbital septum to the inferior orbital rim. The periosteum at the rim is incised with either a #15 Bard-Parker blade or a Freer elevator. Dissection is carried posteriorly to the abscess cavity, which is managed as described before.

The transconjunctival incision involves injecting the inferior fornix with 1–2 cc of 2% lidocaine mixed with 1:100,000 epinephrine. A 4–0 silk Frost suture is placed. A rake retracts the lower lid, and the eye is protected with a shoehorn corneal protector. An incision is made through the conjunctiva and lower lid retractors midway between the inferior edge of the tarsal plate and the inferior fornix (Fig. 8.2d). Gentle dissection is carried down to the periosteum of the inferior rim. Care is taken to avoid damage to the inferior oblique muscle, which can be identified between the central and medial fat pads. The periosteum is incised and dissection carried posteriorly in the subperiosteal plane. The abscess is identified and managed as described above.

Transcaruncular approach to a medial SPA. Another excellent method of accessing the medial orbital wall is through the caruncle. Since the majority of SPAs occur along the medial wall adjacent to the ethmoid sinus, the transcaruncular approach is a useful technique for draining these abscesses [16]. The technique is as follows: approximately 2 cc of 2% lidocaine mixed with 1:100,000 epinephrine is injected into the caruncle and medial conjunctiva. Westcott scissors are used to make a snip in the middle of the caruncle, and relaxing incisions are made in the superior and inferior conjunctiva (Figs. 8.2e and 8.5). The Wescotts are then used to dissect toward the posterior lacrimal crest and then exchanged for Stevens scissors. The Stevens scissors are pointed toward the posterior lacrimal crest and pressed slightly into the medial wall and spread widely. A rake retractor is placed in the medial aspect of the wound,

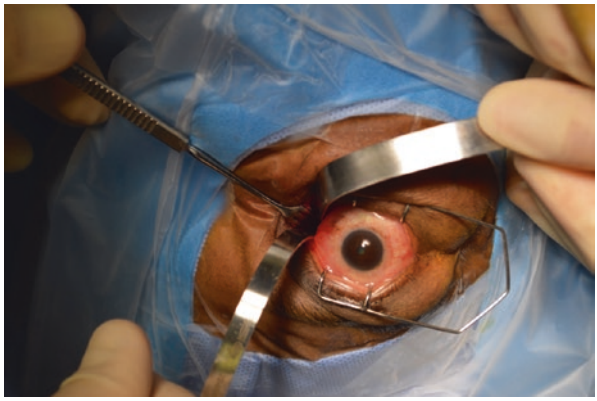

Fig. 8.5 Accessing the medial subperiosteal space using a transcaruncular approach

and a small malleable retractor is placed in the lateral aspect (Fig. 8.5). A Freer periosteal elevator is used to incise the periosteum, and subperiosteal dissection is carried posteriorly until the abscess cavity is identified. Cultures are taken, the pus is suctioned out, and the subperiosteal space is irrigated with an antibiotic solution. A small Penrose drain can be divided in half into a narrow strip and placed in the space, brought out through the caruncle and sutured to the nasal skin. This drain is advanced over 2 days and removed. The main advantage of this approach is the absence of a facial scar. The disadvantage is that it is slightly more difficult to learn, and the drain is more difficult to place and potentially more uncomfortable for the patient.

Endoscopic approach to a medial wall SPA. This surgery is performed through the nose with a nasal endoscope and includes a transnasal endoscopic ethmoidectomy combined with removal of a portion of the lamina papyracae and drainage of the medial wall abscess as first described by Manning in 1993 [17]. This technique should only be performed by a surgeon experienced in endoscopic surgery. Since most of these patients are younger, the nose is smaller, with more nasal congestion and potential for bleeding in the setting of infection. Under general anesthesia, the nose is packed on the affected side with pledgets soaked in oxymetazolone and lidocaine to decongest the mucosa. The nasal endoscope is introduced, and an external ethmoidectomy is performed. Cultures may be taken from the infected ethmoid sinus. The surgeon then gently makes a small opening in the lamina papyracea to enter the subperiosteal space. The abscess cavity is identified and drained. The advantages of this technique include the ability to concurrently drain the involved ethmoid sinus and the SPA, as well as avoiding potential for a facial scar. Potential complications include damage to the medial rectus muscle as well as damage or resection of the optic nerve, resulting in strabismus and possibly blindness [18, 19]. One study noted a trend toward shorter hospitalization in those patients treated with endoscopic drainage compared to those treated with external drainage alone [20]. One study revealed that this technique was often successful for medial SPA without superolateral extension. With superolateral extension, the endoscopic approach was often not successful, and a second surgery using a lateral sub-brow incision was sometimes needed [21].

Combined endoscopic and transcaruncular approach to a medial SPA [22]. Endoscopically the ethmoid sinus can be opened and drained in the usual technique of functional endoscopic sinus surgery. At the same time, a transcaruncular approach is used to enter and drain the abscess. The advantage of using this combined technique is improved visualization of the orbital contents in the setting of infection. The endoscopic surgeon can make a small opening in the medial orbital wall to allow further egress of any pus from the abscess cavity, which obviates the need to place a drain through the transcaruncular incision site. It also ensures complete drainage of the ethmoid sinus, decreasing the likelihood of the SPA reforming.

Minimal endoscopic approach with SPA drainage only. One study revealed that a limited endoscopic approach to the medial SPA was also effective. This approach involved endoscopic opening of the medial wall of the bulla ethmoidalis and lamina papyracea without concomitant ethmoidectomy. This minimal drainage approach combined with intravenous antibiotics was successful without the need for more extensive sinus surgery [23].

Approach to orbital abscess. Rarely, severe or untreated orbital cellulitis can result in a frank intraorbital abscess that is not subperiosteal in location. This type of abscess can also present in immunocompromised individuals with sepsis and hematogenous seeding of the orbit. The approach to these abscess cavities varies depending on the location, and standard orbital approaches are used to drain these infections.

Complications of Surgery

Surgical complications include failure to adequately drain the abscess with the resultant need for a second surgery, damage to surrounding orbital structures, bleeding, scarring, and spread of infection to adjacent areas. If patients present with a medial abscess with superolateral extension, a transnasal endoscopic approach alone has been reported to fail, and a second surgery using an external lateral subbrow incision may be needed [21]. Endoscopic abscess drainage has the added risks of damage to the medial rectus muscle as well as optic nerve damage or avulsion resulting in blindness [18, 19]. Only experienced endoscopic surgeons should therefore use this technique, as the surgeon is usually working in an inflamed, smaller pediatric nose with a tendency toward increased bleeding and poor visualization.

Summary

The complication of a subperiosteal abscess in orbital cellulitis is a true ophthalmic emergency. Improperly treated abscesses can result in permanent visual loss, meningitis, brain abscess, and even death. A careful physical exam and orbital imaging is imperative, and all patients need aggressive broad-spectrum intravenous

antibiotic therapy. Indications for drainage include any patient with vision loss or threat of intracranial extension. Patients younger than 9 years of age meeting strict criteria can often be watched expectantly on medical therapy and may not require surgical intervention if they demonstrate adequate improvement. Older patients develop more complicated, mixed aerobic and anaerobic infection due to sinus maturation, and their abscesses are often refractory to antibiotic therapy alone. Various surgical approaches are available depending on the location and size of abscess and the availability of experienced endoscopic surgical help. With proper diagnosis, good antibiotic therapy, and prompt surgical abscess evacuation when indicated, patients with orbital cellulitis with subperiosteal abscess have an excellent prognosis for a full recovery.

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Chapter 9
Managing Necrotizing Fasciitis of the Eyelids and Orbit

Ran Stein and Morris E. Hartstein

Necrotizing fasciitis is a rapidly spreading infection of soft tissues which can occur in any part of the body but more commonly in the extremities, the perineum, and the truncal area [1]. Although rare, facial involvement including the periorbital region can occur [2].

Necrotizing fasciitis is a devastating, life-threatening condition in which timely diagnosis and aggressive treatment are crucial for reduced mortality and morbidity. Several synonyms for necrotizing fasciitis have been proposed throughout the years, and a partial list appears in Table 9.1. The term, necrotizing fasciitis, was introduced by Wilson in 1952 and describes the most prominent feature of the disease: necrosis of the fascia and subcutaneous tissue [1]. The term, however, is actually a misnomer, as it implies that the process involves only subcutaneous fascial layers. However, the infection may spread to any adjacent soft tissue, including muscles [3].

Table 9.1 Necrotizing fasciitis synonyms

Hospital gangrene
Fournier's gangrene
Streptococcal gangrene
Necrotizing erysipelas
Necrotizing cellulitis
Flesh-eating bacterial infection
Suppurative fasciitis
Progressive bacterial synergistic gangrene

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Demographics

Periocular necrotizing fasciitis is extremely rare: a review by Amrith et al. [2] traced 94 cases reported in the literature between 1991 and 2012. Median age was 46. One-third of the cases were bilateral. A review by Lazzeri et al. [4] collected 104 published reports of periorbital necrotizing fasciitis between 1950 and 2008. In this review, ages ranged from 17 months to 93 years, with an average age of 50 years. Both reviews indicated a slight male predominance. In a prospective BOSU study [5] conducted in the United Kingdom, Flavahan et al. found 30 new cases of periocular necrotizing fasciitis in a two-year period between 2010 and 2012, indicating an incidence of 0.24 per million per annum.

Pathogenesis

Necrotizing fasciitis is caused by soft tissue infection that leads to liquefactive necrosis and extensive soft tissue destruction [5]. The infection and the inflammatory response spread horizontally along the avascular fascial planes, invariably leading to ischemic necrosis of the skin [2]. The superficial avascular musculoaponeurotic system (SMAS) is usually the fascial plane involved first. At this level, resistance to bacterial spread is poor, allowing the process to rapidly extend. When the infection penetrates the fascia, it spreads along longitudinal muscle bundles. Collagenase and hyaluronidase, released from bacteria, aid in bacterial invasion and contribute to aggressive tissue damage. Polymorphonuclear leucocytes infiltrate deep tissues, causing thrombosis of nutrient vessels and suppuration of veins and arteries passing through the fascia [5]. This is accompanied by gangrene of subcutaneous fat and dermis. Bullae and vesicles can be seen, followed by occasional ulceration of the skin. Muscles, bone ligaments, and tendons are usually spared. The process may be limited and localized, or it may evolve into fulminant and have a devastating course. Bacterial toxins that spill into the blood may lead to systemic toxicity and inflammatory response. If prompt medical and surgical treatments are delayed, necrotizing fasciitis often leads to sepsis, organ failure, and eventually death.

Etiology and Predisposing Factors

Periorbital necrotizing fasciitis may be the result of superficial infection that enters the subcutaneous plane, or it can arise from deep soft tissue infection that spreads along fascial planes without interference of the overlying skin [4].

A history of previous penetrating injury or abrasion is the most common etiology for periorbital necrotizing fasciitis, reported in 20–30% of cases [4, 5]. A specific alert should be noted in cases of eyelid lacerations sealed with tissue adhesives in

children. When appearing as a rapidly occurring periorbital cellulitis (approximately 24 h following the injury), it may evolve into life-threatening necrotizing fasciitis and close observation is mandatory [6] (see case persentation later in this chapter).

Other possible etiologies are blunt trauma, reported in up to 17% of cases [4], history of surgical procedure such as blepharoplasty, dacryocystorhinostomy, surgical biopsy or excision, and self-puncture of hordeolum externum in approximately 10% [4, 5]. Retrobulbar injection was reported as a rare but potential etiology for necrotizing fasciitis involving both the orbital and periorbital structures [7]. Periorbital necrotizing fasciitis may also develop after human or insect bites or tooth extraction [4]. Dental infections are the most common cause for head and neck-necrotizing fasciitis [8] and may spread to the periocular area. Upper respiratory tract infection such as pharyngitis can also comprise the source for pathogen spread.

Systemic immunocompromising conditions such as diabetes, alcoholism, rheumatic diseases, HIV infection, chemotherapy, long-term steroid therapy, and immunosuppression are considered predisposing factors to necrotizing fasciitis but are seen in only about half of cases [4].

Pathogens

In general, necrotizing fasciitis has been categorized based on the causative organism: type I is caused by mix of anaerobes, gram-negative bacilli, and enterococci. Type II is caused by group A streptococci, occasionally with coexisting staphylococcal involvement [4]. Necrotizing fasciitis of trunks and extremities tends to be a polymicrobial infection, with up to 11 organisms being isolated in a single case [3]. In contrast, the most commonly reported microorganism associated with periorbital necrotizing fasciitis is β-hemolytic *Streptococcus*. This has been cultured in up to three quarters of cases and is usually the sole and very lethal pathogen [4, 5, 9, 10]. Most reports indicate it as a risk factor for death in periorbital necrotizing fasciitis cases. The virulence of group A streptococcus is attributed to a wide range of factors, both cell associated and secreted, which interact with human inflammatory cells and mediators to promote the pathogen survival and distribution [11]. Membrane-bound antigens, such as M-protein and fibronectin-binding proteins, inhibit antibody-mediated phagocytosis and enable bacterial adherence to host cells and tissue. Exotoxins such as superantigens and proteases support bacterial spread and invasion and facilitate inflammatory response. There are several strains of superantigens, which are considered fundamental for the pathogenesis of streptococcal toxic shock syndrome and the fatal course of necrotizing fasciitis [11].

Staphylococcus is present in up to one quarter of cases and is usually seen as coinfection with β-hemolytic *Streptococcus*. *Pseudomonas aeruginosa* is the second most common pathogen that causes periorbital necrotizing fasciitis as a single agent [2]. *Moraxella catarrhalis*, *Staphylococcus albus*, *Streptococcus viridans*,

Propionibacterium acnes, *Citrobacter*, enterococci, and *Serratia* are less common causative agents. *Cryptococcus neoformans*, candida, and aspergillus are rare and seen mainly in immunocompromised patients [2, 4].

Differential Diagnosis

Differential diagnosis of periocular necrotizing fasciitis is listed in Table 9.2. Contact dermatitis is the most common inflammatory process involving the eyelids [12]. Thin and exposed skin allows for penetration of both contact and airborne allergens. The eyelid skin is typical site for the use of cosmetics. Proximity to the eyes makes this sensitive skin susceptible to the toxic and allergenic effect of ocular topical medications and contact lens solutions.

Erysipelas is a bacterial skin infection of the dermis and superficial cutaneous lymphatics, more common in the face. It appears as a tender, erythematous, indurated, and tense shiny plaque. The borders of the lesion are typically sharply raised, defining the demarcation between the affected and healthy skin. Most cases are caused by group A streptococci, and the age groups most affected are children and elderly between the ages 60–80. Erysipelas may cause gangrene or abscesses but also systemic complications such as pneumonia, glomerulonephritis, endocarditis, and toxic shock syndrome. Flat erythema, crepitus, rapid progression to frank necrosis, and relative resistance to treatment can aid in differentiating between necrotizing fasciitis and erysipelas.

Orbital cellulitis and preseptal cellulitis tend to a much more indolent course, although both may be hard to differentiate from orbital necrotizing fasciitis in its initial presentation. Orbital cellulitis may exhibit systemic manifestations such as fever and septic shock. Devastating neurological complications in orbital cellulitis may be confused with complicated necrotizing fasciitis, including ophthalmoplegia, optic nerve dysfunction, meningitis, and alterations in consciousness in cases of sinus vein thrombosis.

Nonspecific orbital inflammation is an inflammatory condition which involves the periorbital and orbital region. Frequently bilateral, it may cause swelling,

Table 9.2 Differential diagnosis of necrotizing fasciitis

Contact dermatitis or allergic reaction
Erysipelas
Preseptal cellulitis
Orbital cellulitis
Nonspecific orbital inflammation
Blepharochalasis syndrome
Lupus systemic erythematous
Cavernous sinus thrombosis
Rhino-orbital mucormycosis
Periorbital or orbital hematoma

redness, pain, and an ocular motility disturbance which may mimic orbital necrotizing fasciitis. It is noninfectious and usually responds rapidly to steroid treatment. Recurrent episodes are not uncommon.

Blepharochalasis is a rare syndrome, characterized by recurrent episodes of painless eyelid edema, eventually leading to thinning, wrinkling, and discoloration of the eyelids with redundant skin and eyelid malposition. The upper eyelids are more commonly affected, and most cases are bilateral. The cause is unknown, but a hereditary form of the disease exists. Some reports pointed out a preceding period of physical or emotional stress.

The typical malar rash of systemic lupus erythematous (SLE) symmetrically involves the cheeks and the nasal bridge but spares the nasolabial folds and is occasionally painful. It lasts from days to weeks but usually does not spread beyond the cheeks and remains within the erythematous-pruritic range.

Cavernous sinus thrombosis usually follows sinusitis or midface infection and is characterized by headache, fever, cranial nerve palsies, and periorbital edema. Ocular signs include chemosis, elevated intraocular pressure, ophthalmoplegia, and impaired visual acuity. Diagnosis is confirmed by imaging.

Rhino-orbital mucormycosis is caused by fungal infection and is usually seen in immunocompromised patients. Clinical findings include black eschar of the nasal mucosa or palate, sensory loss, and periocular pain. The periocular skin may also exhibit necrosis. Ocular signs include reduced pupillary response to light, impaired visual acuity, exophthalmos, and complete ophthalmoplegia.

Periorbital or orbital subperiosteal hematomas may resemble periorbital necrotizing fasciitis but usually follow traumatic injury, do not share the dramatic local and systemic deterioration that characterizes necrotizing fasciitis, and in most cases resolve spontaneously with conservative treatment.

Signs and Symptoms

Necrotizing fasciitis may present initially as a mild inflammation but exhibits rapid deterioration which must be recognized and treated promptly. Studies have shown that many cases of necrotizing fasciitis are misdiagnosed as non-necrotizing infections. In a large case series of generalized necrotizing fasciitis, approximately 15% of cases were correctly diagnosed as necrotizing fasciitis on admission. Nearly 60% of patients were misdiagnosed with cellulitis [13].

Clinically, three subtypes of necrotizing fasciitis have been identified. The fulminant variant progresses rapidly and may lead to toxic shock and multi-organ failure. The acute variant develops over days and typically affects large areas of the skin. The subacute type advances slowly over a period of weeks and involves localized areas [9]. The fulminant and acute types of necrotizing fasciitis are usually caused by β-hemolytic streptococci, whereas subacute cases are usually polymicrobial [9]. A rise in incidence of necrotizing fasciitis in the last decades is attributed to the increasing prevalence of group A streptococcal infection.

Orbital necrotizing fasciitis introduces a diagnostic challenge similar to that of necrotizing fasciitis of the trunk and extremities. In its early stages, it is occasionally characterized by mild symptoms that fail to imply the severity of the infection and its prognosis. Initially, periorbital necrotizing fasciitis may resemble a simple periorbital cellulitis or erysipelas, with pale red, tense, swollen skin. Patients may appear healthy overall, often with a mild to moderate fever, accompanied by exceptionally exaggerated tachycardia [9]. Severe and disproportionate pain develops at the site of infection and spreads as the process extends, while the involved skin may turn anesthetic due to nerve dysfunction. Crepitus can sometimes be palpated and may be seen as air in the affected soft tissue on plain radiographs or more advanced imaging. These signs are pathognomonic for necrotizing fasciitis; however, their absence does not exclude the diagnosis [1].

Tenderness is remarkable and usually involves areas beyond gross skin involvement. The disease may involve surrounding dermatomes, including V1-V3 [5], but cervical or mediastinal association is rare. As the disease process proceeds, patients feel systemically ill. Within 48 h the skin acquires a typical rose-violet color, which later can progress to fluid-filled bullae. The appearance of black patches is attributed to thrombosis of perforating vessels and indicates progression of the necrotic process. Evident gangrene is seen within 4–5 days, followed by underlying suppuration and sloughing of the skin within 8–10 days.

Laboratory findings include an extreme rise in leukocyte count, elevated C-reactive protein, and increase in the value of glucose, urea, and creatinine. Hypoalbuminemia, acidosis, and alteration in coagulation function can also be seen [4]. Systemic deterioration may manifest as a further elevation in body temperature, as well as signs of toxic shock, including hypotension, renal or multi-organ failure, reduced level of consciousness, and disseminated vascular coagulation. Toxic shock syndrome was reported in up to 30% of periocular NF cases and substantially increases the risk for mortality [2]. Ocular manifestations such as keratitis, uveitis, and chorioretinitis may be seen. Spread of the infection to the orbital region can cause ophthalmoplegia, proptosis, and impaired optic nerve function such as positive relative afferent pupillary defect (RAPD). Necrosis of the medial upper lid was noted as a typical apparent sign affecting patients with orbital disease [5]. Orbital involvement is a predictor of either worse final visual acuity or, in the more severe cases, of the need of exenteration [5].

Specific Considerations in Periorbital Necrotizing Fasciitis

Periorbital necrotizing fasciitis behaves differently than in other body sites, due to specific anatomic characteristics of the region [2]. The eyelid skin is the thinnest in the body and lacks subcutaneous fat. Infection is noticeable in its early course, and evidence of necrosis and gangrene is more obvious. Therefore, the interval between the onset of symptoms and obvious deterioration is short [4, 12]. This should lead patients to seek medical treatment promptly and urge clinicians to act rapidly.

The rich vascularization of the eyelids contributes to eyelid resistance against the pathologic process which tends to spread along avascular planes. It also allows for better antibiotic access to the inflamed regions.

The orbicularis oculi muscle underneath the skin potentially comprises a vascularized barrier to the spreading infection, and the eyelid margins are often spared secondary to their extensive vascularization. Passage of the infectious process through the orbicularis muscle is possible but rare and leads to severe full-thickness eyelid or orbital tissue involvement. Dermal attachments at the nasojugal and malar folds further halt the spread of the infection. Resistant to nasal horizontal spreading, however, is poor, so bilateral involvement of the periorbital skin is not uncommon [4] (Fig. 9.1a, b).

The specific anatomic characteristics of the eyelids may possibly allow for a more conservative treatment in periocular necrotizing fasciitis. Sepsis incidence is lower than in necrotizing fasciitis affecting other body sites. Appropriate antibiotic treatment may inhibit disease progression, and mortality rates are significantly lower in periorbital necrotizing fasciitis than outside the eyelid region. The marginal

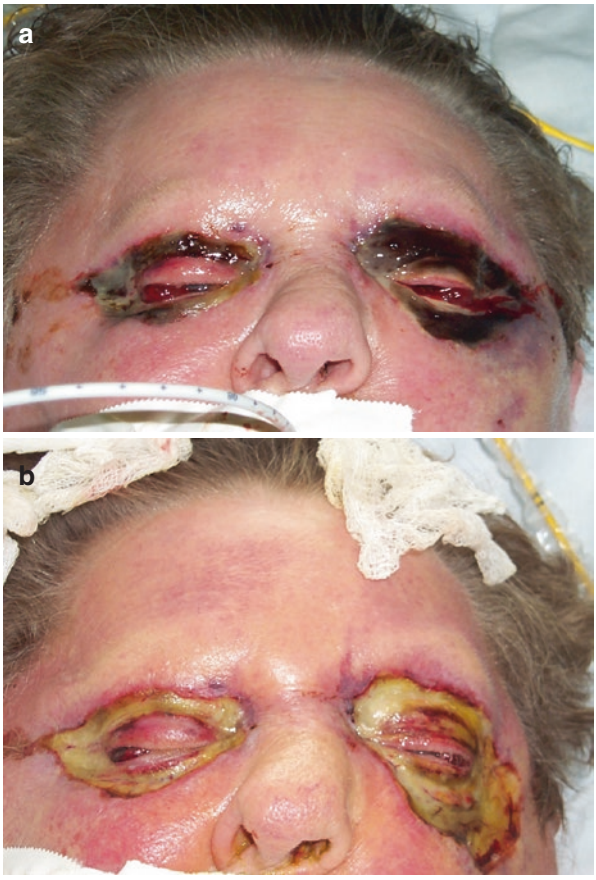

Fig. 9.1 (**a**) Acute necrotizing fasciitis demonstrating gangrene and necrosis of the eyelids. (**b**) The same patient 2 days later after treatment with IV antibiotics, demonstrating autodemarcation. This patient did not undergo debridement

areas adjacent to the necrotic tissue maintain an adequate blood supply, and the border between the affected and healthy tissue may be seen as autodemarcation. This unique phenomenon of autodemarcation in periocular necrotizing fasciitis enables delayed and less extensive debridement in select cases than that indicated in extraocular necrotizing fasciitis [10].

Management

Early diagnosis, aggressive antibiotic treatment, and surgical debridement are the cornerstones to successful outcomes. A multidisciplinary approach, involving oculoplastic surgeons, plastic surgeons, dermatologists, ENT surgeons, and microbiologist, may be necessary.

Evaluation

A thorough history and complete clinical evaluation are mandatory. The patient should be asked about the time of initial symptoms and the rate of deterioration. Emphasis should be made on possible etiologies such as periocular trauma or recent periocular or dental procedures. Predisposing factors, e.g., diabetes, malignancy, HIV, immunotherapy, or long-term steroid treatment, should be evaluated.

Clinical assessment should include observation, palpation of the affected area, and complete ophthalmic examination. The diagnosis of necrotizing fasciitis is mostly clinical and immediate therapeutic measures should be initiated in suspected cases. Disproportionate pain is an alerting symptom, as well as rapid deterioration in the appearance of the affected skin and poor response to antibiotic treatment. Of course, a significant change in or deterioration in systemic status should also raise suspicion for necrotizing fasciitis.

Proptosis and ophthalmoplegia may indicate devastating orbital involvement. Other signs include compromised visual acuity, positive relative afferent pupillary defect, and reduced sensitivity to light or colors. Orbital involvement increases the rate of poor visual outcome. Conversely, vision loss may be a marker for disease severity, because lack of visual impairment has been associated with survival [14]. Anterior and posterior ocular segments should be examined, although in most cases they appear normal. Marking the borders of the affected periocular skin aids in future evaluation of disease progression.

Blood testing is important early in patient evaluation and should include complete blood count, blood electrolytes and urea, liver and kidney functions, C-reactive protein, and erythrocyte sedimentation rate. Blood pressure and body temperature, together with urine analysis, aid in estimating systemic involvement. In cases of suspected toxic shock, blood gases should also be examined. In these cases, urgent

referral to intensive care unit should be made. Both blood and wound swab for culture should be taken immediately when suspicion of necrotizing fasciitis is made and prior to antibiotics treatment.

The laboratory risk indicator for diagnosis of necrotizing fasciitis (LRINEC, see Table 9.3) was published in 2004 as a tool to distinguish necrotizing fasciitis from other soft tissue infections in its early course [15]. The score includes the values of C-reactive protein, white blood cell count, hemoglobin, and the blood concentration of sodium, creatinine, and glucose. LRINEC score ≥6 points was proven to be 74–93% sensitive and 81–92% specific for the diagnosis of necrotizing fasciitis [16]. Maximum score is 13; a score equal to or greater than 6 raises the suspicion of necrotizing fasciitis and a score of ≥8 is a strong predictor of this disease [15]. The LRINEC score is also associated with the outcomes of patients with necrotizing fasciitis. Patients with a LRINEC score of ≥6 have a higher rate of both mortality and morbidity [17].

The relevance of LRINEC as an indicator for the early detection of periocular necrotizing fasciitis has been questioned [9]. In a series of 11 cases of periorbital necrotizing fasciitis, LRINEC score ranged from 0 to 8 and did not correlate with severity of the disease. In fact, only 4 cases had a score of 6 or more. However,

Table 9.3 The Laboratory Risk Indicator for Necrotizing Fasciitis Score (LRINEC)

Variables, units	Score
C-reactive protein, g/L	
<150	0
>150	4
Total white cell count, per mm^3	
<15	0
15–25	1
>25	2
Hemoglobin, g/dL	
>13.5	0
11–13.5	1
<11	2
Sodium, mmol/L	
≥135	0
<135	2
Creatinine, μmol/L	
≤141	0
>141	2
Glucose, mmol/L	
≤10	0
>10	1
The maximum score is 13	

Wong CH, Khin LW, Heng KS, Tan KC, Low CO. *The LRINEC (Laboratory Risk Indicator for Necrotizing Fasciitis) score: a tool for distinguishing necrotizing fasciitis from other soft tissue infections.* Crit Care Med. 2004 Jul;32 (7):1535–41

leukocytosis as a single factor is more than 90% sensitive and specific for necrotizing fasciitis and can also aid in differentiating it from other soft tissue infections [2].

CT and MRI scans are often used in making the diagnosis. Both modalities can detect soft tissue inflammation prior to the appearance of external cutaneous signs. If no fascial or deep tissue involvement is demonstrated, the suspicion of necrotizing fasciitis should be questioned. CT is considered the preferable imaging method since it can aid in recognition of both the initial site of the infection and its extent. CT can easily identify presence of bulla and gas, and its findings can guide surgical debridement [4, 18]. Some authors highlight the superiority of MRI in detecting soft tissue fluid and edema and its multiplanar imaging capabilities, but this modality is often not available [16]. The use of nuclear diagnostic tests such as leucocyte scintigraphy and nuclear medicine tomographic imaging techniques as positron emission tomography (PET)–CT scan and single-photon emission computer tomography (SPECT)–CT scan may be useful, particularly in detecting orbital and retrobulbar abscesses.

The diagnosis of necrotizing fasciitis is confirmed by a tissue sent for culture and pathological examination. It cannot be emphasized enough that the diagnosis is primarily clinical and should call for prompt treatment. Absence of imaging or pathological evidence does not rationalize delay in treatment.

Medical Treatment

Intravenous antibiotics are indicated in all cases suspected as necrotizing fasciitis. The most common pathogen is β-hemolytic *Streptococcus*, but therapy should also target other possible causative agents. Of note, up to 40% of periocular necrotizing fasciitis are polymicrobial [4]. Therefore, empiric antibiotic treatment should include β-lactam antibiotics, such as penicillin or cephalosporin, and clindamycin or metronidazole.

In the BOSU study [5], the most common approach was penicillin and clindamycin at presentation. Treatment was then altered to higher-generation penicillins and atypical antibiotics as required.

Optional regimen is high-dose intravenous benzylpenicillin, flucloxacillin, and metronidazole. Others [19] suggested the combination of a third-generation cephalosporin such as cefotaxime and metronidazole. High-dose clindamycin can be given as a substitute for metronidazole. Imipenem/cilastatin alone also comprises suitable empiric therapy [3].

If a causative agent is isolated and identified, the antibiotic treatment should be adjusted according to type and sensitivity, in consultation with an infectious diseases specialist.

In cases of suspected herpetic coinfection, acyclovir or valacyclovir, either oral or intravenous, may be added [9]. Tetanus toxoid or human tetanus immunoglobulin should be given in cases of traumatic wounds or contaminated sites.

Some researchers have recommended the use of hyperbaric oxygen or intravenous immunoglobulins [9, 20] as an adjunct to the standard antibiotic and surgical treatment. The potential benefits of the hyperbaric oxygen treatment are elimination of anaerobic bacteria and inhibition of exotoxin production, improvement in leucocyte function through oxygen-dependent oxidases, and facilitating healing of affected tissue. These can eventually lead to better overall prognosis and outcome by reducing the amount of the debrided tissue and increasing the amount of viable skin [4]. Whereas hyperbaric oxygen is advocated as a beneficial adjunctive therapy in cases of necrotizing fasciitis, its use in periocular cases has been described in a few case reports only [20]. Thus, more studies are required to establish the efficacy of this treatment. However, considering the lethality of the disease and the potential benefit of this treatment, it seems reasonable to use it in selected cases, as long as this does not interfere with other essential treatment modalities.

The benefit of adjunctive intravenous immunoglobulins (IVIg) is still in question. IVIg is produced from a pooled human plasma of approximately 15,000 healthy people and is usually administered in multiple doses. Side effects are seen in 2–6% of patients and include flushing, anaphylaxis, aseptic meningitis, renal failure, and transmission of pathogens from donors [21]. IVIg contains broad-spectrum antibodies to M-proteins and to group A streptococcus superantigens. It also functions as an immunomodulator through pathways not yet completely understood [11]. Studies confirming its clinical efficacy in severe streptococcal infections are few and limited in numbers but indicate increased survival rate and improvement in factors such as bacterial load, superantigens, and cytokines activity [22]. IVIg treatment in periocular necrotizing fasciitis has been reported anecdotally [21] but has not been yet been proven to be beneficial over conservative treatment alone.

When signs of systemic involvement are suspected, the patient may require urgent referral to an intensive care unit.

Surgical Treatment

Urgent debridement of the necrotic skin and subcutaneous tissue is considered the hallmark of management in necrotizing fasciitis. Widespread excision of the affected tissue halts the spreading of the pathological damage to adjacent structures, reduces bacterial load, and decreases the production of enzymes required for tissue destruction and of toxins that enter the blood stream. Immediate debridement is considered an essential component of the medical treatment that fails to effectively reach the avascular planes and tissue distal to the thrombotic blood vessels. Specimens from the resected tissue are sent to histopathological examination. It should be noted that the overlying demarcation usually fails to reflect the subcutaneous necrosis. Therefore, debridement must continue until viable and vascularized tissue is identified. Conservative exploration can be performed, guided by CT findings, in order to minimize the area excised. The depth should be limited to the fascial layer, with sparing of the underlying muscles if possible. Re-exploration

is usually performed 24–36 h following the initial surgery in order to confirm that all necrotic tissue is removed. Additional debridement is executed as required; however, aggressive excision may complicate further reconstruction. Debridement may produce substantial bleeding, depending on the amount and location of resected tissue. In cases of necrotizing fasciitis in the trunk or the limbs, the surgeon should consider obtaining whole blood and clotting products, especially in cases of disseminated intravascular coagulation [1]. In periocular cases this is usually unnecessary. The exposed skin should be allowed to recover under the treatment of sterile normal saline wet-to-dry dressings. When the infection is eliminated and the wound is stable, reconstruction of the deformed eyelid and periocular region can be performed (Fig. 9.2a–d).

A recent case series advocated the use of negative-pressure wound therapy (NPWT) as an adjuvant to surgical debridement. In this method, the wound is filled with foam or gauze and then covered with an adherent airtight drape. This is connected to a canister attached to a pump to maintain a subatmospheric pressure on the wound bed [23]. NPWT has been shown to promote healing by decreasing edema, stimulation of angiogenesis, cell proliferation, and granulation and by reducing the

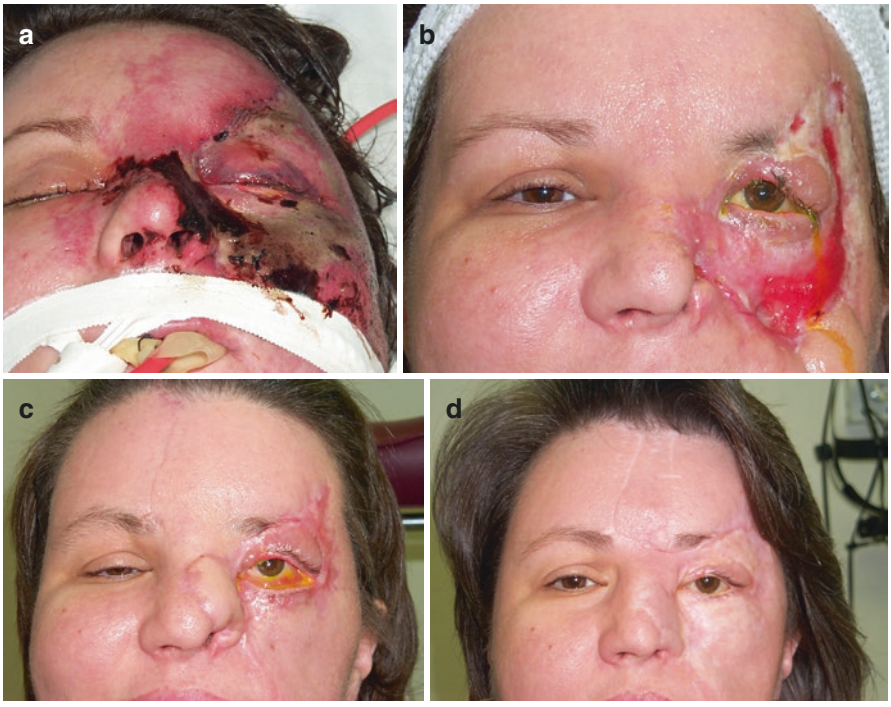

Fig. 9.2 (**a**) Acute NF demonstrating gangrene and necrosis of the lids, cheek, and nasal ala. Despite debridement, this patient also lost vision in the left eye. (**b**) The same patient during the healing phase. (**c**) The same patient after early reconstruction with residual ectropion. (**d**) The same patient after late reconstruction

bacterial load. NPWT is beneficial in avoiding the need for further debridement and may act as a bridging technique that can decrease wound healing time and may even obviate or minimize the need for reconstruction [23].

The majority of periocular necrotizing fasciitis cases reviewed in the literature involved surgical management. In retrospective studies, debridement was found to be carried out in approximately 85% of periocular necrotizing fasciitis cases. This methodology was derived from the common approach to non-periorbital necrotizing fasciitis, which relied on prompt and aggressive surgical removal of the affected tissue and its surrounding. However, some authors believe that owing to the rich vascular supply and the thin eyelid skin, periorbital cases may be treated with intravenous antibiotics and strict observation, whereas the surgical intervention can be delayed or not performed at all [10] (Fig. 9.1a, b). Periorbital necrotizing fasciitis tends to be limited in distribution at presentation. A conservative approach with appropriate antibiotic treatment can lead to arrest of progression, followed by autodemarcation of the necrotic tissue (Fig. 9.1a, b). Allowing delayed conservative debridement reduces the extent of residual structural and functional damage and decreases further morbidity and the need for additional surgical reconstruction.

In a case series of periorbital necrotizing fasciitis published in 2002 by Luksich et al., inclusion criteria were suggested for a conservative approach. The authors recommended that in necrotizing fasciitis which is localized to the eyelids without evidence of orbital or systemic involvement, antibiotic treatment combined with close observation until spontaneous arrest and autodemarcation should be considered. Once autodemarcation occurs, usually within a few days, careful debridement of the necrotic tissue can be performed either bedside or in the operating room, usually without anesthesia. The authors pointed out the preservation of the eyelid margin and the adjacent skin and subcutaneous tissue in the cases that reviewed. The infection was not seen spreading beyond the demarcation line, and the extent of the resected tissue was significantly less than that debrided if the surgery had been done early in the course of the disease, as commonly recommended [10].

Mutamba et al. [24] described three cases of "stalled" periocular necrotizing fasciitis treated medically alone. They suggested that in such cases, genetic factors related to fewer pro-inflammatory polymorphism may be responsible for decreased pathogen-host reaction and therefore a reduced systemic inflammatory response. This effect on clinical course and outcome has been found for other streptococcal infections, e.g., streptococcal septic shock and meningitis.

Prognosis

The prognosis of periocular necrotizing fasciitis is directly related to initial management, whereas early recognition and aggressive multidisciplinary treatment comprise critical milestones. Delay in diagnosis and deferred medical and surgical treatment are considered the main factors affecting morbidity and mortality.

Mortality rate of necrotizing fasciitis involving the trunk, pelvis, and extremities may be as high as 70% if left untreated [9] but is significantly lower with appropriate treatment. Type I necrotizing fasciitis was reported to cause mortality in 20% of cases, whereas in type II mortality rates may exceed 30% [4]. Necrotizing fasciitis of the head and neck regions is substantially less common [10]. Mortality was found to be higher in necrotizing fasciitis involving the lower part of the face than that involving the upper part, presumably due to spreading to structures such as the carotid sheath, chest, and mediastinum. Other mortality risk factors are age above 50 and associated chronic illnesses [4].

Some hypothesize that due to the unique anatomic and physiological features of the eyelids, necrotizing fasciitis involving the eyelid region is less likely to follow the characteristic devastating course of the disease when it occurs in other body sites, including sepsis and death.

Indeed, mortality caused by periocular necrotizing fasciitis is less frequent than elsewhere in the body. The mortality rates do not exceed 10–15% in most reports and seem to be declining in more recent reviews. Unlike in other body sites, the main risk factor for mortality in necrotizing fasciitis affecting the periorbital region is the causative agent, as most deaths were attributed to group A β-hemolytic *Streptococcus* [4]. Loss of vision was reported in 14% of cases and may be the result of orbital involvement or, in some cases, of central retinal artery occlusion [10]. In the rare cases of orbital involvement, exenteration and loss of the eye may be necessary.

While mortality from periocular necrotizing fasciitis is rare, significant morbidity and vision loss may occur. Dry eye symptoms are common, and impaired visual acuity may be seen in approximately one-third of survivors [5]. In up to 80% of survivors, further surgical measures are required for correction of complications, such as ptosis, eyelid malposition, ectropion, lagophthalmos, and corneal exposure [9]. Reconstruction is usually delayed weeks or even months following the extinction of the infection. This allows for relaxation of fibrosis and contractions and reduces the possibility of undercorrection or overcorrection. The main goals of surgery are to retain upper and lower eyelids with adequate function to protect the eyeball, avoid malposition or lagophthalmos, and achieve a good cosmetic outcome. Reconstructive methods depend on the extent of the damage, availability of adjacent tissue, and other factors including age and general systemic condition. Most commonly, split of full-thickness skin grafts are used, occasionally with cartilage or artificial implants to tarsal replacement. In cases of extensive damage, fasciocutaneous free flaps can be used in attempt to restore the facial contour [4].

Treating conservatively, in cases where it is determined to be safe as described above, may carry significant advantages regarding the need for further surgeries and reconstruction measures. Delayed debridement allows for more tissue to remain intact, therefore increasing the chance for secondary healing. In particular, the eyelid margin region and the orbicularis oculi muscle tend to survive the necrotic process and act as promoters for spontaneous resolution. In most cases described, this resulted in good lid function without need for surgery after healing was completed.

Case Presentation

A healthy 3-year-old girl was brought to the ophthalmology emergency unit following an eyelid injury from a corner of a coffee table at her home. Examination revealed swollen left upper eyelid and a two centimeters horizontal simple cut right below the left eyebrow. Ophthalmic examination in both eyes was unremarkable. The cut was cleaned with sterile saline solution, disinfected with iodine 5%, and then sealed with Histoacryl® (TissueSeal, Michigan, USA) and Steri-Strip. The girl was discharged but was brought back to the emergency room twelve hours later with massive swelling of the upper eyelid (Fig. 9.3), fever (40°C), and tachycardia (190/min). The clinical sign led to the suspicion of orbital cellulitis; however, there was no evidence for orbital involvement in both clinical examination and CT scan. Blood tests revealed leukocytosis (19,000) with neutrophilia; blood chemistry was normal. The girl was admitted to the pediatric department with diagnosis of preseptal cellulitis, and treatment with intravenous ceftriaxone and clindamycin was initiated.

The following day the eyelid and systemic parameters remained the same, but eyelid fluctuance was noted (Fig. 9.4a). The girl underwent incision and drainage of the eyelid under sedation. A large amount of pus was drained and a sample sent for bacterial smear and cultures. Because of persistent tachycardia and swelling of the right eyelids, left cheek, and neck, a repeat imaging study was ordered. The second CT demonstrated extensive swelling of the left face and neck with fluid around the sternocleidomastoid muscle (Fig. 9.4b). Repeat blood tests revealed worsening of the leukocyte count (24000), extremely elevated C-reactive protein (92), low hemoglobin levels, and metabolic acidosis. Bacterial smear of the samples taken before discovered gram-positive cocci in chains, consistent with streptococcus. There was

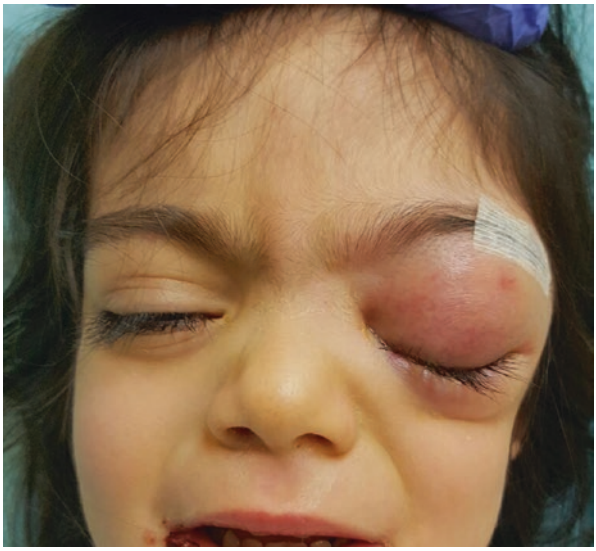

Fig. 9.3 Day 1 following the injury. Notice massive swelling 12 h after the injury

further rapid clinical deterioration and signs of severe sepsis including tachycardia and the need for blood pressure support. Intravenous immunoglobulin (IVIg) treatment was initiated and the patient taken to the operating room for emergent surgery, six hours after the eyelid drainage. At that stage the left eyelids had acquired the typical rose-purple color, and crepitus was palpated in the eyelids of both eyes (Fig. 9.4c).

An extensive debridement of ischemic, necrotic, and edematous tissue was performed on the left upper eyelid (Fig. 9.4d). Exploration of the right eyelids, cheek, and neck was negative for ischemic tissue. The surgical wound was left open with wet-to-dry normal saline dressing, and the girl was transferred to the intensive care unit. Systemic parameters improved rapidly as the same IV treatment continued.

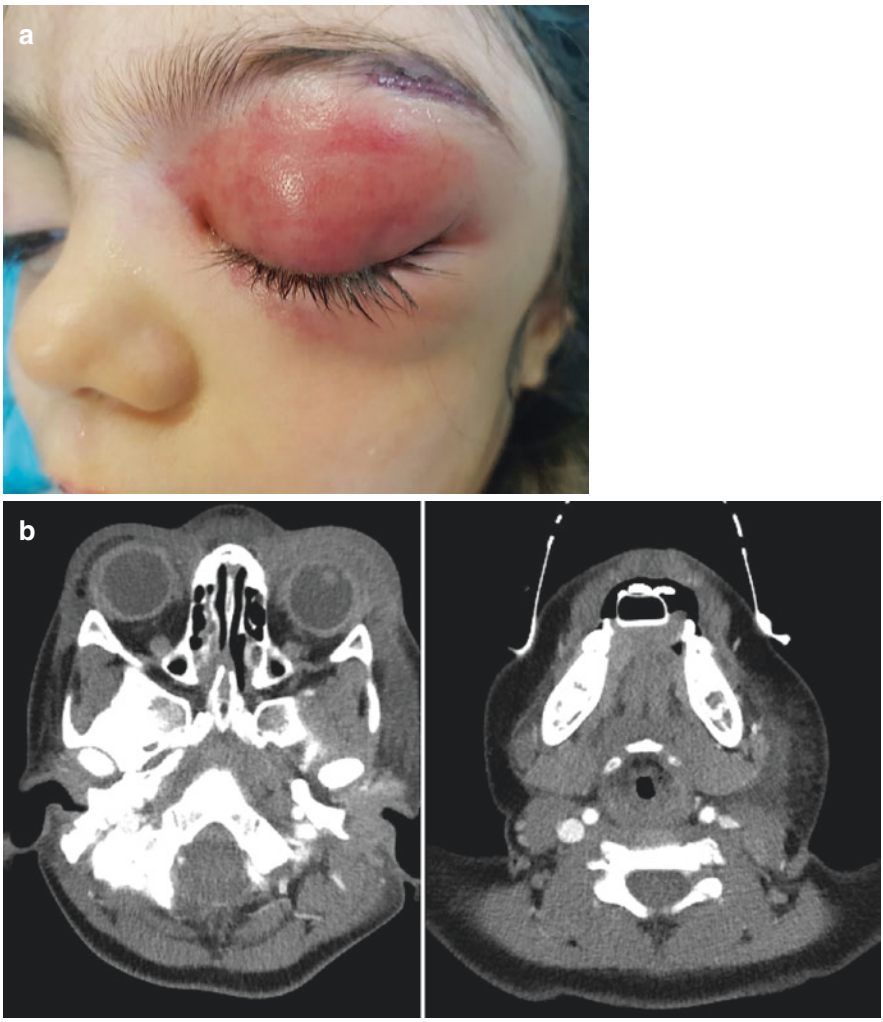

Fig. 9.4 Day 2. (**a**) Palpation called for abscess drainage. (**b**) CT scan demonstrating extensive soft tissue swelling of the left face and neck. (**c**) In the operating room. Notice the rose-purple color of the left eyelids and the involvement of the right eyelids. (**d**) Debridement of ischemic tissue

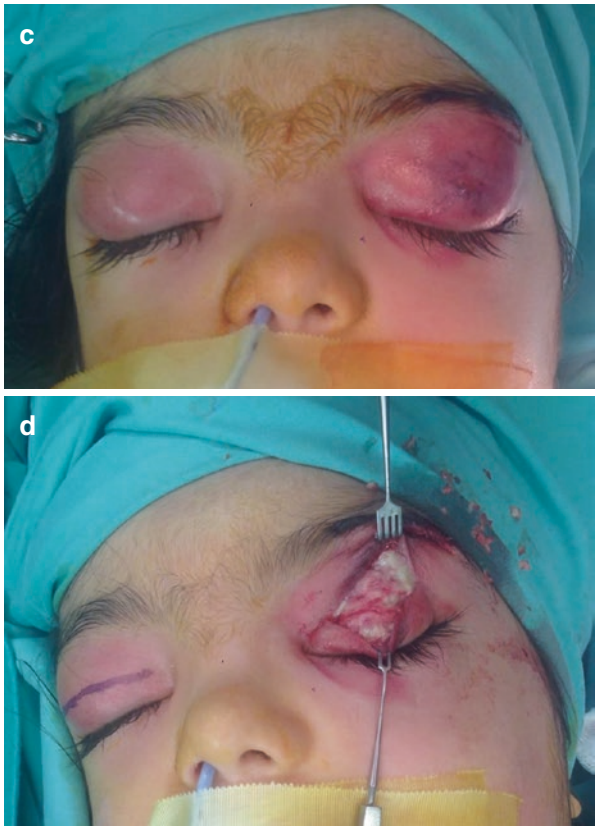

Fig. 9.4 (continued)

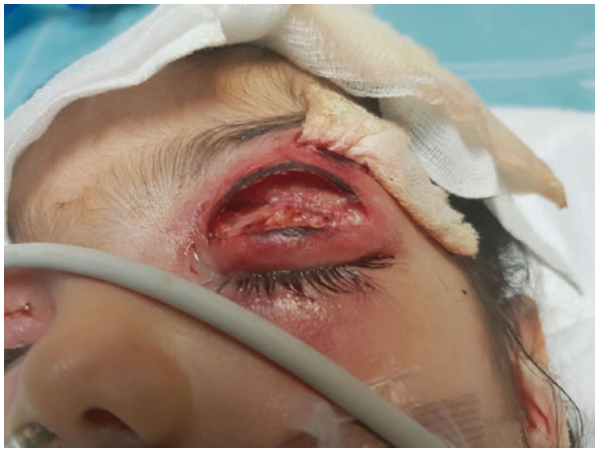

Fig. 9.5 Day 3. Notice necrotic wound edges

Necrotic edges of the wound were seen the following day (Fig. 9.5), and bedside debridement was performed. Three days postoperatively the girl was extubated, as she demonstrated remarkable wound healing (Fig. 9.6). She was discharged after two weeks of IV antibiotic therapy (Fig. 9.7). Follow-up examination revealed that

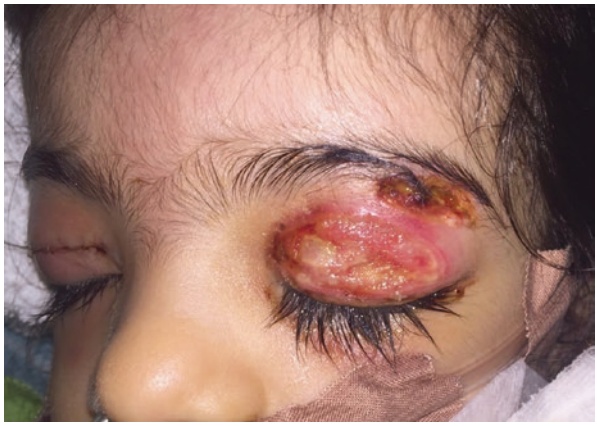

Fig. 9.6 Day 5. Reduced wound swelling and granulation tissue formation

Fig. 9.7 Day 14. Consistent secondary healing and wound closure

the eyelid defect had healed completely by primary intention with only minor scarring and negligible lagophthalmos (Figs. 9.8 and 9.9).

In this case, a few alarming signs were exhibited: rapid local deterioration and a clinical picture of preseptal cellulitis within less than 24 h following the initial injury; systemic involvement, fever, and persistent tachycardia which later evolved into a fulminant septic shock; and horizontal spreading of the inflammation to near

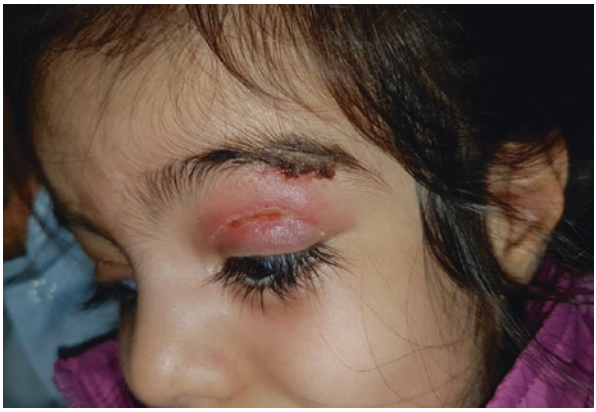

Fig. 9.8 Day 18. Only minor residual wounds are seen

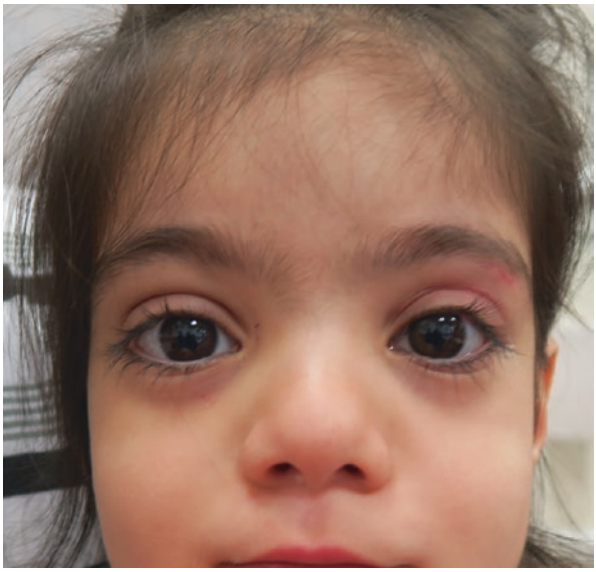

Fig. 9.9 Day 30. Excellent eyelid contour and only mild scarring

structures. Management was based on early diagnosis, broad-spectrum intravenous antibiotic treatment, and surgical debridement – all of which eventually lead to a favorable outcome.

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Chapter 10
Infections of the Lacrimal Drainage System

John D. Ng and C. Blake Perry

Introduction

Infections of the lacrimal drainage system may occur anywhere along its course from punctum to nasolacrimal duct.

Anatomy

The lacrimal drainage system starts at the puncta. Located at the medial margin of both the upper and lower eyelids with slight inversion, the puncta are the first entry point of tears through the lacrimal excretory apparatus. The normal puncta is approximately 0.3 mm in diameter at its opening but widens to 2–3 mm to form the ampulla. The lower puncta sits slightly more lateral than its upper counterpart. Each punctum connects to its respective canaliculus which runs 2 mm vertically then turns approximately 90° medially and travels 8–10 mm between the orbicularis muscle fibers before connecting with the lacrimal sac. In most patients, the canaliculi join together to form a single common canaliculus just prior to entering the lacrimal sac. Before entering the sac, the opening has a mucosal fold known as the valve of Rosenmuller. This valve in conjunction with the natural posterior to anterior bend of the common canaliculus is thought to prevent tear reflux. Patients who develop acute dacryocystitis have a more competent valve of Rosenmuller when compared to patients with chronic dacryocystitis and reflux from the sac onto the ocular surface with pressure over the medial canthal tendon.

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Anatomically, the lacrimal sac and nasolacrimal duct are a continuous structure that extends 3–5 mm above the medial canthal tendon superiorly and empties into the inferior meatus. The combined length of the lacrimal sac and nasolacrimal duct is approximately 30 mm. The lacrimal sac is situated in the lacrimal sac fossa which is bordered by the anterior and posterior lacrimal crests, composed of the maxillary and lacrimal bone, respectively. The nasolacrimal duct travels interosseously through the nasolacrimal canal to enter and drain into the inferior meatus. This opening which lies under the inferior turbinate may be covered by a mucosal fold known as the valve of Hasner. It is this distal portion of the system that is often implicated in congenital nasolacrimal duct obstruction. In total, the lacrimal system spans approximately 35–40 mm from the punctum to the inferior meatus in adults. This is helpful to remember when probing or intubating the lacrimal system to avoid advancing the probe too deep, making it difficult to retrieve [1].

Canaliculitis

Canaliculitis is a relatively uncommon infection of the proximal portion of the lacrimal drainage system. Because it is not commonly seen in clinic, it often is misdiagnosed and undertreated. Canaliculitis can be categorized as primary or secondary, with the secondary group including infections related to dacryocystitis, foreign bodies, or punctal and intracanalicular plugs (Herrick and Smart plugs). Classically, actinomyces was thought to be the most common bacterial cause of primary canaliculitis. However, recent studies have shown staphylococcus and streptococcus to be emerging pathogens along with polymicrobial infections. Concretions have been reported with numerous types of bacteria [2–4].

Clinical Presentation

This disease can present with a variety of signs and symptoms including epiphora, ocular irritation, punctal regurgitation or discharge, punctal or canalicular edema and erythema, and unilateral conjunctivitis (see Table 10.1). A pyogenic granuloma

Table 10.1 Canaliculitis presenting signs and symptoms

Unilateral conjunctivitis
Epiphora
Punctal discharge/regurgitation
Pouting punctum
Punctal/canalicular swelling
Eyelid erythema/edema
Irritation
Mattering
Pain/discomfort

extending out of the punctum can also be seen with retained plugs and canalicular stones. Classically, a "pouting punctum" is described with punctal regurgitation, but this is not necessary for diagnosis. One study showed a pouting punctum to be present in only 50% of patients diagnosed with canaliculitis [3]. Canaliculitis has been found to be more common in women than men for reasons that remain unclear. One theory involves hormonal changes in postmenopausal women [4]. Because of its broad symptoms, it is often mistaken for conjunctivitis, dacryocystitis, chalazion, or blepharitis [2–4].

Evaluation

Evaluation should begin with a thorough history with emphasis on previous punctal plug placement and trauma. The examiner should inspect the medial eyelid margin paying close attention to the punctum and conjunctiva. The canalicular margin is usually swollen, erythematous, and tender to palpation. Gentle pressure should be placed along the medial eyelid margin looking for any punctal discharge. If any discharge or material is present, a culture should be taken. The lids should be everted to examine the palpebral conjunctiva and posterior surface of the tarsus. It remains controversial as to whether irrigation and probing should be performed. Some authors believe canalicular irrigation will only lodge current debris and concretions further distal into the lacrimal drainage system.

Treatment

There are numerous treatment approaches for canaliculitis. These treatments can be broken down into medical versus surgical interventions. Conservative medical treatment with topical or systemic antibiotics can often achieve temporary success but has a high recurrence rate. Lack of eradication is thought to be due to a poor penetration of antibiotics secondary to the concretions that the bacteria form. Retained foreign bodies and stones are also a nidus for recurrence. Success from medical therapy is most likely to occur if treated early on in the course of infection and there is no foreign body or stone present. Other nonsurgical methods include canalicular irritation with antibiotics and/or steroids. However, this may take numerous sessions and in theory can push infected particles more distal into the lacrimal sac. In a recent study, irrigation with antibiotic and steroid solution was nearly 73% effective. This was more successful than conservative medical treatment but less successful than surgical intervention in the study [2]. Punctal dilation with curretage or "milking" of the canalicular system has been advocated by some authors but has reported high recurrence rate.

The most definitive treatment for canaliculitis is complete surgical removal of the canalicular contents. This is particularly important if there is any history of previous punctal plug placement. Punctoplasty with curretage or "milking" from distal to proximal to express canalicular contents has reported success. Epiphora is a possible side effect due to the distortion of the punctal anatomy.

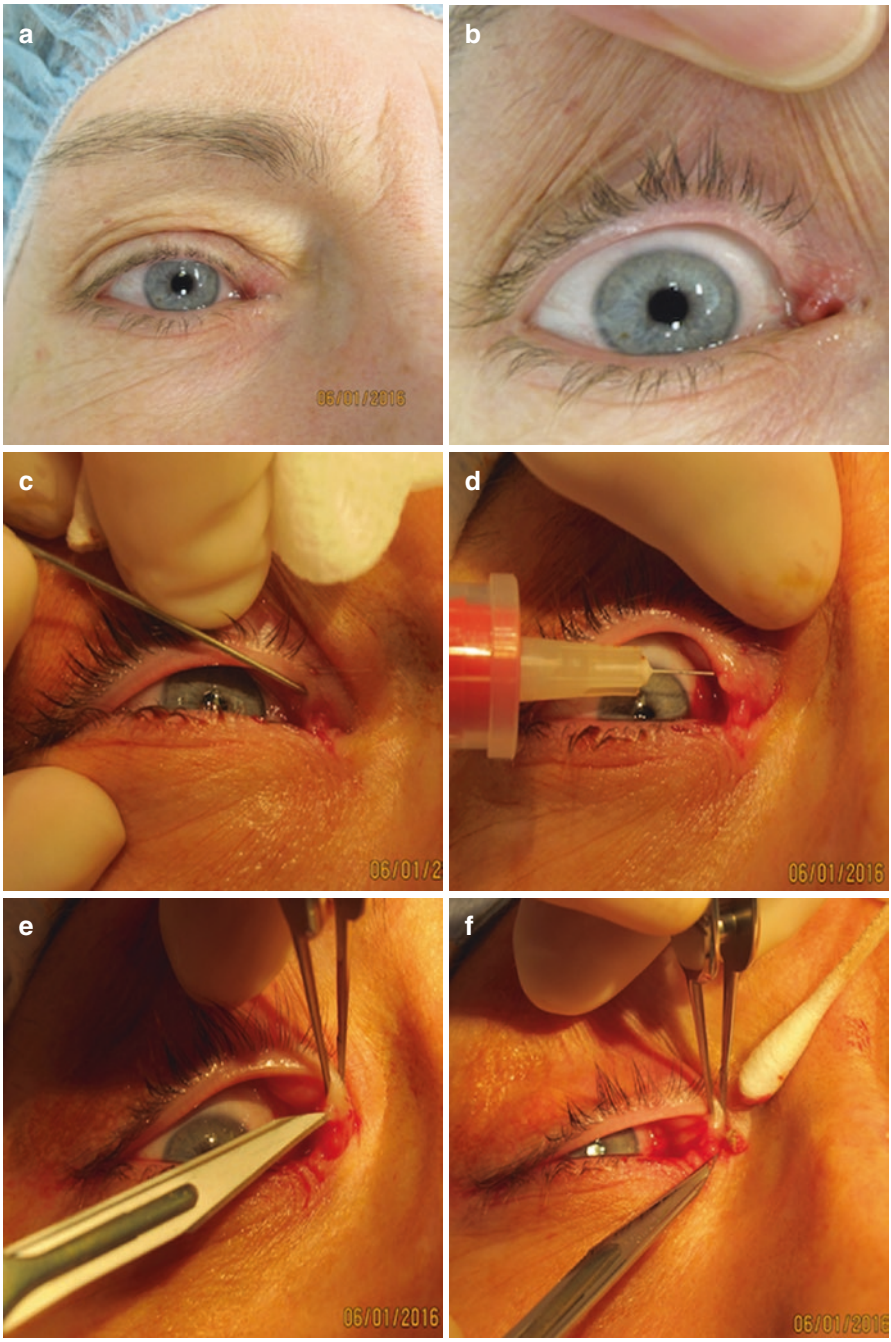
Canaliculotomy with curretage is another option that provides excellent exposure while preserving punctal integrity [5]. This allows direct visualization to look for any foreign body or punctal plug and provides easy access to large stones or concretions that otherwise may be difficult to remove. There have been reports of scarring and stricture of the canalicular system following this procedure, but it is rare. Intubation of the lacrimal system can be performed at the time of canaliculotomy in hopes of preventing these complications but is usually not necessary. Postsurgical tearing is not usually a problem in patients who had plugs placed for dry eye symptoms. Canaliculotomy with curettage is the author's procedure of choice and is described below.

Canaliculotomy

The affected punctum is dilated with a punctal dilator. Local anesthetic is then injected to the area of concern. A #11 blade is used to make a punctal sparing incision medial to the punctum over the area of the canaliculus. Expression of any stone or foreign body is performed with cotton tip applicators and sent to the pathologist for further examination. Mucopurulent material should be cultured. The canaliculus is further examined more distally for any retained foreign body, especially a retained punctal plug. A Westcott scissors can be used to extend the incision distally if greater exposure is needed. A chalazion curette is used to explore the canalicular system. At the end of the case, the canalicular system can be irrigated with antibiotics if the surgeon so desires. The canaliculus is left to heal by secondary intention (Fig. 10.1).

Overall surgical treatment has an excellent prognosis with low rates of recurrence. However, this comes with the theoretical increased risk of damage to the canalicular system. If the canalicular system is damaged and nonfunctioning, patients may require a conjunctivodacryocystorhinostomy (CDCR) with insertion of a Jones tube to correct any postsurgical epiphora (Table 10.2).

Fig. 10.1 Canaliculotomy. (**a**) Right upper eyelid canaliculitis. (**b**) Erythema and edema over right upper canalicular system. (**c**) Punctal dilation. (**d**) Injection of local anesthetic. (**e**) #11 blade used to make a punctal sparing incision over the area of the canaliculus. (**f**) Incision carried distally to expose canalicular stone. (**g**) Expression of canalicular stone. (**h**) Canaliculus further explored more distally using chalazion curette. (**i**) Additional stones removed with curette. (**j**) Lid inspection at end of case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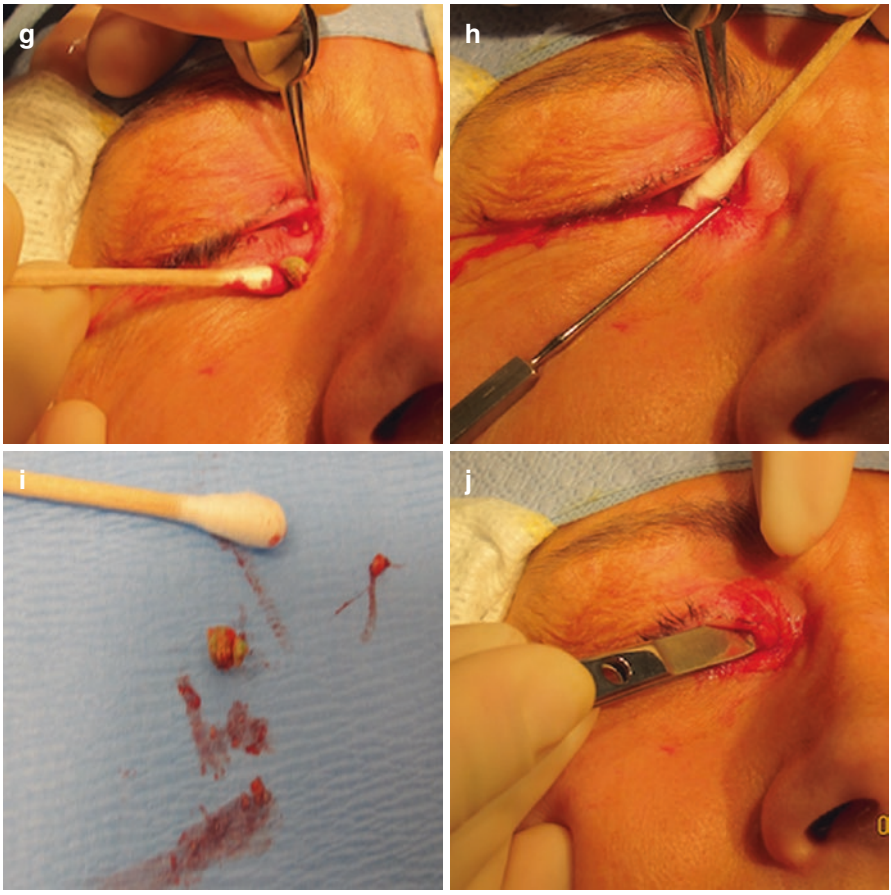


Fig. 10.1 (continued)

Table 10.2 Canaliculitis treatment options

Medical
– Topical antibiotics
– Systemic antibiotics
– Intracanalicular antibiotics
– Intracanalicular antibiotics and steroids
– Punctal dilation with canalicular curettage
Surgical
– Punctoplasty with curettage
– Canaliculotomy with curettage

Lacrimal Sac Infections: Dacryocystitis

Dacryocystitis is defined as an infection of the lacrimal sac. In adults, the most common cause of dacryocystitis is secondary to nasolacrimal duct obstruction. Nasolacrimal duct obstructions can be idiopathic in nature or caused by dacryoliths, sinus disease, trauma (including naso-orbital fractures), iatrogenic (sinus and nasal surgery), radioactive iodine, inflammatory disease, or neoplasm [1, 6, 7]. In pediatric cases, dacryocystitis is most commonly secondary to congenital nasolacrimal duct obstruction with a non-patent valve of Hasner. However, it can also be caused by dacryocystocele, tumors, congenital lacrimal system anomalies, sinusitis, foreign bodies, and post-traumatic nasolacrimal duct obstruction [8]. Despite the cause, the common factor for dacryocystitis is usually complete nasolacrimal duct obstruction that causes stasis and tear retention that lead to an infection of the lacrimal sac.

Clinical Presentation

Dacryocystitis can be grouped into acute and chronic disease. Patients with acute disease generally present with rapid onset of painful swelling over the lacrimal sac and medial canthal area. Classically, the erythema and edema of the lacrimal sac is below the medial canthal tendon. There is often mucopurulent material expressed with digital pressure on the lacrimal sac. In severe cases there can be an associated localized abscess of the lacrimal sac or cellulitis of the periorbital and facial soft tissues. Although uncommon, orbital cellulitis is another potential complication that would require immediate intervention. In contrast, patients with chronic dacryocystitis present with less profound symptoms thought to be due to an incompetent valve of Rosenmuller. Although tearing and swelling of the lacrimal sac occur, there is typically much less pain and a more indolent course. Mucopurulent discharge is expressed with palpation of the sac or with irrigation of the lacrimal system. These patients often have an elevated tear lake on exam [7] (see Table 10.3).

Table 10.3 Dacryocystitis presenting signs and symptoms

Pain and redness in medial canthal area
Swelling over the lacrimal sac
Epiphora
Lacrimal sac discharge with palpation

Organisms

Numerous organisms can be pathogenic in dacryocystitis. Gram-positive organisms (staphylococcus and streptococcus) are the most common in acute dacryocystitis followed by gram-negative and anaerobic organisms [8]. Fungi have also been reported but are much less common. Gram-negative bacteria tend to be more common in patients with chronic dacryocystitis or in immunocompromised patients [7, 8].

Evaluation

A thorough history should be taken followed by a slit lamp examination. Digital palpation should be placed over the lacrimal sac to look for any mucopurulent discharge. If the lacrimal sac and surrounding tissue is not severely swollen, probing and irrigation can be performed. However, this should be avoided in adult patients with clinical evidence of acute dacryocystitis. Any discharge produced with palpation or irrigation should be cultured for organisms and sensitivities. If there is a localized abscess, the lacrimal sac should be incised and drained while taking appropriate cultures. Special attention should be given to any history or evidence of bloody discharge on exam that could suggest possible malignancy (lymphoma/squamous cell carcinoma). Imaging should be considered in post-traumatic, suspected sinusitis, or patients with orbital signs. Pediatric patients should have a nasal exam to exclude an intranasal cyst from possible congenital dacryocystocele with concurrent dacryocystitis.

Associated issues including periorbital and orbital cellulitis must be excluded on examination.

Treatment

Pediatric Acute Dacryocystitis

Acute dacryocystitis in pediatric patients requires close monitoring and immediate intervention. Generally, intravenous antibiotics are started followed by surgical intervention with lacrimal system probing to open the distal blockage. This is typically done at the bedside unless the patient is older and uncooperative. Debate exists in regard to the specific timing of probing following the initiation of antibiotics with concerns over probing-induced bacteremia [8]. The author typically has the patients on intravenous antibiotics for at least 24 h prior to probing. Once the patient starts to improve clinically, they can be transitioned to oral antibiotics.

In patients who fail probing by having return of their symptoms or develop chronic dacryocystitis, the nasolacrimal duct is intubated with silicone stents in the operating room. An inferior turbinate infracture is usually performed at the time of stenting. Balloon dacryoplasty can also be used at the time of stenting, but the author prefers to reserve this for recalcitrant cases. If symptoms persist despite these interventions, then a dacryocystorhinostomy (DCR) is performed (see Algorithm chart). This is most commonly needed in patients with abnormal nasal anatomy.

Pediatric Chronic Dacryocystitis

Pediatric patients with chronic dacryocystitis can be managed more conservatively. Topical antibiotics can be tried for a period of time to keep the infection at bay and allow time for the facial bones to grow. If intervention is indicated, the same treatment algorithm is followed as above (see Algorithm chart).

Adult Dacryocystitis

The treatment of choice for adult lacrimal sac infections is surgical. The goal is to create a new drainage system for tears that bypasses the obstructed nasolacrimal duct. In acute disease, patients are placed on oral antibiotics for 7–10 days prior to surgery to help reduce the inflammation. Topical antibiotics are generally not necessary. Intravenous antibiotics should be considered in patients with severe disease associated with orbital or facial cellulitis.

Dacryocystorhinostomy can be performed from an external or endoscopic approach. If any abnormal tissue of the lacrimal sac is encountered during surgery, a biopsy should be taken. If a patient has failed a previous DCR, one could consider the use of mitomycin c.

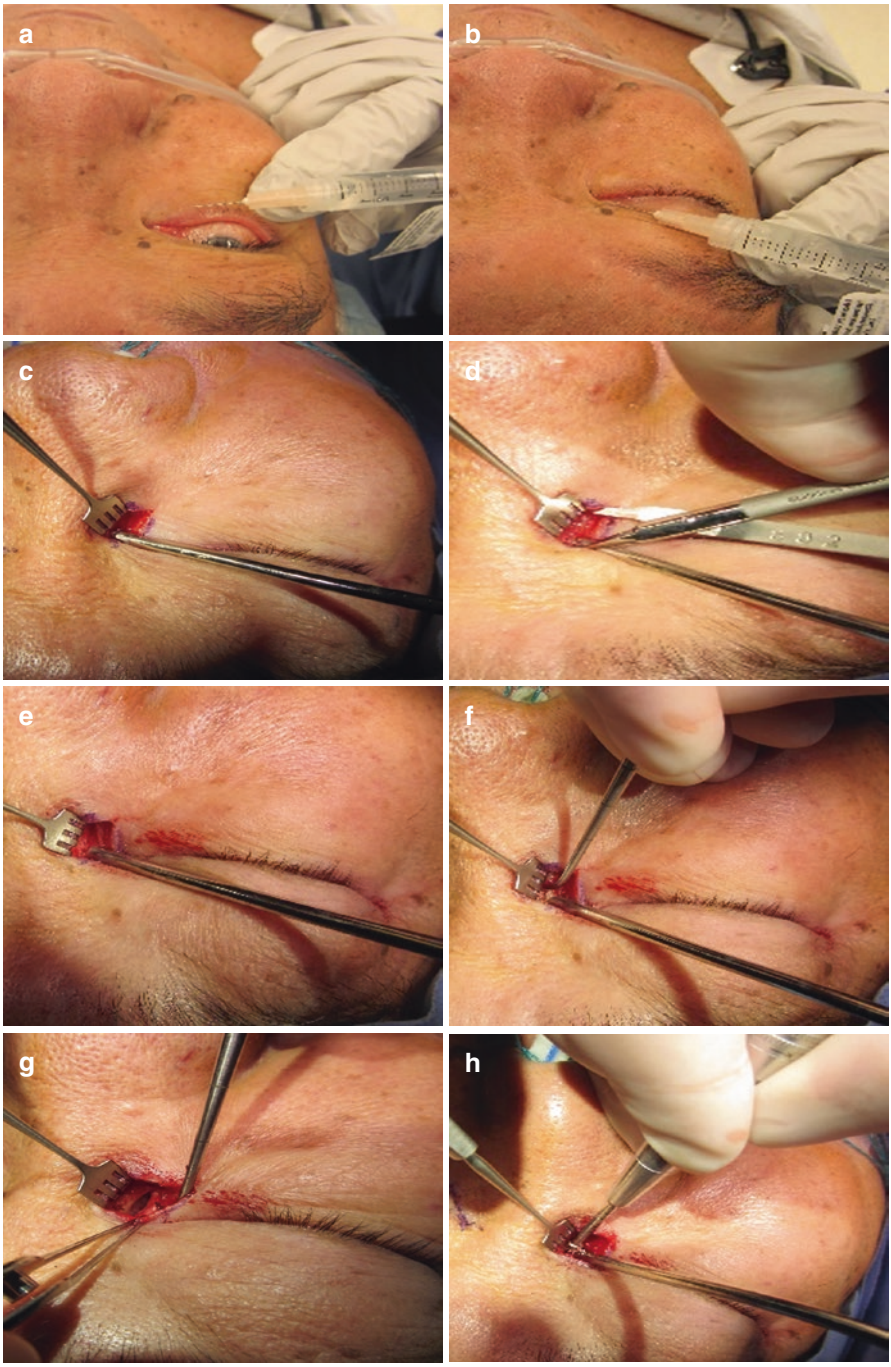
External Dacryocystorhinostomy

External DCR is technically easier than an endoscopic approach and offers the advantage of avoiding general anesthesia. Adequately performed surgery yields a greater than 90% success rate. Care must be taken to remove adequate bone and open the full length of the lacrimal sac to avoid stasis issues (sump syndrome) or closure of the ostium.

Technique

External dacryocystorhinostomy can be performed under Local anesthesia with IV sedation or general anesthesia. Local anesthetic is injected into the medial canthal area, lacrimal sac, and nasal mucosa of the lateral wall of the nose. The nose is packed with neurosurgical cottonoids saturated in adrenaline 1:1000 solution to aid in vasoconstriction. The skin incision is made halfway between the bridge of the nose and medial canthus extending inferiorly for approximately 1.0 cm toward the ala of the nose. A sharp scissor is used to divide the subcutaneous tissue. A freer elevator is used to dissect through the periosteum down to the maxillary bone. The angular vessels are avoided if possible or hemostasis is confirmed with cautery. The periosteum is elevated posteriorly to expose the anterior lacrimal crest. This dissection is carried further to elevate the lacrimal sac from the lacrimal sac fossa. The freer elevator is then used to fracture the thin bone of the posterior lacrimal fossa. Alternatively, a DCR burr can be used to burr down the anterior lacrimal crest. Rongeurs of increasing size are then used to enlarge the bony opening. The osteotomy should include the removal of the lacrimal sac fossa and anterior lacrimal crest. The presence of agar nasi cells may require a limited anterior ethmoidectomy. The lacrimal sac is then vertically incised and anterior and posterior flaps are created. A corresponding incision is made in the adjacent nasal mucosa and again anterior and posterior flaps are created. The posterior flaps are then excised or sutured together with a 5–0 Vicryl suture. Stents are then placed through the lacrimal system and retrieved through the nose. The anterior flaps are then sutured together with the same 5–0 Vicryl suture. The skin is closed with deep 5–0 Vicryl suture followed by 5–0 fast-absorbing suture. The stents are tied and allowed to retract into the nose (Fig. 10.2).

Fig. 10.2 External DCR. (**a**) Local anesthetic injected into medial canthal region: lower eyelid. (**b**) Local anesthetic injected into medial canthal region: upper eyelid. (**c**) A skin incision was made halfway between the bridge of the nose and medial canthus extending approximately 1 cm toward the ala of the nose. (**d**) Sharp scissors used to divide subcutaneous tissue. (**e**) Periosteum identified. (**f**) Freer elevator used to dissect through periosteum down to maxillary bone. (**g**) Periosteum elevated to expose the anterior lacrimal crest and to elevate the lacrimal sac from the lacrimal sac fossa. (**h**) DCR burr used to remove the anterior lacrimal crest. (**i**) Lacrimal sac and nasal mucosa incised for creation of flaps. (**j**) Groove director in place for placement of stents. (**k**) Anterior flaps sutured together. (**l**) Subcutaneous sutures placed to approximate the wound. (**m**) Skin closed with running 5–0 fast-absorbing suture. (**n**) Stents tied with Vicryl suture, cut, and then allowed to retract into the nose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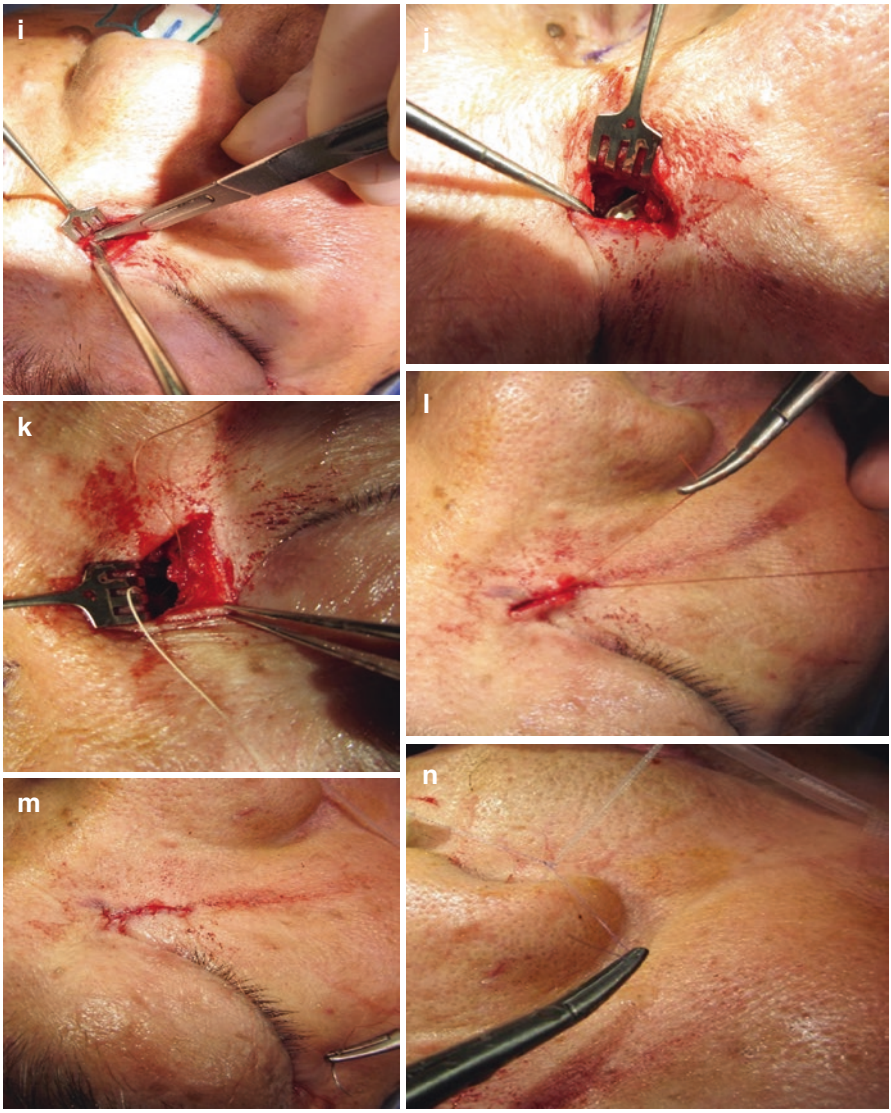


Fig. 10.2 (continued)

Endoscopic Dacryocystorhinostomy

The endoscopic DCR has a greater learning curve but offers the advantage of no external skin incision. This surgery is typically performed under general anesthesia due to nasal mucosal bleeding. Like the external approach, adequate bone removal and the full opening of the sac are imperative for success. It was previously thought that endoscopic DCR has a slightly decreased success rate comparted to external DCR. However, numerous studies now demonstrate at least equal success rates [9–11].

Technique

Similar to the external approach, local anesthetic is injected into the medial canthus, lacrimal sac, and lateral nasal wall. Neurosurgical cottonoids soaked in adrenaline are used to pack the nose.

A zero degree endoscope is used for visualization. A curvilinear incision is made with a crescent knife or sharp end of a freer elevator that outlines the lacrimal sac and mirrors the middle turbinate. The elevator is used to elevate the mucosa off the nasal wall. Cutting forceps are then used to remove the mucosa to visualize the underlying bone. This process can be done with a microdebrider if available. The osteotomy is then created using Rongeurs or DCR burr to completely uncover the lacrimal sac. A DCR burr can be used as needed to remove bone that is difficult to extract with the Rongeurs, often in the axilla of the middle turbinate. Once the appropriate amount of bone has been removed, a Bowman probe is used to tent up the lacrimal sac. The sac is incised along its vertical length. A dental burnisher can be used to further enlarge the opening. The anterior and posterior leaflets are then trimmed. Stents are placed and tied (Fig. 10.3).

Dacryocystectomy

Dacryocystectomy is an excellent option for patients who are poor surgical candidates or have significant dry eye. This can be done under local anesthesia or MAC.

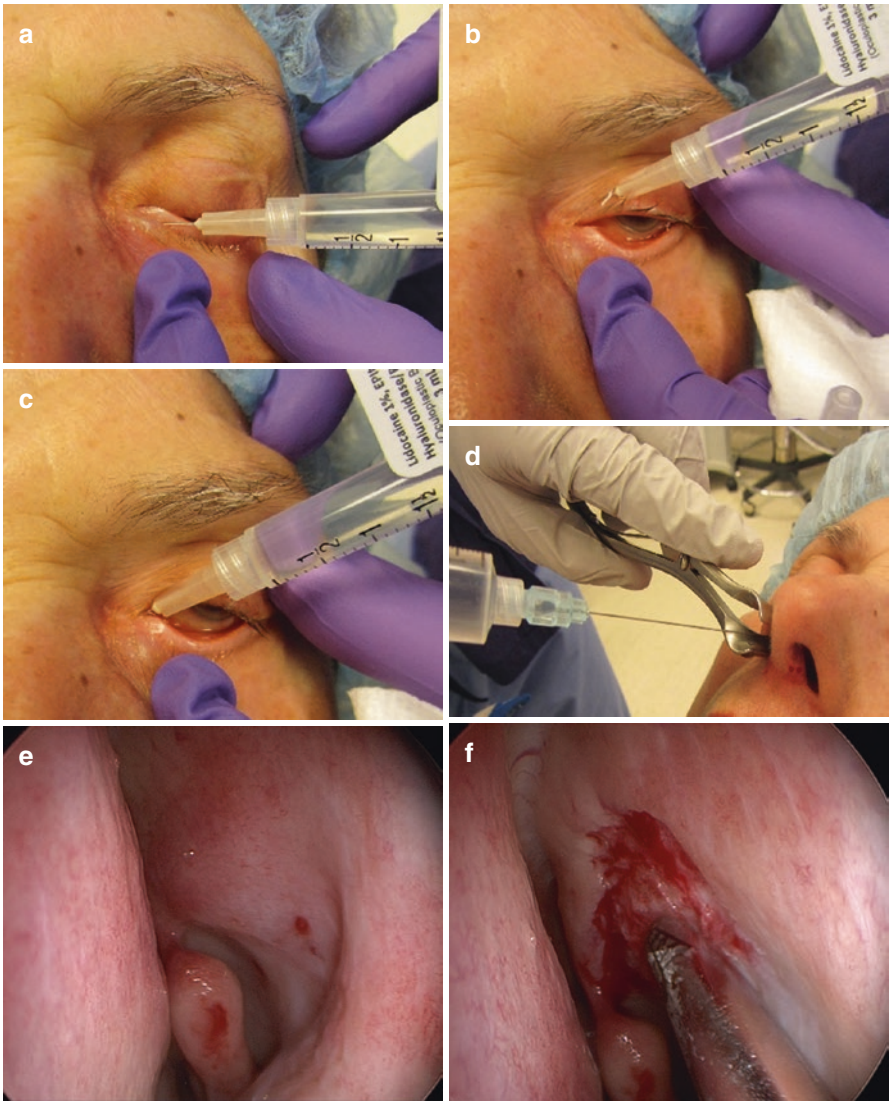


Fig. 10.3 Endoscopic DCR. (**a**) Local anesthetic injected into medial canthal region: lower eyelid. (**b**) Local anesthetic injected into medial canthal region: upper eyelid. (**c**) Local anesthetic injected into lacrimal sac. (**d**) Local anesthetic injected into lateral nasal wall. (**e**) Endoscopic view of left middle turbinate and lateral nasal wall. (**f**) Removal of nasal mucosa using microdebrider. (**g**) Nasal mucosa removed in area mirroring middle turbinate. (**h**) Rongeurs used to create osteotomy. (**i**) Rongeurs used to enlarge osteotomy. (**j**) Lacrimal sac visible with superior bone still in place. (**k**) Bells Rongeur used to remove superior bone overlying lacrimal sac. (**l**) Lacrimal sac exposed with Bowman probe tenting sac. (**m**) Keratome blade used to incise lacrimal sac. (**n**) Sac now completely open. (**0**) Bowman probe visible. (**p**) Dental burnisher used to enlarge opening superiorly. (**q**) Dental burnisher used to enlarge opening inferiorly. (**r**) Microdebrider used to trim posterior leaflet. (**s**) Microdebrider used to trim anterior leaflet. (**t**) Lacrimal sac now open with anterior and posterior flaps trimmed appropriately. (**u**) Stents passed into lacrimal sac. (**v**) Grasping forceps used to retrieve stent. (**w**) Second stent placed. (**x**) Both stents retrieved and in proper position

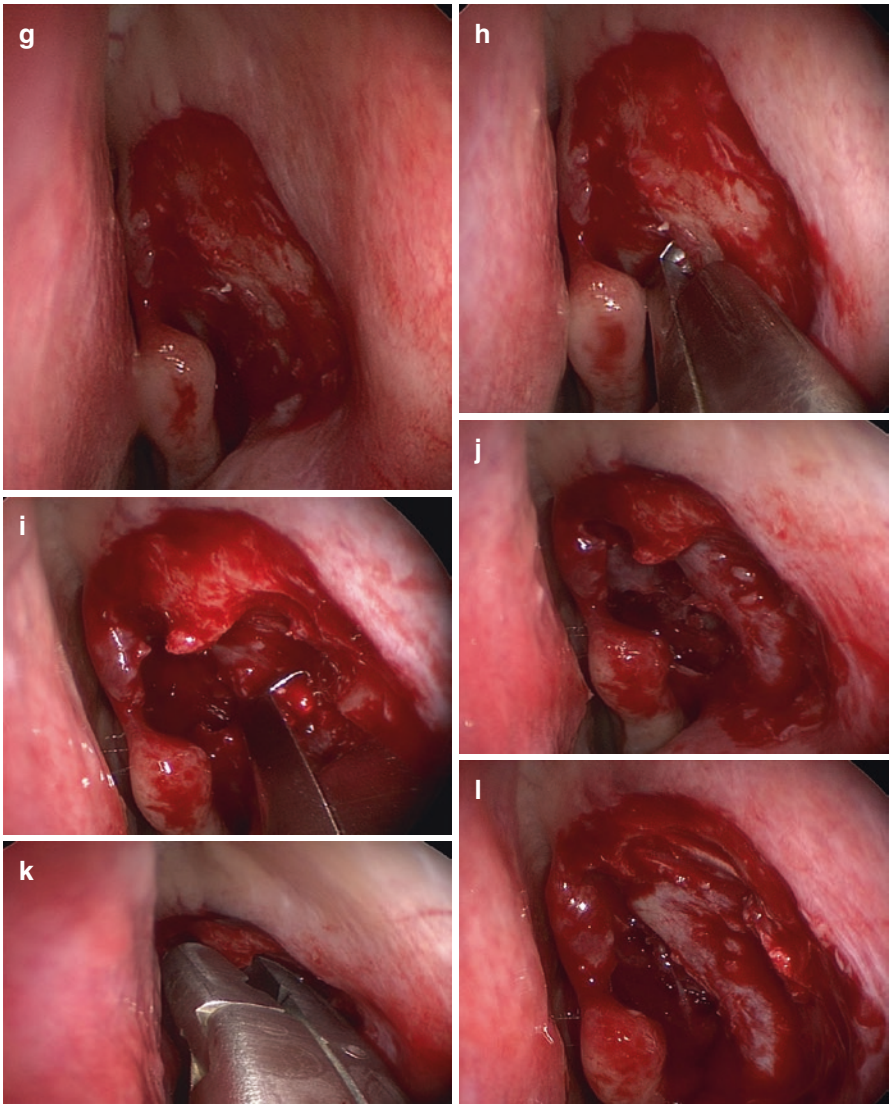
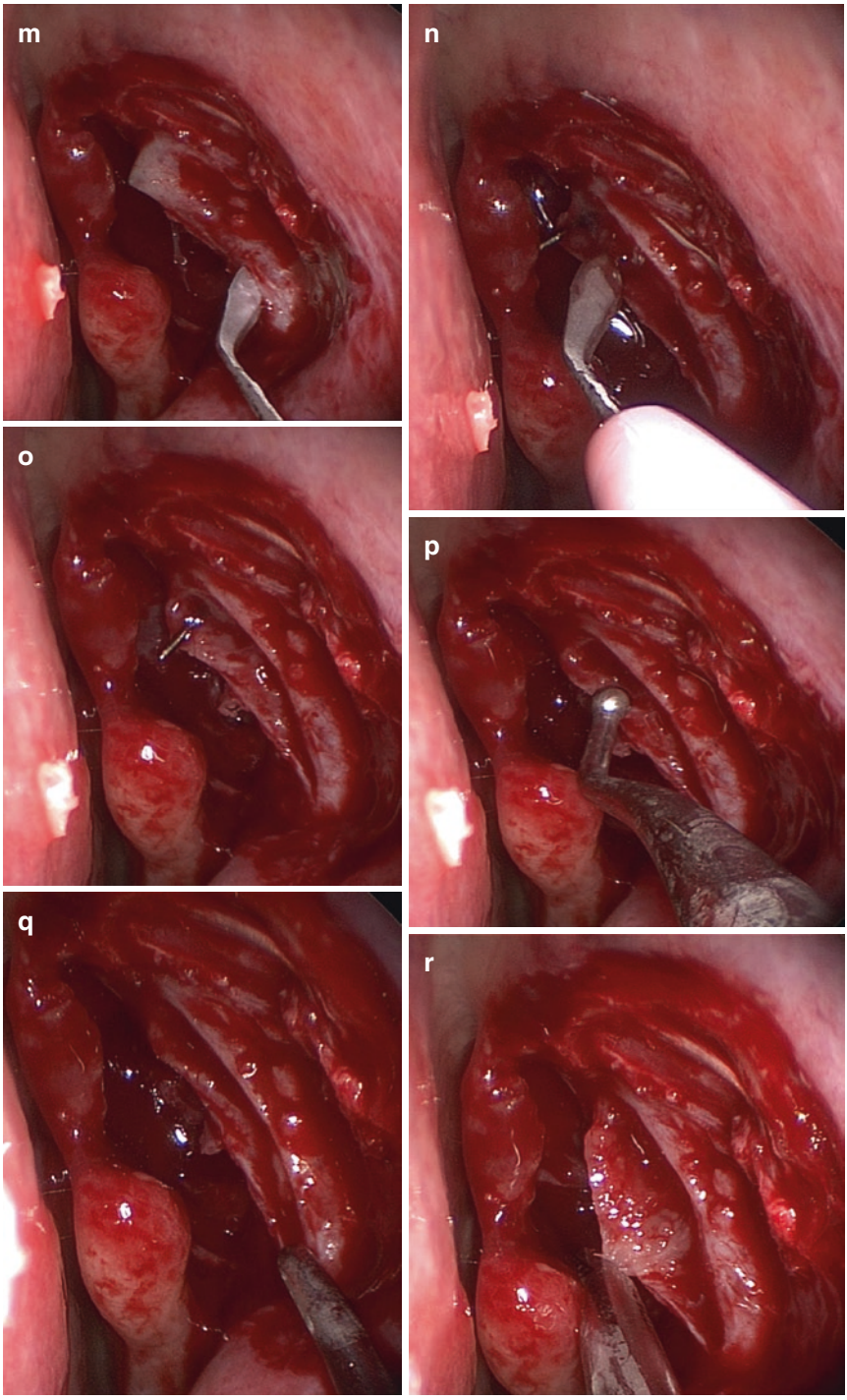


Fig. 10.3 (continued)



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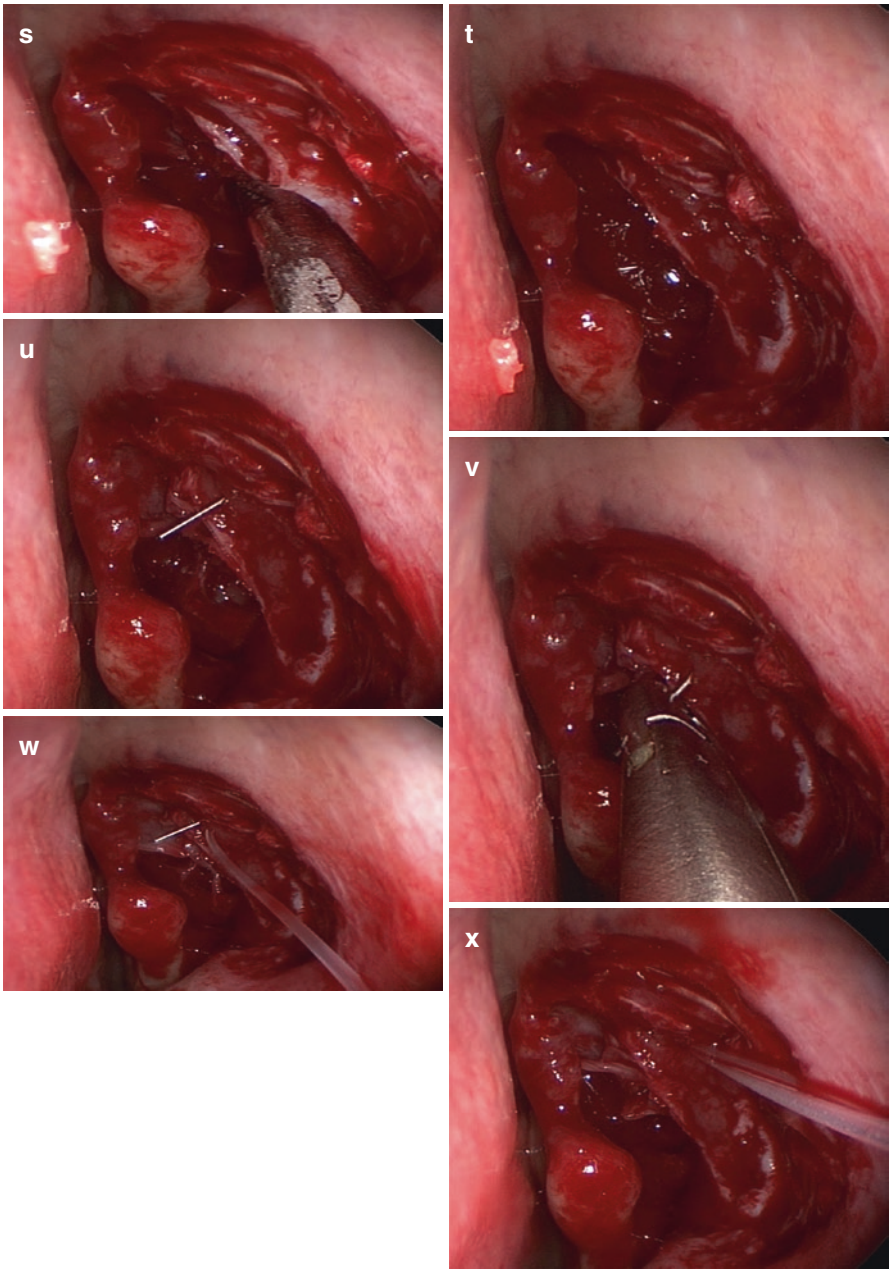

Fig. 10.3 (continued)

Technique

Local anesthetic is injected into the medial canthal area and lacrimal sac. The skin incision is made halfway between the bridge of the nose and medial canthus extending inferiorly for approximately 1.0 cm toward the ala of the nose. A sharp scissor is used to divide the subcutaneous tissue. A freer elevator is used to dissect through the periosteum down to the maxillary bone. The angular vessels are avoided if possible or hemostasis is confirmed with cautery. The periosteum is elevated posteriorly to expose the anterior lacrimal crest. This dissection is carried further to elevate the lacrimal sac from the lacrimal sac fossa medially. The lateral portion of the lacrimal sac is dissected free from the periorbita with blunt dissection. Once the lacrimal sac is freed from its soft tissue attachments, the lacrimal sac is amputated superiorly at the common canaliculus and inferiorly at the nasolacrimal duct junction. Cautery is then used to ensure hemostasis. The skin is closed with deep 5–0 Vicryl suture followed by 5–0 fast-absorbing suture.

Lacrimal Abscess

Localized lacrimal sac abscesses should be treated with incision and drainage with cultures of the discharge. Appropriate oral antibiotics should be started and tailored to sensitivity results. Due to the risk of fistula formation, some surgeons prefer a trial of conservative therapy with oral antibiotics and warm compresses before performing incision and drainage. While this is a reasonable option for less severe cases, the actual risk for fistula formation is quite low. Once the abscess has resolved, the patient will require a DCR for definitive treatment.

Technique

Local anesthesia is generally not used as this causes additional pain and adds very little anesthetic value given the acidic environment. A #11 blade is used to incise the overlying skin and lacrimal sac with one quick movement. Any discharge is cultured. Gentle pressure can be placed to aid in expression of purulent material. The wound is left open to heal by secondary intention.

Drainage of the abscess can also be performed with an 18-gauge needle on a 3 cc syringe to aspirate sac contents.

Complications

If not treated appropriately, dacryocystitis can have numerous complications. Infection can tract more posteriorly into the orbit and place the patient at risk for meningitis and cavernous sinus thrombosis. Chronic lacrimal sac abscess can create

a fistula through the skin. However, if treated appropriately, dacryocystitis has an excellent prognosis.

Algorithm Chart: Treatment of Pediatric Dacryocystitis

1. Nasolacrimal duct probing without placement of stents
2. Nasolacrimal duct intubation with silicone stents
3. Balloon dacryoplasty followed by repeat nasolacrimal duct intubation with silicone stents
4. Dacryocystorhinostomy with silicone stents

Conflict of Interest None.

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Chapter 11
Managing Trauma-Associated and Foreign Body-Associated Orbital Cellulitis

H.B. Harold Lee

Introduction

Each year, approximately three million patients suffer from traumatic craniofacial injuries in the United States [1]. Consequently, infections may complicate the clinical course of orbital and periorbital traumas. Traumatic and iatrogenic intraocular or intraorbital foreign bodies (IOrbFBs) can further increase the risk for infection.

Concomitant intraorbital foreign bodies can occur in greater than 16% of all traumatic orbital injuries [2]. Orbital trauma with associated penetrating injuries, particularly with vegetative foreign bodies, pose a higher risk of infection compared to closed injuries. Further, surgical implants used in either ocular or orbital surgery can predispose a patient to cellulitis and abscess formation in the setting of orbitofacial trauma.

Fractures

The use of perioperative and postoperative antibiotics in the setting of orbital trauma has been debated. Due to the closed nature of most orbital trauma, infection risks isolated to closed fractures rarely result in orbital cellulitis; however, the risks are increased with preexisting sinus disease [3–5]. Simon reported on four cases of acute, severe orbital cellulitis after a closed fracture [3]. All four patients had sinus disease surrounding the time of the injury. Of note, these patients represented only 0.8% of all orbital fractures seen at their institution [3].

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Antibiotic choice in the surgical management of these patients is also not clearly defined. The ASA (American Society of Anesthesiologists) Committee on Occupational Health Task Force on Infection Control estimates that 5–10% of hospitalized patients acquire one or more hospital-acquired infections (HAI) of which 30% are surgical site infections (SSIs) [3]. The Surgical Care Improvement Project (SCIP) developed out of a conglomeration of many institutions with a goal of reducing SSIs [6]. Guidelines for perioperative antibiotic prophylaxis (PAP) were established generally for many fields of surgical practice. The Set Measure ID (SCIP Inf-2) describes specific guidelines and algorithms for certain surgical procedures, but no clear recommendations are made for orbitofacial surgery with regard to PAPs.

Mundinger found no significant evidence supporting pre- or postoperative prophylaxis for upper or midfacial fractures after a meta-analysis of articles studying PAPs in facial fractures [7]. However, there is evidence supporting the use of PAP in patients with comorbid conditions that may predispose a patient to infection (e.g., sinusitis) [3, 8–10].

Prophylactic antibiotics in the age of multidrug-resistant pathogens should not be taken flippantly. Direct complications of antibiotics include rash, urticaria, gastrointestinal problems, blood dyscrasias, metabolic acidosis, hypertensive crisis, cranial edema, and even death.

There is no professional consensus regarding PAPs in orbitofacial fractures; however, there are clear trends in practice. In a study of 205 facial trauma surgeons from different subspecialties, 100% of the respondents used PAPs either “always” (85%) or “sometimes” (15%) [11]. Up to 60% of surgeons in the study even prescribed antibiotics after the injury for 3–7 days prior to surgery [11].

Guidelines developed jointly by the American Society of Health-System Pharmacists (ASHP), the Infectious Diseases Society of America (IDSA), the Surgical Infection Society (SIS), and the Society for Healthcare Epidemiology of America (SHEA) suggest a role for PAPs in the clean-contaminated environment of facial fracture repair [12]. For clean-contaminated procedures, the preferred agents are (1) cefazolin or cefuroxime plus metronidazole or (2) ampicillin-sulbactam. Clindamycin plus or minus an aminoglycoside, such as amikacin or gentamicin, is a reasonable alternative in patients with a documented β-lactam allergy [13]. The ASHP ranks this recommendation a “B” level strength suggesting a range of evidence from well-conducted case-control studies to conflicting evidence that tends to favor the recommendation.

I advocate the use of prophylactic antibiotics (a second-generation cephalosporin, in general) intraoperatively before the initial incision. I do not recommend antibiotics either postoperatively or immediately after the initial injury, whether the patient will be undergoing a surgical repair for his fractures or not.

Traumatic Foreign Body

Orbital trauma with either orbital or ocular foreign bodies carries significant risks of periocular or orbital infection. The numbers and data are difficult to assess because most patients in this subcategory are treated with prophylactic antibiotics. Vegetative matter further increases the rate and severity of the infection.

Metallic foreign bodies are specific projectile injuries that are commonly seen in the emergency care setting of ophthalmic trauma. Interestingly, BB pellets represent 55–75% of intraorbital, extraocular metallic foreign bodies [14, 15]. However, only 8% of patients presenting with a projectile intraocular metallic foreign body had BB pellet as their mechanism of injury [16].

Norris first described his management of two cases of orbital foreign bodies in 1890 [17]. In one case, where a metallic railroad torpedo struck a patient's orbit, removal of the foreign body initially with finger manipulation followed by forceps extraction rapidly relieved the patient's symptoms. This first documented case description initiates the necessity to remove foreign bodies in the setting of cellulitis. However, not all foreign bodies need removal. Gönül et al. discussed the outcome of 35 patients with penetrating orbitocranial gunshot injuries [18]. He found that complete removal of gunshot fragments in deep anatomical locations was not necessary if thorough debridement was performed.

We can look at the data surrounding intraocular foreign bodies (IOFB) and relate them to some extent to foreign bodies in the periocular area. Ehlers studied 96 patients who sustained metallic IOFB injuries in an 11-year time period [16]. Eighty-eight percent received preoperative systemic antibiotics, and 98% received periocular antibiotics. Endophthalmitis rates were low and developed in only 4% of these patients.

Finkelstein looked at 27 patients who sustained projectile metallic foreign bodies (FBs) to the orbit [14]. He performed surgical removal of 18/27 FBs based on location with anterior foreign bodies more likely to be removed. Posterior FBs were removed if concomitant posterior orbital surgeries were necessary (e.g., posterior rupture repair) and the FB was readily accessible. Most of these FBs were BB pellets. He found that the more posterior the metallic FB, the poorer the visual outcome (Fig.11.1).

BB pellets average 4.5 mm in diameter, weigh approximately 0.35 g, and are fired at velocities of 250–750 ft/s [19]. In contrast, bullets can be three times heavier with velocities in the range of 755–3250 ft/s causing greater damage due to the

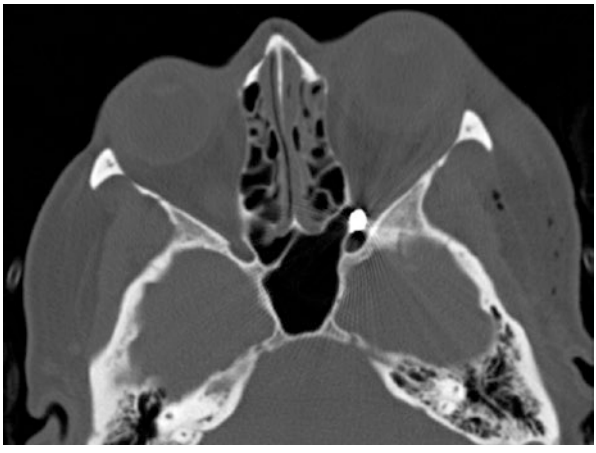

Fig. 11.1 Axial CT scan of patient with posterior intraorbital foreign body. Patient presented with no-light-perception vision in the affected eye

depth of injury in the orbit tissue [14]. In the United States, ammunition for air-powered firearms (typically in the form of BB pellets) is typically steel coated with a zinc (Daisy, Chicago, IL) or copper (Crosman, East Bloomfield, NY) alloy and may not need to be removed surgically [14]. However, shotgun "shot" is generally made of lead and can, thus, carry a theoretical risk of lead poisoning, although no case has been reported from a retained intraorbital lead foreign body [14].

General healthcare initiatives should point toward prevention. Eye protection was worn in only 6% of the 96 patients with IOFB reviewed by Ehlers [16]. Simple polycarbonate lenses would likely prevent the majority of both intraocular and intraorbital foreign body injuries.

As a general guideline, I recommend removal of IOrbFBs in the acute setting if anteriorly located and in the setting of an intact globe. Ruptured globe injuries must be prioritized and often warrant waiting an appropriate timeline for healing prior to orbital exploration. For deeper injuries in the apex, I recommend observation unless there is concern for direct injury to the nerve and compression of the apical tissues. In Fulcher's study of 40 IOrFBs, six patients had their FB left within the orbit [15]. Four out of these six patients were asymptomatic, implying that observation may be the best course of action at times.

The risks of orbital cellulitis are low, but each patient with an IOrbFB should receive prophylactic antibiotics mostly to prevent infection from intrinsic flora and in preparation for possible surgical removal. The surgeon must use his experience and surgical decision-making process to determine whether posterior removal of a metallic foreign body is reasonable.

Intraorbital Wooden Foreign Bodies

Intraorbital wooden foreign bodies (IOrbWFBs) carry a unique dilemma for the orbital surgeon. Often patients can present in a delayed fashion, and standard imaging may miss smaller particulate matter. Injuries may appear minimal or even absent as the entry wound is often missed [20]. Taş found that wooden foreign body size inversely correlated with time of presentation [21]. In his case series of 32 patients, 72 h or more had passed before patients presented with wooden foreign bodies that were less than 2 cm in size.

Typically, CT scans are the standard imaging modality for patients who present with traumatic injuries to the orbit (Fig.11.2). If suspicion is low for orbital foreign bodies, the radiologist may mistake wooden matter for air. Shelsta, in a study of 23 cases, had 13% patients with an unrecognized IOrbWFB after initial imaging [20]. However, Taş found that in all his 32 cases of IOrbWFB, the radiologist either recognized the FB or had a high suspicion of a possible FB [21].

In typical CT images, many types of wood in different hydrated states can be indiscernible in the black background of orbital fat [22]. Wood has absorption coefficients ranging from −999 to +54 HU depending on their origin, hydration, and size [22]. Because standard CT scans are performed at a window width of 200–350 HU, even large pieces of wood can be missed. To improve the context of revealing

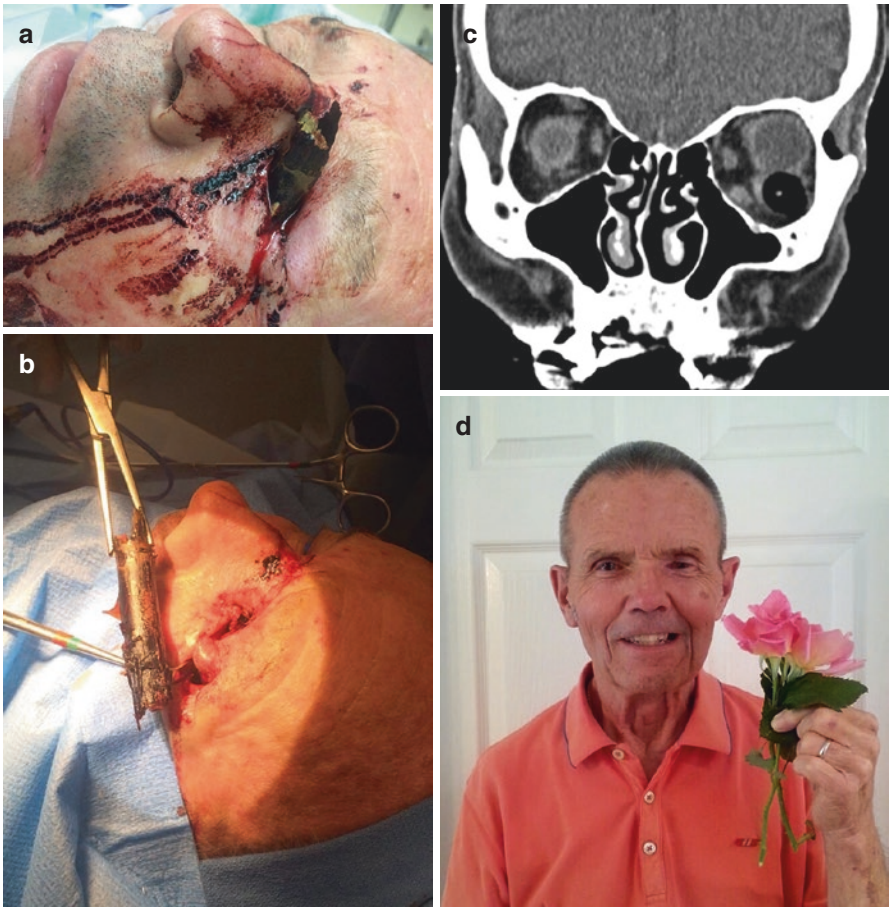

Fig. 11.2 (**a**) External intraoperative photo of patient who sustained a fall onto a rosebush. (**b**) External intraoperative photo of wooden foreign body once removed after orbitotomy. (**c**) Coronal CT scan of the same patient with wooden foreign body visualized along inferotemporal orbit. (**d**) External photograph of the same patient 2 years after injury with flowers from the same rosebush that caused his orbital injury

the FB, the window width should be increased to at least 1000 Hounsfield units (HU) to increase the background signal of the orbital fat. Bone windows (width, 4000 HU) can help discern IOrbWFB far greater than soft tissue windows. Expanding the window width is essential in locating and identifying an IOrbWFB.

If uncertain, an MRI may be an additional modality to help discern IOrbWFB location, size, and severity of injury. Traditionally, green wood or hydrated fresh wooden FB was more difficult to detect than dry wood, typically seen in construction zone accidents [23]. However, newer imaging techniques allow MRI studies to be very accurate in detecting any kind of wooden FB. In T1-weighted images, the IOrbWFB appears hypointense compared to the hyperintense orbital fat. Ring enhancement with gadolinium contrast may be seen particularly with small pieces

of wood which can be surrounded by an artifact consisting of hyperintense spots, known as truncation artifact [22, 24]. Glatt and Custer studied wooden matter in environments consistent with orbital tissue [22, 25, 26]. They found that T1-weighted images created superior imaging quality and required less scanning time. They found MRI useful particularly in small vegetative matter.

Prior to the advent of modern antibiotics, the morbidity and even mortality of intracranial wood-related injuries were quite high [27]. The porous nature of wood and its exposure to the elements present an environment for bacterial growth [28]. A common misunderstanding of IOrbWFB is that they have a high or higher incidence of fungal infection. However, the literature and this author's experience do not support empiric antifungal therapy [20]. No predominant bacterium is present in these injuries. Common species cultured from IOrbWFB include *Staphylococcus epidermidis*, *Staphylococcus aureus*, *Enterobacter agglomerans*, *Clostridium perfringens*, *Escherichia coli*, *Serratia marcescens*, and *Citrobacter freundii* [20, 21]. We recommend broad-spectrum coverage with vancomycin and a third-generation cephalosporin or single therapy with Zosyn and tailoring the antibiotic with patient response and cultured results.

We further advocate timely removal of the IOrbWFB at initial presentation. Although older pieces of literature considered removal of IOrbWFB unwarranted [29], improved orbit training and techniques help outweigh the benefits over the risks. Not only do the retained IOrbWFBs create a nidus for infection, but the extent of inflammation vegetative matter presents to the orbital tissue can be extensive [22]. Delay in treatment may lead to serious complications even months after the injury [30]. Any orbital injury with an extended timeline of recovery or persistent symptoms should be reviewed for a potential IOrbWFB.

Intracranial Penetration

IOrbFB that penetrates the intracranial space can complicate the trauma patient's course. Most of these injuries occur through the thin bone along the roof of the orbit [27]. Other routes of penetration include the posterior foramen such as the superior orbital fissure [31].

Extension into the intracranial cavity can result in traumatic carotid aneurysm [32], cerebral abscess [33], cavernous sinus thrombosis [34], and superior orbital fissure syndrome, cranial nerve palsies, and cerebrospinal fluid leak [28].

Dog Bites

Surgeons practicing all levels of facial trauma will encounter animal bites to the head and face. Traumatic bite injuries specific to the periorbital area can result in complex lacerations, nasolacrimal system injuries [35–37], ruptured globes [38], orbital fractures [39], and even death [40].

Accounting for approximately 1–5% of all emergency department visits, canine bites requiring medical attention occur more than 750,000 times per year in the United States [41, 42]. Four to 27% of all dog bites involve the periorbital area with ocular injuries [35, 43]. Sixty-five to ninety percent of dogs were known to the victim and either the victim's or a friend/neighbor's pet [35, 39]. The majority of patients are children with over 68% under the age of 10 [35–37, 39]. The younger the child (<4 years old), the more common that the injury involves the face [39, 41].

Microorganisms involved in an animal bite are wide ranging including both aerobic and anaerobic pathogens [44, 45]. The most common bacteria isolated from wound infections after bite injuries include *Staphylococcus aureus* and gram-negative organisms [37].

Canalicular injuries are characteristically common in dog bites involving the periocular space. Forty percent of patients with bites involving the eyelids have canalicular injuries often resulting from the lateral shearing forces on the medial lid structures [35]. Slonim advocated the use of Crawford bicanalicular stents, which is the author's preferred technique, in the repair of canalicular injuries with primary closure of associate eyelid lacerations without other drains [37]. Topical antibiotics and oral cephalosporin use were prescribed for 5 days [37].

Initial management includes emergency room triage with airway protection and otolaryngology consultation for any airway or open neck injuries. After stabilization, appropriate broad-spectrum antibiotics should be initiated for deep wounds. Lackmann classified dog bites by level of injury [30]. Stage 3 and 4 injuries included deeper injuries to the level of muscle with a tissue defect. Antibiotic prophylaxis was recommended for these two classes of injury. Surgical management includes irrigation with debridement as necessary and early primary closure for uninfected wounds [35]. Wound culture at the time of injury provides little value because of the multiple organisms involved in both indigenous flora and nonindigenous microorganisms [37]. Additional care items in the initial consultation include following appropriate protocols for both rabies and tetanus treatments and prevention.

Previous management of animal bites to the face supported delayed wound closure while prophylactic antibiotics were initiated overnight [46]. Current large-scale studies establish optimal results with immediate repair with either primary closure or various flap techniques [47–50]. We advocate primary closure for all uninfected wounds. Subcutaneous sutures are kept to a minimum, but skin rotational flaps and microvascular reconstruction can be performed as the initial repair (Fig.11.3) [48].

Oral ampicillin-clavulanate (Augmentin) or intravenous ampicillin-sulbactam (Unasyn) is a reasonable first-line choice for both gram-positive and gram-negative coverage with clindamycin and bactrim/fluoroquinolone for those with penicillin allergy [35, 36, 48]. Recommended duration includes 5 days for prophylaxis and up to 14 days for an infected wound [48].

The unique anatomy of the eyelids includes a large density of blood supply to the periorbital area [37], and resultantly post-injury infections are rare (as low as 2%) and can often be treated with outpatient systemic antibiotic treatment [35].

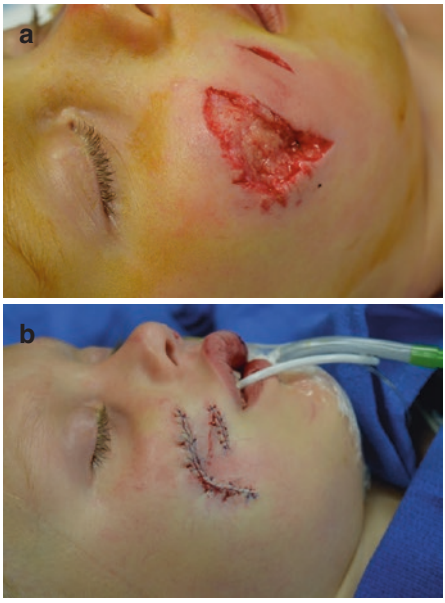

Fig. 11.3 (**a**) External intraoperative photo of tissue injury after dog bite. (**b**) External intraoperative photo of same patient after rotational flap repair (photo credit to Dr. Jeremy Clark)

Wound infection is defined as a bite victim with fever, lymphangitis, frank abscess, or at least four minor criteria (erythema, tenderness, swelling, purulent drainage, and leukocytosis) [48]. We recommended delayed closure for infected bite wounds (which usually present later) after appropriate systemic antibiotic treatment has been completed and the wound is sterile.

Conclusion

Management of complicated orbitofacial trauma relies on a key understanding of complex injury patterns. Working together with the trauma service, infectious disease consultants and other surgical subspecialties is critical to optimize the outcomes of these patients.

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Chapter 12
Fungal Disease of the Orbit

Thomas E. Johnson and Nathan W. Blessing

Introduction

Infectious orbital disease is uncommon but is typically the result of contiguous spread from an adjacent sinusitis. While bacteria are the predominant causative organisms, fungi may also invade and infect the orbit. The majority of patients who develop invasive fungal disease are immunocompromised, but immunocompetent individuals may also be rarely affected. Predisposing factors for invasive fungal sinusitis (IFS) and subsequent secondary orbital infection include poorly controlled diabetes, hematologic malignancies, immunosuppressive therapy, a history of organ transplantation, a history of bone marrow transplant, hemochromatosis, chronic corticosteroid usage, and acquired immunodeficiency syndrome (AIDS). Invasive fungal disease of the orbit is both vision and life-threatening, and prompt diagnosis and treatment are imperative.

The most common fungi implicated in invasive orbital disease belong to either the order *Mucorales* (causing mucormycosis, formerly zygomycosis) or the genus *Aspergillus* (causing aspergillosis). Of these, mucormycosis is thought to have a higher incidence as well as a higher mortality rate when compared to aspergillosis. Delays in diagnosis and treatment are common, as early signs and symptoms may be subtle and may mimic bacterial orbital cellulitis or even giant-cell arteritis. Inadvertent treatment with corticosteroid therapy may result in rapid disease progression. It is important to maintain a high index of suspicion for fungal infection in patients with unusual orbital presentations and characteristic predisposing factors or in those who fail to respond to standard medical therapy for bacterial orbital cellulitis.

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Mucormycosis

Mucormycosis (formerly zygomycosis, phycomycosis) is an aggressive fungal infection that classically arises in the paranasal sinuses and secondarily invades the orbit and subsequently the brain (rhino-orbital-cerebral mucormycosis, ROCM). The causative fungi belong to the order *Mucorales* in the class *Zygomycetes*. The family *Mucoracea*e contains four genera of causative organisms: *Mucor, Rhizopus, Absidi*a, and *Cunninghamella*. Of these four, *Rhizopus* is most commonly isolated from human mucormycosis cases, and *Rhizopus oryzae* is the most frequently reported species [1]. This life-threatening infection often affects poorly controlled diabetics in acute ketoacidosis or severely immunocompromised hosts secondary to hematologic malignancies or chronic immunosuppressive therapy. These fungi are ubiquitous and are generally found throughout our environment in soil, fruits, decomposing plant and animal matter, and old bread [2].

As previously mentioned, mucormycosis typically begins in the nose and paranasal sinuses following the inhalation of fungal spores. Normally these spores are contained and eradicated by an intact immune system. In compromised individuals the spores may be allowed to germinate and proliferate in the nose and sinuses. Mucormycetes have a propensity to invade blood vessels which subsequently causes vessel thrombosis, ischemia, and tissue necrosis [3]. Tissue necrosis may manifest as a characteristic black eschar visible within the nasal cavity [4]. These fungi thrive in an acidic environment setting up a vicious cycle whereby ischemic tissue necrosis drives further fungal proliferation. Eventually, fungal disease in the maxillary and/or ethmoid sinuses progresses to invade the orbit through congenital bony dehiscences in the thin medial wall (lamina papyracea), medial orbital floor, or through neurovascular foramina. Additionally, operative attempts at eradicating the fungus via sinus debridement may inadvertently expose the orbit to subsequent invasion.

Diabetic patients account for 60–80% of those affected by ROCM, particularly those in diabetic ketoacidosis [5, 6]. Hematologic malignancies, such as bone marrow transplantation or solid organ transplantation, also predispose patients to this devastating infection. Neutropenia of any causes is also a risk factor, as neutrophils provide the primary defense against fungal organisms. Mucormycetes require iron for growth, and the presence of increased serum iron availability is an additional risk factor. Diabetic ketoacidosis, hemochromatosis, and treatment with iron all result in the increased bioavailability of iron [7]. ROCM has been rarely reported in immunocompetent individuals without any known predisposing factors; disease has also been reported following extensive trauma in otherwise normal patients [8]. HIV infection with progression to acquired immunodeficiency syndrome (AIDS) is not an independent risk factor as this disease primarily affects lymphocytes without causing neutropenia.

Signs and symptoms of ROCM include fever, sinusitis, pharyngitis, epistaxis, nasal discharge, orbital and periorbital pain, and nasal mucosal ulcerations and necrosis. Ophthalmic signs include ptosis, proptosis, ophthalmoplegia, decreased

vision, chemosis, periorbital redness and edema, pupillary defects, and orbital apex syndrome (OAS). Sudden loss of vision can occur due to ischemia from a central retinal artery occlusion or thrombosis of the posterior ciliary arteries with infarction of the optic nerve. ROCM is generally unilateral, but the disease can progress to involve the contralateral side. Left untreated, the infection spreads to the brain through the orbital apex, cribriform plate, and ophthalmic vessels. Patients with intracranial involvement exhibit obtundation, seizures, hemiparesis, or hemiplegia and can develop cavernous sinus thrombosis. Cerebral infarction and death can occur.

Examination of the skin and nasal mucosa may reveal a black eschar representing tissue necrosis, but this may not be present early in the disease course. If identified, a scraping and a potassium hydroxide (KOH) prep will identify fungal hyphae. Mucor hyphae are broad, irregular, and nonseptate, with wide angle branching approaching 90° (Fig. 12.1). Tissue should also be sent for permanent histopathologic staining and fungal culture. This may require an endoscopic or open biopsy.

Orbital, sinus, and brain imaging using computed tomography (CT) or magnetic resonance imaging (MRI) is imperative. CT often shows sinus opacification (Fig. 12.2) with secondary orbital extension, often into the orbital apex, and sometimes intracranial extension. Bony destruction is common. MRI shows a similar pattern with involved tissue displaying hypo- or isointensity on T1-weighted images, hypointensity to variable intensity on T2-weighted images, and enhancement with contrast (Fig. 12.3a, b) [9, 10]. The MRI appearance relates to the presence of calcium concretions, air, and ferromagnetic elements like manganese, iron, and magnesium [11].

Laboratory evaluation often shows an elevated white blood cell count, and blood cultures are rarely positive. Cerebral spinal fluid analysis is typically nonspecific.

Urgent treatment is imperative given the risk of significant morbidity and mortality and involves a multidisciplinary approach, including ophthalmology, otorhinolaryngology, neurosurgery, and infectious disease [12, 13]. Urgent reversal of

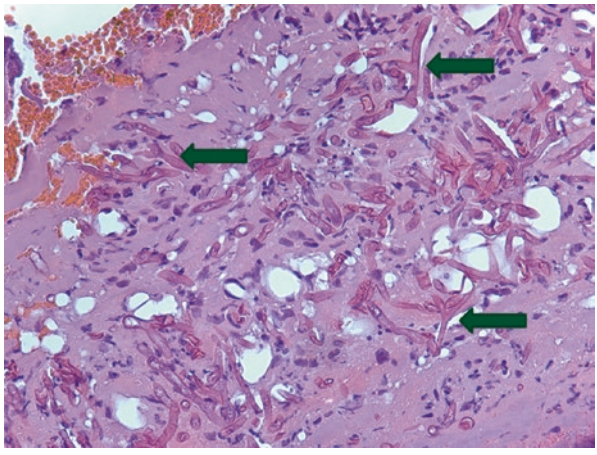

Fig. 12.1 Hematoxylin- and eosin-stained sinus mucosal tissue at 40x magnification taken from a patient with rhino-orbital-cerebral mucormycosis (ROCM) demonstrating multiple irregularly sized nonseptate hyphae branching at 90° and wider angles (*arrows*)

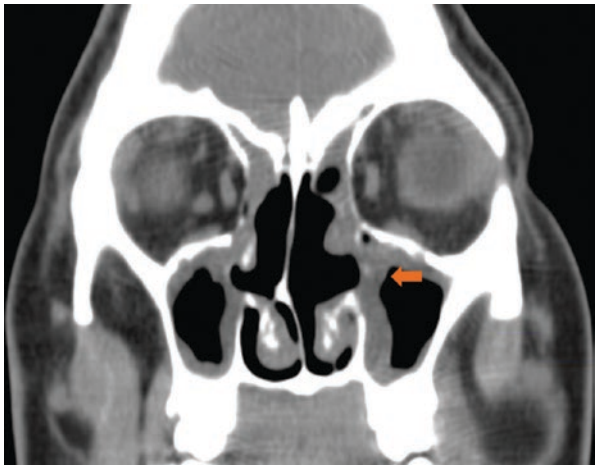

Fig. 12.2 CT scan without contrast in the coronal plane through the central orbits in a patient with left-sided ROCM status post-endoscopic ethmoidectomy demonstrating mucosal thickening suggestive of residual disease (*arrow*)

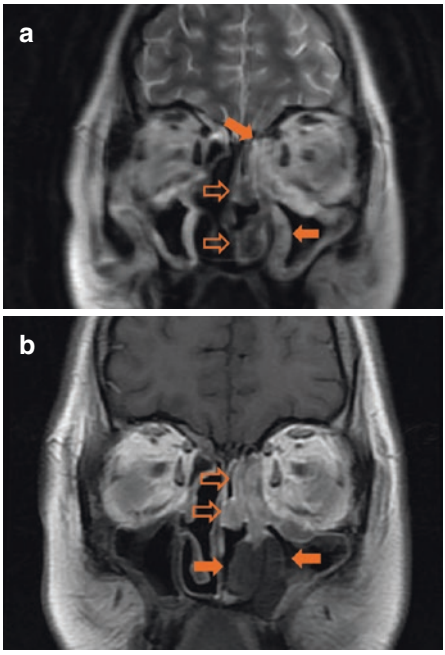

Fig. 12.3 Coronal plane MRI through the mid-orbit without (**a,** T2 weighted) and with (**b**, T1 weighted) contrast taken from the same patient demonstrated in Fig. 12.2 with left-sided ROCM pre-endoscopic ethmoidectomy. (**a**): There is left-sided ethmoid and maxillary sinus mucosal thickening (closed arrows) with associated inferior and middle turbinate enlargement (*open arrows*). (**b**): Contrast-enhanced scan demonstrates enhancing thickened mucosa (*open arrows*) directly adjacent to hypointense ischemic mucosa (*closed arrows*) which is consistent with fungal vascular invasion

immunosuppression is key, and this can often be accomplished quickly in patients with ketoacidosis. Infectious disease consultation directs medical and antifungal therapy, and both otorhinolaryngology and ophthalmology work to surgically eradicate infected tissue. Wide local excision of infected tissue should be performed promptly with establishment of sinus drainage. Infected tissue bleeds very little due to ischemia from angioinvasion by fungi and should be excised until bleeding occurs. Many patients require repeated surgical debridement. Surgery frequently

includes sinus and orbital exenteration. Orbital exenteration can be lifesaving even with intracranial involvement as this procedure decreases the total fungal load. Early cases can sometimes be successfully treated by surgical debridement alone without loss of the eye [14]. Local intraorbital irrigation of amphotericin B has also been reported to allow local infection control without orbital exenteration [15]. Furthermore, local surgical packing soaked with amphotericin B (1 mg/mL) can also improve outcomes by increasing the concentration of drug available to the infected tissues [16].

Medical management should be initiated urgently and includes intravenous amphotericin B (AmB) as a primary agent. AmB is a polyene antifungal agent that is fungistatic. The therapeutic dosage is 1–1.5 mg/kg/day [17]. Treatment is maintained for weeks to months. Nephrotoxicity is a major treatment limiting side effect. Liposomal amphotericin B has fewer renal side effects and is better tolerated at higher dosages. Occasionally the dosage may increasable beyond the traditional limits to provide fungicidal activity and increased efficacy. Locally administered AmB can and may also improve outcomes as mentioned previously. Newer adjunctive therapies include oral posaconazole, a triazole antifungal agent, and the echinocandins, a new class of antifungal drugs [18] that inhibits the synthesis of glucan in the fungal cell wall [19–21]. *Rhizopus oryzae* expresses the target enzyme of echinocandins, 1,3-beta-glucan synthase [12]. Both of these newer agents have been used in combination with liposomal AmB as the backbone therapy [12, 21]. Posaconazole has also been used in combination with liposomal AmB in refractory cases [22]. Both daily irrigation and packing of the surgical site can be helpful in the postoperative management of these patients. Daily intraorbital infusion of AmB may also be advantageous and can be readily achieved using a surgically placed catheter [23]. Kohn and Hepler successfully managed eight patients with limited debridement, intravenous AmB, and daily irrigation of the orbital tissues and involved paranasal sinuses with AmB (1 mg/cc). All eight patients avoided exenteration and retained good vision [14].

Hyperbaric oxygen therapy is another efficacious but adjunctive treatment modality. The exact mechanism of action is not well understood and is most likely multifactorial [24]. Hyperbaric oxygen treatment helps to counteract the tissue acidosis and ischemia caused by fungal angioinvasion by increasing the local oxygen tension. Additionally, the increased oxygen tension improves the action of macrophages and neutrophils and augments the effectiveness of AmB [24–27].

The mortality rate of ROCM ranges from 50 to 90% [9]. Patient prognosis depends upon a multitude of factors, but the most important is the successful reversal of the underlying immunosuppression that precipitated the infection. Therefore, patients with diabetes in ketoacidosis have the best prognosis given that controlling their blood sugar and correcting the metabolic acidosis resolve their immunosuppression. With intracranial extension, the mortality rate approaches 90% [27, 28]. Early diagnosis and prompt treatment improve the chances for survival. Even patients with cavernous sinus invasion can survive with aggressive surgical treatment including sino-orbital as well as cavernous sinus exenteration.

Aspergillosis

Aspergillosis is caused by fungi in the order *Eurotiales* and genus *Aspergillus* [2], a group of ubiquitous filamentous fungi found in decaying vegetation and soil with typically low manifest intrinsic virulence. Similar to mucormycosis, the fungus usually invades the orbit after the inhalation of spores and the spread of infection through an adjacent paranasal sinus. Sino-orbital aspergillosis can be invasive or noninvasive and can affect both immunocompromised and immunocompetent hosts. The three species most commonly involved in orbital infections are *Aspergillus flavus*, *Aspergillus fumigatus*, and *Aspergillus niger.*

Noninvasive variants include localized sinus aspergillomas and allergic fungal sinusitis. Aspergillomas are found in immunocompetent patients with nonatopic disease. These fungus balls are usually caused by *Aspergillus fumigatus*. Allergic fungal sinusitis occurs in immunocompetent young adults with a history of asthma, atopic disease, polyps, chronic sinusitis, and aspirin sensitivity. Symptoms include nasal congestion, pain, and rhinorrhea. Serum IgE is often increased. CT and MRI reveal expanded and opacified sinuses that can mimic a neoplastic process. On MRI, the opacities are usually isointense or hypointense on T1 with a more marked decrease in signal intensity on T2. Orbital involvement occurs in up to 17% of patients and is more often caused by *Bipolaris* species than by *Aspergillus* species. Treatment includes surgical debridement, aeration of the sinuses, and both topical and systemic corticosteroids. Systemic antifungals are not required.

Invasive sino-orbital aspergillosis generally occurs in immunocompromised patients. The lungs are the most common site of infection, but the paranasal sinuses, orbit, and brain may also be involved. Risk factors include an underlying hematologic malignancy such as leukemia or lymphoma, organ transplantation, diabetes, and acquired immunodeficiency syndrome (AIDS). Before modern therapies for HIV were available, sino-orbital aspergillosis was a major fatal complication of AIDS.

Presenting signs include the abrupt onset of proptosis, orbital pain, and visual loss. Inflammatory signs may be minimal. Imaging studies are helpful in establishing a diagnosis. On CT, soft tissue masses are heterogeneous due to the presence of iron, manganese, or calcium (Fig. 12.4). Bony erosion can occur due to the pressure effect from the mass and the presence of inflammatory mediators. MR imaging reveals sino-orbital contrast-enhancing masses that appear hypointense on both T1- and T2-weighted images with surrounding mucosal inflammation (Fig. 12.5a–c). In contradistinction, bacterial infections and neoplasms are more often hyperintense on T2-weighted imaging.

A definitive diagnosis requires a tissue specimen and fungal cultures. A potassium hydroxide prep shows fungal elements, and the hyphae are characteristically regular and septated with acute-angle branching (Fig. 12.6) in contrast to *Mucor* species whose hyphae are large, irregular, and nonseptate with wide angle branching.

Treatment involves the surgical debridement of infected tissues combined with local and systemic antifungal therapy. In advanced cases, exenteration of the affected

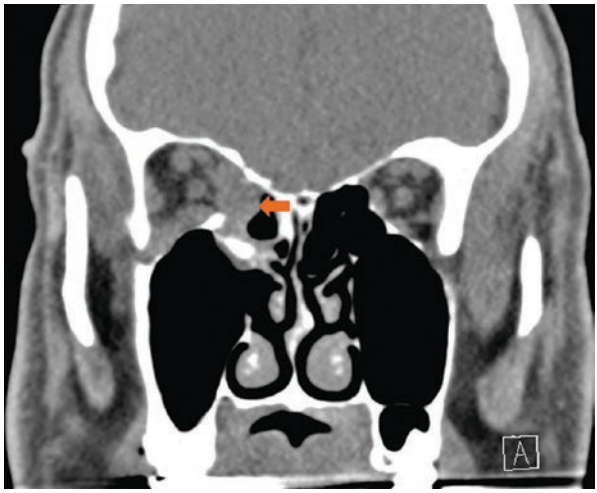

Fig. 12.4 CT scan without contrast in the coronal plane demonstrating an ill-defined soft tissue mass involving the posterior orbit and ethmoid sinus (*arrow*)

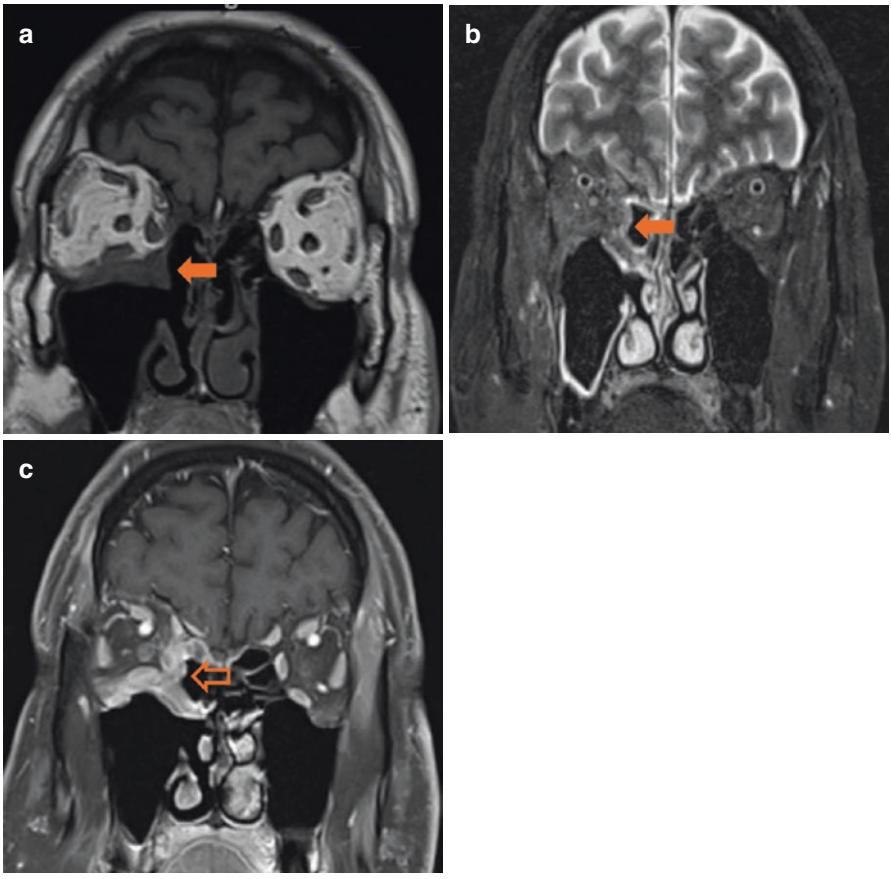

Fig. 12.5 MRI scan in the coronal plane without contrast demonstrating hypointense mucosal thickening (*closed arrows*) on both T1 (**a**)- and T2 (**b**)-weighted imaging. T1-weighted scan (**c**) with contrast demonstrates an ill-defined contrast-enhancing lesion of the maxillary and ethmoid sinuses as well as the posteromedial orbit (*open arrow*)

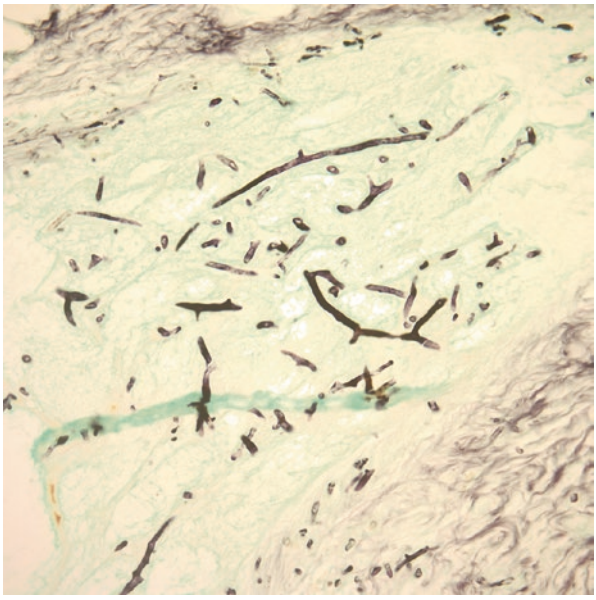

Fig. 12.6 *Aspergillus* infection showing regular septated fungal hyphae with acute angle branching. GMS × 200

sinuses and orbit is often required (Fig. 12.7a, b). Efforts should be made to reverse underlying immunosuppression. If immunosuppression cannot be reversed, the prognosis is guarded even with aggressive surgical and medical management. Like those affected by mucormycosis, patients with poorly controlled diabetes in ketoacidosis tend to have the best prognosis as their immunosuppression can be reversed. AmB used to be the mainstay of medical therapy. However, a recent study showed that systemic voriconazole led to better disease responses and higher survival rates compared with AmB in patients with invasive aspergillosis without concomitant mucormycosis [29]. Similar to mucormycosis, management is multidisciplinary and should be shared among an ophthalmologist, ENT surgeon, neurosurgeon, infectious disease specialist, and the patient's hematologist/oncologist.

During the early years of the AIDS epidemic invasive sino-orbital aspergillosis was a common disease process with a very high mortality rate. Most cases were caused by *Aspergillus fumigatus*. A low CD4 cell count (<50 cells/mL) and a history of marijuana smoking were noted to be risk factors. These patients had a very slow progressive onset of disease with headache and proptosis and showed minimal inflammatory signs [5]. Despite aggressive surgical and medical therapy, most of these patients died from this infection. With modern HIV treatment, this process is now fortunately rare.

In Sudan and other Middle Eastern countries, there is a chronic progressive and sclerosing form of sino-orbital aspergillosis that affects otherwise immunocompetent individuals. The infection is caused by inhalation of *Aspergillus flavus* spores. This fungus is endemic to the region, and frequent dust storms facilitate spore inhalation. Treatment requires surgical excision of the infected tissues along with systemic and local administration of antifungal agents [30].

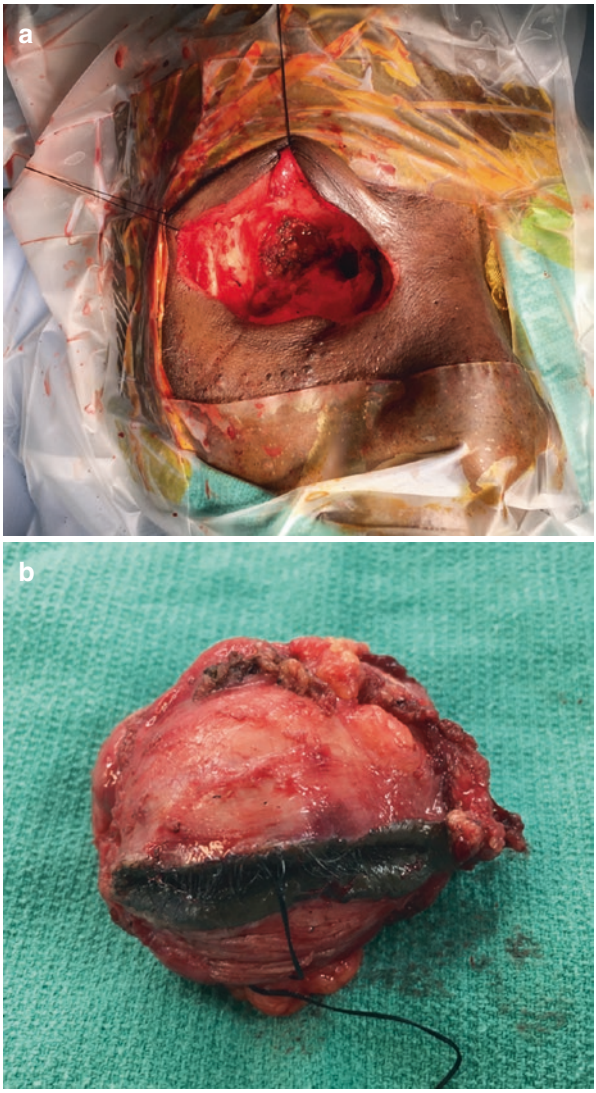

Fig. 12.7 Patient with invasive orbital aspergillosis immediately following lid-sparing orbital exenteration surgery (**a**). Orbital contents (**b**)

Summary

Orbital fungal infections are rare but are vision and life-threatening complications. Mucormycosis and aspergillosis make up the vast majority of these infections and are ordinarily present in immunocompromised patients. Patients are often misdiagnosed and/or diagnosed late resulting in a high mortality rate. One should maintain a high index of suspicion in any patient with a sino-orbital process not responsive to conventional therapy that is also diabetic or otherwise immunocompromised. Orbital disease accompanied by optic neuropathy, decreased ocular motility, and

trigeminal hypesthesia should alert the physician to the possibility of fungal invasion. Treatment includes a prompt multidisciplinary response and should be directed toward reversing causes of immunosuppression, biopsy and confirmation of the diagnosis, surgical debridement (often requiring sinus and orbital exenteration), and both local and antifungal therapy. Adjunctive therapy with hyperbaric oxygen and the emergence of newer antifungal agents with fewer adverse side effects can improve patient prognosis.

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Chapter 13
Orbital Cellulitis in Cancer Patients

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According to the World Health Organization, over 14 million new cases of cancer are diagnosed each year, and over 8 million patients die of cancer each year [1]. Cancer patients present with a unique set of anatomic, physiologic, and treatment-related conditions that may result in immunosuppression and infection. Among the infections that can occur in cancer patients is orbital cellulitis, which may be due to immunosuppression caused by the cancer itself (e.g., leukemia or lymphoma) or due to treatments for cancer (e.g., cytotoxic chemotherapy, immune-targeted therapy, or bone marrow transplant). Tumor-induced, surgery-induced, and radiation-induced changes to the orbital and facial tissues can also contribute to the development of orbital cellulitis in cancer patients. In this chapter, we review the etiology and management of orbital cellulitis in cancer patients and review masquerade syndromes and treatment-induced inflammatory conditions that may mimic this condition.

Etiology of Orbital Cellulitis in Cancer Patients

Cancer-Related Immunosuppression

Hematologic malignancies, such as lymphomas, leukemias, and multiple myeloma, directly alter the functioning of the immune system as they involve the bone marrow and cells primarily responsible for both innate and adaptive immunity. Specifically,

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lymphomas are abnormal proliferations of lymphoid cells; leukemias are abnormal proliferations of single populations of cells that are found in the blood and/or bone marrow; and multiple myelomas are abnormal proliferations of immunoglobulin-producing plasma cells. Not surprisingly, then, infectious disease has been reported to be the most common cause of morbidity and mortality in patients with lymphoproliferative diseases [2].

Interestingly, the literature does not provide us with much information to suggest that lymphomas and leukemias by themselves contribute significantly to orbital cellulitis. Nonetheless, in the experience of the authors of this chapter, orbital cellulitis is not an uncommon finding in patients with hematologic malignancies, although it may be related more to treatment than to the cancer itself, as discussed further below.

Treatment-Related Immunosuppression

Treatment of cancers, especially lymphomas and leukemias, is very well recognized to be a source of altered immune function resulting in infection. In the normal physiologic state, the functioning of the immune system depends heavily on vastly complex interactions between several cell types and their chemical mediators; throwing this system out of balance results in susceptibility to infection. Classic cytotoxic chemotherapies that target highly metabolically active cells destroy most types of immune system cells in the bone marrow. Increased risk of sinus and orbital infections has previously been reported in relation to such treatments [3, 4]. Even the newer targeted therapies, which are directed against single cell types or serum targets, which theoretically minimize the incidence of neutropenia, can have untoward downstream effects altering immune system functionality. Orbital cellulitis is recognized as a potential complication of the use of targeted monoclonal antibodies and other biologic drugs for treatment of autoimmune diseases [5–7].

Anatomical Changes

Given that many orbital infections originate from the paranasal sinuses, it stands to reason that changes in the anatomy of the orbit and paranasal sinuses may contribute to the development of orbital cellulitis. Normally, the maxillary, anterior ethmoidal, and frontal sinuses drain into the middle meatus; the middle and posterior ethmoidal sinuses drain into the ethmoidal bulla and superior meatus, respectively; and the sphenoid sinus drains into the sphenoethmoidal recess. It is well documented that obstruction of these drainage pathways by any of a number of causes, including tumor, leads to opacification of the blocked sinus, ultimately allowing

microorganism overgrowth and infection [8]. If a sinus were to become obstructed as a result of surgical removal of a tumor or placement of tissue flaps to repair a large defect in the sinonasoorbital area, and if no alternate drainage pathway were established, infectious sinusitis would be expected to develop and potentially evolve into an orbital cellulitis.

At the cellular level, radiation has long been known to cause a myriad of changes to upper respiratory mucosal tissue, including loss of cilia, dysmorphism of cilia, and intercellular and intracellular vacuolation [9]. These alterations of the tissue significantly reduce local control of microorganism populations and are associated with an increased incidence of paranasal sinus infection after head and neck radiotherapy [10]. Persistent or recurrent orbital cellulitis has previously been reported as a frequent (more than 70% of patients) complication of radiation treatment for paranasal sinus rhabdomyosarcoma [11].

Organisms Implicated in Orbital Cellulitis

Most reports of orbital cellulitis in the literature are reports of single cases or small case series. However, even though few cases of orbital cellulitis in cancer patients have been reported in the literature, the causes of orbital cellulitis due to cancer-related immunosuppression and the causes of orbital cellulitis due to other causes of immunosuppression, such as AIDS, are likely to be similar. Organisms commonly implicated in orbital cellulitis include *Streptococcus* species, including *Streptococcus pneumoniae*, staphylococci, and a variety of Gram-negative rods, such as *Klebsiella* and *Pseudomonas* species, especially in profoundly neutropenic patients with hematologic cancer [12–14]. In the latter group of patients, orbital cellulitis could be the result of contiguous extension from a concomitant invasive fungal sinus infection. A variety of opportunistic molds, such as *Aspergillus*, *Fusarium*, and *Mucor* species, have been implicated. Mycobacteria, parasites, and *Pneumocystis* species are extremely rare causes of orbital cellulitis in cancer patients [15].

Extension of Organisms from the Paranasal Sinuses

Orbital cellulitis is often a result of infection or organisms originating from the nearby paranasal sinuses. While some of these organisms have gained the ability to elude the body's natural defenses and thus cause infection in an otherwise healthy patient, other organisms are kept at bay until the defenses break down and thus cause what is known as an opportunistic infection. This is particularly common for fungal species; multiple papers in the literature describe cases of fungal orbital cellulitis in patients with immunosuppression due to various causes [16]. Only rarely do fungi cause orbital cellulitis in otherwise healthy patients; there are only a few

published case reports describing this [17, 18]. Mortality rates associated with fungal orbital cellulitis have been reported to be as high as 85% in patients with suppressed immune systems [19].

Evaluation of Cancer Patients with Suspected Orbital Cellulitis

In the care of a cancer patient with suspected orbital cellulitis, a thorough history and physical examination are essential. Early and aggressive clinical monitoring of the patient for evolution of signs and symptoms is necessary. Any history of systemic or malignant disease warrants careful consideration. Particular attention should be paid to systemic risk factors for immunocompromise: current or previous chemotherapy or treatment with immunomodulatory drugs, diabetes mellitus, recent history of other atypical infections, and low blood cell counts. The history should also cover other plausible direct causes of orbital cellulitis, such as previous orbital or sinus surgery, the presence of an upper respiratory tract infection or sinusitis, a previous skin infection (or preseptal cellulitis), periodontal disease, an underlying systemic infection, and a recent local trauma, which could be associated with a retained intraorbital foreign body.

Aggressive imaging is also probably necessary. It is important that baseline imaging be obtained at the initial suspicion of orbital cellulitis in a cancer patient to assess the extent of orbital and periorbital soft tissue involvement and to rule out obvious fungal sinusitis. Repeat imaging should be obtained if the patient's clinical findings worsen despite treatment. The use of diagnostic imaging, including contrast-enhanced computed tomography (CT) and magnetic resonance imaging (MRI), can demonstrate extensive sinus mucosal thickening in up to 68% of patients with upper respiratory infections [20]. Therefore, in patients without cancer, imaging is recommended only when symptoms of sinusitis are persistent. However, in immunocompromised patients, a much lower threshold is often applied because of the increased risk of and potentially devastating consequences of serious infections such as fungal cellulitis and sinusitis. Typical findings on orbital CT of a patient with orbital cellulitis include proptosis (best assessed on axial view), preseptal diffuse soft tissue thickening with areas of enhancement (indicative of edema or cellulitis), poor definition of the orbital planes, intraconal fat stranding, and extraocular muscle edema (Figs. 13.1c, d and 13.2b). Intraorbital abscess formation, either in the subperiosteal plane of a bone adjacent to an infected sinus or elsewhere in the orbit, should be sought for on the CT scan. MRI is usually not indicated, but if MRI is done, any abscess will be hypointense on

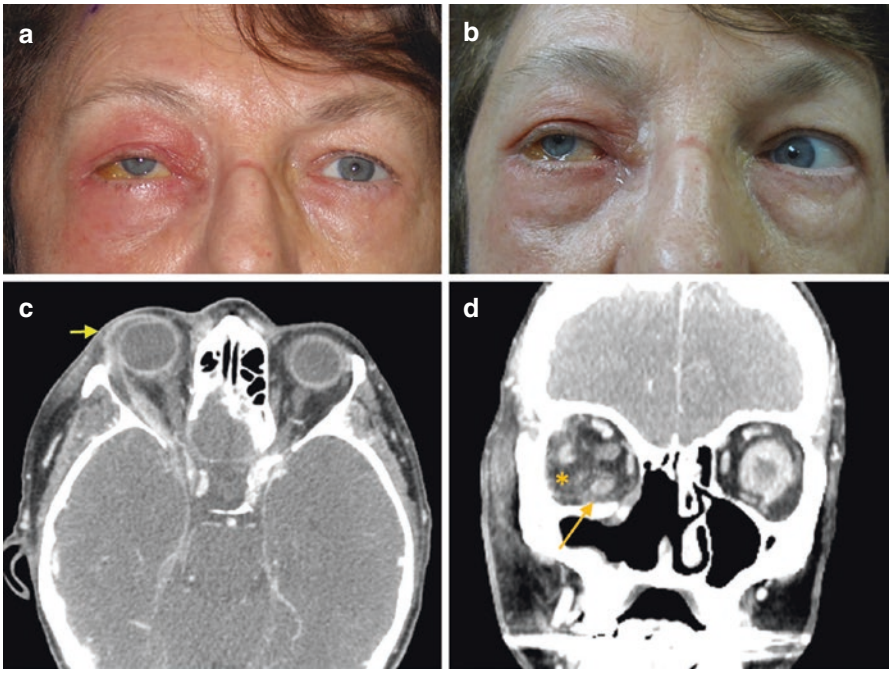


Fig. 13.1 Orbital cellulitis in a cancer patient after a sinus surgery. A 69-year-old woman presented to our service with swelling, decreased visual acuity, and pain in the right eye. She had a history of a recurrent atypical pituitary macroadenoma with extension into the sinuses and CREST (calcinosis, Raynaud phenomenon, esophageal dysmotility, sclerodactyly, and telangiectasia) syndrome. She had undergone multiple surgical resections and received a total of 70 Gy of radiation. On examination, she was afebrile, the visual acuity was 20/60 in the right eye (compared with 20/25 at baseline), and there was a positive afferent pupillary defect. The patient had right eye proptosis, upper eyelid ptosis, restriction in movements, and pain in all directions of gaze (**a**, **b**). Ocular examination revealed conjunctival chemosis; there were no other intraocular findings. A laboratory work-up revealed leukocytosis (leukocyte count, 17.6×10^9/L) and an absolute neutrophil count of 14.2×10^9/L. Computed tomography showed right eye proptosis, periocular soft tissue thickening (**c**, *arrow*), intraorbital fat stranding (**d**, *asterisk*), enlargement of the extraocular muscles (**d**, *arrow*), and a bony defect in the medial wall from a previous sinus surgery (d). The patient was treated with broad-spectrum systemic antibiotics and antifungals, and the orbital cellulitis gradually resolved over 13 days of treatment

T1, will be hyperintense on T2, will show diffusion restriction on diffusion-weighted imaging, and may show rim enhancement on T1 after contract injection.

We also routinely obtain a consultation from an ear, nose, and throat specialist to make sure that nasal endoscopy is performed to rule out obvious fungal sinusitis.

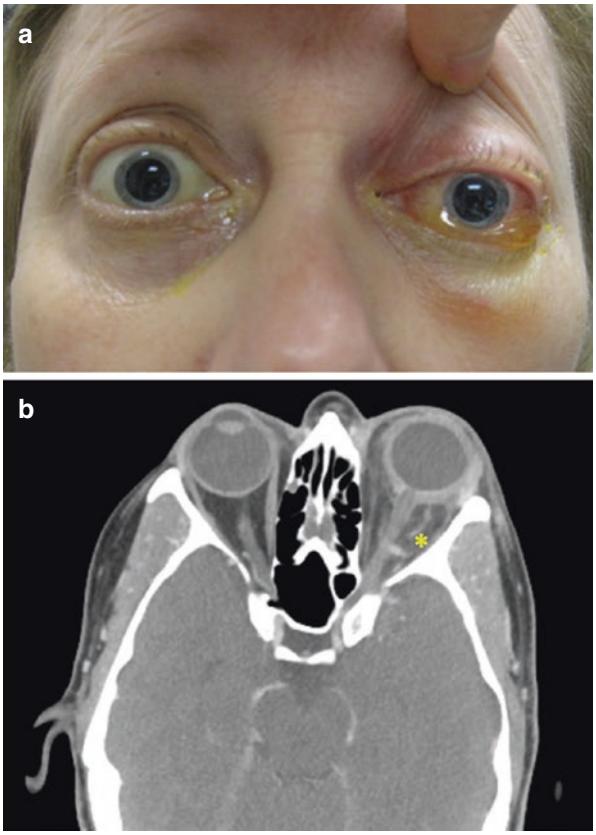


Fig. 13.2 Orbital cellulitis in a cancer patient treated with chemotherapy. A 56-year-old woman with lung adenocarcinoma treated with local resection, radiation therapy, and chemotherapy presented to our service with worsening left eye irritation and progressive swelling during chemotherapy. On examination, she was afebrile, the best corrected visual acuity was 20/40 (compared with 20/25 at baseline), and the patient had full color vision and no afferent pupillary defect. The patient had left eye periocular edema and erythema with upper eyelid ptosis. She had left eye hypoglobus and proptosis of 2 mm compared to the right eye. Prominent conjunctival chemosis was noted with conjunctival exposure on eyelid closure (**a**). Extraocular movements were restricted in all directions of gaze; no further findings were noted on dilated fundus examination. A laboratory work-up demonstrated white blood cell count within normal limits. Computed tomography showed left eye proptosis and hypoglobus, periocular soft tissue thickening, induration and stranding of the intraconal fat (*asterisk*), and abnormal enhancement of the extraocular muscles (**b**). The patient was treated with broad-spectrum antibiotics, and clinical improvement was noted after 6 days

Clinical Findings in Cancer Patients with Orbital Cellulitis

The clinical examination findings in cancer patients with orbital cellulitis may be similar to the findings in patients with orbital cellulitis in the general population and often include fever, periorbital soft tissue edema, erythema, warmth, tenderness,

upper eyelid ptosis, chemosis, limitation of and/or pain with extraocular motility, and proptosis (Figs. 13.1a, b and 13.2a). Deeper orbital soft tissue involvement (postseptal involvement) may be accompanied by gradual visual loss, but in the absence of an orbital abscess, acute optic nerve compromise is unlikely. Since neutropenia is common in cancer patients, inflammatory signs in cancer patients with orbital cellulitis may be less severe than inflammatory signs in immunocompetent patients with orbital cellulitis.

The physician should assess functionality of all orbital structures, including the optic nerve (by testing for visual acuity, pupillary reaction, color vision, and visual field); motor cranial nerves III, IV, and VI (by testing for limitation in ductions); and sensory cranial nerves V1 and V2 (by testing for hypoesthesia of the cornea and periocular skin). A full ophthalmic examination including dilated fundoscopy should be performed with special attention to the optic disk and engorgement of venous vessels. Neurological signs and symptoms, such as headache, meningismus, multiple cranial neuropathies, and progression to involve the contralateral side, seizures, focal neurological deficits, and altered mental status, should alert the clinician to the possibility of intracranial involvement. In cancer patients, all these signs and symptoms should be sought. Further work-up and close monitoring are recommended even in patients with only preseptal signs without evidence of orbital involvement because patients with cancer and orbital cellulitis are prone to more rapid deterioration than is observed in patients without cancer.

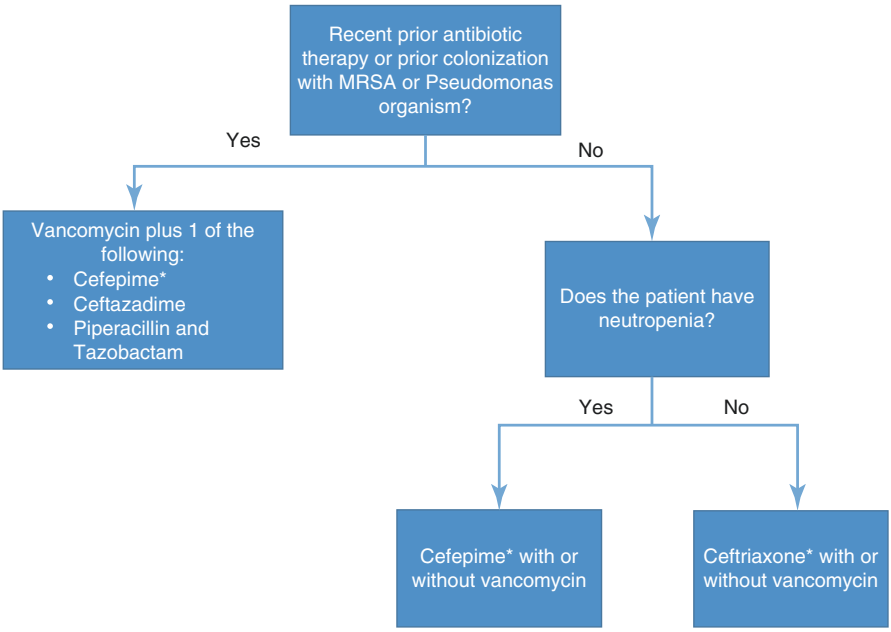
Progression of Orbital Cellulitis to Orbital Abscess

The frequency of abscess in patients with orbital cellulitis is a subject of debate. One paper in the literature proposes immunocompromise as a risk factor for progression of paranasal or orbital cellulitis to the development of an abscess; however, the paper provides no data to support the claim [21]. Interestingly, in a review by the senior author (B.E.) of radiographic studies in all cancer patients treated for orbital cellulitis at our tertiary cancer center over the past 10 years, no classic subperiosteal orbital abscess was found (unpublished data). The rarity of progression of orbital cellulitis to orbital abscess may be due to an alteration in the normal function of the immune system and lack of a robust inflammatory response to infectious agents in cancer patients. One study of the milieu of cytokines expressed in children with orbital cellulitis with a subperiosteal abscess revealed elevation in interleukin-1 (IL-1), IL-1 receptor antagonist, IL-6, and tumor necrosis factor as significant components [22]. In cancer patients, changes in cellular physiology due to immune suppression may affect the expression of these inflammatory mediators and other cytokines, and this phenomenon may explain the rarity of orbital abscesses in the setting of orbital cellulitis in cancer patients.

In a 2015 review from the United Kingdom of 54 non-cancer patients with a diagnosis of orbital cellulitis seen between January of 2008 through December of 2012, 11 patients (20%) had subperiosteal abscesses, and an additional 5 patients (9%) had an orbital abscess [23]. A retrospective review published in early 2015 showed that an abscess of any kind developed in 32 of 83 children (39%) with orbital cellulitis [24]. In contrast, in the reports of orbital cellulitis in immunocompromised patients published thus far, no patients were found to have subperiosteal abscesses. Careful review of the literature reveals rare case reports of soft tissue abscess formation in the orbital and ocular adnexal tissues in immunocompromised patients, but none of these abscesses are subperiosteal abscesses [25, 26]. In a 2004 case series of seven immunocompromised patients with fungal orbital cellulitis, no abscesses were noted; however, nearly all patients had extensive opacification of the sinuses with varying degrees of bony destruction [18]. In 18 years of practice at our tertiary cancer center, we have not encountered a single instance of an orbital subperiosteal abscess in a patient with orbital cellulitis in either the outpatient or inpatient setting. However, we have encountered isolated cases of soft tissue abscess in the area of the lacrimal sac or in connection with large flaps used for reconstruction; these have generally been localized to a heavily surgically treated and irradiated area near the nasal cavity or other part of the paranasal sinuses. Thus, the absence of a subperiosteal abscess in a patient with suspected orbital cellulitis and a history of malignancy should not put the clinician's mind at ease.

Treatment of Orbital Cellulitis in Cancer Patients

As soon as orbital cellulitis is suspected in a cancer patient because of clinical findings of periorbital soft tissue edema or erythema, empirical broad-spectrum antibacterial and antifungal treatments should be initiated. The use of broad-spectrum bactericidal or fungicidal agents given intravenously in appropriate doses is of paramount importance. This therapy should be instituted before imaging studies of the orbit are arranged and before ophthalmology and ear, nose, and throat consultations are obtained. In the majority of patients, broad-spectrum antibiotics are started empirically; subsequently, careful clinical evaluation indicates whether de-escalation or further intensification of antibiotics is needed. Finally, it is important to correct underlying metabolic abnormalities in patients with orbital cellulitis (e.g., to obtain glucose control in patients with uncontrolled hyperglycemia). Figures 13.3 and 13.4 depict a reasonable approach to the

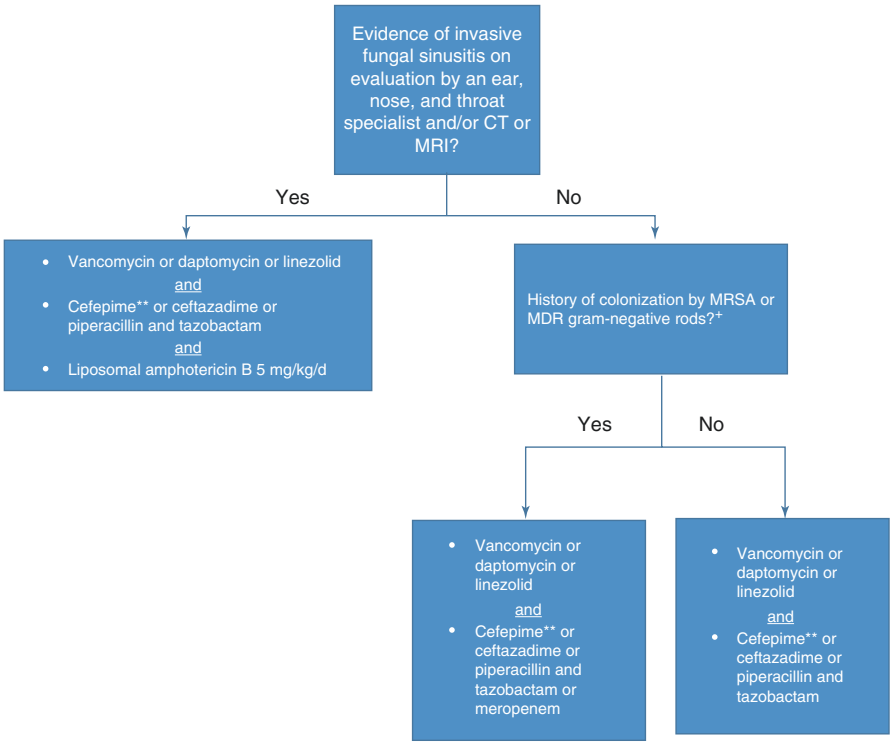


*Fluoroquinolone should be used instead for patients with a history of severe penicillin or cephalosporin allergy. MRSA, methicillin-resistant *staphylococcus aureus*

Fig. 13.3 Empiric treatment of acute orbital cellulitis in patients with solid tumors

empirical choice of anti-infectives in patients with cancer and suspected orbital cellulitis at our institution. This approach, however, is not necessarily applicable to every patient.

In view of the relative rarity of orbital cellulitis in cancer patients, there is no consensus regarding the optimal management of this condition. Treatment is individualized and depends on factors such as the presence of comorbidities (especially kidney or renal dysfunction), drug-drug interactions, prior exposure to antibiotics, and the possibility of selection for resistant organisms and local epidemiology of resistance. In addition, the choice of antibiotic is individualized and depends on the rapidity of symptom onset (rapid onset favors bacterial etiology), the presence of features suggestive of adjacent fungal sinusitis, and the possibility for intraorbital or even central nervous system (e.g., cavernous sinus thrombosis) involvement.



*Typically patients with leukemia and/or transplant recipients are on prophylaxix with a quinolone or an oral cephalosporin as well as with a mold-active triazole. ** Aztreonam or meropenem or and aminoglycoside should be used instead in patients with a history or severe penicillin or cephalosporin allergy. + Local antibiogram and prior information about the susceptibility of colonizing bacterium drive the selection. CT, Computed tomography; MDR, multi-drug-resistant; MRI, magnetic resonance imaging; MRSA, methicilin-resistant *Staphylococcus aureus*

Fig. 13.4 Empiric treatment of acute orbital cellulitis in patients with leukemia and/or transplant recipients*

CT or MRI of orbit to evaluate the extent of cellulitis and to check for the presence of a drainable focus is critical. Blood culture should be performed in patients with septicemia and secondary "seeding" to the orbit, and the use of biomarkers (beta-D glucan, *Aspergillus* galactomannan) might be helpful in selected patients. Biopsy is reserved for rare cases in which tumor infiltration masquerading as infection (discussed in the next section of the chapter) cannot be ruled out.

An infectious disease consultation is highly recommended in patients with severe or atypical orbital cellulitis or in patients in whom resistant strains of bacteria are suspected.

Regarding the need for surgical intervention, cancer patients with orbital cellulitis often have accompanying thrombocytopenia due to cancer treatments such as chemotherapy or bone marrow transplant. Thus, surgical intervention for orbital or sinus infection is often not an early consideration as it might be in healthier patients. Obviously, should an abscess actually be present, it should be managed acutely with

surgical drainage. However, as we have already established, a subperiosteal abscess is a very rare finding in cancer patients with orbital cellulitis. The current philosophy is to employ watchful watching after rapid initiation of broad-spectrum antibiotics and reserve surgery for selected patients who have an intraorbital abscess or necrotic lesions in the sinuses.

Masquerade Syndromes

Malignancies can present with signs and symptoms suggestive of orbital cellulitis. For example, there are numerous reports of cancer masquerading as invasive fungal sinusitis with signs of cavernous sinus involvement, a scenario seemingly overrepresented in patients with T-cell lymphomas [27–33]. Lesions such as Langerhans cell histiocytosis have also been treated as orbital cellulitis before the correct diagnosis was made [34]. Additionally, the scientific literature contains multiple reports of intraocular or orbital tumors and metastases in the orbit or paranasal sinuses that presented the like and were initially misdiagnosed as orbital cellulitis [35–42]. Retinoblastoma can masquerade as orbital cellulitis, as indicated in multiple reports [43–46]; so can pleomorphic adenoma [47]. Interestingly, there are also reports of orbital masses initially believed to be tumors but later confirmed to be chronic infectious abscesses [48].

More recently, noninfectious orbital inflammatory conditions have emerged that are related to treatment for cancer. Subtenon injection of carboplatin for the treatment of retinoblastoma has been associated with noninfectious orbital inflammation [49]. Bisphosphonates, often used in cancer patients with abnormal bony metabolism, have long been known to cause various types of ocular or orbital inflammation [50, 51]. Intravesical bacille Calmette-Guérin immunotherapy used for bladder cancer has been reported to cause orbital inflammation [52]. Such scenarios are expected to become more frequent as oncologists treat more diseases with immune-modulating therapies. It is therefore prudent in all cases of suspected orbital cellulitis in patients with a history of cancer to note of all treatments rendered for their disease.

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Chapter 14
Intracranial Complications of Orbital Cellulitis

Karolyn Au and Jacques J. Morcos

Introduction

Intracranial complications of sinus and orbital infection are uncommon but can lead to significant morbidity and mortality. They include cavernous sinus thrombosis, epidural abscess, subdural empyema, cerebritis and brain abscess, and meningitis. These processes can occur in combination, at any stage of orbital cellulitis, and with rapid progression, so a high index of suspicion must be maintained when managing patients with orbital cellulitis.

Anatomy

The intimate association of the orbit with the anterior skull base allows intraorbital infectious processes to extend into the intracranial compartment. The roof of the orbit is formed by the orbital plate of the frontal bone, with variable interposition of the frontal sinus depending on its extent of pneumatization. Diploic channels and occasional areas of dehiscence form direct communications from the extracranial space to the dura. The cells of the ethmoid sinus, separated from the medial orbit only by the thin lamina papyracea, lead posteriorly to the sphenoid sinus, which abuts the sella turcica, optic canal, and cavernous sinus.

At the orbital apex, multiple neural and vascular structures enter and exit the orbit: the optic nerve and ophthalmic artery via the optic canal, and divisions of the oculomotor (CN III), trochlear (CN IV), ophthalmic (CN V1), and abducens (CN

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VI) nerves, the recurrent meningeal branch of the ophthalmic artery, and the superior ophthalmic vein via the superior orbital fissure (SOF). The optic nerve sheath is continuous with the intracranial dura and remains applied to the bone, so that the optic nerve freely traverses the subarachnoid space toward the optic chiasm. Posteriorly, the periorbita of the SOF is continuous with the connective tissue layer arising from the epineurium of the cranial nerves that forms the lateral wall of the cavernous sinus.

The paired cavernous sinuses are venous channels situated on either side of the sella, formed between the periosteal and meningeal layers of dura. They are connected by the anterior and posterior intercavernous sinuses and have venous communications with the cerebrum, cerebellum, face, orbit, nasopharynx, mastoid, and middle ear [1]. Anteriorly, the cavernous sinus is bounded by the medial end of the SOF and posteriorly by dura at the petrous apex and dorsum sellae. The roof is formed by a fold of dura attached to the anterior and posterior clinoid processes and petrous apex and the floor by the endosteum of the greater sphenoid wing. The oculomotor, trochlear, ophthalmic, and maxillary nerves run in the lateral wall and the cavernous segment of the internal carotid artery and abducens nerve within the sinus.

Tributaries of the anterior facial vein communicate with the superior ophthalmic vein, which drains to the cavernous sinus. In addition, the cavernous sinus receives blood from the inferior ophthalmic vein, the sphenoparietal sinus, the superficial middle cerebral vein, and variably the central retinal vein and middle meningeal vein tributaries. Emissary veins traverse the sphenoid emissary foramen, foramen ovale and foramen lacerum. The superior and inferior petrosal sinuses form a confluence with the basilar venous plexus and, respectively, drain the cavernous sinus to the transverse sinus and jugular bulb. These venous channels do not contain valves, so the direction of flow within the system is determined by relative pressure and can be altered by the presence of pathology.

Etiology

Intracranial complications of sinusitis and orbital cellulitis arise through two major mechanisms: retrograde thrombophlebitis and direct extension [2]. The shared venous drainage of the face and paranasal sinuses and the intracranial structures facilitates the spread of infectious thrombophlebitis. As these veins are valveless, thrombophlebitis or septic emboli can progress in retrograde fashion into the cavernous sinus. Less commonly, direct extension of osteomyelitis of the sinus or orbital walls or suppurative penetration through natural or traumatic bony defects can admit infection to the epidural space. Purulence can then further penetrate through the dura to the subdural space, subarachnoid space, and brain parenchyma. The frontal bone is particularly vulnerable to infectious spread, likely due to its extensive network of diploic veins, and in adolescents, rapid growth of the frontal sinuses.

Clinical Presentation

In the modern era, intracranial complications are seen in 1–2% of cases of orbital cellulitis [3]. Demographics parallel the incidence of orbital cellulitis, more commonly affecting older children and males. In the same way that orbital infection most commonly results from sinusitis, so does intracranial suppuration, although symptoms of sinusitis may be variable or absent. Clinical findings depend on the site or sites of involvement, although most patients have fever and headache. Altered mental status, focal neurological deficit, seizure, meningismus, and signs of increased intracranial pressure (ICP) may be present in intracranial infection, while proptosis, periorbital edema, and chemosis may reflect cavernous sinus pathology. The presentation of meningitis, subdural empyema, and cavernous sinus thrombosis may be acute and progress rapidly, while development of epidural abscess and focal encephalitis may be more insidious. It is important to note that patients may not have focal neurologic findings, and radiographic studies should be considered to identify intracranial complications prior to development of irreversible sequelae.

Management

The initial medical management of orbital cellulitis includes broad-spectrum intravenous antibiotic coverage using agents with adequate central nervous system penetration, with consideration for local resistance patterns. In keeping with typical pathogens causing acute sinusitis in children, the most common agents include *Streptococcus* spp. and *Staphylococcus* spp., while introduction of the *Haemophilus influenzae* type B (HiB) vaccine has reduced the incidence of HiB-associated infection and complications. Polymicrobial infection, often on a background of chronic sinusitis, is more common in adults, and initial antibiotic selection should include coverage of anaerobic bacteria. Upon identification of the causative organisms and their sensitivity profile, a tailored choice of antibiotic should be made.

Contrast-enhanced CT scan provides distinct bony resolution and is readily available on an emergent basis, and has long been the imaging study of choice to evaluate patients with suspected orbital infection. However, MRI should be obtained when an intracranial abnormality is suggested on CT or when contrast-enhanced CT fails to provide adequate explanation for a patient's clinical presentation. Contrast-enhanced MRI is highly sensitive for detection of inflammation and focal fluid collections, and diffusion-weighted imaging (DWI) can provide additional diagnostic certainty for identifying abscesses even without contrast administration. CT or MR venography can help define abnormalities of the dural sinuses and cortical veins. Findings of intracranial pathology necessitate close neurological monitoring and urgent consultation with neurological surgery. The presence of intracranial complications is generally an indication for functional sinus surgery to treat an underlying sinusitis, which can be performed at the same sitting as surgical management of intracranial and orbital infection.

Cavernous Sinus Thrombosis

The inclusion of cavernous sinus thrombosis (CST) as group 5 in Chandler's classification of orbital complications of sinusitis reflects its involvement in both orbital and intracranial processes [4]. CST is an infectious thrombosis of the cavernous sinus, due to retrograde propagation of thrombophlebitis and/or septic embolism along the superior or inferior ophthalmic vein or direct spread of infection from the sphenoid sinus or orbit. Signs of sepsis, including spiking pyrexia, tachycardia, hypotension, and rigors, may be present. Periorbital edema, chemosis, and proptosis reflect venous hypertension of the orbit and are seen in over 90% of cases. Retinal edema and retinal vein engorgement with hemorrhages may be evident on fundoscopy. An afferent pupillary defect and decreased visual acuity may result from increased intraocular pressure. Cranial neuropathy can result in internal and external ophthalmoplegia, ptosis, mydriasis, abnormal periorbital sensation, and corneal anesthesia. Many of these findings are present in the setting of orbital cellulitis alone, but CST should be suspected if clinical signs worsen rapidly. The cardinal sign of cavernous sinus involvement is the development of bilateral orbital findings.

CST is most commonly demonstrated as cavernous sinus filling defect(s) and outward lateral wall bowing on contrast-enhanced CT and MRI. Narrowing of the cavernous and petrous segments of the internal carotid artery and arterial wall enhancement is frequently seen. Associated findings include dilatation or filling defect of the superior ophthalmic vein, thrombosis of cavernous sinus tributaries, and thrombus in the sigmoid sinus and internal jugular vein, as well as suppurative intracranial collections [5]. Susceptibility weighted MR imaging is highly sensitive to blood breakdown product and can demonstrate venous thrombi, and restricted diffusion in thrombosed venous structures can be seen. Areas of high DWI signal intensity within the bran parenchyma may reveal infarction due to emboli or hypoperfusion.

Bacteria may persist in septic thrombi until canalization occurs, allowing for antibiotics to penetrate. Anticoagulation therapy has therefore been advocated in the treatment of CST, and some retrospective series found a reduction in morbidity [6] or mortality [7] when anticoagulation was added to antibiotic treatment. Major hemorrhagic complications did not seem to be increased. Rapidly reversible intravenous heparin may be used for initial management of CST, followed by conversion to a longer-acting agent in the stable patient. In the absence of an underlying thrombophilia, anticoagulation may be discontinued when there is radiographic evidence of thrombus resolution [8].

The potential benefits of steroids in CST include decreased orbital inflammation and reduced cranial nerve and cerebral edema. However, these may be outweighed by immunosuppressive and prothrombotic effects. One study of steroid use in aseptic cerebral venous and sinus thrombosis showed no benefit and some harm. Steroids should therefore not be used in CST without evidence of parenchymal lesions or a specific indication such as adrenal insufficiency [9].

A rare complication of septic CST is the development of infectious aneurysms of the internal carotid artery [10]. Infectious intracranial aneurysms overall carry a high risk of hemorrhage and death, and some studies have shown improved survival with surgical treatment compared to antimicrobial therapy alone. However, one series found that although CST was a risk factor for development of infectious aneurysm, the response of these lesions to medical treatment alone was better than in other locations [11].

Although mortality from CST is uncommon in the modern era, up to half of patients are left with cranial neuropathy and a sixth have visual deficits [8]. Anterior hypopituitarism, likely due to venous thrombosis involving the hypophyseal vessels, may persist [12]. Parenchymal regions affected by arterial embolic or venous infarction may result in long-term neurological deficits or seizure.

Epidural Abscess

Most intracranial suppurative complications are associated with frontal sinusitis, due to the spread into the anterior cranial fossa directly through bony dehiscences or from osteomyelitis of the frontal bone. Outward spread of osteomyelitis results in frontal subperiosteal abscess, known as Pott's puffy tumor, and presents as tenderness and swelling of the forehead [13]. The spread of infection from the frontal sinus into the anterior cranial fossa can result in epidural abscess. The adherence of dura to the calvarium constrains the spread of purulence through the potential epidural space, and the thick dura itself forms a relatively protective barrier. The clinical course may therefore be indolent, with headache and fever developing over weeks. If the abscess grows to sufficient size, signs of increased ICP and focal neurological deficits may develop.

CT and MR imaging demonstrate a collection of extra-axial fluid with a biconvex shape, typically with rim enhancement. Large collections may exert mass effect on the adjacent brain. CT may show bone erosion, indicative of osteomyelitis. DWI may show low or mixed signal within the abscess. With routine imaging for orbital cellulitis, epidural abscess may be detected prior to development of specific symptoms.

The standard management of epidural abscess involves urgent surgical evacuation of purulent material added to systemic antibiotic-based therapy.

Subdural Empyema

Infection may penetrate through the dura to the subdural space, where an absence of anatomic barriers allows for rapid spread over the brain surface. Initial headache, fever, and neck stiffness can evolve to focal neurological deficit, signs of intracranial hypertension, and depressed level of consciousness within hours. Seizures are

more common in subdural empyema than with other intracranial complications. Thrombophlebitis of bridging and cortical veins can lead to venous stasis and cerebral infarction, with worsened cerebral inflammation and edema.

A different pathogenesis of subdural empyema occurs in infants; most commonly, meningitis leads to formation of a sterile subdural effusion from increased efflux of intravascular fluid, which becomes secondarily infected.

A fluid collection may not be apparent on CT imaging in early cases of subdural empyema, so MRI should be considered if the clinical presentation is suspicious. When seen, subdural empyema appears as a hypodense extra-axial fluid collection following the contour of the brain surface, which can track into the interhemispheric fissure. Rim enhancement is typical, particularly of the brain-adjacent side. Mass effect is generally due to edema and ischemia and can be disproportionate to the size of the fluid collection [14]. On T1-weighted MRI images, the purulent area is typically hypointense with a hyperintense rim, which enhances upon contrast administration. High signal is seen on T2-weighted images. In contrast to subdural effusions, which are also hyperintense on T2-weighted images, empyemas have high signal on DWI, while effusions have low signal similar to CSF.

Subdural empyema is a neurosurgical emergency, and surgical intervention to evacuate the purulent collection and decompress the brain should be carried out without delay. This is typically performed by craniotomy; burrhole drainage is an option but is associated with a higher rate of recurrence [15]. Broad-spectrum systemic antibiotics are administered until pathogen sensitivities are determined, then tailored as appropriate. Anticonvulsant therapy is indicated for seizure treatment and may be considered for prophylaxis given the frequent occurrence of seizure in patients with subdural empyema.

Cerebritis and Brain Abscess

The spread of infection from the extra-axial space to the brain parenchyma can result in cerebritis and subsequent brain abscess, which proceeds in defined histopathological stages [16]. Bacterial seeding incites focal inflammation, called early cerebritis. After ~3 days, the area of inflammation expands as the center develops coagulation necrosis in the late cerebritis phase. By 1–2 weeks, a well-vascularized capsule is walled-off by host defenses, marking the formation of an early abscess. Collagen deposition over the capsule and gliosis on the parenchymal surface are associated with a mature abscess. The extent of inflammation and tissue destruction depends on virulence of the pathogen and exuberance of the immune response and contributes to cerebral edema, mass effect, and neurologic injury. Infrequently, an abscess may rupture into the ventricular space, which is associated with a high mortality rate [17].

The pathological progression is reflected on imaging findings, with a ring-enhancing intraparenchymal lesion consistent with development of an encapsulated abscess. Cerebritis may appear as an irregular hypodensity on CT and may or may

not enhance. MRI is more sensitive than CT and is particularly useful during the early cerebritis stage; an area of low intensity on T1-weighted imaging and high intensity on T2-weighted imaging is readily detected. Restricted water diffusion within suppurative abscess fluid gives a high-intensity signal on DWI, which can help distinguish an abscess from a neoplastic ring-enhancing lesion should the clinical context be unclear.

Presentation of brain abscess may have a relatively indolent course, and the classic triad of fever, headache, and focal neurological deficit is seen in less than 20% of cases [18]. However, the development of focal deficit may correlate with the area of infection and local brain destruction. Headache is common and often nonspecific, although sudden worsening may signal intraventricular rupture of an abscess and attendant poor outcome. Seizure and signs of intracranial hypertension may develop.

Recognizing the pathological stage of infection is necessary in planning management, as cerebritis can be treated medically, while the formation of an abscess capsule prevents penetration of antibiotics and necessitates surgical intervention to drain the purulent core. The presence of associated extra-axial infection must be considered in developing a surgical plan.

Meningitis

Meningitis is the infection of the arachnoid membrane, subarachnoid space, and cerebrospinal fluid (CSF). The classic clinical triad of fever, headache, and neck stiffness occurs in less than half of adults with bacterial meningitis [19]. Patients may also have photophobia, nausea, seizure, and altered mental status, with no focal neurological deficits. An acute and rapidly progressive clinical course is typical. Cerebral edema causes increased intracranial pressure (ICP) and decreased cerebral perfusion, resulting in neuronal hypoxia/ischemia, and is an important cause of death. Cranial nerve deficits may develop either as a result of intracranial hypertension or of exudates encasing nerve roots. Inflammatory infiltrates can cause necrosis of blood vessel walls resulting in thrombosis and subsequent cerebral infarction.

CT imaging may appear normal or demonstrate sulcal effacement and small ventricles. Late findings may include venous infarction and communicating hydrocephalus. MRI studies may demonstrate leptomeningeal enhancement and high FLAIR signal within sulci.

Acute bacterial meningitis is a medical emergency, and effective antimicrobial therapy must be rapidly established to avoid excess morbidity and mortality. A lumbar puncture is indicated when the diagnosis of meningitis is considered and imaging has ruled out an intracranial mass lesion. Opening pressure exceeding 20 cm H_2O suggests increased ICP and correlates with worsened outcome. Analyses of CSF, showing neutrophilic pleocytosis, reduced glucose and increased lactate and protein levels, and positive Gram staining, support the diagnosis of bacterial meningitis and guide initial management [20]. CSF culture establishes the responsible pathogen.

Conclusion

While intracranial complications of orbital cellulitis are uncommon, they carry risk of significant morbidity. A high index of suspicion must be maintained when evaluating and managing patients with orbital infection. Broad-spectrum systemic antibiotic therapy is indicated to treat the primary infectious site as well as secondary locations and should be initiated promptly. Contrast-enhanced MRI is useful to identify and characterize intracranial pathology. Urgent neurosurgical intervention is generally needed for abscess evacuation. Long-term sequelae may include visual deficit, neurological impairment, and seizure.

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Chapter 15
Overview and Current Recommendations for the Treatment of Bacterial Endophthalmitis

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Abbreviations

BRE	Bleb-related endophthalmitis
EE	Endogenous endophthalmitis
EVS	Endophthalmitis Vitrectomy Study
PK	Penetrating keratoplasty
POE	Postoperative endophthalmitis
PPV	Pars plana vitrectomy
Va	Visual acuity

Introduction

Endophthalmitis is a severe infection that affects the contents of the entire globe, resulting in serious and potentially vision-threatening injury to the eye. It should be distinguished from localized infections that affect only part of the globe, such as blebitis or keratitis, and infections which also affect other surrounding structures,

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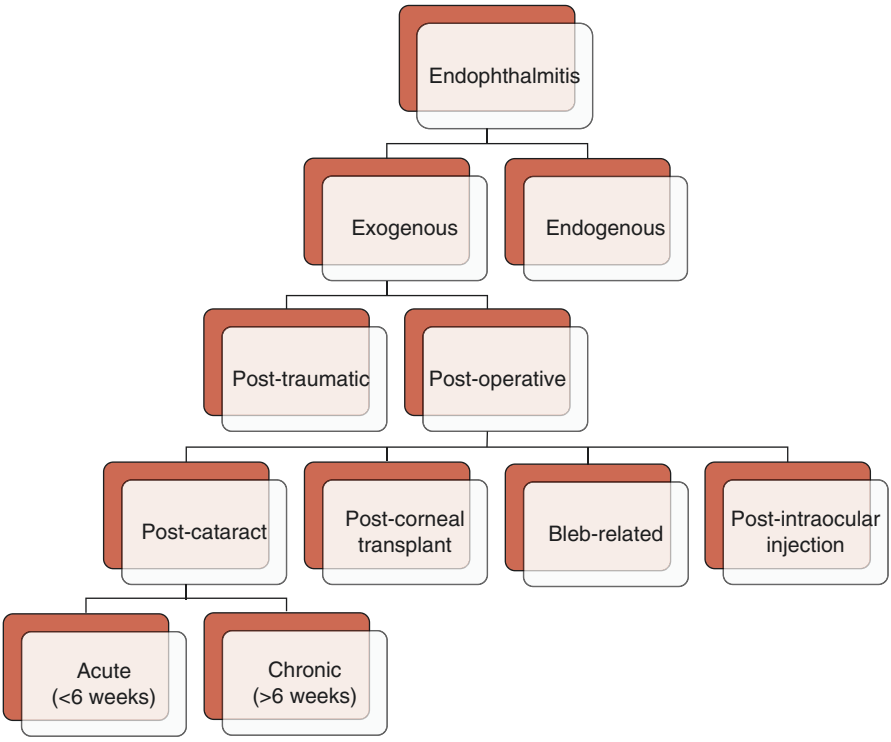

Fig. 15.1 Types of endophthalmitis categorized by route of infection

such as panophthalmitis. Exogenous endophthalmitis is caused by direct inoculation of an organism that invades the eye following a disruption of the outer ocular tissues, often after surgery or ocular trauma. Endogenous endophthalmitis is caused by introduction of an infectious agent into the eye via hematogenous dissemination from a distant internal source of infection (Fig. 15.1). Although fungi and parasites can cause endophthalmitis, the bacterial type is most common and will be the focus of discussion here.

Routes of Infection

Exogenous Endophthalmitis

Postoperative

Postoperative endophthalmitis can be classified into two broad categories: acute-onset (<6 weeks after surgery) and delayed-onset (>6 weeks after surgery). The overall incidence of acute-onset postoperative endophthalmitis is

approximately 0.1% [1–3]. Endophthalmitis can occur after any type of surgery; the most common procedures associated with postoperative endophthalmitis are discussed below.

Acute Post-cataract Surgery Endophthalmitis

Cataract surgery is one of the most common intraocular procedures and accounts for the majority of postoperative endophthalmitis cases [2, 4, 5]. The incidence of acute postoperative endophthalmitis (POE) after cataract extraction ranges from 0.028 to 0.16% in the literature [1, 2, 4, 6–12]. A variety of factors are associated with the risk of acute endophthalmitis including extracapsular or intracapsular extractions, surgeries combined with lacrimal or eyelid procedures, postoperative wound defects, preoperative eyelid abnormalities, and intraoperative complications, namely, posterior capsular rupture, which can increase the risk 8- to 11-fold [11, 13–16]. Nonsurgical risk factors for endophthalmitis after cataract surgery include age over 80 and diabetes [4, 16].

The pathogenic microorganisms are most commonly innate bacteria that reside on the eyelid margin and within the tear film [17, 18]. Coagulase-negative *Staphylococcus* is the most commonly isolated organism comprising 54–70% of culture-positive cases of POE [19–21]. *Staphylococcus aureus* and *Streptococcus* species also cause a significant number of cases [1, 19, 20, 22–24]. Negative cultures account for 16.7–35% of cases in the United States [1, 20, 21, 24, 25].

Chronic Post-cataract Surgery Endophthalmitis

Chronic post-cataract endophthalmitis is less common than acute POE and is marked by insidious inflammation. It can manifest weeks to months after surgery and is typically associated with less virulent bacterial and fungal pathogens. The incidence of chronic post-cataract endophthalmitis is 0.017% based on a single-center study [26]. *Propionibacterium acnes* is the most commonly isolated pathogen comprising 41.2–63% of positive cultures [26–30]. Coagulase-negative *Staphylococcus* [27, 31], *Corynebacterium* [31], *Candida* [27], *Actinomyces* [32], and *Nocardia* [33] species can also produce a similar chronic, smoldering presentation to that of *P. acnes* [27].

Bleb-Related Endophthalmitis

The incidence of bleb-related endophthalmitis (BRE) after trabeculectomy ranges from 0.061 to 2.6% [4, 34–40] for early-onset POE and 0.19–0.6% for late-onset POE [38–40]. Antiproliferative agent use [38, 39, 41, 42] and inferiorly-located trabeculectomies [35, 42, 43] significantly increase the risk of BRE. The

most significant postoperative risk factor is bleb leakage [41–43]. Gram-positive organisms, most commonly *Staphylococcus* and *Streptococcus* species, are responsible for the majority of cases [44–46]. Culture positivity is present in 64–86% of BRE cases, notably higher than rates associated with other causes of POE [45–47].

Post-corneal Transplantation Endophthalmitis

The incidence of endophthalmitis after penetrating keratoplasty (PK) ranges from 0.08 to 0.67% [1, 2, 4, 8, 48–51]. A downward trend in the incidence of post-PK endophthalmitis has been observed since 1991, probably due to increased iodine use on the donor tissue prior to harvest as well as on the recipient tissue prior to surgery. Other factors that may have contributed to the decrease in post-PK endophthalmitis include the addition of antibiotics for gentamycin-resistant species in the tissue storage media and use of fluoroquinolones for surgical prophylaxis [8].

Risk factors for post-PK endophthalmitis include death of donor by infection and high-risk graft indications such as ulcerative keratitis and trauma [51]. A positive donor rim culture significantly increases the risk of the recipient developing endophthalmitis [52, 53]. Postoperative risk factors including graft ulceration [54], suture abscess, and wound gape [55]. Gram-positive bacteria, such as *Streptococcus* species, are the most common culprit of post-PK endophthalmitis cases where an organism is identified [49, 50, 53, 56–58]. Negative cultures account for approximately 10.9% of cases based on a single-center study [49].

Post-intravitreal Injection Endophthalmitis

There has been exponential growth in the use of intravitreal injections over the past decade. This can be attributed primarily to the advent of anti-vascular endothelial growth factor (anti-VEGF) agents which are used to treat numerous conditions like exudative age-related macular degeneration and diabetic macular edema. Although one study found that intravitreal injections accounted for 8.5% of all endophthalmitis cases [59], most studies estimate the incidence of postinjection endophthalmitis to be much lower, ranging from 0.00 to 0.095% [60–74]. The largest study evaluating this issue analyzed 316,576 injections and observed 65 cases of endophthalmitis, equating to an incidence of 0.021% [72]. Gram-positive organisms are the most frequent culprit of postinjection endophthalmitis cases, and coagulase-negative *Staphylococcus* and *Streptococcus* species are the most commonly isolated organisms [66, 72, 75]. Negative culture rates vary significantly in the literature. Postinjection endophthalmitis generally presents earlier and has poorer visual outcomes compared to post-cataract endophthalmitis [76].

Risk factors for post-intravitreal injection endophthalmitis have been difficult to identify due to the low overall incidence of endophthalmitis and the wide variety of injection techniques. Suggested preventative measures include administering postinjection topical antibiotics, wearing a face mask, and utilizing a speculum; however, there is no definitive evidence to support the efficacy of any of these methods [66, 68–71, 77]. The only practice with substantial evidence for endophthalmitis prevention is the use of povidone-iodine in the preparation process [69, 78–81].

Post-traumatic Endophthalmitis

Post-traumatic endophthalmitis accounts for 20–30% of infectious endophthalmitis cases [3, 82]. Its incidence following penetrating trauma ranges from 0.0 to 12% [83–90], although this can be as high as 30% in rural settings [85, 90]. Lens violation, contamination of the wound, delayed primary globe repair, and retained intraocular foreign bodies are the most commonly identified risk factors for development of post-traumatic endophthalmitis [83, 84, 86, 91, 92]. Traumatic endophthalmitis is frequently caused by polymicrobial infections [85, 93, 94]; coagulase-negative *Staphylococcus* and *Bacillus cereus* are the most commonly cultured organisms [85, 93–97]. *Bacillus cereus* infections are common in penetrating eye injuries contaminated by soil and are characterized by rapid destruction of the intraocular contents and dismal visual outcomes resulting from a severe enterotoxin-mediated reaction [82, 94].

Endogenous Endophthalmitis

Endogenous endophthalmitis (EE) accounts for 2–11% of all cases of infectious endophthalmitis [98–100]. Risk factors include diabetes mellitus, gastrointestinal disorders, hypertension, cardiac disorders, malignancy, AIDS, immunosuppressive therapy, renal failure, intravenous drug abuse, indwelling catheters, and history of invasive surgery [98, 101]. The liver, lung, and endocardium are common sources of endogenous infection [102]. Causative organisms vary based on geography and population demographics (Table 15.1). In the developed world, fungal organisms account for most endogenous cases. One study reported fungal pathogens in 66% of culture-positive cases, with a predominance of *Candida albicans* [103]. Conversely, a study from Hong Kong identified bacteria as a more common cause [104]. In the context of bacterial EE, gram-positive organisms are more prevalent in the Western world, whereas gram-negatives are more prevalent in Asian countries [98, 100, 103, 104]. For instance, *Klebsiella* endophthalmitis is frequently seen in patients with liver abscesses, a condition frequently seen in Asia [30, 105–107].

Table 15.1 Most common causative organisms for the various types of endophthalmitis

Causative organisms in various endophthalmitis types	
Endophthalmitis type	Causative pathogen
Acute post-cataract [19–21]	Gram-positive Coagulase-negative *Staph.* (54–70%) *Staphylococcus aureus* (6.8–13%) *Streptococcus* species (8.2–9%) Gram-negative (5–9.6%)
Chronic post-cataract [26–28]	Gram-positive *Propionibacterium acnes* (41.2–63%) Polymicrobial (17.6%) *Staph.* species (16–17.6%) Fungal (16–17.6%)
Post-penetrating keratoplasty [49]	Polymicrobial (40%) *Streptococcus pneumoniae* (27%) *Staphylococcus epidermidis* (21.8%) *Propionibacterium acnes* (14.5%) *Staphylococcus aureus* (12.7%) Negative (10.9%)
Post-intraocular injection [66]	Gram-positive (92.8%) Negative (40.4%)
Blebrelated [44–46]	*Streptococcus* species (30–55%) Coagulase-negative *Staphylococcus* (14.6–20%) Gram-negative (20.8–28%) Polymicrobial (12–27%)
Post-traumatic [95, 97]	*Staphylococcus epidermidis* (21.5–21.8%) *Bacillus* species (18.5%) Polymicrobial (3.2–15.6%)
Endogenous [30, 98, 101, 103, 104]	Fungal (27.3–65.9%) Western world Gram-positive (e.g., *Staph.*, *Strep.*) Eastern world Gram-negative (e.g., *Klebsiella*)

Clinical Assessment and Diagnosis of Endophthalmitis

Signs and Symptoms

The classic presentation of endophthalmitis is a red, painful eye accompanied by a significant inflammatory reaction that often manifests as a hypopyon (Fig. 15.2) with vitritis [3]. However, different etiologies of endophthalmitis may cause slight variations in the presenting signs and symptoms of a patient. In the Endophthalmitis Vitrectomy Study (EVS), 94% of patients with acute-onset endophthalmitis following cataract surgery or secondary intraocular lens implantation presented with decreased visual acuity, 82% with conjunctival injection, 74% with eye pain, and approximately 35% with eyelid edema [108] (Table 15.2). Bleb-related endophthalmitis (BRE) presents similarly, although a relative afferent pupillary defect can also

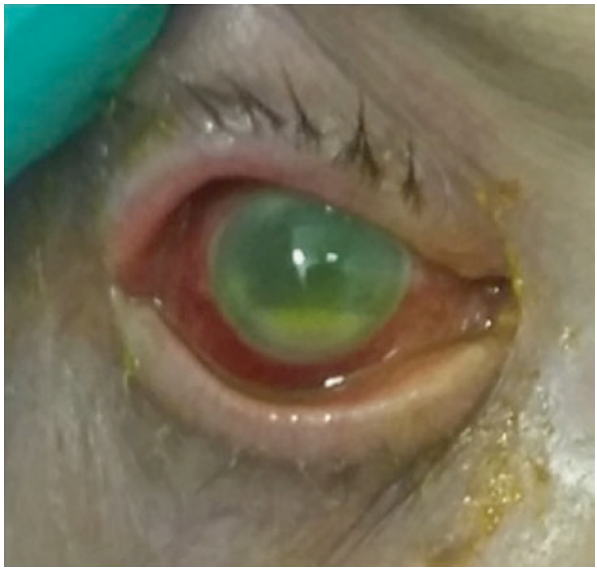

Fig. 15.2 External photograph of patient with a hypopyon, conjunctival injection, and corneal edema in the setting of endophthalmitis, postoperative week 1 following cataract surgery

Table 15.2 Symptoms and signs of endophthalmitis

Classic symptoms and signs of endophthalmitis	
Symptoms	Signs
Vision loss Pain Photophobia Floaters Headache Systemic symptoms including nausea,vomiting, chills, and fever (endogenous endophthalmitis)	Conjunctival injection/chemosis Corneal edema Hypopyon Anterior chamber cells/fibrin Vitritis Eyelid edema Discharge Subconjunctival hemorrhage Deposits on remaining lens capsule Reduced/absent red reflex Iritis Papillitis Retinitis/retinal necrosis Periphlebitis

be seen [109]. In contrast, delayed-onset postoperative endophthalmitis typically progresses more slowly and may induce only mild inflammation. The provider must look carefully for white plaques within the remaining capsule where the infectious nidus may dwell [28]. Post-intravitreal injection endophthalmitis usually manifests acutely within the first few days following injection. While anterior chamber cells are often present, a hypopyon and vitritis can initially be subtle [64, 110, 111]. Post-traumatic endophthalmitis may be the most highly variable in terms of presentation. While similar signs and symptoms are seen [88, 112], their onset can range

anywhere from hours to years after the injury depending on the mechanism of injury, foreign body presence, and type of microorganisms involved [112].

Endogenous endophthalmitis (EE) presents in a similar fashion, but due to hematogenous spread of infection in 19–33% of cases [88, 113, 114], the patient may also have constitutional symptoms such as fever, chills, or vomiting. The clinical presentation of EE may also depend on the immune status of the patient. A blunted clinical appearance in immunocompromised patients can lead to a delay in diagnosis [3]; in these circumstances, a detailed patient history can help identify risk factors such as intravenous drug use, sickle cell disease, foreign bodies including intravenous catheters, malignancy, neutropenia, diabetes, corticosteroid use, and acquired immunodeficiency syndrome (AIDS) [3].

Common masqueraders of endophthalmitis include several conditions associated with a pseudohypopyon such as Behcet's disease, rifabutin use [115], HLA-B27 uveitis, toxic anterior segment syndrome (TASS), multiple myeloma [116], retinoblastoma [117], and certain leukemias and lymphomas [118, 119]. Other conditions include the use of intravitreal triamcinolone acetonide [120, 121], heavy oil emulsification [120, 122], retained lens fragments following cataract surgery [123], and injection of intravitreal aflibercept which produces a sterile inflammatory reaction that often lacks pain or conjunctival erythema and typically responds to topical steroids [124].

Diagnosis and Further Evaluation

Once endophthalmitis is suspected, it is considered an emergency given the potential for severe ophthalmic damage and vision loss. As such, a complete clinical evaluation and work-up should commence immediately. Focus should be placed on identifying the causative microbe and initiating treatment with broad-spectrum intravitreal antibiotics. To address the former, a sample of intraocular fluid must be collected for analysis. The most common and widely accepted method is a vitreous humor tap. Tapping through areas with scleral thinning or hardware (e.g., tube shunt) should be avoided if possible.

Given the severe inflammation associated with endophthalmitis, affected patients are extremely sensitive to pain, and anesthesia is critical. Some providers use topical proparacaine (0.5%) or hold localized pressure on the globe with a proparacaine-soaked cotton-tip applicator. Subconjunctival lidocaine (2%) without epinephrine can be injected on a 30-gauge 0.5-in. needle. Peribulbar or retrobulbar blocks (2% lidocaine/0.5% bupivacaine) injected on a 25-gauge 1.5-in. needle may be considered in patients with extreme discomfort, although these injections can be painful in themselves. It is important to note that due to the severe degree of inflammation often present, the penetration and efficacy of anesthesia—regardless of route—can be lower than that typically observed in routine settings.

Once the eye is anesthetized, the actual vitreous tap is done. The steps utilized by the retina providers in our department are described next. The patient is reclined into

a supine position. Gloves are worn by the provider and the patient is asked not to talk so as to avoid contamination by oral flora. Povidone-iodine (5%) is dropped directly onto the ocular surface, and then 10% povidone-iodine swabs are used to clean the eyelids, eyelashes, and periorbital skin [125]. An eyelid speculum is inserted. Calipers are used to mark the position of entry through the pars plana (3.5 mm posterior to the limbus for pseudophakic patients, 4.0 mm for phakic patients), and another drop of povidone-iodine (5%) is applied over the mark. A 23- or 25-gauge needle attached to a 3-mL syringe is inserted perpendicular to the ocular surface. Slow, steady aspiration of 0.1–0.3 mL of vitreous humor is conducted [126]. In young patients with formed vitreous, gentle aspiration is especially important in order to avoid an iatrogenic retinal break or detachment. Once the specimen has been collected, the syringe is withdrawn while rolling a cotton-tip applicator over the site to prevent vitreous reflux; generally, injection of intravitreal antibiotics will follow, as discussed below.

An anterior chamber paracentesis (tap) can be beneficial in certain situations. Vitreous taps in young patients can be dry with no yield; these patients should undergo an aqueous tap or vitreous biopsy [115]. Collection of aqueous can also be done to increase sample yield for cultures. Finally, aqueous taps can be considered in endophthalmitis cases with concurrent retinal detachment or tractional membranes so as to avoid further retinal damage. An anterior chamber tap is performed by entering the anterior chamber through the limbus and parallel to the iris plane with a 30-gauge 0.5-in. needle on a 1-mL syringe [115]. Care should be taken to avoid contact of the needle with the lens.

Another method for sample retrieval is a vitreous biopsy. This invasive approach is usually reserved for cases unresponsive to broad-spectrum antibiotics with a prior unsuccessful vitreous tap or negative culture results. Moreover, in cases of trauma or severe inflammation where a complete pars plana vitrectomy (PPV) will be performed anyway, a concurrent biopsy can be done for organism identification [115, 127]. Details of the technique will be described below.

Collected specimen must be carefully handled to avoid contamination, and physicians must be aware of their specific laboratory facility's specifications for processing specimens. Although specific tests should be individualized to the patient based on clinical suspicions, the specimen should at least be sent for Gram stain as well as aerobic and anaerobic cultures [108]. Specifically, it can be plated on chocolate agar, enriched thioglycolate broth, anaerobic blood agar, and fresh Sabouraud dextrose agar. One should also send for KOH prep and fungal culture if fungal endophthalmitis is a concern.

Imaging and Other Ancillary Testing

Although the clinical examination and vitreous tap are the primary components of the work-up, ancillary testing can assist in the diagnosis of endophthalmitis. B-scan ultrasonography can further characterize the extent of posterior involvement if direct visualization is limited; it can also detect potential complications such as a retinal detachment or be used serially to monitor treatment response (Fig. 15.3).

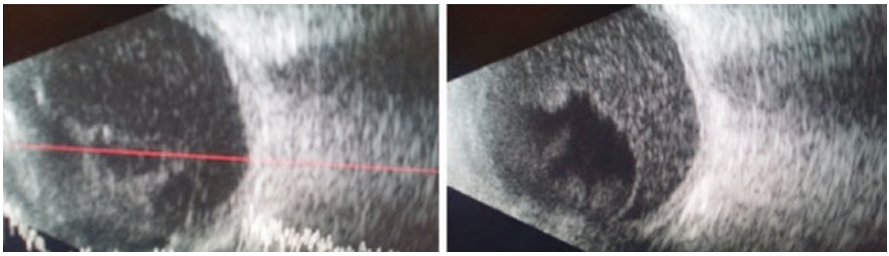

Fig. 15.3 B-scan ultrasound images of a patient with endophthalmitis, illustrating consolidated vitritis and fibrinous debris

If endogenous endophthalmitis is suspected, the work-up may also include an echocardiogram, gastrointestinal endoscopy, chest X-ray, abdominal ultrasound, and CT scan. Cultures of blood, urine, cerebrospinal fluid, sputum, and indwelling catheters should also be performed [128]. Lastly, orbital or intracranial CT scan may be done to differentiate endophthalmitis from panophthalmitis [129].

Management of Bacterial Endophthalmitis

Early treatment of endophthalmitis is critical in optimizing visual outcomes and preventing loss of the eye. Endophthalmitis was historically treated with intravenous antibiotics in the 1940s–1960s, but suboptimal visual outcomes were observed due to poor drug penetration into the ocular tissues [3, 130, 131]. Advances in management such as intraocular sampling, intravitreal antimicrobial injections, and early surgical intervention have brought improved outcomes [3, 108].

Medical Therapy

Systemic Antibiotics

Since their advent in the 1940s and subsequent development over decades, intravitreal antibiotics have replaced systemic antibiotics as the primary treatment for exogenous endophthalmitis [131, 132]. Even as supplemental treatment, systemic antibiotics do not seem to provide additional benefits [106, 133]. In endogenous endophthalmitis, however, systemic antibiotics are a critical adjunctive therapy to intravitreal injections. Oral or parenteral antibiotics are able to target the primary source of infection, while local intravitreal antibiotics address the endophthalmitis itself [113].

Intravitreal Antibiotics

Intravitreal antibiotics are the mainstay of endophthalmitis treatment (Table 15.3). These allow for high concentrations of therapeutic agents to be delivered directly to the vitreous cavity while limiting systemic toxicity and side effects [134, 135]. Unfortunately, due to their short duration of action, multiple injections are sometimes required.

Generally, broad-spectrum coverage is initiated to cover both Gram-positive organisms, the predominant pathogen of exogenous endophthalmitis, as well as Gram-negative organisms, which can be more virulent and convey a poorer prognosis. Most providers use intravitreal vancomycin (1 mg/0.1 mL), and a third-generation cephalosporin such as ceftazidime (2.25 mg/0.1 mL) until treatment can be tailored based on bacterial sensitivity studies [115, 127, 130, 131]. Injection of antibiotics typically immediately follows the vitreous tap, so the field is usually already prepared; if not, details for preparing the semi-sterile field are discussed above. The 0.1-mL injections should be delivered sequentially via a 30-gauge needle through the pars plana (3.5–4.0 mm posterior to the limbus in pseudophakic or phakic patients, respectively) directed toward the optic nerve. The needle should be withdrawn while rolling over the site with a cotton-tip applicator to prevent vitreous reflux. If the intraocular pressure is subsequently elevated, an anterior chamber paracentesis can be done.

Table 15.3 Common intravitreal antibiotics used to treat bacterial endophthalmitis

Common intravitreal antibiotics			
Drug name	Concentration	Mechanism of action	Coverage
Vancomycin	1 mg/0.1 mL	Inhibits cell wall synthesis	Gram-positive (e.g., *Staphylococcus aureus*)
Cefazolin	2.25 mg/0.1 mL	First-generation cephalosporin: inhibits cell wall synthesis	Gram-positive and some Gram-negative
Ceftazidime	2.25 mg/0.1 mL	Third-generation cephalosporin: inhibits cell wall synthesis	Gram-positive and some Gram-negative
Amikacin	0.4 mg/0.1 mL	Aminoglycoside: binds 30S ribosomal unit to inhibit protein synthesis	Gram-negative (e.g., *Pseudomonas*, *Serratia*)
Gentamicin	200 μg/0.1 mL	Aminoglycoside: binds 30S ribosomal unit to inhibit protein synthesis	Gram-positive and Gram-negative (e.g., *Pseudomonas*, *Klebsiella*)
Gatifloxacin/moxifloxacin	400 μg/0.1 mL	Fluoroquinolone: inhibits DNA gyrase	Gram-positive, Gram-negative, and anaerobes

Sensitivities of Gram-positive organisms to vancomycin were previously thought to be approximately 99% [4, 21], while sensitivities of Gram-negative organisms to ceftazidime ranged from 63 to 90% [108, 136]. Unfortunately, resistance to these medications may be emerging [137–139]. Fluoroquinolones and aminoglycosides (e.g., amikacin) are other treatment options and can be used in patients with a penicillin allergy. However, the growing use of fluoroquinolones has contributed to increasing resistance of *S. aureus* and other Gram-positive organisms to this drug class [5, 140–142]. Aminoglycosides have waned in popularity due to their potential retinal toxicity that can induce macular infarction [143, 144, 154].

Topical Pharmacotherapy

Topical antibiotics are far inferior to intravitreal therapies for treating endophthalmitis due to their poor penetration and resultant low intravitreal concentrations. Still, they can be beneficial as an adjunctive treatment. In bleb-related and keratitis-associated endophthalmitis, it is recommended that intravitreal antibiotics be used alongside topical therapies such as fortified vancomycin (50 mg/mL), fortified ceftazidime or cefazolin (50 mg/mL), fortified tobramycin (14 mg/mL), or a fluoroquinolone (gatifloxacin 3 mg/mL, ciprofloxacin 3 mg/mL, or moxifloxacin 5 mg/mL) [145, 146].

Other topical therapies to consider are cycloplegics to help control pain and prevent synechia formation and topical intraocular pressure-lowering medications if the intraocular pressure is elevated. Topical steroids may be considered to help control inflammation [130].

Intravitreal and Periocular Steroids

The use of intravitreal or periocular steroids in the treatment of bacterial endophthalmitis remains controversial given the lack of convincing data [147, 148]. A prospective randomized clinical trial described early improvement in intraocular inflammation at 1 and 4 weeks following adjunctive administration of intravitreal dexamethasone 400 μg; however, there was no significant difference in the level of inflammation or visual acuity at 12 weeks between eyes that had received intravitreal steroid and those which did not [149]. Another smaller prospective study showed trends of improvement in visual acuity 3 months and 12 months after intravitreal dexamethasone, but results were not statistically significant [150].

Surgical Therapy

Aside from those outlined in the Endophthalmitis Vitrectomy Study (EVS), no general guidelines exist as to when surgical intervention is indicated in patients with endophthalmitis. The EVS was a multicenter randomized controlled study which

included patients who developed endophthalmitis within 6 weeks after cataract surgery or secondary intraocular lens implantation. In this study, there was no apparent benefit in performing an immediate vitrectomy (versus tap/inject) if patients had hand motions visual acuity (Va) or better. For patients with light perception Va, an immediate vitrectomy (versus tap/inject) led to a threefold increase in the frequency of achieving Va 20/40 or better (33% vs. 11%), twofold improved likelihood of achieving Va 20/100 or better (56% vs. 30%), and a 50% decrease in the frequency of severe vision loss (20% vs. 47%) [108].

Under real-world conditions that may not mimic those of the study, whether or not to proceed with pars plana vitrectomy (PPV) for endophthalmitis is left to the discretion of the treating physician. Surgical intervention might be considered in patients who do not respond to medical therapy or in those with chronic post-cataract endophthalmitis due to *Propionibacterium acnes* in which a PPV along with a total capsulectomy and intraocular lens explantation are recommended [151]. For endogenous endophthalmitis, there is data to suggest that earlier surgical intervention when the Va is counting fingers or better may be beneficial [115, 152]. Regardless of the endophthalmitis type, patients can develop a large intraocular pus-like consolidation. In these cases, a PPV may be advantageous in order to debulk the eye and remove necrotic tissue and bacteria. Doing so can lessen inflammation, maintain vitreous transparency, and hasten visual recovery [127].

During a PPV, a vitreous sample can also be collected for culture. One technique involves a three-port setup where the infusion line is placed, but deliberately left off [108]. The aspiration tubing is disconnected, and a syringe with in-line stopcock is attached. The cutter is introduced into the mid-vitreous cavity and then 1 mL of vitreous is cut and aspirated while the assistant gently draws back on the syringe; the assistant should be directed to suction only while active cutting is occurring. The surgeon should expect to see mild collapse of the ocular walls, and care should be taken not to insult retinal tissue. Once the undiluted specimen has been collected, the syringe is handed off and a new one is attached. The infusion line is turned on and the process is repeated to collect the diluted specimen. Finally, the aspiration tubing is reconnected to the cassette and the remainder of the vitrectomy is completed.

Intraoperative visualization is often poor due to corneal edema, hypopyon, lens opacity, or a profound fibrinous reaction. The view sometimes improves with anterior chamber washout or lensectomy (intraocular lens placement should be deferred). If it does not, an endoscope can be utilized. As a last resort, a surgeon can perform a blind vitrectomy where the cutter is held in the mid-vitreous cavity without much manipulation. If the view permits, careful evaluation for retinal tears should be performed. Sclerotomies should be sutured given compromised tissue integrity and risk for postoperative hypotony. Finally, intravitreal antibiotics with or without steroids should be injected at case conclusion. The vitreous aspirate collected in the cassette should be sent for culture along with the diluted and undiluted specimens. Each specimen is filtered through a sterile 0.45-μm membrane filter and then plated on culture media as discussed earlier [108]. If sufficient material is available, specific polymerase chain reaction (PCR) studies should also be ordered based on clinical suspicions [115].

Table 15.4 Advantages and disadvantages associated with pars plana vitrectomy in the treatment of bacterial endophthalmitis

Pars plana vitrectomy for endophthalmitis treatment	
Advantages	Disadvantages
Debulk infectious nidus and debris	Surgical complications
Improve view to retina	Anesthesia risk
Address concurrent retinal pathology	Intraoperative/postoperative pain
Collect specimen for culture	No change in final visual acuity outcome

The decision for surgical intervention is multifactorial and case-dependent. While there are advantages to debulking the intraocular debris, addressing retinal pathology, and obtaining an abundant vitreous sample for microbial identification, disadvantages also exist (Table 15.4). There are anesthesia risks and surgical complications, and patients can experience immense postoperative pain and hypotony as a result of operating on an inflamed eye. The surgeon must weigh these carefully and remember that surgery may not improve the ultimate outcome.

Follow-Up

Patients with endophthalmitis should be followed daily until clinical improvement is seen. Improved visual acuity, level of pain, and vitreous haze (via exam or B-scan ultrasound) are initially the most important indicators of progress. Other signs include decreased hypopyon height and conjunctival injection. Once improvement is observed, follow-up intervals should remain short until the infection is stabilized. Return precautions should be discussed with the patient; if worsening is seen within the first 48–72 h after treatment initiation, a repeat injection of intravitreal antibiotics or pars plana vitrectomy should be considered.

Complications

Multiple complications can arise from endophthalmitis treatment or from the infection itself. Perhaps the most common sequela is a severe inflammatory response that can lead to retinal necrosis, ocular ischemia, or even retinal detachment despite resolution of the infection. Inflammation with or without elevated intraocular pressure can also cause optic neuropathy, glaucoma, or persistent hypotony.

Potential complications related to treatment include adverse effects of intravitreal aminoglycosides such as retinal ischemia and destruction of the nerve fiber layer [153]. Retinal detachment can occur after vitrectomy as was seen in 8% of eyes in the EVS [107]; other studies have reported an even higher incidence [155, 156]. This may be due to compromised retinal tissue integrity or media opacities from the cornea, anterior segment, lens, or vitreous, which make retinal breaks

difficult to visualize during vitrectomy. Post-vitrectomy hypotony is frequently seen in endophthalmitis patients due to persistent inflammation or wound leak from poor tissue integrity. Often accompanied by corneal edema or choroidal detachments, hypotony often signifies a poorer prognosis [3].

Rarely, the infection may be resistant to therapy and continue to progress. In these settings, the blood-retinal barrier can be violated, and the infection can spread to the orbit. This results in a condition called panophthalmitis which is discussed in the next section.

Panophthalmitis

Rarely, endophthalmitis can be intractable to medical and surgical therapy; this is perhaps the context in which this condition becomes especially relevant to the oculoplastic provider. Panophthalmitis is a rare but serious complication of endophthalmitis that occurs when the intraocular infection spreads outward to involve Tenon's capsule and other surrounding orbital tissues. Patients present with signs and symptoms similar to those of endophthalmitis, but may also have periorbital erythema and edema, headache, profuse purulent discharge, proptosis, fever, and malaise (Fig. 15.4).

Pseudomonas aeruginosa and *Bacillus cereus* are known virulent organisms that often result in poor vision in spite of intravitreal antibiotic treatment. These pathogens along with other Gram-positive cocci, such as *Staphylococcus epidermidis* and *Streptococcus pneumoniae*, have been implicated in panophthalmitis [157–159]. *Bacillus cereus* has been associated with exogenous panophthalmitis in intravenous drug-abusing patients as well as in trauma patients [160, 161]. Case reports of endogenous panophthalmitis have named causative pathogens like methicillin-sensitive *S. aureus* [162], *E. coli* [129], *Klebsiella* pneumonia [163], *Salmonella typhi* [164], and *Pseudomonas aeruginosa* [158].

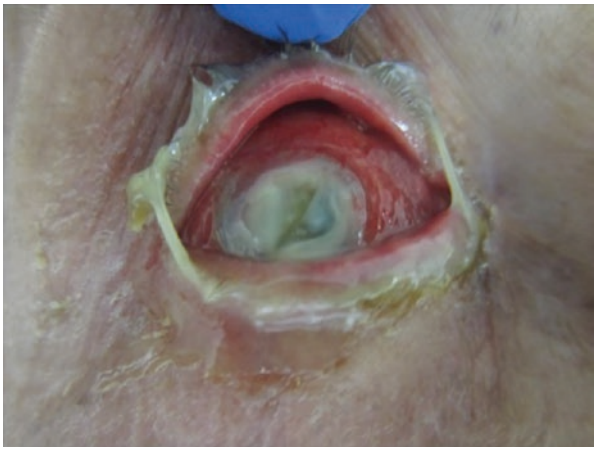

Fig. 15.4 External photograph of patient with panophthalmitis. Notice the evident pus seen within the anterior chamber, diffuse injection of the ocular coats, and mild erythema of the surrounding periorbital skin (Image courtesy of Sophie D. Liao, M.D.)

Treatment of panophthalmitis requires the addition of broad-spectrum systemic antibiotics. Unfortunately, prognosis for panophthalmitis is even poorer than that for endophthalmitis. Evisceration or enucleation is often necessary to control the infection and prevent devastating sequelae such as intracranial dissemination of infection or cavernous sinus thrombosis. Primary orbital implants during evisceration or enucleation can be used in these cases, although it is important to note that the presence of infected orbital tissue is associated with a higher postoperative risk of exposure or extrusion [165].

Prevention

Endophthalmitis prophylaxis is commonplace in ophthalmic procedures and should occur preoperatively, intraoperatively, and postoperatively. Adnexal disease, such as blepharitis and canaliculitis, should be treated with eyelid hygiene regimens and antibiotics prior to ocular surgery [166]. It is usually advised that elective ophthalmic surgery be postponed if there are other active systemic infections in the body.

Careful preparation of a sterile field is critical in the prevention of post-procedural infection. Standard sterile procedures should be followed in the operating room with use of povidone-iodine (5% on the globe, 10% on the eyelashes and periorbita), appropriate draping, and speculum insertion to isolate the globe from the eyelids and eyelashes [125]. For semi-sterile intravitreal injection procedures, minimizing talking or using masks may decrease the aerosolization of oral flora. Povidone-iodine can be applied to the eyelids, but aggressive eyelid scrubbing and meibomian gland expression should be avoided. Povidone-iodine (5%) should be the last agent applied to the conjunctiva prior to injection.

Intracameral antibiotics have been shown to decrease the risk of post-cataract surgery endophthalmitis four- to tenfold [167–169]. Moxifloxacin is a common agent used intracamerally and has a good overall safety profile [130, 150, 170, 171]. However, the use of intracameral antibiotics has not been universally implemented in perioperative prophylaxis, and many practitioners continue to use postoperative topical antibiotics alone [172].

Because ocular trauma carries such a high risk of endophthalmitis, prompt prophylaxis with broad-spectrum intravitreal antibiotics should be considered in all open-globe injuries [173]. Systemic prophylactic antibiotics (e.g., parenteral moxifloxacin) have also been suggested as an adjunctive therapy to possibly decrease intraocular infectious seeding following disruption of the blood-retinal barrier [174].

Prognosis

Prognosis of endophthalmitis is generally poor, but depends on a variety of factors including time to initial treatment, virulence of the causative organism, and route of injury. At the final follow-up visit 9 to12 months after treatment in the EVS, 53% of

patients had a final visual acuity of 20/40 or better, 74% had Va 20/100 or better, 15% had Va 5/200 or worse, and 5% had no light perception [108]. Visual outcomes of 20/100 or better were most commonly seen with coagulase-negative *Staphylococci* (84%) and *Staphylococcus aureus* (50%). More severe vision loss was observed with *Streptococcus* species, *Pseudomonas aeruginosa*, and *Bacillus* organisms [3, 157, 175]. Severe vision loss at initial presentation (light perception or worse), advanced age, diabetes mellitus, coexisting corneal ulcer, abnormal intraocular pressure, afferent pupil defect, and absence of a red reflex were also associated with poorer prognosis [108].

Conclusion

Endophthalmitis is a rare but devastating ocular condition that can progress rapidly and lead to visual demise. Despite advances in intravitreal antibiotics and vitrectomy techniques, many patients affected by endophthalmitis continue to suffer poor outcomes. It is imperative for all ophthalmologists to practice up-to-date perioperative prophylaxis techniques to prevent postoperative infection. While traumatic injury and endogenous spread of infection might seem unavoidable at times, practitioners should be able to recognize signs and symptoms of endophthalmitis as early diagnosis with prompt treatment is essential to optimizing outcomes. With continued advancements in preventative measures, diagnostic technologies, and antibiotic therapies, we strive to improve the prognosis of this serious disease.

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Chapter 16
Evaluation and Management of Orbital Cellulitis Secondary to Endophthalmitis

Thomas E. Johnson and Brian C. Tse

Introduction

Endophthalmitis is an intraocular infection caused by bacteria or fungi that can occur following trauma, intraocular surgery, corneal ulcer, or hematogenous spread of a systemic infection (endogenous endophthalmitis). Patients typically will present with pain, redness, decreased ocular motility, and decreased vision. Treatment consists of vitreous culture to identify the causative agent, broad-spectrum intravitreal and systemic antibiotics, and, in some cases, pars plana vitrectomy.

Severe infections with virulent organisms or untreated infections can result in panophthalmitis, an infection that extends outside the globe and results in intra-orbital inflammation and secondary orbital cellulitis. Complete loss of light perception can occur in these cases, as the eye becomes filled with pus. The eye itself becomes an abscess cavity and focus of the secondary orbital cellulitis. Presenting symptoms include intense pain, fever, eyelid swelling and redness (Fig. 16.1), loss of vision, and decreased motility of the eye. Patients with *Pseudomonas* endophthalmitis often end up needing to have the eye removed to resolve their infection [1]. At this point medical treatment alone is often inadequate, and surgical intervention is required to help clear the infection. Untreated or inadequately treated patients are at risk for intracranial extension of the infection, meningitis, cavernous sinus thrombosis, and even death. Options for surgery

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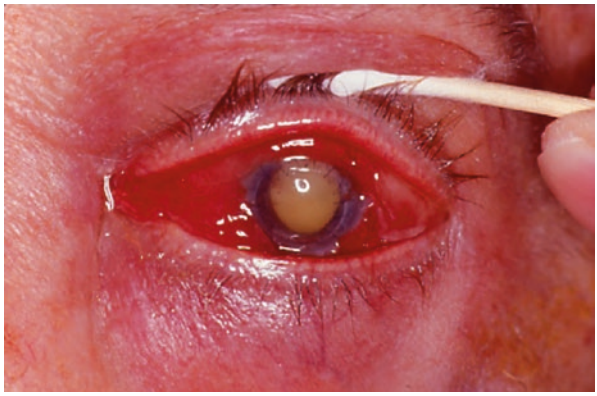

Fig. 16.1 Patient with a history of penetrating keratoplasty presents with vitritis and conjunctival injection consistent with endophthalmitis

include either evisceration or enucleation. A preoperative CT or MRI scan is useful to delineate the extent of the infection.

There has been a long-standing controversy concerning which procedure is best in the setting of endophthalmitis with complete visual loss—enucleation or evisceration. Evisceration offers the advantages of being a shorter and less traumatic procedure that does not disrupt the extraocular muscle insertions or suspensory attachments. Additionally, there is usually less bleeding during an evisceration when compared to enucleation, which is an important consideration in an acutely inflamed orbit. Postoperative fornices are usually deeper than in enucleation and may lead to easier prosthesis fitting [2]. Finally, evisceration offers theoretical advantages of better motility and improved cosmesis. However, evisceration does leave a small risk of developing sympathetic ophthalmia in the contralateral eye and may lead to the inadvertent orbital spread of a previously undetected intraocular melanoma. In patients with phthisical eyes, an adequate-sized orbital implant can be difficult if not impossible to place at the time of surgery, leading to postoperative orbital volume deficit and poor cosmesis.

In an enucleation, the whole globe is removed, which includes the sclera that, if left behind, may continue to harbor infection and place the patient at risk for postoperative implant extrusion. After globe removal, a large orbital implant can be easily placed. On the contrary, enucleation requires more dissection in an acutely inflamed orbit, leading to increased bleeding and longer procedure times. Disruption of the extraocular muscle attachments during enucleation can theoretically lead to poorer implant motility when compared to evisceration. Additionally, enucleation can increase the risk of posterior spread of the infection owing to removing the scleral barrier and cutting across the optic nerve with exposure of the meninges and CSF to infectious material. However, studies have not demonstrated any increased risk of infection or meningitis after enucleation and have reported similar outcomes between enucleated and eviscerated patients after endophthalmitis [3].

Evisceration

During an evisceration, the intraocular contents are removed while leaving the extraocular muscle insertions and majority of the sclera intact. The surgery can be performed under general anesthesia or retrobulbar block along with monitored anesthesia care. A lid speculum is placed, and a 360° conjunctival peritomy is performed. Gentle dissection with Stevens scissors is carried out between the sclera and Tenon's capsule in each of the four quadrants between the rectus muscles. A number 11 Bard-Parker blade is used to make a paracentesis, entering the anterior chamber at the corneoscleral limbus. Keratectomy is performed using Westcott scissors. Often an abundant amount of purulent material presents during keratectomy. Cultures should be taken at this point, and antibiotic therapy can later be adjusted depending on culture results. An evisceration spoon is then used to gently separate the scleral spur and uveal contents off the scleral wall 360° just behind the iris plane. The spoon is run along the inside of the sclera from the anterior lip toward the posterior pole, detaching the uveal contents from the sclera, clock hour by clock hour. Attempt should be made with a larger evisceration spoon to remove the uveal contents intact, but this may not be possible. The surgeon should make every effort to remove all of the uveal tissue to minimize the risk of sympathetic ophthalmia. The inside of the sclera is next scrubbed with cotton tip applicators soaked in absolute ethanol, taking care to avoid the alcohol from coming into contact with the conjunctiva. After several sweeps with the absolute ethanol, copious irrigation is then performed with an antibiotic solution such as gentamicin to remove any residual alcohol. Posterior sclerotomies can be performed to allow placement of a large implant and facilitate vascularization of a porous implant. If the sclera looks healthy and noninfected, an acrylic or porous orbital implant is placed in the sclera, and the sclera is closed over the implant using 5–0 Vicryl or Mersilene sutures. Tenon's capsule is then closed with interrupted sutures of 5–0 Vicryl, taking care to bury the knots. The conjunctiva is closed with a running 6–0 plain gut suture. Subconjunctival injection of an antibiotic is then placed. Finally, a proper-sized conformer and a firm pressure patch are placed, with the pressure patch staying in place for 1 week. Treatment with systemic antibiotics is continued for another week. If the sclera appears necrotic, as often happens with *Pseudomonas* or streptococcal infections, the necrotic sclera can be trimmed and the sclera packed with Betadine gauze. The gauze is then removed a few days after the procedure, and the tissues are allowed to heal by secondary intention. A secondary implant can be placed later when the infection is completely cleared. Usually it is best to wait about 3 months to ensure complete healing and resolution of infection and inflammation.

Enucleation

Enucleation involves the complete removal of the eye. As in evisceration, it can be performed under general anesthesia or local anesthesia with retrobulbar block and sedation. The procedure starts with the placement of a lid speculum, and a 360°

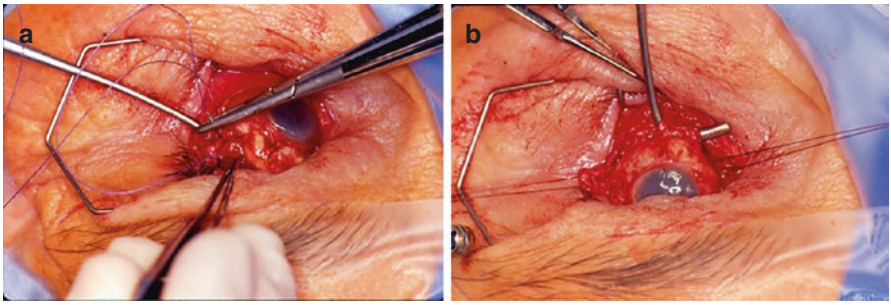

Fig. 16.2 (**a**) Rectus muscles are secured using 5–0 double-armed Vicryl on a spatulated needle with locking bites. (**b**) Rectus muscles are disinserted from sclera; von Graefe muscle hook has hooked the next muscle to be disinserted

conjunctival peritomy is performed with Westcott scissors. Stevens scissors are then used to clear the quadrants between the rectus muscles separating Tenon's capsule from the underlying sclera. The four rectus muscles are then isolated with muscle hooks, and a 5–0 Vicryl suture is woven through the muscle insertions and locked on each end (Figs. 16.2a, b). Each of the rectus muscles is then disinserted from the globe, and the sutures are secured to the surgical drapes with seraphim clamps to keep them from becoming tangled together. The superior and inferior oblique muscles are next isolated with muscle hooks and disinserted from the globe and allowed to retract into the orbit. Stevens scissors are used to gently dissect tissue off the sclera back to the posterior pole of the eye. The optic nerve is palpated with a hemostat and then clamped posterior from its medial aspect. The clamp is left in place for 1 min to help with hemostasis before it is removed. The optic nerve is cut with an enucleation scissors. Care is taken to remove a long segment of the nerve and not to cut into the back wall of the eye. The globe is gently lifted out of the orbit and inspected to ensure an adequate resection of the optic nerve before being passed off and sent for histopathology. Hemostasis is then obtained by packing the socket with gauze soaked in gentamicin solution. After hemostasis has been secured, acrylic implants are then tried to determine the size of the orbital implant to select. Usually one places the largest orbital implant that can be inserted that allows closure of the Tenon's and conjunctiva without tension. In adults this is usually a 20–22 mm sphere. Either a porous or nonporous implant can be placed. This author usually selects a nonporous implant in severely infected cases. The socket is irrigated with an antibiotic solution before placing the implant. A wrapping material such as eye bank sclera can be used to encase the implant, and the windows are cut corresponding to the rectus muscle insertions (Fig. 16.3a, b). A tulip inserter is often used to inject the implant deep into the socket and to avoid dragging anterior tissues posteriorly and causing a "cactus syndrome" with late exposure and extrusion of the implant. The double-armed 5-0 Vicryl sutures connected to the extraocular muscles are then brought into the windows of the wrapping material and tied (Fig. 16.4). Tenon's and conjunctiva are then closed in an identical fashion as that described for evisceration. Subconjunctival injections of antibiotics are given, and a conformer is placed. Pressure patch is placed for a week. Systemic antibiotics are continued for another week.

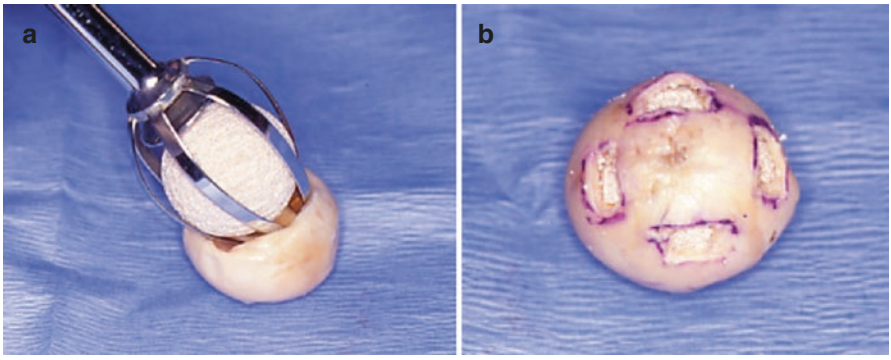

Fig. 16.3 (**a**) Tulip inserter placing porous polyethylene implant into the donor sclera. (**b**) Windows are cut into the donor sclera at the locations that the rectus muscles will be sutured

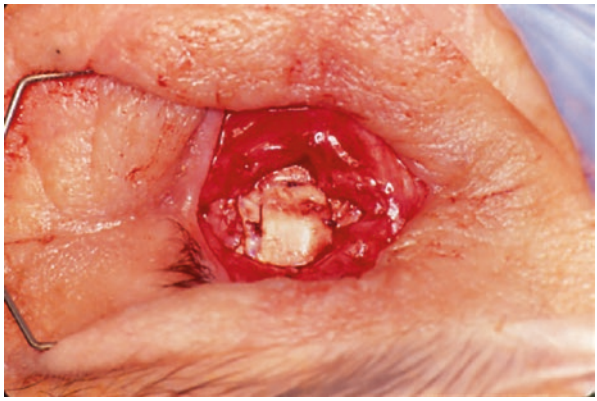

Fig. 16.4 After tulip inserter has placed implant into the socket, the rectus muscles are sewn to the donor sclera through the windows with the 5–0 Vicryl sutures that were used to initially secure the muscle. The anterior positioning of the scleral windows allows the rectus muscles to hold the implant in the socket and help to prevent extrusion

Implant Placement

An area of controversy concerns the placement of a primary implant after either enucleation or evisceration in the setting of endophthalmitis. Advocates of a two-staged approach (enucleation or evisceration followed by delayed secondary orbital implant insertion) argue that primary placement of an implant in this infected setting would result in a high incidence of implant extrusion [4]. Proponents of a one-staged procedure point to decreased recovery time, lower cost, fewer surgical procedures, less patient anxiety, and decreased hospitalization time [5, 6].

Dresner and Karesh evaluated 11 patients who underwent evisceration for endophthalmitis with placement of a primary implant [7]. They found that 10 of 11 patients had an uneventful postoperative course with successful prosthesis fitting. One patient with *Pseudomonas aeruginosa* endophthalmitis had an implant exposure. Ozgur and coworkers reported the results of 25 patients with endophthalmitis treated with evisceration and primary implant placement [6]. With a mean follow-up of 25.4 months, they found three patients (12%) developed implant exposure and one patient (4%) developed a pyogenic granuloma. Additionally Tawfik and Budin

reported 67 patients with endophthalmitis who underwent evisceration with primary implant placement and found 63 successfully retained their implant [5]. These studies concluded that primary implant placement with evisceration patients with endophthalmitis is an acceptable treatment. These findings are in concert with other studies that have shown that primary implant placement is safe in the majority of cases when antibiotic therapy is used in the perioperative period. However, in patients in whom there is concern for or documentation of more virulent infections (i.e., *Pseudomonas aeruginosa, Streptococcus,* or *Bacillus cereus*), consideration should be given to delaying implant placement, as there may be greater risk of extrusion [8]. Some advocate for secondary implant placement only after the initial infection has been cleared [7].

Another debate centers on the type of implant (porous or nonporous) to be placed after enucleation or evisceration in the setting of endophthalmitis. Originally it was thought that nonporous implants should be used after evisceration or enucleation in endophthalmitis cases because of the risk of implant infection. Recent studies have found that porous implants such as hydroxyapatite and porous polyethylene can be safely implanted [2]. Abel and Meyer described 22 patients with advanced endophthalmitis or panophthalmitis who underwent enucleation with primary implant placement, 11 with hydroxyapatite and 11 with silicone implants [3]. All were treated during surgery with intravenous antibiotics. No patients had persistent orbital cellulitis and none developed meningitis. Only two patients with silicone implants had implant extrusions. There appears to be a trend toward the placement of porous polyethylene implants over nonporous implants [8].

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Index

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