Endocarditis

Kwan-Leung Chan and John M. Embil (Eds)

Endocarditis

Diagnosis and Management

With 62 Figures
including 43 Color Plates

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Foreword

Infection remains the number one killer worldwide. Nevertheless, it is the expectation that bacterial infections can be eliminated with antibiotics. Unfortunately, there remain infections due to bacteria that are difficult to detect and difficult to reach, because of minimal blood supply, with even the most potent of antibiotics. One of the diseases in this category is infections that initiate on the inner lining of a vital organ, the heart. These infections are referred to as endocarditis since they involve the endocardium, the inner lining of the heart and valves. The initial site of infection is generally in areas exposed to mechanical trauma or prosthetic device. Unfortunately the damage to the heart if not treated can be fatal and often survival requires surgical replacement of one of the valves. Despite the tremendous array of antibiotics and the marked increase in potency of these drugs to eradicate bacterial infection, the efficacy of treating the relatively avascular lining of the heart or its valvular apparatus often eludes the desired effect. This is further complicated by the changing substrate for bacterial endocarditis, namely, artificial valves and devices and the increasing number of individuals who are imuno-suppressed because of drug use, human immuno deficiency virus infections or other debilitating conditions. Endocarditis due to bacteria and other agents remains a continuing threat as well as a challenge in terms of diagnosis, management and treatment.

Drs Chan and Embil have brought together the expertise of pathologists, infectious disease experts, cardiologists, pharmacologists and surgeons to provide a comprehensive approach to the problem of endocarditis. The book is organized to include a chapter on the pertinent pathology followed by population studies. The diagnostic section is extensive, comprehensive and very clearly written so that both medical and paramedical personnel can appreciate the armamentarium and its application. The management section is broad based to include treatment of the acute and chronic forms as well as potential sequelae that may occur. Echocardiography has become a major tool in the management of endocarditis and transesophageal echocardiography is now essential in the diagnosis and management of suspected prosthetic valve endocarditis. The role of echocardiography is critically assessed in several chapters dealing with specific clinical situations. The chapters reflect the authors' first-hand experience in dealing with endocarditis. The book in essence brings together the most current and evidence-based approaches as practiced by a group of experts who are intimately involved in the management of this disease.

In a world in which longevity is sought by all and lifespan has doubled just in the past century, it is expected that bacterial infections will not rob us of this expanding lifespan. The fact that they can and do in today's world of modern technology and ever revolving therapies remains a sobering thought. This book is an example of the thoughtful analysis that is required if we are to prevail in our long battle with serious infections such as endocarditis. It is a gem for the student, the teacher and the practitioner.

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Preface

Despite advances in medical and surgical treatments, infective endocarditis continues to be an important clinical problem. It has an in-hospital mortality of 10–20%, and many patients will require valve surgery during long-term follow-up. The diagnosis is difficult since it is based on a constellation of findings and none of the clinical findings alone is pathognomonic. Unequivocal diagnosis is often made only at surgery or autopsy.

Our aim is to provide an up-to-date approach to the diagnosis and management of endocarditis based on a critical analysis of recent studies. The book is structured in a format that is easy to follow, clinically relevant, and evidence-based. Key points are listed at the end of each chapter for quick review. It is divided into three sections. The first section provides a comprehensive review of the basic principles underlying the management of endocarditis. In addition to chapters on etiologic agents and pathologic findings, the changing epidemiology and the vexing issue of antibiotic prophylaxis are discussed. The second section presents the clinical principles underlying the diagnosis and treatment approaches, both medical and surgical. The role of transthoracic and transesophageal echocardiography is discussed in detail, particularly in relation to false-positive and false-negative test results. The third section focuses on difficult clinical scenarios frequently encountered in patients with this disease, including culture-negative endocarditis, prosthetic valve endocarditis, natural history and management of perivalvular abscess, systemic embolism, and etiologies and treatments of neurologic events. The practical clinical approach of this section is underscored by the inclusion of an illustrative case in each of the clinical chapters in the book.

We sincerely hope that this book will serve as an important source of clinical information on diagnosis and management of endocarditis that is useful to all practitioners involved in the care of these critically ill patients.

We would like to thank all the authors for their thoughtful and erudite contributions covering the protean facets of this challenging disease. We are indebted to our colleagues, past and present, for their support and inspiration. Finally, we would like to express our sincere appreciation to our families for their understanding, patience and encouragement without which this text would not have become a reality.

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Perspectives on the History of Endocarditis

Allan Ronald

Case Study

Alfred Reinhart was born in 1907 with a brilliant mind. He contracted rheumatic fever at age 13 and was hospitalized at Peter Bent Brigham Hospital in Boston. Despite losing a year of school, he excelled in his studies. He was admitted to Harvard College at age 17 and subsequently to Harvard Medical School in 1928 at age 21. Rheumatic fever left him with severe aortic insufficiency and for about 10 years he had 0 diastolic blood pressure. His own onset of endocarditis, caused by *Streptococcus viridans,* was recognized by him in May 1931, many months before the diagnosis was accepted by his treating physicians. He faced this "incurable" disease with dignity and went on to provide a vivid and detailed chronicle of his symptoms.

The following is his description of extrasystoles, which troubled him greatly [1]:

> The extrasystole has always affected me as if it were a cannon ball, shot point blank at my brain. The sensation is that of a terrific explosion, occurring within the narrow and limited confines of a calcified skull, which refuses to yield to the compressive force. It is like an irresistible force against an immovable object. Most of the time I am helpless before it and simply wait patiently in terror until the ordeal has passed.

Reinhart was convinced he had endocarditis when he noticed petechiae on his wrist [1]:

> At any rate, at approximately one-quarter to twelve that night, I remember distinctly getting up from my chair and from the table, where my books lay, and taking off my suit coat. No sooner had I removed the left arm of my coat, than there was on the ventral aspect of my left wrist a sight which I never shall forget until I die. There greeted my eyes about fifteen or twenty bright red, slightly raised, hemorrhagic spots about 1 millimeter in diameter which did not fade on pressure and which stood defiant, as if they were challenging the very gods of Olympus. I had never seen such a sight before, I have never seen such a sight since, and I hope I shall never see such a sight again. I took one glance at the pretty little collection of spots and turned to my sister-in-law, who was standing nearby, and calmly said, "I shall be dead within six months."

He died of endocarditis in October 1931, after suffering complications including splenic infarcts, retroperitoneal hemorrhage, embolic stroke, subarachnoid hemorrhage, and pulmonary edema.

The case of Alfred Reinhart illustrates many of the protean manifestations of endocarditis, vividly described by a keen observer with medical knowledge. Despite major advances in the diagnosis and treatment of endocarditis since Reinhart's death, endocarditis remains an elusive diagnosis, and the complications which afflicted Reinhart are still observed today.

Historical Perspectives

Historical perspectives are fraught with interpretation and bias. For this author, particular points of interest include recollections and reminiscence from almost 50 years of medical learning and practice, as an observer to both the science and the management of endocarditis and the personal triumphs and failures in the care of patients with endocarditis. Although these biases will be apparent in this review, my goal is to

provide my perspective on what many regard as the most fascinating of infectious diseases.

Several authors attribute the initial description to clinicians and pathologists in the 17th and 18th centuries who described the clinical course and autopsies in patients who in retrospect almost certainly had bacterial endocarditis. This includes Rivierins in 1646, Lancisi in 1707, Glynn in 1749, Morgagni in 1769, and Baillie in 1793 [2]. Baillie clearly differentiated rheumatic endocarditis from what we now know as bacterial endocarditis [3]. Corvisart in 1806 described the "warty" lesions on heart valves and some of these appear, in retrospect, to have been bacterial vegetations [4].

Over the next 75 years, however, rheumatic endocarditis and bacterial endocarditis were not clearly differentiated clinically or pathologically. In1852 Kirkes was the first to describe emboli arising from heart valves in cerebral, renal, splenic and other arteries [5]. Subsequently Virchow and Beckmann each described embolic phenomena and showed that they contained elements which appeared to be bacteria [6,7]. Specifically, Heiberg described chains of cocci in vegetation [8].

In 1859 Quinquaud used the term "chronic" to describe a patient and this allowed subacute bacterial endocarditis to be differentiated from acute [9]. Cayley in 1877 first used the term "infective endocarditis" and this replaced the earlier term "ulcerative endocarditis" [10]. A major advance occurred when Osler in his Gulstonian Lecture in 1885 reported on the clinical course and outcome of 209 cases [11]. He first identified the tendency of bacteria to localize on "diseased valves." He also was the first to mention the importance of bacterial culture.

Meanwhile in Paris, Jaccoud had described endocarditis, and subsequently in France it is often referred to as "Jaccoud's disease" [12]. The long duration of the illness and its subacute presentation was emphasized by both Osler and Jaccoud [11,12].

Numerous other individuals have made important contributions. At the end of the 19th century, the clinical course of endocarditis and its microbial etiology were described fully [11–15]. Thayer and Blumer recovered gonococci in the bloodstream of a patient with endocarditis in 1895 and subsequently reviewed a 100 cases of gonococcal endocarditis [13]. Lenhartz introduced material from a vegetative lesion into the urethra of a male patient and produced classical gonococcal urethritis [14]. Schottmuller isolated the organism which he initially called *Streptococcus mitiorseu* viridans [15].

The clinical features, including fever and murmur, were well described by Osler in his classic presentations [11,16,17]. The appearance of a new murmur and the clinical features of embolic phenomena were identified as being particularly important for the diagnosis of bacterial endocarditis.

In 1893 Osler saw one of his initial patients and described the "red swollen areas on her fingertips" [16]. Janeway in 1899 described the painless lesions on the palms and soles which now bear his name [18].

Horder carried out classical studies linking ante-mortem blood cultures to post-mortem valve cultures and published these in 1905 [19]. From this time on, positive blood cultures became the sine qua non for diagnosing endocarditis in the vast majority of patients and this remains as important today as it was in 1906.

A paradigm shift in management occurred in 1944 when Loewe and colleagues treated seven consecutive patients successfully with penicillin [20]. Change occurred rapidly with increasing access to penicillin and other antibiotics. By 1947 Seabury reported on the Penicillin Era and showed that it completely changed the practice of infectious diseases and cardiology as it pertained to bacterial endocarditis [21].

These advances were occurring as a part of medical practice as I commenced medical school in 1957. Infectious or bacterial endocarditis was still largely cared for, at least in Canada, by cardiologists, who had a variable interest in microbes and antibiotics. The importance of blood cultures and antimicrobial susceptibility tests including bactericidal tests had been identified. The broad-spectrum bacteriostatic drugs, such as the tetracyclines and chloramphenicol, were shown to be relatively ineffective. The dose of penicillin was gradually increased, initially from 100,000 units a day, which cured only 41% of patients, to 600,000 units a day, which was still associated with a substantial mortality [21,22] At 5 million units daily, the mortality was reduced to 36%. Increasing the dose of penicillin now administered intravenously and in association with streptomycin was quickly recognized as the regimen of choice for penicillin-susceptible streptococci [23].

Anderson and Keefer followed 222 patients who were "responsive to antibiotic therapy" [24]. Of those who responded with negative blood cultures, 21 died within a year—12 from

heart failure, 3 from cerebral emboli, and 2 from renal failure. An additional 10% died between one and three years, primarily of heart failure. The risk of reinfection/year was about 2%.

Huge advances have occurred in the diagnosis and management of bacterial endocarditis during the past 40 years and this history is documented within the remaining chapters in this book. The important of enterococcal, staphylococcal, and fastidious Gram-negative rod endocarditis have all been recognized, and strategies for early diagnosis and treatment are now routine in most centers. The Duke criteria for diagnosis and its continued modification has made the diagnosis more precise [25]. The diagnosis and management of prosthetic valve infections have also become an important part of the overall management of endocarditis. The appropriate timing for surgical interventions has also become more evidence based.

The role of echocardiography has markedly changed the management of bacterial endocarditis and given us a tool that has enabled more sensitive and specific diagnosis to occur. Today it is difficult to envision management of endocarditis without access to this technology. In particular, transesophageal echocardiography has become routine for excluding this diagnosis in patients with bacteremia, particularly with staphylococci [26].

Recent advances have enabled the diagnosis of very fastidious microorganisms, including *Coxiella bruneti*, Bartonella sp., and others to now occur with both serologic and cultural tests [27]. Infective endocarditis of unknown etiology is now less common due to continued improvements in microbial diagnosis particularly with the advent of nucleic technologies.

The prevention of endocarditis remains controversial and largely expert consensus-based rather than based on solid scientific evidence. Our current dilemmas in this regard are well reviewed in a subsequent chapter.

Infective endocarditis remains a fascinating illness and continues to intrigue us as clinicians and as individuals attempting to understand the complex biologic processes of host and microbe interactions. Certainly there will be more to learn about this disease. However, we have reached the point in 2006 where we can usually precisely diagnose the infection, localize it to a site on the endocardium, treat it with an established effective regimen, manage complications including surgical interventions with a low mortality, and expect a favorable outcome in over 90% of patients. This is remarkable progress over the past six decades since the advent of penicillin.

Only the future will identify further landmark events that will be highlighted by individuals recording their memories of this disease. In the meantime, as physicians seeing patients with a wide variety of symptoms, we must continue to remember the lessons learned, obtain blood cultures before antimicrobial therapy is instituted and be aware of the many, many presentations of this fascinating illness.

Key Points

1. There have been major advances in the diagnosis and treatment of endocarditis over the past 60 years.
2. The advent of antibiotics has dramatically improved the prognosis of patients with endocarditis.
3. Endocarditis remains an elusive diagnosis because of its many disguises.
4. Early diagnosis and prompt antibiotic therapy are the most effective way to minimize mortality and morbidity.

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2

Pathologic Findings: Valvular Destruction, Perivalvular Abnormalities, and Extracardiac Findings

John P. Veinot

Case Study

A young man presented to hospital with acutely painful legs. He had chronic osteomyelitis and took chronic oral antibiotics. Leg ischemia was diagnosed and surgical thrombectomy yielded large pale thrombi from both leg arteries. Due to the suspicion of a potential cardiac source, an echocardiogram was performed, which demonstrated aortic and mitral vegetations with valve destruction and an aorto-right atrial fistula. Surgical replacement of the aortic and mitral valves was performed and the intracardiac fistula was closed. The excised leg thrombi and the valve vegetations all grew Aspergillus (Figure 2.10). Antifungal medications were administered. Postoperatively the individual continued to be septic with recurrent strokes and died a few weeks after surgery.

At autopsy the fistula between the aorta and right atrium was still infected (Figure 2.14). The tricuspid valve had new fungal vegetations. The strokes were due to embolic cerebral infarctions, as the intracardiac fungal vegetation had massively re-occurred at the aortic valve prosthesis site partially immobilized the valve discs and parts of the vegetation had embolized to the brain (Figure 2.18).

Infective endocarditis (IE) has many clinical manifestations, not just limited to the heart. Pathology is important in the diagnosis of endocarditis and assessment of valvular and perivalvular complications.

Introduction

Infective endocarditis (IE) may give rise to numerous extracardiac, cardiac, and valvular findings, including infected thrombi (vegetations), sequelae of local tissue destruction, and systemic manifestations including vasculitis, emboli, and ischemic events. This is an appropriate term as the causal organisms may be bacterial, fungal, rickettsial, or even viral or mycoplasmal. Traditionally a distinction between acute and subacute IE was made depending upon the severity and rate of disease progression. This reflected an organism's virulence and the presence of underlying cardiac disease. With antimicrobial treatment these clinical divisions have little pathologic significance, and it is preferable to think in terms of active, healing, and healed IE [1,2]. The disease is now probably best described by its anatomical location and the organism involved.

Infective endocarditis may arise in normal hearts with normal valves, or more commonly in patients with abnormal cardiac anatomy [2,3]. The most common preexisting cardiac valvular lesions are left-sided ones, including aortic stenosis (especially the congenitally bicuspid aortic valve), aortic insufficiency, and mitral insufficiency [4–6]. Valves damaged by rheumatic fever continue to be the most common type of predisposing cardiac valvular abnormality in developing countries. However, in developed countries degenerative or age-related diseases, including mitral valve prolapse, degenerative

aortic stenosis, and mitral annular calcification are becoming a more predominant background for IE [2,5].

Other important predisposing conditions are congenital heart diseases, including ventricular septal defect, patent ductus arteriosus, coarctation, transposition of the great arteries, tricuspid and pulmonary atresia or stenosis, and tetralogy of Fallot [7]. Hypertrophic cardiomyopathy and prosthetic grafts or valves may also predispose to IE [8].

For IE to occur there are usually three features—valvular thrombus, circulating bacteria, and bacterial growth on the valve [9,10]. Hearts may develop valvular thrombus due to abnormal flow and anatomy. Thrombus may develop due to regurgitant jet lesions, on contact surfaces, or other areas of mechanical trauma. It should be realized that many phenomena of modern medicine, including prolonged intubation, immunosuppression, chemotherapy, complex surgical procedures, and increased use of antimicrobial agents might contribute to increased susceptibility to develop IE. Other predisposing conditions include immunodeficiency, alcoholism, malnutrition, and diabetes. Intravenous drug use (IVDU) may give rise to a repetitive bacteremia and is an important risk factor for IE.

Catheter and Line-Related IE

Intravascular and intracardiac catheters and devices have proliferated and now include pacemakers, defibrillators, indwelling heart catheters, grafts, and valve or non-valve prostheses. These foreign bodies may be the nidus for infection and may also lead to thrombus formation on a neighboring structures or heart valves [11]. Insertions of catheters, pacemakers, and cannulas are routine procedures in modern medical therapy for resuscitation, feeding, hemodynamic monitoring, and therapy of disease [12,13]. Lines or catheters may contuse, tear, penetrate, perforate, tangle, or thrombose the intracardiac structures. Biofilms of infecting organisms and extracellular matrix may form on the surface of lines or devices and serve as a protective environment for the infective organisms [11,14].

The most common catheter- or line-related lesions involve the right atrium, right ventricle, pulmonary, and tricuspid valves [12,15]. These lesions are rarely important unless they are infected [12]. The catheter lesions are located on the atrial side of the tricuspid valve or on the ventricular side of the pulmonary valve [15]. The lesions usually follow the line of the catheter and the catheter may be surrounded by thrombus which chronically may organize and fibrose.

Infections in defibrillators and pacemakers may occur anywhere along the electrode and are not limited to the tricuspid valve [11]. Pacemakers and defibrillators may have infection involving either the lead or the pouch, and Staphylococci are the most common pathogens involved [16]. Fungal infection may also be seen [17]. Septic and bland pulmonary emboli may complicate pacemaker/defibrillator infection. If the device has been in place for some time, lead extraction is usually impossible and open-heart surgery may be necessary.

Approach to Infective Endocarditis at Surgery or Autopsy

At surgery or autopsy examination of hearts, valves, and vascular prostheses, clinical suspicion that the patient has IE may or may not be present. The presence of unexpected but suspicious valvular lesions should prompt a proper workup for IE. Before immersion of the heart or resected valve in fixative, a thorough examination should be made to visualize all the valves and perivalvular structures. Sterile instruments should be used if a suspicious lesion is encountered (Figure 2.1). Since the proper approach is to assume that all valvular thrombi are infected until proven otherwise (this is the author's personal practice), portions of the thrombus should be submitted for culture. Swabs of the lesions are not recommended. Cultures should never be interpreted in isolation. Pre-mortem or pre-operative blood cultures should be consulted. Microscopy of the valve or thrombus to confirm the presence of microorganisms is essential [18].

Special stains are useful to detect microorganisms; however, treatment with antimicrobial agents has changed the utility of these stains. Gram stain is useful to detect bacteria, but after a few weeks of antimicrobial treatment the organisms may not stain (Figures 2.2, 2.3) [2]. Therefore silver stains should always be performed not only to detect fungi but also to

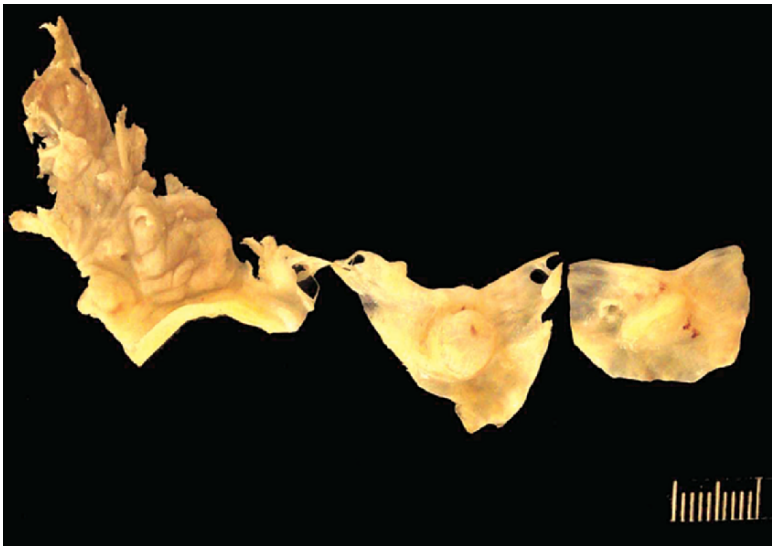

Figure 2.1. Gross photograph of excised three cusp aortic valve with infective endocarditis. The left cusp has adherent infected thrombus (vegetation). The middle cusp has a small nonruptured acquired aneurysm (windsock lesion) related to the infection. Ruler = 1 cm.

detect bacteria that have lost their positive Gram staining, yet still can be detected with silver stain of their cell walls (Figure 2.4). Care must be exercised with silver stain interpretation as this stain also highlights cellular debris and some intracellular organelles. Giemsa stain is useful to detect rickettsial organisms, which may not stain with the other stains.

Correlating the blood culture result with cultures of the tissues and vegetation is essential. Communication with the clinicians may save much frustration if the special stains are negative and the organism is known from prior cultures. This is common in patients who have received prior antimicrobial agents. In culture-negative IE, the common culprit organisms include Eikenella, Brucella, Neisseria, fungi, Chlamydia, acid-fast bacilli, or right-sided endocarditis, where the lungs filter out the organisms. HACEK (Hemophilus,

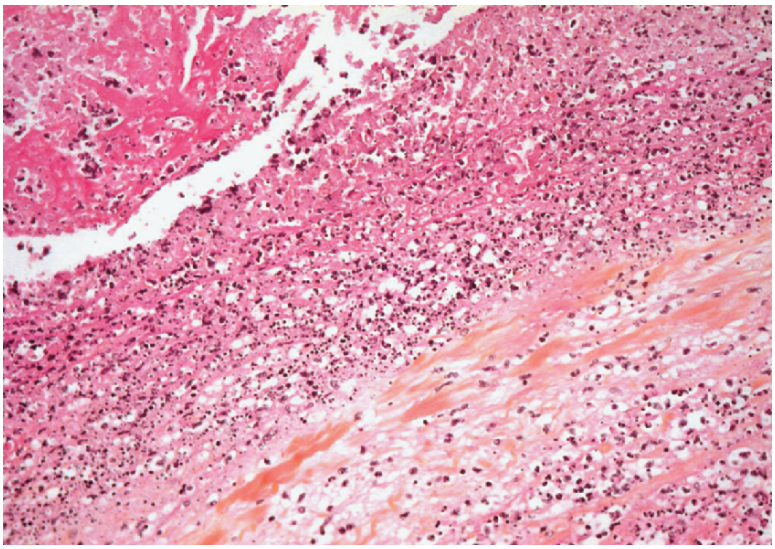

Figure 2.2. Photomicrograph of valve cusp with infective endocarditis. The valve cusp tissue is heavily infiltrated by acute inflammatory cells and there is inflamed thrombus **(left)**. (hematoxylin phloxine saffron, ×200).

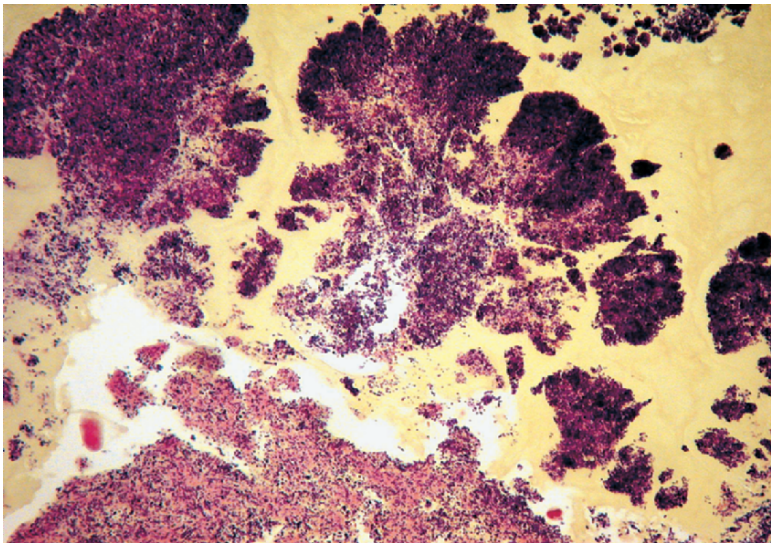

Figure 2.3. Photomicrograph of valve cusp. This is a Gram stain demonstrating large clusters of blue-staining Gram-positive cocci bacteria (Gram stain, ×200).

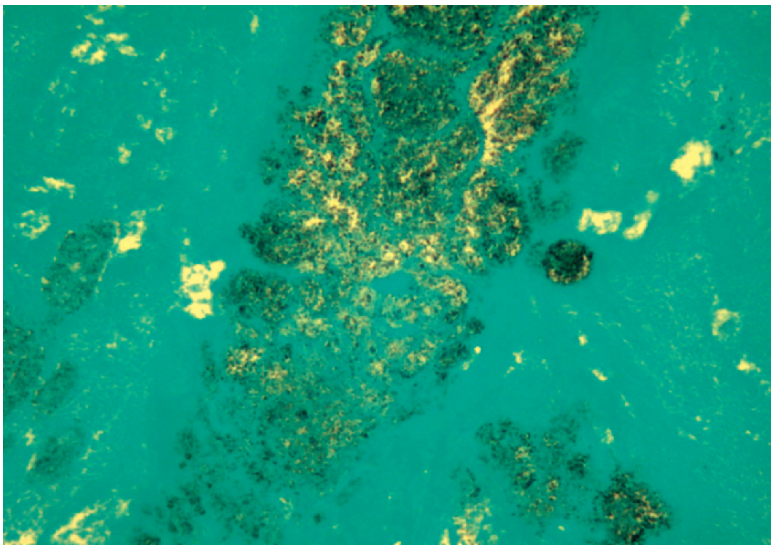

Figure 2.4. Photomicrograph of valve cusp. This is a silver (Grocott) stain demonstrating degenerating clusters of cocci bacteria. This is an excellent stain for fungi, but it is also useful to detect degenerating or dying bacteria after antibiotic treatment (Grocott, ×200).

Actinobacillus, Cardiobacterium, Eikenella, Kingella) organisms may be particularly difficult to grow [19,20]. Clinical history and history of treatment and exposures may be very relevant [21]. Electron microscopy, immunofluorescence, polymerase chain reaction (PCR), or other molecular techniques may be contributory in the search for these often culture negative organisms [18,21–23]. Studies have suggested that PCR may be a better diagnostic tool than culture, especially after antimicrobial therapy, but there remains concern about false positives and background contamination [18,23,24].

Pathological diagnosis of healed IE can be difficult, as the findings may be nonspecific and organisms frequently cannot be found. The diagnosis can only be made with confidence when the gross and microscopic features are typical, and there are collaborative clinical findings. This is quite common in patients with adequate preoperative antibiotic treatment.

Active Infective Endocarditis Pathology (Table 2.1)

Table 2.1. Pathology of Valvular Sequelae of Infective Endocarditis

Acute
Vegetations—infected thrombi
Valve ulcers or erosions
Aneurysms
Chord rupture
Annular and ring abscess
Endocardial jet lesions
Flail leaflet or cusp
Chronic
Perforations
Calcified nodules
Valve tissue defects
Valve fibrosis

On gross examination, infected thrombi of variable size, commonly known as "vegetations," are detected along the lines of valve closure or at the low pressure end of jet lesions [2,9]. They are usually gray, pink, or brown and are often friable (Figures 2.1, 2.5). They may be single or multiple and may affect more than one valve. Common sites are usually on the downstream side of the intracardiac high-velocity flow jets, such as the atrial side of the mitral valve or the left atrial endocardium in cases of mitral insufficiency, the ventricular side of the aortic valve, the ventricular septum or the anterior mitral leaflet in cases of aortic insufficiency, or on the right ventricular endocardium in ventricular septal defects. Infection may also involve the intima of a blood vessel distal to a coarctation or involve the pulmonary artery side of an infected patent ductus arteriosus (Figure 2.6). Left-sided valve lesions are more common than right-sided lesions except for cases related to interventional devices, catheters, or IVDU [9].

Vegetations may be located anywhere on the valve cusp or leaflet or endocardial surface. In fact this is an important distinguishing feature to note, as valve thrombi associated with nonbacterial thrombotic endocarditis (NBTE) and those related to rheumatic fever do not have this variability in location, and are usually along the lines of valve closure. Libman Sacks lesions in lupus patients may be on both sides of the valve. Thrombi from NBTE, rheumatic fever, Libman Sacks, are not associated with valve destruction.

The valve structures may also manifest destructive lesions leading to perforations, defects, aneurysms, erosions, and chordal ruptures (Figures 2.7, 2.8). The amount of thrombus and destruction may completely mask the underlying predisposing valve disease. Thrombi may obstruct the valvular orifice, creating stenosis, but valvular insufficiency is a much more common complication. Chordae may rupture resulting in flail leaflets [25]. Leaflet or cusp aneurysms bulge toward the flow surface and may resemble "windsocks," and IE is the most common cause for leaflet aneurysm or diverticulum (Figure 2.9). If the aneurysm tip ruptures,

Figure 2.5. Gross photograph of excised tricuspid valve from a patient with intravenous drug use related bacterial infective endocarditis. Numerous large, infected vegetations are present. Ruler = 1 cm.

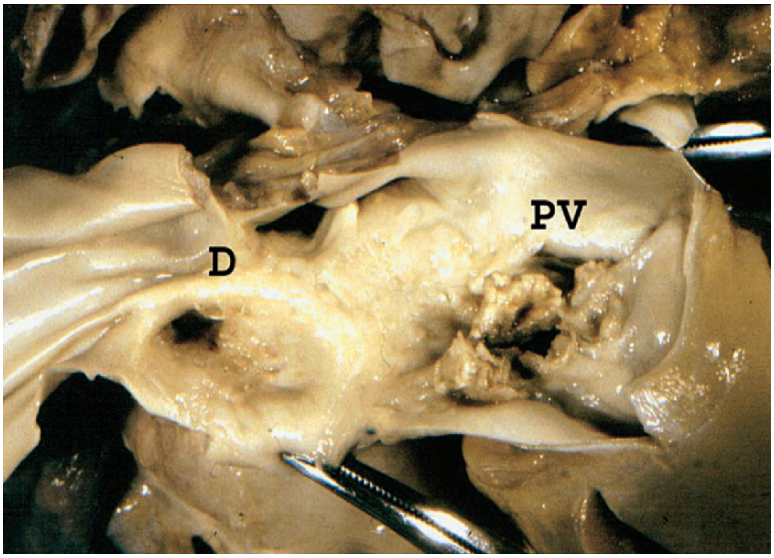

Figure 2.6. Gross photograph of an opened pulmonary trunk artery with the opening of a patent ductus arteriosus that had become infected. There is ragged material surrounding the ductus opening (**D**), and the pulmonary valve (**PV**) is also destroyed by the infection.

the valve may become severely regurgitant due to cusp or leaflet defects.

On microscopic examination, the appearance of the vegetation depends upon both the virulence and destructiveness of the organism and the duration of the infection. Early in the disease course there are fibrin, neutrophils, and clumps of organisms (Figure 2.2). With therapy the organisms may calcify, and the thrombi organize from the base. Organizing thrombus may show no easily recognizable organisms and only show acute and chronic inflammation with neovascularization and fibroblastic proliferation. With thrombus organization giant cells may be seen. If giant cells are prominent one should consider serology for Coxiella or fungi. Pathological changes in the infected valve tissue depend on the chronicity or duration of the infection, the virulence of the organism and the status of the original valve itself. Electron microscopy, immunofluorescence, polymerase chain reaction or molecular techniques are contributory in the search for organisms [18,21–23].

Figure 2.7. Gross photograph of excised aortic valve with infective endocarditis. There are diffuse ragged cusp defects and the right cusp has a ruptured cusp aneurysm. Ruler = 1 cm.

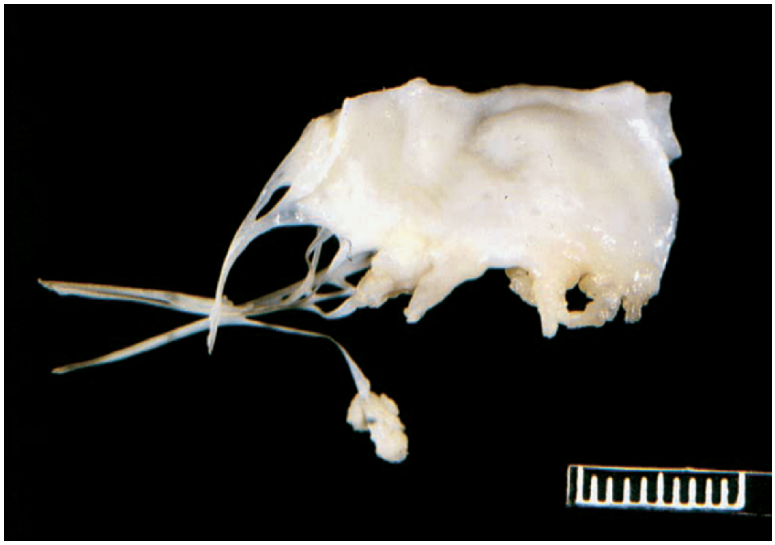

Figure 2.8. Gross photograph of an excised mitral valve leaflet with infective endocarditis. There is chordal vegetation with chord destruction. Most of the leaflet has no remaining intact chords. Ruler = 1 cm.

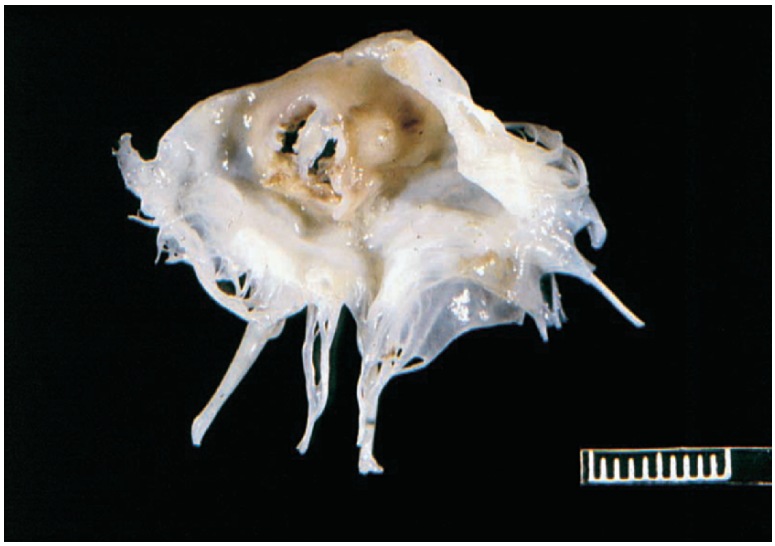

Figure 2.9. Gross photograph of excised anterior mitral leaflet with infective endocarditis related aneurysm (windsock lesion) formation. These infected aneurysms eventually erode through and form valve perforations. Ruler = 1 cm.

Fungal Endocarditis

Fungal endocarditis is usually encountered when there are preexisting risk factors such as intravenous drug use, prior cardiac surgery, immunosuppression, intravenous hyperalimentation, antibiotic therapy, long-term venous catheters, pacemakers, defibrillators, and other intravascular devices [26]. Fungi may infect either native or prosthetic valves. The common organisms are Candida and Aspergillus. Classical clinical manifestations of bacterial IE are often absent. Fungal infected thrombi are usually quite large and friable (Figure 2.10) [2,27]. Valve orifice obstruction leading to clinical valve stenosis may occur if the size of the thrombus is large [14,17,28,29]. Embolic events are not unusual and blood cultures are often negative [29]. The organs receiving the emboli frequently develop abscesses [17].

Whipple Disease

Patients with Whipple disease have been reported to have symptoms of cardiovascular

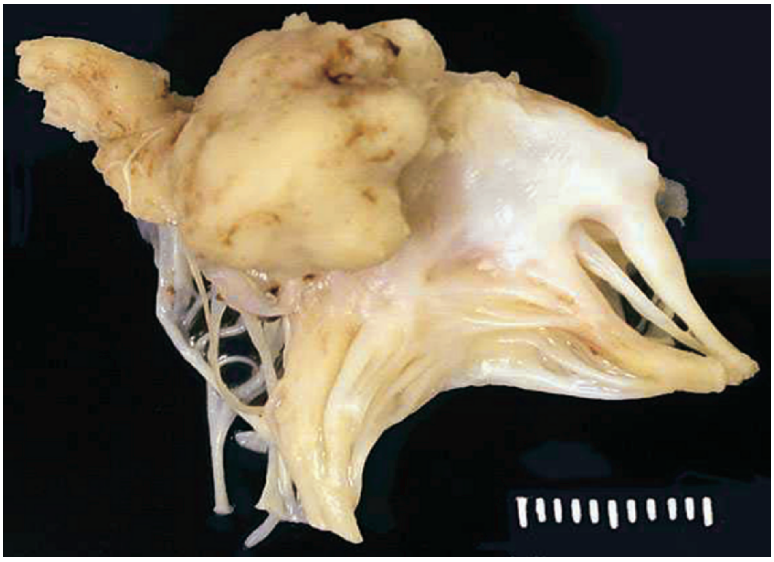

Figure 2.10. Gross photograph of excised anterior mitral leaflet with large bulky fungal vegetation. This was present on both sides of the leaflet (the back is shown). The infecting organism was *Aspergillus*. Ruler = 1 cm.

disease in 58% of cases. However, at autopsy 79% have gross evidence of cardiac involvement, and of these 53% have valvular disease [30,31]. The mitral valve is the most common valve affected, with the aortic and tricuspid valves also reported to be involved at times. There are periodic acid Schiff reaction (PAS)-positive macrophages on light microscopic examination and bacilliform organisms on electron microscopy. Polymerase chain reaction performed on blood may be helpful for diagnosis [22]. The organism is a Gram-positive actinomycete, *Tropheryma whippelii* [31]. The infection may lead to fibrosis and chronic inflammation giving rise to a valve with similar appearance to a post-rheumatic one. The deposits may be nodular and are often not calcified. Similar pathological changes are found in the myocardium, endocardium, and pericardium [32]. History of gastrointestinal disorder should be questioned for, as the diagnosis is usually made by small intestinal biopsy.

Chronic Infective Endocarditis Pathology (Tables 2.1 and 2.2)

With successful medical treatment of infective endocarditis the infected vegetations may organize and the thrombi may form calcific valve nodules. Destructive sequelae of the infection are common (Figure 2.11). The valve may have defects at the edges or central defects forming irregular perforations. Around the holes or perforation there may be brown nodules of organisms that eventually form fibrocalcific nodules. The destruction of the valve tissue may lead to defects at the margins resulting in poor valve coaptation. Distinguishing a post-IE perforation from a congenital accessory orifice may be difficult. In atrioventricular valves congenital orifices should have surrounding chordae, while a post-IE perforation would not. Fenestrations, an age-related finding, are also confused with perforations. These fenestrations are located laterally on the valve cusps near the commissures and always beyond the line of valve closure.

Chordae may rupture resulting in flail leaflets and valve regurgitation. The ruptured chords may knot and calcify along with the organizing

Table 2.2. Pathology of Perivalvular Sequelae of Infective Endocarditis

Perivalvular leaks
Prosthesis dehiscence
Annular and root abscess
Pseudoaneurysm
Fistula or sinus formation
Conduction system destruction
Myocardial abscess
Pericarditis
Hemopericardium
Coronary artery compression
Coronary artery erosion, thrombosis, or rupture

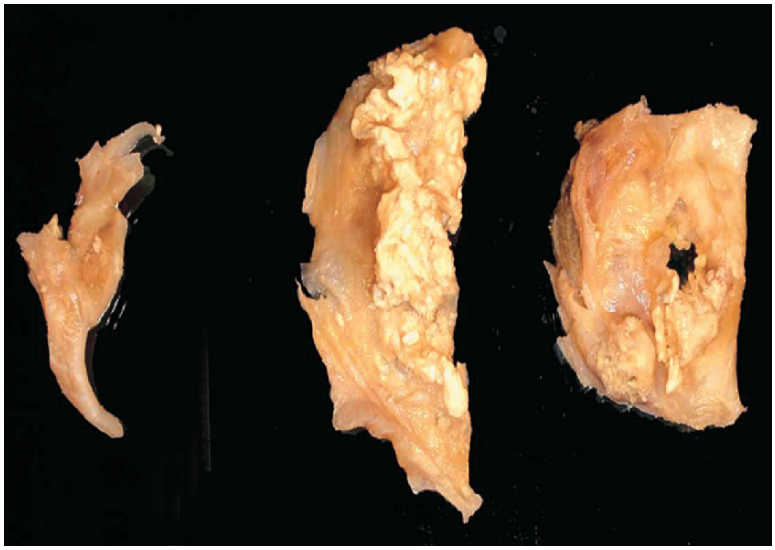

Figure 2.11. Gross photograph of an excised aortic valve with destructive sequelae of prior infective endocarditis. The right cusp has a defect surrounded by calcified material (old vegetation). Similar material is noted on the other two cusps.

infected thrombi. The valve itself may thicken and the chords may fuse. All these are significant contributors to chronic valve regurgitation.

Ventricular papillary muscles may rupture for multiple reasons due to IE. The infection may extend from an adjacent chord and cause myocardial necrosis and rupture. A coronary arterial embolus may cause a myocardial infarct with papillary muscle rupture, similar to any acute myocardial infarct. Finally an embolus may lead to a myocardial abscess with local tissue destruction.

Perivalvular Lesions of Infective Endocarditis (Table 2.2)

Extension of the valve infection into surrounding structures predicts a higher mortality, higher risk of significant heart failure, and the need for cardiac surgery [22]. In the early stage, perivalvular abscess is largely composed of inflammatory infiltrate, but at later stages necrosis and cavitation usually develop leading to destruction of perivalvular tissue [33]. Perivalvular abscess is not a static complication but is progressive and can evolve into serious perivalvular complications including perivalvular leak, fistula and pseudoaneurysm. These perivalvular complications may develop in spite of early valve surgery. Perivalvular leak due to annular abscess may be seen with native valve IE (aortic more than mitral), but are especially common adjacent to infected valve prostheses [6]. Although a perivalvular leak may be technically related to poor tissues, suture unraveling, suture tissue cut-through, and other technical matters, it is important to keep the possibility of IE in mind with all perivalvular leaks. These leaks may cause clinically significant congestive heart failure and sometimes hemolysis.

Extension of an active valve infection to adjacent cardiac structures is common, including infected lesions where adjacent valves come in contact or are contiguous—such as from the aortic valve to the base of anterior mitral leaflet, from the posterior leaflet mitral valve to the left atrial endocardium, and from the aortic valve to the ascending aorta [34]. Jet lesions as a result of valvular insufficiency may cause infected endocardial lesions to form along the path of the regurgitant jet [9,34].

Infections may also extend from the mitral and aortic valves to the valve annuli (Figure 2.12) [35]. This complication is considerably more common in the aortic position as compared to the mitral. This may manifest as an aortic root abscess, or the mitral annulus or mitral annular calcification (MAC) may become infected. MAC is a common finding in the hearts of elderly patients [36]. It is considered to be an age-related finding, but it probably represents degenerative changes in the mitral annulus [37]. It is associated with mitral valve disease, especially mitral valve prolapse due to myxomatous/floppy

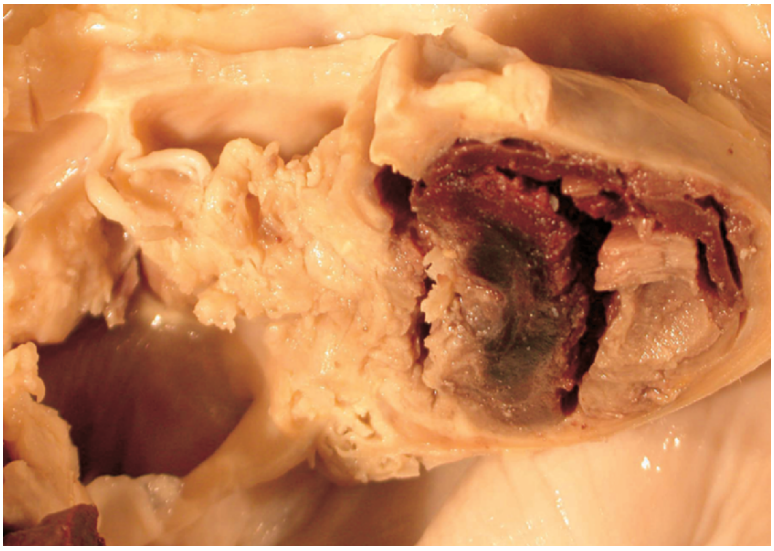

Figure 2.12. Gross photograph of opened aortic root and aortic valve at autopsy. The aortic valve is destroyed by vegetations (**center**) and to the right there is a large paravalular aortic root abscess. This root abscess contained infected laminated thrombus material.

mitral valve. Uncommonly the calcium extends onto the leaflet, producing a mass and the calcium may undergo liquefactive necrosis and grossly mimic IE [38–40]. MAC may ulcerate giving rise to thrombus deposition with potential for embolization and infection. If infected, there is usually leaflet perforation and myocardial abscess formation (Figure 2.13) [41]. If the infection spreads into the lateral atrioventricular groove, the circumflex coronary artery may thrombose because of distortion from the local effects of the infection, and development of arteritis. Annular abscesses may also erode into to the pericardial surface, producing fibrinous or suppurative pericarditis and hemopericardium with tamponade.

Aortic root abscesses may become a significant source of embolic material and they may compress adjacent structures around the aortic root. If the proximal coronary arteries are distorted, myocardial ischemic sequelae may result. The formation of annular abscess is not an end event. Rather these structures are progressive with potential formation of perforations or fistulas [33]. Due to the central position of the aortic valve, infection of this valve may form fistulas with practically any chamber (Figure 2.14) [42]. Each aortic cusp and sinus has its own pattern or

Figure 2.13. Gross photograph of longitudinal section through the mitral valve, the mitral annulus, and left ventricle. There is mitral annular calcification (**MAC**) with large abscess formation in the calcific material.

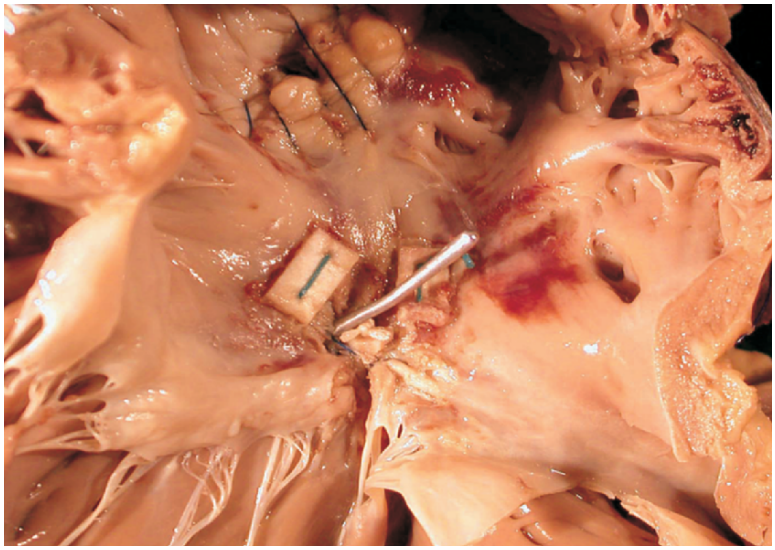

Figure 2.14. Gross photograph of a heart opened to demonstrate the right atrium and tricuspid valve. Aortic valve fungal endocarditis had caused a fistula to the right atrium. This was closed with pledgets but the disease reoccurred. The metal probe is passed from the aortic region and the fistula is still infected and patent. This is the same patient as Figure 2.10 (aortic and mitral valve *Aspergillus* endocarditis).

propensity for fistula formation and complication (Figure 2.15). Infection in the left aortic cusp or sinus may spread through the aortic wall and cause pericarditis or tamponade, or a fistula may extend into the left atrium. Infection of the posterior (non-coronary) aortic cusp or sinus may cause a fistula to either the left or right atrium. Infection of the right aortic cusp or sinus may cause a fistula to the right atrium, and the right ventricle or right ventricular outflow tract. An aorto-right ventricular fistula is possible due to the presence of the atrioventricular component of the interventricular septum. Extension into the myocardium and the conduction system may be found when the infection involves the valve ring or annulus. Fistulas and abscesses are important problems particularly with prosthetic IE, as discussed below.

Involvement of the coronary arteries may be due to distortion from an aortic root abscess or they may become directly infected by local extension through the coronary ostia or by formation of mycotic aneurysms. The latter may occur in normal arteries but also may be superimposed

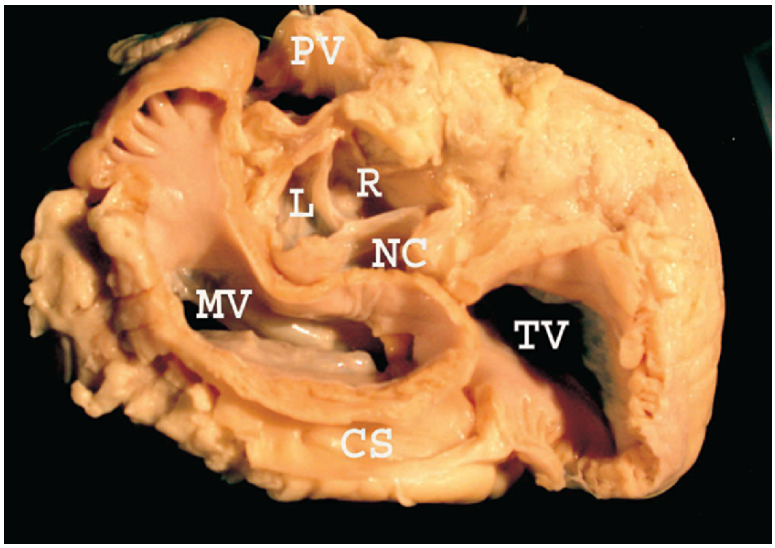

Figure 2.15. Gross photograph of the base of the heart. The central aortic valve may form fistulas to nearly any chamber. Infections from the right cusp or sinus (**R**) may extend to the epicardium, the right atrium and the right ventricle outflow tract. Infection of the non-coronary cusp or sinus (**NC**) may form fistulas to both the right and left atria. Infections of the left cusp or sinus (**L**) may form fistulas to the epicardium, and the left atrium. Additional abbreviations: **CS** = coronary sinus; **MV** = mitral valve; **PV**= pulmonary valve; **TV** = tricuspid valve.

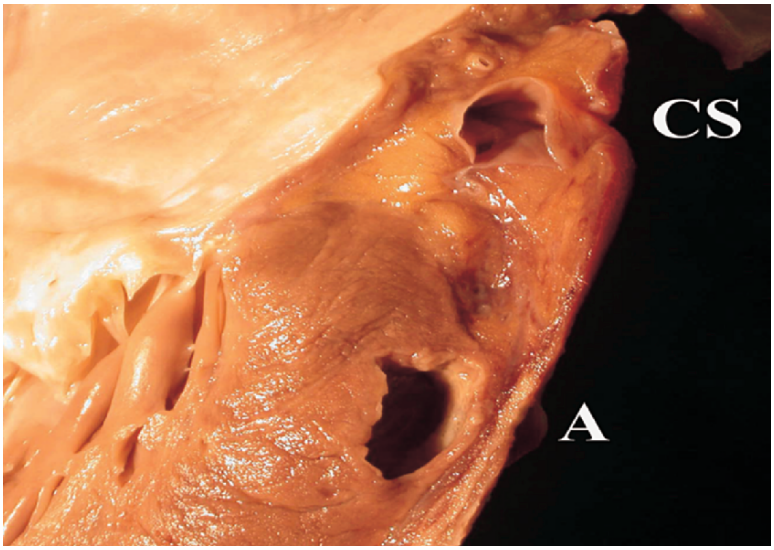

Figure 2.16. Gross photograph of longitudinal section of the left ventricle wall. The upper defect (**CS**) is the normal coronary sinus near the atrioventricular groove. The lower large intramyocardial defect (**A**) is an abscess cavity that contained purulent material. The patient had a floppy myxomatous mitral valve that became infected leading to coronary arteritis and myocardial abscesses.

on an underlying atherosclerotic plaque. Mycotic aneurysms may thrombose and are a source of infected emboli that may seed the myocardium leading to myocardial abscesses. Myocardial abscesses may also form as a result of local valvular IE extension into the adjacent myocardium (Figure 2.16). Aortic root abscesses and myocardial abscesses may impinge upon or destroy the conduction system in the areas of the atrioventricular node and His bundle. Clinically this manifests as a progressively worsening degree of heart block and may be an important clinical sign that treatment is failing or disease is progressing.

Extension of infection to the pericardial space may lead to hemopericardium and tamponade or to pericarditis. Fibrinous pericarditis is a common finding with IE, but the pericardium may also become infected, leading to suppurative pericarditis.

Infective Endocarditis of Valve Prostheses (Table 2.1 and 2.2)

Infection of valve prostheses may manifest early after surgery or long after hospital discharge [43–46]. Both bacteria and fungal organisms are important causes of prosthetic IE [28]. Valvular bioprostheses have vegetation, cusp thrombi, destruction, erosion, and perforation similar to native valves (Figure 2.17). With infection of mechanical prostheses, the actual prosthesis usually remains intact and the infection is mainly in the sewing ring and surrounding tissues. The thrombi on a mechanical prosthesis or bioprosthesis may interfere with normal function, as the prosthesis may become dysfunctional with disc or cusp immobility (Figure 2.18) [9,27]. Peripheral emboli are not uncommon [43].

In any prosthesis, sewing ring and perivalvular tissue infection is common, and the valve prosthesis may dehisce or become loose when the surrounding tissues develop necrosis [9,45]. Annular abscess and fistulas are much more common with prostheses, as compared to native valves. It is a disturbing and memorable experience to image a near totally dehisced valve prosthesis by echocardiography and for the surgeon to be able to remove such a valve prosthesis from the patient without much need for dissection. Sutures, pledgets, as well as the aortotomy site may become infected.

A large perivalvular leak results in severe perivalvular regurgitation and heart failure, but even a small perivalvular leak can be significant due to the development of severe hemolysis. Destruction of the adjacent tissues may lead to intracardiac fistulas, conduction system destruction and arrhythmias, and coronary artery inflammation and thrombosis [43]. The mortality of prosthetic IE remains high, with or without surgery, and perivalvular complications can develop despite surgery. Fungal infection of

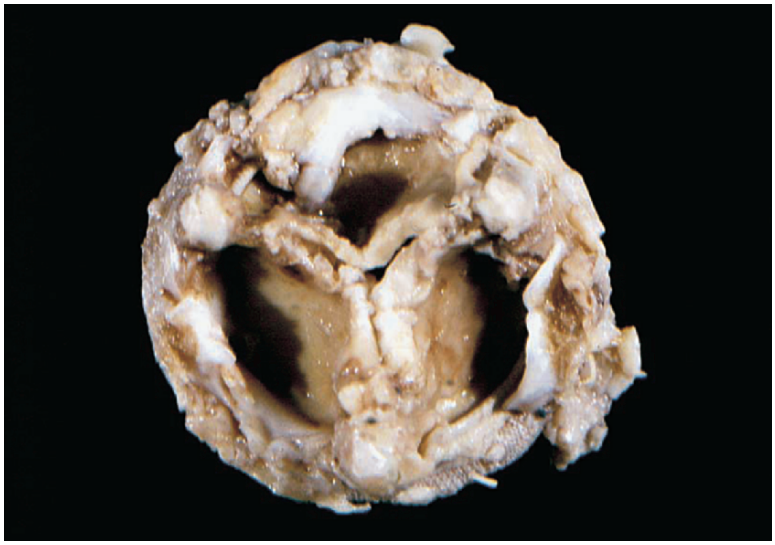

Figure 2.17. Gross photograph of an infected Carpentier Edwards bioprosthesis. The ring and cusps have ragged thrombus material that contained bacterial colonies.

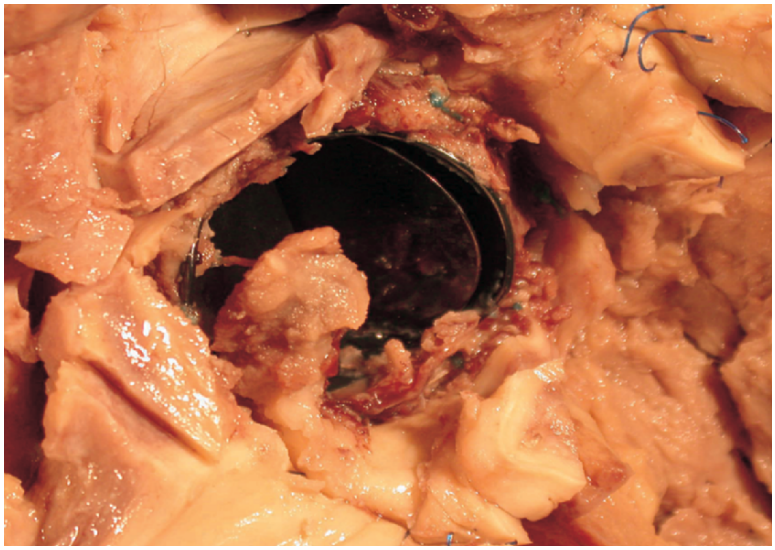

Figure 2.18. Gross photograph of opened aortic root with a mechanical tilting disc prosthesis placed in the aortic valve position. A large amount of thrombus at the edge of the prosthesis is interfered with the disc movement. This is recurrent *Aspergillus* infection (same patient as Figures 2.10 and 2.14). There was recurrent stroke after valve replacement.

a valve prosthesis is a surgical indication due to near total mortality without surgery [14,29,44].

Systemic Pathology of Infective Endocarditis (Table 2.3)

Systemic manifestations of IE may be due to generalized sepsis, immune reactions—including immune complex disease—or related to emboli or ischemia with organ atrophy, ischemia, or infarction. Classic peripheral stigmata of IE may not be evident with right-sided IE or with infections due to HACEK organisms [22]. Similar to all disseminated infections, IE related sepsis may present with fever (or fever of unknown origin), leukocytosis, disseminated intravascular coagulation (DIC), adult respiratory distress syndrome (diffuse alveolar damage), jaundice, and other sequelae of hypotension including multiorgan failure.

Table 2.3. Pathology of Systemic Sequelae of Infective Endocarditis

Sepsis
Diffuse alveolar damage
Cholestasis
Systemic emboli
Infarct / atrophy
Abscess
Roth spots
Osler nodes
Janeway lesions
Splenic infarct or rupture
Mycotic aneurysms
Pulmonary emboli
Infarct
Abscess
Empyema
Immune complex phenomena
Vasculitis
Glomerulonephritis

Renal manifestations include interstitial nephritis and pyelonephritis. There may be immune complex formation between bacterial antigens and antibodies, which deposits in the glomeruli leading to glomerular damage [47]. Focal necrotizing and diffuse proliferative glomerulonephritis may manifest as acute nephritis and renal failure. Type 1 membranoproliferative glomerulonephritis may lead to nephrotic syndrome. Crescentic glomerulonephritis with rapidly progressive glomerulonephritis can also occur. Emboli to the kidney may cause infarction, hematuria, flank pain, and renal abscesses.

Emboli may occur in right- and left-sided IE [48]. Emboli can occur before therapy, during therapy, or even after therapy [22]. Emboli from left-sided valve or cardiac lesions may affect any systemic organ leading to visceral infarction, ischemia, or organ atrophy. Either bland fibrin platelet material of the vegetation or infected components containing microorganisms may embolize. The propensity for embolization may be related to the size and mobility of the vegetation, as seen on echocardiogram [48].

The effect of the embolic material depends upon the size of the embolus, whether it contains microbes, the size of the occluded blood vessel, the degree of collaterals in the organ, and the metabolic demand of the organ. Vascular spasm may also contribute. If there are prominent numbers of organisms in the embolic material, the organ may form an abscess, in addition to an infarct, which is referred to as a septic infarct. Coronary arterial emboli may lead to angina, myocardial infarction or sudden death. Embolic myocardial infarcts are usually large, and myocardial abscesses may develop.

The central nervous system is the most common site involved by IE and neurologic deficits may be due to many different causes [22,48]. Cerebrovascular embolism may manifest as transient ischemic attacks or stroke. Cerebral infarcts may be hemorrhagic and non-hemorrhagic [49]. Mycotic aneurysms of infected cerebral arteries may thrombose or rupture (Figures 2.19, 2.20).

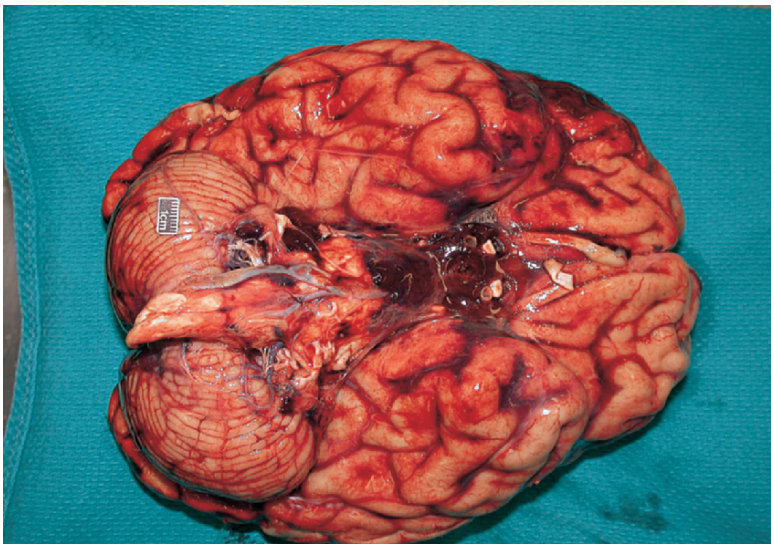

Figure 2.19. Gross photograph of the base of the brain with adherent blood clot. Subarachnoid hemorrhage occurred due to a ruptured mycotic cerebral artery aneurysm. The mitral valve was infected with bacteria. Ruler = 1 cm.

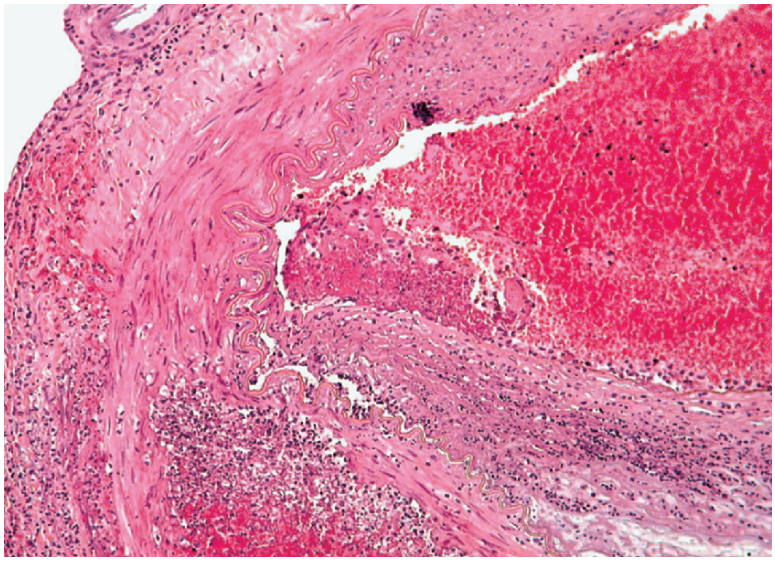

Figure 2.20. Photomicrograph of the mycotic aneurysm of the cerebral artery from patient with subarachnoid hemorrhage (Figure 2.19). The artery is acutely inflamed and even has dissection with destruction and splitting of the wall. Thrombus is present in the lumen. Gram stain (not shown) had numerous Gram-positive cocci (hematoxylin phloxine saffron, ×100).

Other serious neurological complications are cerebral abscesses and meningitis.

Splenic infarcts may cause abdominal, back, or flank pain. Splenic infarcts may be bland ischemic infarcts or septic infarcts both of which may lead to abscess formation [22]. Rarely the spleen may rupture, leading to intra-peritoneal bleeding. Gut ischemia and infarction may occur if the mesenteric circulation is embolized. Emboli to the limbs may cause acute ischemia or gangrene. When a vascular surgeon performs a thrombectomy or embolectomy in a patient with acute limb ischemia the removed material should be examined for infection with bacterial and fungal stains.

Right-sided endocarditis may lead to infected pulmonary emboli, pulmonary infarction, abscesses, and empyema. If large, these pulmonary emboli may cause sudden death. If there is an intracardiac shunt, either preexisting or developed due to IE, paradoxical embolism is possible with vegetation fragments embolizing into the systemic circulation bypassing the lung.

Osler nodes (tender subcutaneous nodules on the digits), Janeway lesions (red or hemorrhagic nontender lesion on the palms or soles), and Roth spots (retinal hemorrhages) are due to emboli to small blood vessels. These are now rarely encountered with modern medical care. Petechiae and subungual hemorrhages may be seen on the skin. Small-vessel vasculitis may be due to an infected embolus (a mycotic aneurysm) or immune complexes [50].

Mycotic aneurysms may occur in any circulation, but are most common in the central nervous system circulation [22,51]. Cerebral vessels are commonly involved, followed by visceral arteries and arteries of the extremities. Branch points are usually affected. They may develop in the aortic wall adjacent to the valve or distant to it. These aneurysms weaken the vessel wall and may rupture and hemorrhage even after the infection has been treated (Figures 2.19, 2.20]. Subclinical rupture may lead to pseudoaneurysm formation. They also may thrombose. Surgical intervention is usually required [22].

Summary

Infective endocarditis continues to be a medically challenging disease despite modern medical advances. In fact, modern medical therapy, such as intracardiac catheters and devices, may contribute to the underlying predisposition of some individuals. In many cases careful clinical assessment and blood cultures remains important to determine the infecting organism. The anatomical pathologist, cardiologist, cardiac surgeon, infectious disease consultant, and microbiologist all play an important role in diagnosis and treatment. Many of the classically described clinical and pathological manifestations are no longer commonly encountered because of timely and effective antimicrobial treatment. In addition to the well-recognized

local valvular complications, spread of the infection to perivalvular structures is clinically relevant and contributes to the therapeutic challenge. Patients with culture-negative fungal and prosthetic IE have a poor prognosis and pose a major clinical challenge.

Key Points

1. Infective endocarditis may be definitely diagnosed from surgical or post mortem material. It may be an unexpected finding, and suspicious pathologic specimens should always be evaluated for microbes.
2. It is useful to consider valve thrombus to be infected until proven otherwise. Multiple special histological stains to look for bacteria and fungi are recommended and complimentary.
3. Gram stain may become negative after antibiotic treatment.
4. Infective endocarditis produces valve destruction usually resulting in valve regurgitation, but rarely stenosis.
5. Very large vegetations are often from culture negative organisms (HACEK) or from fungi.
6. Local perivalvular destructive lesions such as abscesses and fistulas may cause significant complications such as heart failure and arrhythymias. This is a dynamic process and generally progressive, resulting in perivalvular regurgitation, pseudoaneurysm, or fistula.
7. Prosthetic valve endocarditis may involve both mechanical and bioprosthetic valves. It may be difficult to treat without surgical intervention.
8. Some of the clinical manifestations related to infective endocarditis are due to systemic sequelae including sepsis, embolization, and immune-related complications.

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3

Changing Populations: The Elderly, Injection Drug Users, Health-Care-Associated and Immunocompromised Patients

Yasmin Maor and Ethan Rubinstein

Case Study

A 38 year old man presented to hospital with a 10 day history of bloody sputum, left sided chest pain aggravated by inspiration and movement, dyspnea, fatigue and pyrexia. He had been using intravenous heroin and crack cocaine for the past 10 years and was diagnosed to be infected with both the human immunodeficiency virus and hepatitis C virus 5 years ago, but he declined therapy for both infections. He had just finished a 6-month course of directly observed antituberculous therapy. Hospital record from an admission 3 months previously disclosed that at that time he was colonized with methicillin resistant *Staphylococcus aureus* (MRSA) in his nostrils and throat.

On examination, he was cachectic and jaundiced. The blood pressure in the right arm was 110/35 mmHg, his heart rate 110 beats per minute and the respiratory rate 36 per minute. His oxygen saturation on room air was 94%. Old and fresh track marks were present in both arms. Evaluation of fundi revealed multiple hemorrhages. His jugular venous pressure was markedly elevated at 15 cm. In addition to S_3 and S_4 gallop, there were a 3/6 holosystolic murmur over the second intercostal space radiating to the neck, a 3/6 systolic ejection murmur over the right sternal border and a 2/6 diastolic murmur over the left second intercostal space. Dullness to percussion was appreciated in the right lower lung field with decreased breath sounds and bronchial breathing. Also present were hepatosplenomegaly, ascitis and ankle edema. The neurological examination was normal.

The chest radiograph showed consolidation and a cavity with an air fluid level in the right lower lung field. The electrocardiogram revealed second degree A-V block, left axis deviation and left ventricular hypertrophy.

The hemoglobin was 66 g/L with normal indices, the white blood cell count 32 x 10^9 cells/L with the majority being polymorphonuclear cells and the platelet count 850 x 10^9 cells/L. The INR is 3.2 with elevated liver enzymes. The viral load was > 100,000 copies/ml and the urine contained 100 red blood cells, 100 white blood cells and red blood cell casts.

A transthoracic echocardiogram showed two pedunculated vegetations about 2 cm in length on the anterior and posterior cusps of the aortic valve and an additional vegetation on the tricuspid valve, associated with severe aortic and tricuspid insufficiency.

In light of the history of injection drug use and previous colonization with MRSA, decision was made to initiate empiric therapy with vancomycin and ciprofloxacin which was used instead of an aminoglycoside because of renal failure. Within 72 hours of their collection all 3 sets of blood cultures grew MRSA and *Candida albicans* was recovered from all blood cultures at 96 hours. Parenteral fluconazole was then added

to his treatment. Unfortunately, he became progressively more dyspneic and hemodynamically unstable. Despite emergency valve replacement surgery 6 days after admission, profound hypotension, third degree heart block, ischemic bowel and coagulopathy ensued. He died 3 days after the emergency valve replacement surgery.

This case illustrates the challenges in the treatment of endocarditis in patients with complex concomitant illnesses.

Introduction

Over the past 100 years the incidence of infective endocarditis has not changed significantly. This may seem surprising as the detection of bacteremia has improved significantly during this time period and the introduction of two-dimensional (2-D) echocardiography has revolutionized the diagnosis of bacterial endocarditis. Epidemiological studies demonstrate that infective endocarditis accounts for about 1 case per 1,000 hospital admissions (range 0.16 to 5.4 cases per 1,000 admissions) [1]. The incidence of endocarditis depends on the criteria used to identify cases and on referrals to tertiary medical centres and publication bias. When strict criteria were applied to identify all definite, probable and possible cases of endocarditis in residents of Olmsted County, Minnesota, U.S.A from 1950 through 1981, the mean annual age- and sex-adjusted incidence rates per 100,000 person-years were 3.8 for total cases and 3.2 for definite and probable cases only. Total rates were 4.3 for 1950 through 1959, 3.3 for 1960 through 1969 and 3.9 for 1970 through 1981 [2]. A follow-up publication from the same region for the years 1970–2000 demonstrated that age- and sex-adjusted incidence of infective endocarditis ranged from 5.0 to 7.0 cases per 100,000 person-years during the study period and did not change significantly over time (P = 0.42 for trend). Nonetheless, an increasing temporal trend was observed in the proportions of prosthetic valve infective endocarditis cases (P = 0.09). Among individuals with underlying heart disease, there was also an increasing temporal trend in endocarditis complicating mitral valve prolapse (P = 0.04) and a decreasing trend in endocarditis complicating rheumatic heart disease (P = 0.08). However, the absolute numbers were small [3].

This rather stable incidence of endocarditis occurs despite the fact that the epidemiological, microbiological and clinical features of the disease have changed substantially. In particular, the age distribution of patients has increased from a mean of 30 years in the pre-antibiotic era to about age 50 years to date [1]. In addition, new populations at risk have been added, such as injection drug users and immunocompromized patients. These include human immunodeficiency virus (HIV) patients, cancer patients receiving chemotherapy and a growing population of patients receiving particularly aggressive chemotherapy such as bone marrow transplant recipients and patients with solid organ transplants. This chapter is devoted to the changes in the epidemiology and to new insights gained into the clinical presentation, treatment options and outcomes of these special populations that occurred during the past decade.

The Elderly

Epidemiology

Despite the fact that the incidence of infective endocarditis has not changed, recent studies have shown remarkable changes in the epidemiology and clinical features of the disease. In the 1950s, when rheumatic fever was prevalent, particularly during World War II and before the wide use of penicillin, the incidence of endocarditis was highest in patients aged 20–30 years old and only 5% of patients with endocarditis were over 60 years of age. More recent publications show that the incidence of infective endocarditis has increased in patients older than 50 years, reaching a peak at 70–74 years of age. Currently, more than 50% of patients are older than 50 years [4–7]. Data from the International Collaboration on Endocarditis (ICE) which encompassed in 2003 over 2,200 well-characterized patients from seven countries with definite infective endocarditis by the Duke criteria, demonstrated that the median age of these patients was 58 years [8]. Hoen et al. [9] performed a population-based survey during 1999 in all hospitals in six French regions representing 26% of the French population (16 million inhabitants). Three hundred ninety adult inpatients diagnosed with infective endocarditis according to the Duke criteria were identified. The annual age- and sex-standardized incidence was 31 (95% confidence interval [CI] 28–35) cases per million, not including the region of New Caledonia, which had 161 (95% CI 117–216) cases per million. Incidence increased

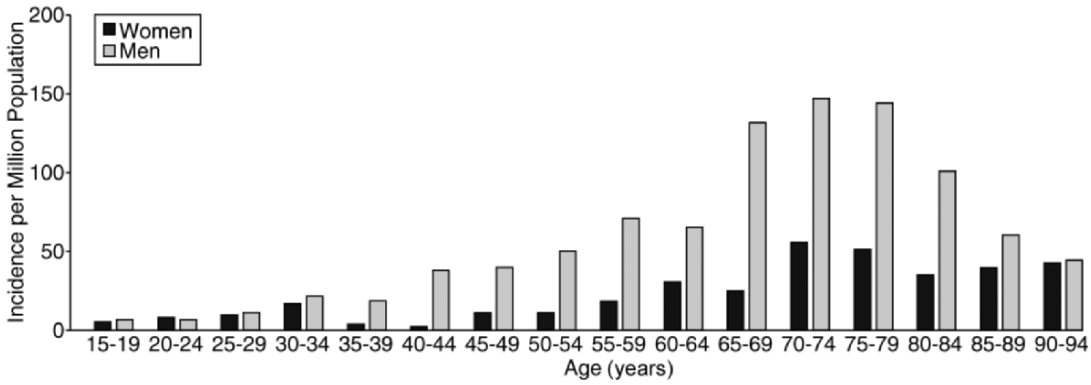

Figure 3.1. Incidence of infective endocarditis by age and sex in the study population [9].

in patients older than 50 years and peaked at 145 cases per million in males between 70 and 80 years (see Figure 3.1). Fefer et al. [10] collected 108 episodes of infective endocarditis during the years 1990–1999 admitted to a community hospital. The annual admission rate was stable at around 0.4 patients with endocarditis per 1,000 admissions. Sixty episodes (56%) involved males and 48 (44%) females, a ratio of 1.3:1. The mean age was 57 (SD 22) years. Thirty-three patients (31%) had prosthetic valve endocarditis and 75 (69%) patients had native valve endocarditis. Patients with prosthetic valve endocarditis were significantly older than those with native valve endocarditis [66 years (standard deviation [SD] 12) versus 54 years (SD 24), $P < 0.05$].

Selton-Suty et al. [11] studied the characteristics of infective endocarditis in the elderly in a university hospital that is both a referral and a primary care centre. They identified 114 consecutive patients treated for infective endocarditis from 1990 to 1993. Of the 114 patients, 25 (22%) were older than 70 years [mean age 76 (SD 6) years, range 70–91] and 89 were younger than 70 years [mean age 51 (SD 15), range 19–69]. In both groups there was a predominance of males in a ration of 2:1. According to the Duke criteria, the distribution of diagnostic categories was significantly different in the two groups, with a lower percentage of definite infective endocarditis in the older patients. The distribution of underlying heart disease was significantly different between the two groups. Infective endocarditis complicating intracardiac prosthetic devices (valve prostheses or pacemakers) was more common in the older compared to the younger patients. The location of infective endocarditis, when vegetations were seen, was similar in the two groups with most cases involving the mitral valve. There were no significant differences between the two groups with respect to clinical signs, auscultatory findings changes or extracardiac manifestations. Emboli were three times less common in the older patients [2 (8%) vs. 25 (28.1%), $P < 0.04$]. Echocardiographic findings were also similar between the two groups. Younger patients underwent more surgery operated but this may reflect the reluctance to operate on elderly individuals rather than a true difference related to the actual disease process. To conclude, this detailed investigation demonstrates the clinical significance of infective endocarditis in the elderly. These findings are in accord with other publications demonstrating the increasing prevalence of infective endocarditis in the elderly [8–10].

Why are the elderly more prone nowadays than previously to have infective endocarditis? There are several possible explanations. On the one hand, the wide and early use of antibiotics in proven or suspected infections prevents many cases of endocarditis that were common in the past—when antibiotics were prescribed sparingly. In addition, antibiotic treatment decreased the prevalence of rheumatic heart disease, once the most common predisposing factor for infective endocarditis in younger patients. These factors among others, have contributed to the decline in endocarditis—particularly in the young, but at the same time life expectancy has substantially increased so that the total time a person is at risk for infective endocarditis has increased. Also, as people age, the prevalence of degenerative heart disease increases. The aortic valve undergoes

degenerative calcification and such a valve becomes functionally stenotic because of the restricted mobility of the cusps. The resulting turbulence predisposes to endocarditis. As people live now much longer than before, various minor cardiac lesions can become hemodynamically important creating turbulent flow and allowing for a fibrin-thrombus clot, the basic mechanism of endocarditis, to form. In addition, in the elderly, hypertension, atherosclerosis and kidney disease are more common allowing for turbulent flow in diseased vessels to develop. Mouth sanitation of the elderly tends to decline with age increasing the risk of local oral infections and subsequent bacteremia, thus increasing the risk of developing infectious endocarditis [12]. The decline in rheumatic infective endocarditis is counterbalanced by the increased prevalence of infective endocarditis due to degenerative valve disease. In addition, prosthetic heart valves are more common in the elderly and the eligible age for cardiac surgery (excluding bypass surgery) is constantly being pushed up [13]. Other medical devices, such as implantable pacemakers, defibrillators and stents, have become more common, increasing the risk of these groups of patients to infectious endocarditis [14,15]. Current data suggest that the prevalence of endocarditis in patients with foreign objects is between that of valvular infective endocarditis in the general population and prosthetic valve infective endocarditis in the range of 550 cases/million patients per year ~100 times more common than non-foreign-body-associated endocarditis [14]. Finally there are some neoplastic diseases that are more common in the aged that may be associated with infectious endocarditis. Among them ulcerating skin cancers (like basal cell carcinoma, melanoma, etc.), polyps and cancers of the large bowel (associated with *S. bovis* endocarditis). Other factors, such as increasing incidence of nosocomial bacteremia in the elderly and an impaired host immune system, may also contribute to the increase prevalence in the elder. As the world's population is becoming older it is to be expected that in the future more endocarditis cases will be encountered in the very old. In the year 2030, there will be >1 billion individuals > 65 years of age; 19.6% of the North American population, 23.0% of the European population, 11.5% of the Latin American and Asian population and 4.6% of the African population will be elderly; and thus this population will become the prime population segment from which endocarditis cases originate [16]. It is thus expected that the shift in patients with endocarditis belonging to the older age will continue and even increase in the coming decades.

Bacteriology and Age

Several publications have demonstrated the increased frequency of enterococcus and other streptococci of group D (e.g, *S. bovis*) in causing bacterial endocarditis in the elderly. In the publication of Selton-Suty et al. [11] older patients (≥70 years) with infective endocarditis had a significantly higher percentage of group D streptococci and enterococci compared to the younger patients (<70 years) [10 patients (47.6%) versus 15 patients (19.5%), $P < 0.04$]. A recent publication [17] also demonstrated that among 1,285 patients with left-sided native valve endocarditis, 107 (8.3%) had enterococcal endocarditis most frequently seen in elderly men, frequently involving the aortic valve, tending to produce heart failure rather than embolic events and associated with relatively low short-term mortality. Compared to patients with streptococcal endocarditis, those with enterococcal endocarditis were more likely to be nosocomially acquired (15% vs. 1%; $P < 0.0001$) and have heart failure (46% vs. 35%; $P = 0.03$). Compared to patients with *S. aureus* endocarditis, patients with enterococcal endocarditis were less likely to embolize (26% vs. 49%; $P < 0.0001$) and less likely to die (11% vs. 27%; $P = 0.001$). Multivariable analysis showed that enterococcal endocarditis was associated with lower mortality than other etiologies in patients with left-sided endocarditis (odds ratio [OR] 0.49; 95% CI 0.24–0.97). As far as culture-negative endocarditis is concerned, there was no significant difference in the number of culture negative endocarditis between the older and younger patients.

Di Salvo et al. [18] studied 315 consecutive patients with definite infectious endocarditis. Patients were separated into three groups: group A included 117 patients aged < 50 years, group B included 111 patients aged ≥50 and ≤70 years and group C included 87 patients aged ≥70 years. A digestive presumed port of entry was more commonly detected in group C (19%)

and in group B (16%) than in the younger patients (5%), $P < 0.0001$. Similarly, the urinary tract as the presumed port of entry was more frequent in group C (13%) than in the other groups (group A = 2% and group B = 6%, $P < 0.005$). The presumed port of entry was supported by the distribution and etiology of the pathogens. The most frequent isolated pathogens were *Streptococci* found in 45% of patients. The proportion of *S. bovis* endocarditis was higher in groups B and C than in group A [25 (22%), 14 (16%) and 6 (5%), respectively, $P < 0.001$]. The proportion of *enterococci* was highest in group C [5 (5%) in group A, 5 (4%) in group B and 8 (9%) in group C] while *S. aureus* was more frequent in younger patients [34 (29%) in group A, 19 (17%) in group B and 15 (17%) in group C]. Thus, the bacteriological features of endocarditis in the elderly reflect the common sources of bacteremia relating to the co-morbidities typical of this age group. *S. bovis* probably relates to colonic lesions and enterococci relates to urogenital infections.

The high incidence of *S. bovis* endocarditis in the elderly as well as the difficult clinical course related to this pathogen is also evident when studying the clinical course of these infections compared to other pathogens. Pergola et al. [19] studied the clinical, echographic and prognostic features of *S. bovis* endocarditis compared to endocarditis caused by other streptococci and "other pathogens" in a large sample of patients. Two hundred six patients with a mean age of 57 (SD 15) years with a diagnosis of infective endocarditis formed the study population. *S. bovis* endocarditis was documented in 40 patients, other Streptococci were identified in 54 and "other pathogens" were documented in 112 patients. The mean age was 64 (SD 12) years in the *S. bovis* group, 55 (SD 15) years in the other Streptococci group and 56 (SD 16) years in the "other pathogens" group, $P < 0.05$. Multiple valve involvement, native valves and large vegetations (>10 mm) were more frequent in patients with *S. bovis*. There was a significantly higher rate of embolism in the *S. bovis* group. Splenic infarcts and multiple embolisms were significantly more frequent in patients with *S. bovis*. Gastrointestinal lesions, anemia and spondylitis were also observed more frequently with *S. bovis* endocarditis. The relationship between age and prevalence of *S. bovis* endocarditis is depicted in Figure 3.2 [20].

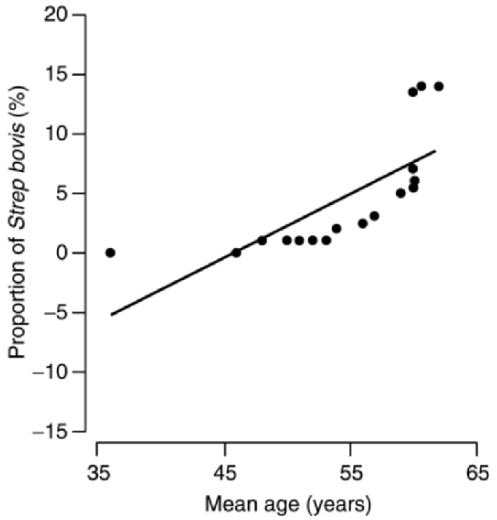

Figure 3.2. Microbial epidemiology of infective endocarditis. Linear regressions between proportion of S. bovis disease and mean age [20].

Clinical Presentation and Echocardiography Findings

In the study by Di Salvo [18] age was not found to be corelated to the echocardiographic presentation of endocarditis, nor was age related to the incidence and localization of embolic events regardless to the pathogen involved. Elderly patients were operated on as frequently as younger patients and their operative risk of dying and complications was similar to that of younger patients (11%, 3% and 5% in groups C, B and A, respectively). In two reports however, renal failure, as a complication of endocarditis was more common in the elderly patients compared to younger patients [21,22]. An additional report [23] documented decreased use of echocardiography in the aged despite the fact that perivalvular complications were more common in this age group.

Treatment and Outcome

Age, not surprisingly, is correlated with higher endocarditis caused mortality. In the study by Selton-Suty et al. [11], mortality was 28% in the older patients (> 70 years) double of that (13.5%) in the younger patients (< 70 years) ($P < 0.08$). Multivariate analysis showed that age ($P < 0.02$) and the presence of at least one vegetation at echocardiography ($P < 0.04$) were

independent risk factors for a fatal outcome. Elderly patients with enterococcal endocarditis had similar mortality to younger patients with streptococcal endocarditis [17]. Di Salvo et al. [18] demonstrated that the overall mortality was clearly higher in elderly (17%) group aged >70 years compared to the younger patients (10% versus 7%, respectively, $P = 0.02$). Surgical treatment was performed slightly less frequently in the elderly compared to the other groups, although 41% of elderly patients underwent surgery. Mortality was relatively high in non-operated elderly patients (21%), but only 11% in elderly patients who could be treated surgically. This difference may reflect a hidden bias were less severe patients were more likely to receive a surgical intervention. For the entire population, including the younger patients, mortality was lower in operated patients than in patients treated conservatively with antibiotic alone (6% vs. 15%, respectively, $P = 0.04$). Among the 51 non-operated elderly patients, seven (14%) patients had undisputed indication for surgery (severe heart failure, persistent sepsis, or multiple embolisms). Of them, five were not considered good candidates for surgery because of very poor general condition and two patients declined surgery.

In a logistic regression analysis independent predictors of in-hospital mortality were age ($P = 0.003$), prosthetic valve ($P = 0.002$) and cerebral embolism ($P = 0.006$). Conversely, surgical management was associated with a lower in hospital mortality (regardless of age) ($P = 0.03$).

In a report by Netzer et al. [21], 82 younger patients (17–59 years) were compared to 53 elderly patients (65–90 years). There were no significant differences between the two groups regarding co-morbidities or clinical presentation except that renal failure was more common in the elderly. Mortality was significantly higher in the elderly patients [13 (25%) vs. 9 (11%) respectively, $P < 0.04$].

In contrast to these publications which demonstrate a higher mortality in elderly patients, Gagliardi et al. [22] reported similar outcomes in the young and the old. They compared 44 episodes of definite native valve infective endocarditis in patients >64 years with 64 similarly defined episodes in patients >29 years but <64 years old, who were not using intravenous drugs. Clinical presentations, characteristics and outcome were similar in the two groups. Elderly patients were hospitalized for an average of 12 days longer compared to the younger patients. The occurrence of renal failure and cerebral embolism during an episode of infective endocarditis was associated with higher rates of death (odds ratios, 4.8 and 4.0, respectively). Age, however, was not a significant contributor to mortality. These results differ from the other authors' sited above. It is important to note that in this group of patients the rate of enterococcal endocarditis and *S. bovis* endocarditis were not significantly higher in the elderly and this peculiarity might explain the lack of difference in outcomes between the two groups of patients.

To conclude, it seems that the elderly may fare worse, however, not significantly so, during an episode of infective endocarditis, although the extent of excess mortality differs between various studies. Aggressive intervention, including early surgery should not be excluded in the elderly, merely because of the age, as better outcomes especially in the group of patients without severe co morbidities are to be expected.

Injection Drug Users

Infective endocarditis is one of the most common and serious complications of intravenous drug use (IVDU) [24]. In parallel with the increase in the incidence of drug use in the past 30 years the incidence of infective endocarditis in IVDU has increased as well.

Epidemiology

The incidence of infective endocarditis in IVDU is 2–5%/year and is responsible for 5% to 8% of hospital admissions among IVDU. The overall incidence of infective endocarditis in this population is estimated to be 1 to 20 cases per 10,000 injection drug users per year [26] and is responsible for 5% to 10% of the overall death rate of IVDU [24]. Levine et al. [27] followed all IVDU admitted to the Detroit Medical Center with infectious endocarditis (74 cases) during the early 1980's and compared them with a control group of bacteremic addicts who had other infections (106 cases). They found that acute infection accounted for approximately 60% of hospital admissions and that infective endocarditis was implicated in 5% to 15% of these episodes. The

male:female ratio was 5.4:1. Men with infective endocarditis were somewhat older than females (mean age, 32.7 years vs. 31.4 years) and had significantly longer histories of addiction (10.2 years vs. 7.1 years) than women. Chambers et al. [28] compared 102 IVDU with endocarditis to IVDU with other causes of fever. Bacterial endocarditis was diagnosed in 23% of hospitalizations. Logistic regression analysis showed the following variables to be predictive of infective endocarditis in IVDU: cocaine use (OR 138, CI 8–2,318), mitral or aortic valve murmur (OR 51, CI 3–779), haematocrit < 40% (OR 25, CI 2–318), proteinuria (OR 14, CI 1–127) and signs of septic emboli, cavity, or effusion on chest x-ray (OR 165, CI 9–3067). Although heroin was the most common drug used, it was not independently associated with the development of endocarditis in this study and nor was the combination of heroin and cocaine. The mechanism by which cocaine increases the risk of infective endocarditis has not been elucidated. Nevertheless, in other circumstances when heroin was mixed with non-sterile adjunctives, the risk of endocarditis with IV heroin use was high. In the last 20 years the rate of HIV in IVDU has been reported to be in the range of 30–70%; thus the prevalence of the disease in recent series reflects the risk attributed by both conditions. Needle exchange programs and a massive intervention programs among these individuals has resulted in a decreased rate of HIV in some countries and therefore the risks for endocarditis are expected to diminish over time as well.

Bacteriology

In the study of Levine et al. [27] endocarditis was caused by *Staphylococcus aureus* in 60.8% of the cases, streptococci in 16.2% of cases, *Pseudomonas aeruginosa,* in 13.5% of cases, mixed bacteria in 8.1% of cases and *Corynebacterium JK* in 1.4% of cases. *Staphylococcus aureus* endocarditis most frequently involved the tricuspid valve and streptococci infected left-sided valves significantly more often than other organisms ($P = 0.001$). Biventricular and multiple-valve infections were commonest in patients with pseudomonas endocarditis ($P = 0.05$). In Miro's Spanish series [26] *S. aureus* was also the most common etiological agent, usually being sensitive to methicillin (MSSA). HIV-positive IVDU had a higher ratio of right-sided infective endocarditis and *S. aureus* infective endocarditis than HIV-negative IVDUs and the tricuspid valve was the most frequently affected (60–70%), followed by the mitral and aortic valves (20–30%) [26].

Clinical Presentation

IVDU and particularly HIV-positive IVDU are prone to acquire right-sided endocarditis and this has been well documented in older as well as in newer series [26,27]. Two-thirds of IVDU with infective endocarditis have no clinical evidence of underlying heart disease. Despite the fact that heart murmurs are predictive of infective endocarditis in IVDU, only 35% of addicts demonstrate heart murmurs on admission [27]. In recent years a higher prevalence of left-sided endocarditis has been reported in IVDU. For example, in a retrospective study of infective endocarditis in IVDU, 67 patients had vegetations documented by two-dimensional echocardiogram. Left-sided involvement was present in 38 (57%) of these patients, a higher prevalence than reported in older series. Right-sided involvement was limited to only 27 (40%) cases. This change in epidemiology is important as left-sided endocarditis carries higher morbidity and mortality. In this study, valvular involvement was as follows: tricuspid valve alone or in combination with others, 52.2% of cases; aortic valve alone in 18.5% of cases; mitral valve alone in 10.8% of cases; and aortic plus mitral valves in 12.5% of cases [29]. Similarly, in the recent Spanish series the tricuspid valve is the most frequently affected (60–70%), followed by the mitral and aortic valves (20–30%) [26].

When patients have right-sided endocarditis, pulmonary symptoms such as pleuritic chest pain, cough, dyspnea and lung infiltrates representing septic emboli tend to dominate the clinical picture as well as signs and symptoms of right heart strain and failure. Many patients have in addition extravalvular sites of infection.

Treatment and Outcome

As mentioned before, many IVDU with infective endocarditis have right-sided endocarditis. This prompted researchers to assess the feasibility of shorter antibiotic courses in this population, as right-sided endocarditis has a better prognosis

than left -sided infection. This approach is particularly attractive as the compliance of IVDU to prolonged hospitalization or home care is low. Chambers [30] in 1988 published a report confirming the possibility to treat right-sided endocarditis in IVDU with as two-week course of antibiotics. Fortun [31] confirmed these results by performing a prospective, randomized clinical trial among drug abusers to assess the efficacy and safety of a short course of a combination of a glycopeptide (vancomycin or teicoplanin) and gentamicin compared with a combination of cloxacillin and gentamicin for treatment of right-side endocarditis caused by *S. aureus*. Therapeutic success was significantly more frequent with cloxacillin than with a glycopeptide. No adverse effects were noted among patients in the cloxacillin group. Ribera et al. showed similar results [32]. Thus, a shortened course of penicilliase-resistant penicillin with or without the addition of an aminoglycoside for right-sided infective endocarditis in IVDU infected with *S. aureus* sensitive to methicillin seems and acceptable alternative.

Another issue is the best surgical approach for IVDU with endocarditis. To determine the early and late results of surgical treatment for infective endocarditis in IVDU, Mathew et al. [33] observed IVDU undergoing surgical treatment for infective endocarditis. Eighty patients underwent cardiac surgery for the following indications: acute congestive heart failure in 44 (56%) patients, persistent sepsis in 21 (26%) patients and multiple systemic embolization in 15 (19%) patients. Six patients (7.5%) died within 30 days of surgery and 13 of 69 patients (17.6%) died during the follow-up from cardiovascular causes. The probability of survival at 36 months and at 60 months was 0.74 and 0.70, respectively. Seventeen (30%) of the survivors had at least one major cardiovascular event, 6 (8.8%) patients had recurrent endocarditis, 10 (14.6%) patients experienced central nervous system complications and 3 (4.4%) patients required repeated valve replacement. Probability of event-free survival at 36 months and 60 months was 0.65 and 0.52, respectively. These authors conclude that since the expected mortality without surgery in patients with infective endocarditis in whom medical treatment fails is almost 100%, surgical treatment should be advised liberally as it substantially improves the outlook for early and late survival of IVDU with endocarditis.

HIV

HIV-seropositive patients are at risk for infective endocarditis because of three main reasons: intravenous drug abuse, long-term use of central venous catheterization for administration of medications and as a consequence of immune suppression. Infectious endocarditis is responsible for 5–20% of hospital admissions and for 5–10% of total deaths in IVDU patients with HIV infection, but the clinical outcome of the patients depends on the affected valve and the culture germen rather than the HIV serostatus. HIV stage C was found in six cases and the median (range) CD4 cell count was 22/μL (4–274 cells/μL [34]). *Staphylococcus. aureus* is the most common pathogen involved .and the infection is more commonly localized to the right side of the heart. It is not clearly defined whether HIV infection is responsible for the worst evolution in these patients and if treatment should be the same as that used in HIV seronegative subjects [26,35].

Epidemiology

To determine the effect of HIV infection and other factors on infective endocarditis among IVDU Wilson et al. [36] examined the incidence of endocarditis according to HIV status in a cohort of IVDU. Endocarditis incidence (117 cases) was higher among HIV-seropositive than HIV-seronegative IVDU (13.8 vs. 3.3 cases/1,000 person-years). Multivariate analysis of HIV-infected case patients revealed an inverse association between infective endocarditis and CD4 lymphocyte count (OR for 200–499 cells/mm^3, 2.01, OR for <200 cells/mm^3, 3.61) and with alcohol intake (OR for 1–21 drinks/week, 0.43; OR for >21 drinks/week, 0.32). Women had an increased risk of endocarditis (OR, 3.26), as did persons with increasing injection drug use frequency (OR for less than daily use, 3.15; OR for at least daily use, 6.07) (see Figure 3.3). This study confirmed that infective endocarditis is more common among IVDU with advanced HIV immunosuppression even after accounting for injection drug use behaviors. The higher incidence found in woman is surprising as in other populations including IVDU without HIV a higher incidence is found consistently in men. Conversely, infective endocarditis in HIV-infected persons who do not use drugs is rare. In

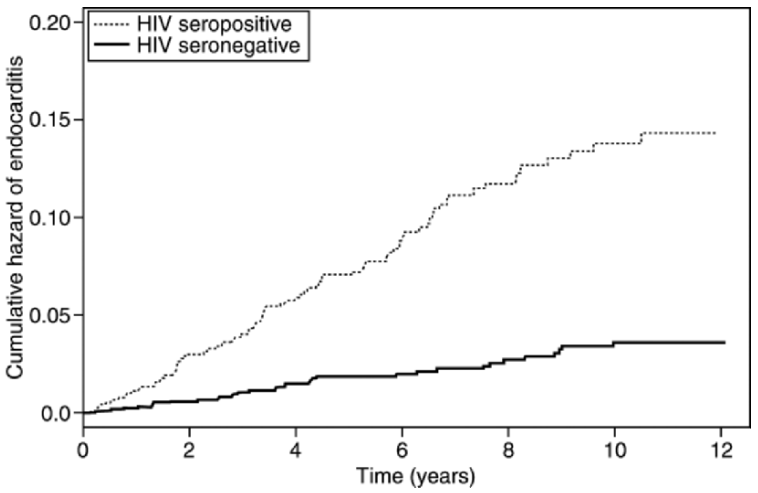

Figure 3.3. Cumulative hazard of first episode of infective endocarditis over time, by HIV serostatus [36].

the absence of intravenous drug abuse, HIV-seropositive patients develop left-sided and right-sided infective endocarditis with equal frequencies. In contrast, in the setting of intravenous drug abuse, HIV-seropositive patients develop predominantly right-sided infective endocarditis. The related morbidity and mortality rates in HIV-seropositive patients who do not have an AIDS-defining illness or criteria are similar to rates in HIV-seronegative counterparts [37,38].

Clinical Presentation and Echocardiography Findings

To determine the clinical features in HIV-positive patients with and without infective endocarditis Smith et al. [39] retrospectively reviewed all bacteremic, HIV-positive patients with suspected infective endocarditis admitted over a four-year period that underwent either transesophageal echocardiography (TEE) or transthoracic echocardiography (TTE). Ten (11.5%) of 87 HIV-positive patients had a clinical diagnosis of infective endocarditis based on the Duke criteria. The mean age of patients with endocarditis was 37.8 years—similar to those without endocarditis, i.e., 39.9 years (P = NS).

Both patient groups were similar with respect to gender, race, IVDU, renal failure requiring hemodialysis, history of predisposing heart disease, origin of infection and causative organism. The mean CD4 count (cells/μL) was 200.7 in patients with infective endocarditis and 95.9 in patients without infective endocarditis (P = NS). Of ten HIV-positive patients with infective endocarditis, seven had left-sided heart involvement, two had complications related to infective endocarditis, three required cardiothoracic surgery and three died.

Abraham et al. [40] retrospectively reviewed the records of patients with suspected infective endocarditis who were referred to the echocardiography laboratory for evaluation and had ≥2 positive blood cultures for the same microorganism.

One hundred seventy-seven cases of bacteremia involving 169 patients were evaluated. Fifty-two patients were HIV positive and 125 were HIV negative. One hundred sixty-eight of the patients (95%) underwent TEE. HIV-positive patients were on average 12 years younger than HIV-negative patients ($P < 0.0001$). HIV-negative patients were more likely to have a cardiac predisposition to endocarditis ($P < 0.003$). There was a higher rate of diabetes in HIV-negative patients ($P < 0.002$), which likely corresponded to their older age. There was also a higher incidence of renal failure requiring hemodialysis in HIV-negative patients ($P < 0.03$), which was likely due to their older age and higher rate of diabetes. More men comprised the HIV-negative group ($P < 0.017$) (for unknown reasons). There was no difference in the rates of active IVDU between the two groups and the percentage of patients with documented sources of infection that would explain bacteremia, including line infections, was similar.

Staphylococcus aureus was the causative organism for bacteremia in almost half of all patients in both groups. There was no sta-

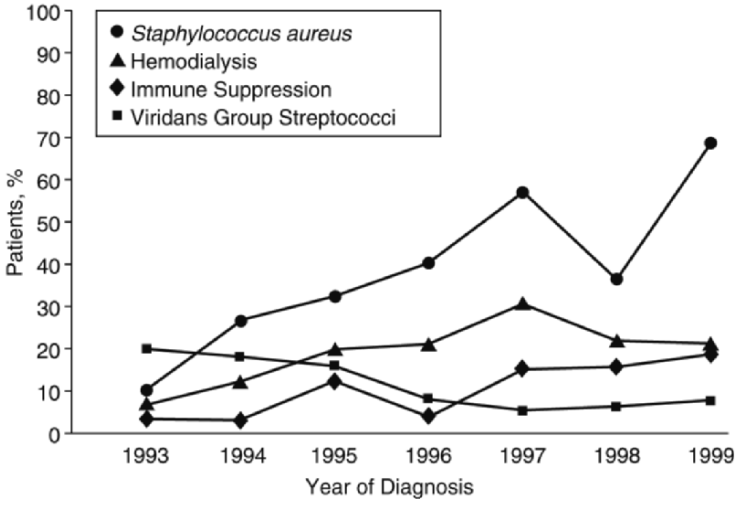

Figure 3.4. Changing characteristics from 1993 to 1999 of 329 patients with infective endocarditis: The increase in nosocomial infective endocarditis [43].

tistically significant difference in the microorganisms between the HIV-positive and HIV-negative patients, although most involved small numbers of patients. When considering all organisms, the rate of endocarditis in HIV-positive patients was lower than in HIV-negative patients (12% vs. 42%, $P < 0.0001$). There was no correlation between the CD4 count and the presence or absence of endocarditis in the HIV-positive group. Multiple logistic regression analysis revealed five clinical factors that were predictive of infective endocarditis: HIV status, presence of IVDA, predisposing heart disease, *S. aureus* bacteremia and bacteremia caused by modified Duke criteria 1A organisms. In conclusion, the bacteremic HIV-positive patients in this study had less infective endocarditis than bacteremic HIV-negative patients.

Robinson et al. [41] attempted to determine if HIV seropositivity alters the maximum temperature and WBC count of febrile IVDU users with infective endocarditis. In their review of 158 episodes of infective endocarditis among 126 patients HIV infections were not associated with lower maximal temperature. Mean WBC counts were significantly lower in the HIV-positive patients.

Treatment and Outcome

Despite the fact that HIV patients are immune suppressed, in various series their outcome whether treated medically or surgically does not seem to differ from non-HIV patients with infective endocarditis. In a retrospective study Mestres et al. [42] described 31 HIV-1-infected patients that underwent cardiac surgery due to infective endocarditis. Hospital mortality was 22.6. Nine patients (37.5%) died between 2 and 171 months (mean 54.5) after surgery. Overall mortality was 50%. In this small European series, cardiac surgery did not blunt CD4 response induced by antiretrovirals. The late causes of death were not AIDS-related events.

Immunocompromised Patients and Health-Care-Associated Endocarditis

Epidemiology

As medical technology advances, more and more patients have prolonged hospitalizations, are subject to invasive procedures, receive high-dose chemotherapy and corticosteroids, spend more time in intensive care setups and have more central lines, intubations, catheters and other foreign objects inserted. These trends have caused an increase in nosocomial bacteremia and as a result an increase in nosocomial endocarditis.

Cabell et al. [43] studied the demographic and microbiological changes that occurred in patients with infective endocarditis during 1993 to 1999 and their impact on survival. Among the 329 study patients, rates of hemodialysis dependence, immunosuppression and *S. aureus* infection increased during the study period ($P = 0.04$, $P = 0.008$ and $P < 0.001$, respectively),

while rates of infection due to viridans group streptococci decreased ($P = 0.007$). Hemodialysis was independently associated with *S. aureus* infection (odds ratio, 3.1; 95% confidence interval, 1.6–5.9). Patients with *S. aureus* endocarditis had a higher one-year mortality rate (43.9% vs. 32.5%; $P = 0.04$) that persisted after adjustment for other illness severity characteristics (hazard ratio, 1.5; 95% confidence interval, 1.03–2.3). In a recent international study initiated by the International Collaboration for Endocarditis (ICE), health-care-associated infection was the most common form of *S. aureus* infective endocarditis. Most patients with health-care-associated *S aureus* endocarditis (131 patients, 60.1%) acquired the infection outside of the hospital. Persistent bacteremia was independently associated with MRSA infective endocarditis (OR 6.2; 95% CI 2.9–13.2). Patients in the United States were most likely to be hemodialysis dependent, to have diabetes, to have a presumed intravascular device source, to receive vancomycin, to be infected with MRSA and to have persistent bacteremia [44].

Mourvillier et al. [45] reviewed charts of 228 consecutive patients admitted to two intensive care units with infective endocarditis between 1993 and 2000. Again, *S. aureus* emerged as the leading pathogen. The overall in-hospital mortality rate was 45% (102/228). Multivariate analysis revealed the following clinical factors in patients with native valve endocarditis as independently associated with outcome: septic shock (OR 4.81), cerebral emboli (3.00), immunocompromised state (2.88) and cardiac surgery (0.475). Clinical factors in patients with prosthetic valve endocarditis independently associated with outcome were septic shock (4.07), neurological complications (3.1) and immunocompromised state (3.46).

The increase in nosocomial bacteremia and the related burden of nosocomial endocarditis in newborns is also reflected by the data presented by Opie et al. [46]. In this publication, the incidence of bacterial endocarditis in a level III neonatal nursery was 0.07%. As expected in such young babies the presenting symptoms and signs were often vague and nonspecific. Gestation less than 32 weeks, birth weight less than 1,500 g, thrombocytopenia and neutropenia or neutrophilia were common features. The tricuspid valve was involved in seven infants. Of the eight babies six (all of them with tricuspidal endocarditis) had a percutaneous central venous catheter in situ before diagnosis. Mitral valve involvement occurred in two infants, neither of whom had central lines inserted. However, compared to infants without endocarditis, the placement of a central venous line was not of statistical significance.

Nosocomially acquired infective endocarditis carries a worse prognosis compared to infective endocarditis acquired outside in the community. This is due to several reasons: hospitalized patients are usually "sicker," with significant comorbidities, such as diabetes, renal failure, heart disease, hypertension and malignancies. In addition, many of these patients are immune suppressed—whether this reflects their primary disease or is a cause of the treatment they are receiving (e.g., patients receiving chemotherapy). In addition, these patients have a higher rate of *S. aureus* infective endocarditis, which may cause substantial valvular damage and is harder to cure.

To conclude, in recent years a change in the epidemiology of infective endocarditis has been taking place. The combination of prolonged longevity, the burden of chronic disease and the burden of iatrogenesis have combined to change the features of patients at risk for infectious endocarditis. Thus, the challenge of endocarditis has remained unchanged—timely diagnosis and optimal medical and surgical treatments are still essential for optimal outcome.

Key Points

1. Empiric therapy for the management of endocarditis in injection drug users (IVDUs) must target *S. aureus* particularly MRSA and should therefore contain an agent such as vancomycin which is effective against MRSA.
2. In addition to *S. aureus* and MRSA, Gram negative bacilli such as *P. aeruginosa* and fungi, such as *Candida* spp must be considered when initiating treatment of endocarditis in an IVDU.
3. For IVDUs with right sided endocarditis caused by methicillin susceptible *S. aureus*, a 2 week course of cloxacillin and gentamicin may be sufficient. However, the standard regimen must be used in the following circumstances:
    - Delayed clinical or microbiologic response (> 96 hours)

- Right sided endocarditis complicated by the presence of right sided heart failure, large vegetation (>2 cm in diameter), respiratory failure, empyema, the presence of extrapulmonary metastatic foci such as osteomyelitis.
- Severe immunosuppression (<200 CD for cells/uL)
- Polymicrobial endocarditis or endocarditis caused by MRSA
- Therapy with agents other than cloxacillin

4. Surgery must not be delayed until blood cultures become negative, if the patient's condition warrants immediate intervention because of severe valvular destruction.

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Microbiology of Infective Endocarditis and Microbiologic Diagnosis

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Case Study

A 46-year-old homeless male with a history of excessive alcohol consumption presented to the emergency department with a two-week history of fever and night sweats. The diagnosis of infective endocarditis was considered when he was found to have a systolic ejection murmur in the aortic area as well as an early diastolic murmur along the left sternal border. A transthoracic echocardiogram revealed an aortic valve vegetation with moderate aortic regurgitation. Two sets of blood cultures drawn prior to initiation of intravenous ceftriaxone and vancomycin yielded no growth after extended incubation in the microbiology laboratory. Valve tissue obtained at the time of aortic valve replacement was sterile despite five days of culture. Polymerase chain reaction (PCR) of the 16S-23S rDNA intergenic spacer region with sequencing of the PCR product confirmed the causative agent to be *Bartonella quintana*.

Microbiology

Trends

The microbiology of infective endocarditis (IE) has evolved significantly over the last century [1]. Previously a community-acquired disease affecting predominantly patients with rheumatic heart disease, IE is now being seen in new populations including IV drug users (IVDU), patients with prosthetic valves, and patients infected through health-care-associated bacteremia. Improved blood culture technologies and non-culture laboratory methods have also resulted in a lower rate of culture-negative cases. Because of differing proportions of particular risk groups, the etiologic agents responsible for causing IE vary significantly among continents, countries, regions within countries, and even among different years in an individual hospital. The approximate proportions of IE cases caused by different groups of microorganisms as recently published by Mylonakis and Calderwood are provided in Table 4.2 [2].

This discussion of the etiologic agents of IE will begin with native valve endocarditis followed by consideration of special situations including prosthetic valve endocarditis, IE in injection drug users, and culture-negative endocarditis.

Community-Acquired Native Valve Endocarditis

The common causes of native valve endocarditis are members of the normal flora of the skin, oropharynx, and the gastrointestinal and genitourinary systems. The vast majority of native valve endocarditis cases are caused by *Staphylococcus* and *Streptococcus* species. Several recent publications show that *Staphylococcus aureus* seems to have overtaken the viridans group Streptococci as the most common cause of native valve IE [3]. However, a

Table 4.1. Microorganisms (%) in Endocarditis by Decade

	Viridans Group	Other Strept	*S. aureus*	Coagulase Negative Staphylococci	Gram–Negative	Other	No Growth
Prior to 1970	43	12.5	14	4	5.5	3	18
1970s	42.5	16	13	3	5	10	10
1980s	29	19	24	9	4	7.5	7.5
1990s	28	23	28	7	4	5	5

Source: Cabell et al. [1], © 2002 by permission of Elsevier, Inc.

Table 4.2. Microbiologic Features of Native–Valve and Prosthetic–Valve Endocarditis

	Native-Valve Endocarditis (approximate % of cases)			
Pathogen	Neonates	2 mo–15 yr	16–60 yr	>60yr
Streptococcus species	15–20	40–50	45–65	30–45
Staphylococcus aureus	40–50	22–27	30–40	25–30
Coagulase-negative staphylococci	8–12	4–7	4–8	3–5
Enterococcus species	<1	3–6	5–8	14–17
Gram-negative bacilli	8–12	4–6	4–10	5
Fungi	8–12	1–3	1–3	1–2
Culture–negative and HACEK organisms*	2–6	0–15	3–10	5
Diphtheroids	<1	<1	<1	<1
Polymicrobial	3–5	<1	1–2	1–3

	Prosthetic-Valve Endocarditis (approximate % of cases)		
Pathogen	Early <60 days after procedure)	Intermediate (60 days–12 mo after procedure)	Late (>12 mo after procedure)
Streptococcus species	1	7–10	30–33
Staphylococcus aureus	20–24	10–15	15–20
Coagulase-negative staphylococci	30–35	30–35	10–12
Enterococcus species	5–10	10–15	8–12
Gram-negative bacilli	10–15	2–4	4–7
Fungi	5–10	10–15	1
Culture-negative and HACEK organisms*	3–7	3–7	3–8
Diphtheroids	5–7	2–5	2–3
Polymicrobial	2–4	4–7	3–7

*Patients whose blood cultures were rendered negative by prior antibiotic treatment are excluded. HACEK denotes *Haemophilus* species (*H. parainfluenzae, H. aphrophilus, H. paraphrophilus*), *Actinobacillus actinomycetemcomitans*, *Cardiobacterium hominis*, *Eikenella corrodens,* and *Kingella kingae*.
Source: Mylonakis et al. [2], Copyright © 2001 Massachusetts Medical Society. All rights reserved. With permission.

population-based study of IE cases in Olmstead County, Minnesota, from 1970 to 2000 revealed no significant trends over time with respect to either the overall incidence of IE or the relative proportion of cases caused by Staphylococci and Streptococci [4]. These apparently contradictory observations likely result from differences in patient risk factors (e.g., low IVDU rates in Olmstead County) and referral patterns (more *S. aureus* IE referred to tertiary care centers).

Staphylococci

Staphylococcus aureus

Two recent publications from the International Collaboration on Endocarditis (ICE) provide an international perspective on *S. aureus* native valve endocarditis. In one report, the authors used a merged database derived from data collected between 1979 and 1999 at seven sites in five countries. The database included 2,212 cases

defined as definite IE based on the Duke criteria; 566 (34%) of 1,640 native valve IE cases were caused by *S. aureus* [5]. Compared to the patients with native valve IE caused by organisms other than *S. aureus*, these patients were younger (median age 46.0 vs. 60.0 years) and more likely to have a history of IV drug use (36.9% vs. 5.5%). The valves involved were significantly different between the two groups, with tricuspid involvement much more common in the *S. aureus* cohort (31.3% vs. 5.0%) and aortic valve involvement less common (15.9% vs. 31.2%). Although outcomes varied by center, embolic events (60.6% vs. 30.7%), central nervous system events (20.6% vs. 13.3%) and in-hospital mortality (19.9% vs. 12.2%) were all higher for the subset infected with *S. aureus*. The mortality rate was particularly high (28.6%) for patients with *S. aureus* infecting a left-sided valve. The other publication from the ICE investigators was based on data collected prospectively at 39 participating centers in 15 countries between 2000 and 2003 [6]. In this cohort, *S. aureus* was again observed to be the most common etiologic agent of definite IE both overall (558/1,779, 31.4%) and in the native valve IE subset (401/1,247, 32.2%).

Medical procedures and (often intravascular) devices that place patients at risk for bacteremia appear to be at least partly responsible for the observed increase in some centers of the proportion of IE cases caused *S. aureus*. Fowler et al. [6] found *S. aureus* IE to be health-care associated in a substantial proportion of cases. Overall, 218/341 (39.1%) of *S. aureus* IE cases were health-care associated compared to 211/1,221 (17.3%) of non-*S. aureus* cases. Approximately 60% of the health-care-associated *S. aureus* IE cases were nosocomial, with the remainder acquired outside of hospital. The patients with health-care-associated *S. aureus* IE had a higher average age, an increased likelihood of mitral valve involvement, and higher in-hospital mortality compared to those with community-acquired *S. aureus* IE.

The incidence of MRSA IE has also been noted to be increasing, particularly within the health-care-associated IE subgroup. Excluding community-acquired IVDU-associated IE, Fowler et al. reported MRSA as the cause in 100/289 (34.6%) of native valve *S. aureus* IE in the prospective ICE cohort [6]. The majority (75.9%) of MRSA IE cases were health-care associated, with intravascular devices as the presumed source in the majority (60.3%). Diabetes mellitus (34.0%) and immunosuppressive therapy (17.7%) were more common in the MRSA-infected patients than in the non-MRSA *S. aureus* IE group. Patients with MRSA IE had a lower rate of embolic events, but persistent bacteremia was more common and there was a trend toward higher in-hospital mortality. The proportion of *S. aureus* IE caused by MRSA varied considerably, ranging from 43.5% in US centers to 19.1% in Australia/New Zealand.

Coagulase-Negative Staphylococci

In most published case series, coagulase-negative staphylococci (CoNS) are reported to cause approximately 5% of cases of native valve endocarditis [2,3]. A review of 99 native valve IE cases caused by CoNS was recently published based on information obtained from the ICE merged database, which is composed of IE case data collected between 1979 and 1999 at seven sites in Europe and the United States [7]. CoNS strains were determined to be the cause of native valve IE in 6.6% of 1,504 adult patients in the database (excluding those with a history of injection drug use) who met Duke criteria for definite IE. The species was identified as *S. epidermidis* in 55/65 (85%) of cases for which specific organism identification was available. Although CoNS are often not considered to be virulent organisms, the rates of heart failure and in-hospital mortality were similar to those observed in patients with *S. aureus* native valve IE in the same database. When compared to cases caused by viridans group streptococci, the CoNS patients were older overall, had a much greater likelihood of health-care-associated acquisition (40% vs. 1.3%), and had a more complicated clinical course as indicated by higher rates of heart failure, intracardiac abscess, cardiac surgery and mortality.

One particular CoNS species that has been associated with more aggressive disease is *S. lugdunensis*. In a recent review of 48 published IE cases, Seenivasan and Yu reported that 39 (81%) involved native valves and 74% had an acute presentation, with an overall mortality rate of 49%. [8] Valve destruction was common, with over half of the patients (25/48) proceeding to cardiac surgery; the mortality rate was 65% among those who did not have surgery.

Streptococci

The viridans group streptococci remain among the most common causes (30–40% in most series) of community-acquired native valve IE in individuals without a history of IV drug use. The most common species include *S. oralis*/*S. mitis, S. sanguis, S. mutans*, and *S. salivarius*. These alpha hemolytic organisms are members of the normal flora of the gastrointestinal tract, and they usually cause a subacute presentation of IE. They are the most common causative agents among children and young women with mitral IE. Members of the *S. anginosus* (or *S. milleri*) group most often grow as pinpoint alpha hemolytic colonies on sheep blood agar. Although often considered to be part of the viridans group, the distinction is important because infections with these organisms are associated with abscess formation, possibly impacting the duration of therapy [9]. The organisms previously designated as nutritionally variant streptococci are now classified as *Abiotrophia defectiva* and *Granulicatella* species. These organisms can be challenging because media supplemented with pyridoxal hydrochloride or L-cysteine are required to support growth, and treatment success requires more aggressive therapy than for viridans streptococci.

Non-enterococcal group D streptococci, the *Streptococcus bovis/S. equinus* complex, are an important cause of IE in certain geographical areas. A recent analysis of the ICE merged database yielded 136 IE cases caused by these organisms, of which 109 (80.1%) involved native valves [10]. When compared to cases caused by viridans group streptococci, patients were older with more co-morbidities, and multiple valve involvement was more common. When data from two decades of the database were compared, the proportion of streptococcal IE caused by *S. bovis/equinus* increased from 10.9% (1979–89) to 23.3% (1990–99). This proportion was particularly high in France (58%) compared to other sites in Europe (9.4%) and the US (16.7%). Previous studies have shown a strong association between *S. bovis* bacteremia and colorectal cancer.

S. pneumoniae was an important agent of IE in the pre-antibiotic era. Its incidence has decreased to 1–3% in recent series, though a recent small Scandinavian study showed a fourfold increase from 1981 to 1996 [11]. *S. pyogenes* and Lancefield groups B, C, and G streptococci are also rare causes of native valve IE.

Enterococci

The enterococci are the third most common agents of IE overall, causing 5–20% of cases. In a prospective analysis over a five-year period in a center in Spain, IE was found to be present in 17/116 (14.6%) patients with enterococcal bacteremia [12]. Enterococcal IE was caused by *E. faecalis* in 16/17 (94%)cases. Endocarditis was hospital acquired in 6/17 (35.3%) cases, and 10/17 (59%) patients had preexisting valvular abnormalities. Health-care-associated infection was also noted in an early retrospective review of 38 cases of enterococcal IE published in 1970 by Mandell et al., in which 47% of infections had developed in elderly men who had undergone GU tract procedures or in younger women following gynecological procedures [13]. In a recent publication based on the ICE merged database (1970–1999), 107 definite left-sided native valve IE cases caused by enterococci were compared to cases of other etiologies in the same database [14]. Among the 62.6% of isolates that were fully identified, 92.5% were *E. faecalis*, 6.0% *E. faecium* and 1.5% *E. durans*. Patients with enterococcal endocarditis were older (mean age 66.4 vs. 58.2 years) and more likely to have cancer (21% vs. 8%) when compared to those with non-enterococcal IE. Enterococcal IE was more likely than streptococcal IE to be nosocomially acquired (15% vs. 1%). When compared to *S. aureus* IE, systemic embolization (26% vs. 49%) and in-hospital death (11% vs. 27%) were significantly less common in the enterococcal IE cohort.

Infective endocarditis caused by vancomycin-resistant enterococci (VRE) is rare. Stevens and Edmond have reviewed the literature, finding 12 reports of native valve IE out of a total of 19 IE cases, all of which were health-care associated [15]. The patients were 80% male with a median age of 59.5 years, and had multiple co-morbidities, including diabetes (25%), dialysis dependency (25%), cancer (25%), recent surgery (42%) and transplantation (42%). The infection involved left-sided valves in 70% of the cases and the aortic valve was involved most commonly (50%). Overall survival was 9/12 (75%), including all 3 patients that required surgical management; 2 of the 3 deaths were attributed to VRE IE.

Gram-Negative Endocarditis

Overall, Gram-negative agents cause 1–5% of IE cases. Although *Pseudomonas* spp. and the Enterobacteriacae are rare causes, the most common Gram-negative agents of native valve IE are members of the HACEK group. The HACEK group includes *Haemophilus* spp. (*H. paraphrophilus, H. parainfluenzae, H. aphrophilus, H. influenzae*), *Actinobacillus actinomycetemcomitans*, *Cardiobacterium hominis*, *Eikenella corrodens*, and *Kingella* spp. (*K. kingae*, *K. denitrificans*). These slow-growing, fastidious Gram-negative bacilli cause IE with a subacute presentation and large vegetations with a propensity for embolization. In a recent review of studies published from 1993–2003, HACEK organisms were found to be responsible for 4% of native valve IE [3]. *Actinobacillus actinomycetemcomitans* is the most common HACEK organism, with 93 published cases as of 2001 [16]. Prior dental disease was reported in half of patients and underlying valvular disease in nearly three-quarters. About 1% of endocarditis is caused by *Haemophilus* spp.; a recent review of 42 cases by Darras-Joly et al. showed *H. parainfluenzae* to be the most common cause (26/42, 62%) [17]. Approximately 10% of patients with *Haemophilus* spp. IE had a history of recent dental work, and 71% had underlying valve disease.

Prosthetic Valve Endocarditis

Overall, prosthetic valve endocarditis (PVE) accounts for 10–30% of all IE cases. The risk of endocarditis is highest in the first few months following surgery, with cumulative rates of 1.0–1.4% at one year and 3.0–5.7% at five years after valve replacement [18]. When compared to native valve IE, (CoNS) infection is much more common in PVE; Gram-negative bacilli, fungi and diphtheroids are also more likely to cause PVE, while *S. aureus* enterococci are less frequently causes of PVE than they are of native value IE. The relative importance of the causative organisms in PVE depends on the timing of infection in relation to valve replacement surgery. We accept the definitions of early PVE as infection developing <60 days after surgery, late PVE as >12 months post-replacement, and intermediate PVE as those cases occurring between 2 and 12 months (see Table 4.2).

Early PVE is most often related to intraoperative contamination of the surgical field or postoperative bacteremia. As such, the bacterial flora of the skin and hospital-associated pathogens predominate. CoNS (most frequently *S. epidermidis*) are responsible for about 30–50% of PVE within this group, *S. aureus* (with an increasing proportion of MRSA) causes 15–20%, and Gram-negative bacilli causes 10–20%. Fungi (*Candida* species), diphtheroids and enterococci (with rare cases of VRE) each cause at least 5% of early PVE cases, and the streptococci are very rare causes of PVE in the early postoperative period.

The distribution of etiologic agents causing late PVE is very similar to that for native valve IE, with the streptococci being the most frequently isolated organisms in most reported series. Patients with late PVE tend to have more CoNS and less *S. aureus* when compared to those with native valve IE. The Gram-negative bacilli and fungi seen in the early period after valve replacement are recovered infrequently in late PVE. The HACEK organisms are isolated in up to 5% of patients presenting with late onset PVE. In a recent review of 121 PVE cases over 34 years at a single center in Spain, Rivas et al. found that enterococci and *S. aureus* had overtaken the viridans group streptococci as the leading causes of late PVE when cases occurring between 1987 and 2003 were compared to those from 1970 to 1986 [19]. This change in microbiology was attributed to a higher proportion of hospital-acquired late PVE (22% vs. 7%) in recent years.

Intermediate-onset PVE includes a mixture of patients who are presenting relatively late with peri-operatively acquired infections and individuals who have developed community-acquired endocarditis. As a result, the pattern of organisms causing PVE developing at this time is essentially an average of the proportions of cases caused by each group of organisms observed in the early and late periods.

Intravenous Drug Users (IVDU)

The majority of IE in the IVDU group is caused by *Staphylococcus aureus*, which is responsible for 50–75% of cases [20,21]. The streptococci and enterococci are the next-most-common

organisms (7–10%), with small percentages caused by CoNS, Gram-negatives, and *Candida* species. Polymicrobial IE is relatively common in the IVDU population, occurring in up to 5% of cases.

S. aureus most commonly causes right-sided (tricuspid) endocarditis in the IVDU setting. In the review of definite *S. aureus* native valve IE cases from the ICE merged database (1979–1999) published by Miro et al., 131/149 (88%) cases in patients with a history of injection drug use involved the tricuspid valve [5]. Of 170 patients with right-sided *S. aureus* IE, 131 (77%) provided a history of IV drug use. In the same study, MRSA was observed infrequently in the IVDU population: 6/43 (14.0%) patients with MRSA IE used IV drugs compared to 136/248 (54.8%) of those with infection caused by susceptible strains. However, increasing rates of MRSA in IVDU have been observed and outbreaks have been documented.

Gram-negative IE in drug users can be caused by organisms that are encountered only rarely in non-IVDU patients. *Pseudomonas aeruginosa* endocarditis is uncommon and occurs nearly exclusively in IVDU. *Pseudomonas aeruginosa* IE is usually right sided, but can involve left-sided valves, in which case the clinical course is more complicated [22]. A cluster of 36 cases of *Serratia marcescens* IE was seen among heroin users in San Francisco in the 1970s, with high associated mortality [23]. *Campylobacter fetus, Pasteurella* spp., *Brucella* spp., *Bordetella* spp., *Franciscella tularensis, Aeromonas hydrophila*, and *Yersinia enterocolitica* are other Gram-negative bacilli that are occasionally encountered in the setting of IV drug use.

Blood-Culture-Negative Endocarditis

Reported blood culture-negative endocarditis (BCNE) rates have historically varied by study population, ranging from 2.5% to 31% [24]. These rates are still consistent among recent studies conducted in Spain (13.7%) [25], London (12.2%), and Sweden (20%) [26]. A recent review of 26 case series published between 1993 and 2003 showed BCNE rates of about 10% [3]. These rates are likely artificially high because of preceding antibiotic therapy. This effect was quantified in a retrospective review of 107 definite IE cases at a center in Spain, in which 14/20 patients with negative blood cultures had received prior antibiotics, leaving 6/107 (5.6%) with BCNE [27]. Thus, excluding the cases confounded by antibiotic therapy prior to blood cultures, the frequency of "true" culture-negative endocarditis is much less, likely around 5%.

By definition, standard culture methods are inadequate to allow detection of the causative agents of BCNE. The largest study to address the etiology of BCNE, published by Houpikian and Raoult, involved 348 patients with suspected BCNE in France [28]. The authors attempted to determine the causative organism using a comprehensive serology panel, shell vial cultures and analysis of valve specimens by multiple methods, including PCR. These investigations showed that 167 cases (48%) were due to *Coxiella burnetti*, 99 (28%) due to *Bartonella* spp., 5 (1%) due to rare fastidious organisms, and 73 (21%) without an identified cause. Of the 73 undiagnosed cases, 58 had received antibiotics before the blood cultures, leaving only 15 (4.3%) unexplained cases.

Coxiella burnetti is reported to cause 3–5% of all endocarditis in France, Israel, and Great Britiain [16]. Underlying heart disease, immunocompromising conditions and animal contact are the major risk factors. Houpikian and Raoult's review of BCNE in France included 167 cases of Q fever IE [28]. Of these, 53 patients (35%) had underlying immunodeficiency and 139 (91%) had valvular disease, including 27 with prosthetic valves, and 70% had a history of contact with domestic animals. Reported outcomes of *C. burnetti* IE were previously poor with nearly two-thirds of patients developing congestive heart failure (CHF), but in this cohort only 38% developed CHF and mortality was only 3% (4/150). This improvement likely reflects better and more rapid diagnostics and more timely treatment.

Bartonella spp. are reported to cause 3% of all endocarditis [16]. In a recent review of *Bartonella* endocarditis, 75% of identified cases were caused by *B. quintana* and 25% by *B. henselae* [29]. Epidemiology was distinct for the two species, with *B. quintana* seen in patients who were homeless or alcoholic with exposure to body lice, and *B. henselae* in individuals with a history of exposure to cats.

Trophyrema whipplei, the Whipple disease bacterium, is an emerging cause of culture-negative endocarditis. In a review of 35 cases

published in 2001, the disease was predominant in men, occurring on previously healthy valves in 88%, with a mortality rate of 57% (20 of 35 cases) [30].

Microbiologic Diagnosis

Blood Cultures

Blood culture remains the single most important investigation in a patient suspected of having infective endocarditis. If appropriately collected prior to antibiotic administration, blood cultures can be expected to yield growth of the causative organism in over 90% of cases of infective endocarditis. Identification of the organism may allow the treating physician to determine the original source of bacteremia, and facilitates the choice of the appropriate therapeutic agent(s) and treatment duration.

The Modified Duke Criteria include blood culture as one of the major diagnostic criteria. In order to fulfill the major microbiologic criterion, blood culture support for the diagnosis of IE is defined as isolation of "typical" microorganisms (viridans streptococci, *Streptococcus bovis*, HACEK group, *S. aureus*, community-acquired *Enterococcus* spp.) from at least two separate blood cultures, blood cultures persistently positive for "microorganisms consistent with IE," or a single culture positive for *Coxiella burnetti*. Rognon et al. [31] retrospectively applied the Duke criteria to 179 IE cases over a 10-year period, and found blood culture to be the most important criterion in establishing a diagnosis of definite IE. Over half of 52 pathology-proven IE cases in this series that were classified as "definite IE" using the Duke criteria before pathology results were available would have been designated as "possible IE" or "rejected" in the absence of blood culture data.

Intravascular infections including IE are characterized by the presence of continuous bacteremia, and in the majority of IE cases most or all of the pre-therapy blood cultures will be positive. Demonstration of continuous bacteremia by definition requires more than one blood culture result, and the yield of blood cultures is dependent on both the number of cultures obtained and the volume of blood cultured. The effects of blood draw volume and timing on culture yield were investigated by Li et al., who analyzed data from all blood cultures drawn on patients in the Veterans Administration Medical Center in Seattle over an 18-month period [32]. For the majority of patients, one blood culture set consisted of 20 mL divided equally between one aerobic and one anaerobic bottle. The investigators found that a second 20 mL blood draw increased blood culture yield by 17–20%, and that this additional pick-up rate was the same whether the second culture set was drawn immediately after the first, or at any other time within the next 24 hours. The addition of a third 20 mL draw within 24 hours further increased the blood culture yield by 10%. Most experts agree that three separate blood culture sets (20–30 L in two or three bottles) should be sufficient to detect over 95% of IE-associated bacteremias in the absence of preceding antibiotics [33]. In addition to maximizing the diagnostic yield, the practice of obtaining multiple blood cultures can also be useful in determining whether a positive result represents contamination, in which case only one culture would be expected to grow the contaminating organism.

The timing of blood culture draws depends on the overall clinical status of the patient. In the setting of a septic patient with suspected acute IE, therapy should not be delayed to allow blood cultures to be drawn, and two or three separate venipunctures can be performed a few minutes apart while arrangements are made for initiation of empiric antibiotic therapy. This approach is supported by the data reported by Li et al. (see above), who found that the rate of additional positive cultures from a second blood culture set was independent of its timing. Conversely, a clinically stable patient who has been ill for weeks can safely remain off antibiotics for at least 24 hours while serial blood cultures are obtained. In patients who have received antibiotic therapy before being worked up for IE, blood culture media containing antibiotic-inactivating resin should be used, and in selected circumstances withdrawal of antibiotics in order to allow cultures to be drawn would be appropriate.

Newer blood culture media and modern automated blood culture systems represent a significant improvement over older methods. The majority of non-fastidious organisms will trigger a positive signal in blood culture instruments within 72 hours.

Most clinical laboratories incubate routine blood cultures for five days, as most positive cultures appearing after longer incubation represent contaminants. However, some fastidious organisms that cause IE, including the HACEK group, *Brucella* species and others, may require longer periods of incubation before triggering automated blood culture systems. The majority of fastidious organisms causing IE will grow within ten days, but others (e.g., *Bartonella* species) can require several weeks to grow and may not trigger blood culture instruments even when they do grow. In the setting of clinically suspected IE, therefore, blood culture specimens require special management within the laboratory. Approaches vary among institutions and include extended incubation of the bottles collected from patients identified as suspect IE cases, terminal subcultures of negative blood culture bottles to solid culture media at the end of the planned incubation period, or a combination of both. Highly specialized culture techniques can be used for isolation of specific rare causes of IE such as *Coxiella burnetti*, *Bartonella* species, and *Tropheryma whipplei* when they are suspected; these methods and pertinent biosafety considerations have recently been reviewed by Houpikian and Raoult [34].

Candida species cause approximately 50% of proven cases of fungal endocarditis. Although blood cultures are thought to have poor sensitivity for detection of candidemia, more specialized blood culture media have no advantage over standard blood culture bottles for detection of *Candida* species. Special fungal blood culture media such as Bactec Myco-F-lytic bottles are superior in supporting growth of filamentous fungi such as *Aspergillus* species, and could be considered for use in immunocompromised patients or known IV drug users with suspected IE. The lysis-centrifugation (Isolator) method is superior to other available processes for detection of *Histoplasma capsulatum* from blood samples. Emboli leading to operative intervention are seen relatively commonly in cases of fungal endocarditis given the typically large vegetation size. Because blood cultures are frequently negative in fungal endocarditis, these emboli can provide crucial information about the causative organism, and they should be cultured and stained for fungal organisms when they are encountered and removed.

Methods for Diagnosis in Culture-Negative IE

Serology

Serologic testing can be useful in determining the cause of IE in true culture-negative cases, which are usually caused by organisms that are difficult to culture including *Coxiella burnetti, Bartonella* spp., *Chlamydia* spp., and *Legionella* species. The immune response to *C. burnetti* involves development of antibodies against phase 1 and phase 2 antigens. In acute infection, IgM and IgG antibodies develop against phase 2, and only IgM antibodies develop against phase 1. Endocarditis is a manifestation of chronic Q fever, which is characterized by high anti-phase 1 IgG titers. Positive Q fever serology, defined as a phase 1 IgG titer of >1:800, is listed as one of the major modified Duke criteria. A *Bartonella* antibody titer of 1:1,600 has been reported to have a positive predictive value of 88% for *Bartonella* IE [34]. However, titers may not be reproducible given lot-to-lot variability of antigen preparations used for testing. Patients with *Bartonella* infection also frequently develop cross-reacting antibodies that result in false-positive *Chlamydia* spp. serology. Additional assays to be considered in culture-negative IE cases include serologic studies for *Brucella* species and *Legionella* serology or urinary antigen testing.

Molecular Diagnostics

In spite of limitations including the potential presence of PCR inhibitors in clinical samples and the possibility of sample-to-sample contamination, molecular amplification methods can be useful in establishing the cause of IE. To date, PCR methods have been applied with most success to surgically excised valve tissues.

Because several possible etiologic agents are normally being considered in cases of culture-negative IE, the most commonly applied approach involves the use of "universal" PCR primers. These primers are directed against highly conserved sequences that are common to all bacteria, thereby allowing amplification of genetic material from virtually any species of bacteria. The segment to be amplified (most

often genes encoding for 16S rRNA) is chosen based on the presence of intervening regions with sequence variability, allowing identification of organisms by sequencing of the PCR product with subsequent comparison of the result to a sequence database. Podglajen et al. [35] evaluated 16S rDNA PCR/sequencing of valve tissues resected from 36 patients with clinically definite IE by the modified Duke criteria. PCR identification was possible in 26 of 30 cases with positive blood cultures prior to surgery, and in 5 of 6 blood culture-negative cases (four *Bartonella* species, one *S. gallolyticus*).

When a particular diagnosis is suspected, species-specific PCR assays can also be employed. Protocols have been developed for many of the agents of culture-negative IE including *C. burnetti*, *Bartonella* spp., *Brucella* spp., *Tropheryma whipplei*, *Chlamydia* spp. and *Legionella* spp. [34].

Histology

In cases of suspected IE for which the causative organism is not known prior to surgical intervention, heart valve material should be submitted for further investigation by histology and culture. Because of preceding antibiotic therapy, bacterial cultures of valve tissue obtained at surgery are positive in only a minority (10–15%) of cases. Histologic examination of excised valve tissue can be used both to confirm the diagnosis of IE and to determine the probable causative organism. Pathologic findings compatible with IE are considered to be evidence of definite endocarditis within the modified Duke criteria.

Routine stains, including H&E and tissue Gram stains, will show infiltrates of inflammatory cells and can allow common causative organisms to be visualized. Special stains, including Warthin-Starry (*Bartonella* spp.), periodic acid-Schiff (*T. whipplei*, fungi), Gimenez (*C. burnetti*, *Legionella* spp.), and Gomori methenamine silver (fungi) stains, are needed for detection of less common causes of IE.

Key Points

1. The etiologic agents of IE vary between centers due to different risk factor profiles in the patient populations served.
2. Staphylococci and *Streptococcus* species are the most common etiologic agents of endocarditis, accounting for 80–90% of cases in most patient populations.
3. The proportion of IE cases caused by *Staphylococcus aureus* has been increasing due to higher numbers of patients with either health-care-associated IE or a history of intravenous drug use.
4. In addition to appropriately collected blood cultures, microbiologic laboratory techniques useful for determining the causative agents of IE include histology, serologic testing, and molecular diagnostic methods.

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5

Prophylaxis of Endocarditis

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Case Study

An otherwise well 53-year-old man had mitral valve prolapse diagnosed 20 years prior, and had been clinically stable. He presented with an eight-week history of night sweats and a 5-kg weight loss. Approximately one month prior to the onset of symptoms, the patient underwent a dental cleaning and took amoxicillin 2 g, 1 h prior to the procedure. The physical examination revealed a man who appeared well and whose blood pressure in the right arm in the sitting position was 118/64 mm Hg with a heart rate of 84 beats per minute (regular). His chest was clear to auscultation and his heart sounds were normal with the exception of a grade 3/6 systolic murmur radiating to the axilla. The peripheral pulses were all palpable and peripheral edema was absent. A blood culture yielded *Streptococcus mutans*.

A transthoracic echocardiogram revealed significant myxomatous mitral valve disease; marked thickening of the posterior leaflet with a shaggy appearance and flail segment involving predominantly the middle scallop were seen. Severe eccentric mitral regurgitation was present. The left atrium was significantly enlarged. This study was followed up with a transesophageal echocardiogram, which demonstrated that the posterior mitral valve leaflet was diffusely thickened and very redundant. There was severe prolapse of this leaflet. There was at least one small mobile mass at the leaflet tip, but the entire posterior leaflet was thickened and somewhat shaggy. The findings were consistent with endocarditis.

The *S. mutans* had a minimal inhibitory concentration (MIC) to penicillin of 0.008 g/mL. Since the patient was stable, it was elected to initiate home parenteral antimicrobial therapy with penicillin G, 18 million units per day administered by continuous infusion pump for 4 weeks. The patient had an uneventful course of therapy and underwent an elective mitral valve replacement one year later.

Introduction

Infective endocarditis (IE) is a potentially fatal disease. Even with appropriate antimicrobial treatment, mortality rates range from 10% to 25% [1]; therefore, prevention of disease is very important. Guidelines have been created to estimate which patients with certain risk factors would most benefit from IE prophylaxis. However, there have been no controlled, clinical trials to demonstrate the protective efficacy of antibiotic regimens in the prophylaxis of IE in humans. Such trials will not likely ever be done for two major reasons: From a study-design perspective, the relative rarity of IE developing after a single transient bacteremic episode would require ≥6,000 patients, all with predisposing cardiac disease [2]. Secondly, such a study would also be considered unethical. Therefore, the guidelines that have been devised have been based on the efficacy of IE prophylaxis in animal models, previous antimicrobial susceptibility testing data of the most likely pathogens, pharmacokinetic studies, and studies on the incidence and prophylaxis of procedure-related bacteremias. Thus, the evidence for these recommendations is at the level of expert opinion, the efficacy is not 100%, and the

changing microbiology of IE may necessitate updated new recommendations.

Pathogenesis and Rationale for Prophylaxis

The fundamental step in the pathogenesis of IE is the development of bacteremia, with subsequent seeding of a previously damaged endocardial surface. Experimental studies suggest that valvular endothelial damage leads to platelet and fibrin deposition and the formation of a nonbacterial thrombotic vegetation. Circulating bacteria can then adhere to these lesions and multiply within the platelet-fibrin complex, leading to an infected vegetation. Dental treatment has traditionally been considered the major cause of the bacteremia that leads to IE [3], mainly because of historical studies that demonstrated a high frequency of bacteremia after various oral invasive procedures, as well as because of previous studies documenting the viridans group streptococci (VGS, the predominant members of the oral microflora) as the leading cause of IE. The initial recognition of a relationship between viridans streptococcal IE and dental procedures is attributed to Horder in 1909 [2,3]. In 1923, Lewis and Grant proposed the hypothesis that abnormally structured heart valves may contribute to the development of IE in healthy adults by trapping and retaining organisms from the transient bacteremia [4]. In 1935, Okell and Elliott, in a series of 138 patients, demonstrated the presence of bacteremia related to tooth extraction; in 64% of the cases, the isolate was a *Streptococcus* spp. [5]. Another study, published in 1937 by Burket and Burn [6], confirmed the biological plausibility of the oral cavity as the source of bacteremia when they painted the gingival crevices of 90 patients with *S. marcescens* (which was felt to be non-pathogenic at the time) before dental extraction. Subsequent to the procedure, the organism was recovered in 20% of the blood cultures. One study demonstrated a "dose-dependent"-like effect, with a significant correlation found between the number of teeth extracted and subsequent positive blood cultures [7]. Thus, it has become well established that bacteremia may occur after dental procedures that compromise mucosal surfaces, especially dental extractions and gingival surgery [8]. This bacteremia, however, is transient, lasting typically no more than 15–30 minutes [9,10], as well as low grade (usually < 100 colony-forming units/mL of blood) [9]. Transient asymptomatic bacteremia also occurs after a variety of other procedures and manipulations, particularly those associated with trauma to the mucous membranes of the respiratory, esophageal, gastrointestinal, and genito-urinary tracts. If the bacteremia following these procedures is a major cause of IE, in theory, maneuvers that decrease the magnitude and/or the duration of this bacteremia could prevent the development of IE in patients at risk for the disease.

Prophylaxis of Experimental Endocarditis

The evidence supporting the use of prophylactic antibiotic regimens in humans derives from its proven efficacy in animal models. Experimental IE has been typically produced in rabbits (e.g., New Zealand white rabbit [11]) or rats (e.g., female Wistar rats [12]) via catheter-induced damage to cardiac valves and subsequent intravenous challenge with various amounts of bacterial inocula. These experimental conditions allowed IE to be more effectively and reliably induced than in other models, with a predictable time of onset, thus facilitating analyses. Antibiotics are administered at the same or similar weight-based dose as in humans. The experimental IE is followed with serial blood cultures, with eventual sacrifice of the animal and quantitative culture of the valvular vegetations. Such experiments have helped to elucidate a hierarchy in the infectivity of the pathogens [13]. Adherence of circulating bacteria to the valvular endothelium/thrombotic vegetation is the most critical factor early in the pathogenesis of infective endocarditis [14,15]. Indeed, *S. aureus*, the VGS, and *Enterococcus* spp., which collectively account for the majority of cases of IE, do so specifically because of virulence factors that permit ligand-receptor interactions between bacterial surface components and constituents of damaged valves. However, the inoculum size (i.e., magnitude of the bacteremia) [13,16], as well as the duration of the bacteremia after inoculation, are also important determinants of infectivity [13].

Based on such models, antimicrobial prophylactic regimens should be predicted to be efficacious by interfering with one or more of these factors. A previously held belief was that

antibiotics prevented IE via elimination of the post-procedure transient bacteremia by killing the microorganisms before, as they entered, or while they were circulating in the bloodstream, before they seeded the endocardial surface. It seems unlikely, however, that any prophylactic agent could prevent the actual lodgement of circulating bacteria on a suitable nidus: seeding of the vegetation occurs within 30 minutes of the bacteria entering the circulation [17], while antibiotics usually require hours to exert their antibacterial effect [18]. The notion that prophylaxis is mediated by a bactericidal effect is the result of misinterpretation of negative blood culture results in earlier studies, which resulted from the continued elimination of the bacteria by the antibiotic after transfer of blood (and antimicrobial) to culture media. Indeed, animal [19,20] and human [21–24] studies with improved culture methods confirm that prophylaxis does not consistently and significantly reduce the incidence of post-procedure bacteremia. Therefore, the operative mechanism by which antibiotic prophylaxis is successful occurs by other means. Prevention of bacterial adherence has been proposed to explain the success of experimental prophylaxis. It was previously demonstrated that inhibitors of cell wall synthesis, such as β-lactams [25] and glycopeptides [20], have the capacity to decrease the adherence of bacteria to platelet-fibrin clots in vitro, possibly by inducing the release of lipoteichoic acid [26]. However, Moreillon and colleagues [27] elegantly demonstrated in the rat model of amoxicillin prophylaxis that inhibition of adherence was not an important mechanism, as the decrease was very marginal and did not prevent infection. Alternatively, successful prophylaxis is mediated by the ability of the administered antibiotic to facilitate elimination of bacteria subsequent to attachment to the vegetation. Studies have demonstrated that such an effect likely occurs by the prolonged inhibition of bacterial growth after inoculation. The determinants of the inhibitory effect include characteristics of the organism (e.g., tolerance), the challenge dose (i.e., the ID_{90}, that is, the minimum inoculum producing IE in 90% of control animals), and the duration of time the serum concentration of the antibiotic remains above the MIC of the pathogen. Studies have shown that for inocula $>ID_{90}$, the longer the duration of growth inhibition, the greater the likelihood of successful prophylaxis [27–29]. Thus, when VGS or enterococci tolerant to amoxicillin are inoculated into the rat model, single-dose prophylaxis with amoxicillin was efficacious only at the ID_{90} [16,30,31]. Against higher inocula, multiple doses of amoxicillin for VGS or amoxicillin and gentamicin for enterococci were necessary for successful prophylaxis [32]. Pharmacokinetic properties inherent in the administered antimicrobial assist in determining the dosage scheme to maximize growth inhibition. For example, single-dose aminopenicillin prophylaxis for *Enterococcus* spp. is likely not effective because blood antibiotic levels are not sustained long enough completely to eliminate the bacteria from the vegetation, whereas single-dose teicoplanin was efficacious [33]. For organisms with demonstrated in vitro susceptibility, amoxicillin has a duration of inhibition of ≥10 hours [13]. These features identified from experimental models have thus allowed recommendations for prophylaxis in humans to be devised. What remains unclear, though, is the mechanism by which prolonged serum inhibitory activity eliminates bacteria adherent to vegetation. It had been postulated that growth-inhibited surface organisms would be susceptible to post-antibiotic leukocyte-enhanced opsonophagocytic activity. Animal studies [28], including a neutropenic endocarditis model [16], have demonstrated that polymorphonuclear leukocytes do not play a role in eliminating bacteria adhered to the vegetation. Therefore, the mechanism by which antibiotic prophylaxis is effective remains undefined.

Although the principle of prophylaxis dictates to administer the antimicrobial agent before commencement of the procedure, experimental studies have demonstrated that prophylaxis may also be effective if given shortly after the procedure. In the rat model, efficacy of prophylaxis could still be maintained if the antibiotic was administered within two hours of the bacteremia-inducing procedure [16]. Administration of antimicrobials at four to six hours post-procedure was not effective in preventing IE [16,34]. Also, although the dogma in the treatment of IE is to use a bactericidal antimicrobial regimen, this philosophy may not necessarily apply to IE prophylaxis, particularly given the lack of evidence that bactericidal properties mediate prophylaxis. In fact, animal studies have confirmed that while bactericidal antimicrobial agents are required for large inocula, bacteriostatic antimicrobial agents are effective for inoculum sizes $\leq ID_{90}$ [35]—hence, the rationale for agents, such as the macrolides (e.g., clarithromycin [36]) and

lincosamides (e.g., clindamycin [37]) for penicillin allergic patients.

The applicability of the results from animal studies to humans remains debated. Major issues relate to the size of the inoculum used and the route of challenge. The bacteremia post-procedure in human is estimated to be $<1 \times 10^2$ CFU/mL of blood [9], whereas in experimental models, the inocula used is in the order of 10^6–10^8 CFU/mL [38]. Such large inocula are required to ensure that IE consistently developed in all (90%) of tested animals, but it may lead to an inaccurate model of disease. Furthermore, most animal models are challenged via the intravenous route to mimic a presumed mucosal micro-trauma-related bacteremia, again potentially introducing sources of error. Lastly, the experimental models used (i.e., rabbits, rats) may not reliably reproduce the pharmacokinetics of the antibiotics in humans, since these small animals clear drugs from their blood more quickly than humans [2].

Patients at Risk

The American Heart Association (AHA) [39], British Cardiac Society (BCS) [40], and French [41] guidelines stratify cardiac conditions into high- and moderate-risk categories, based on studies that have shown that certain types of structural heart disease are associated with higher risks of developing IE. Although the exact degree of risk for IE for certain cardiac lesions is difficult to assess, conditions deemed high-risk are inferred from the relative frequencies that particular cardiac lesions occur in a large series of patients with IE. For example, the incidence rates for IE are highest for patients with a previous history of native valve endocarditis (300–740/100,000 patient-years) and for patients with mechanical or bioprosthetic cardiac valves (300–600/100,000 patient-years); these rates are approximately 60–185-fold higher than that of the general population [42]. Presumably, damaged valvular endothelium from a previous IE episode predisposes to subsequent nidus formation for a second episode. In the case of prosthetic valves, IE can occur by seeding of the foreign-body valvular apparatus. Patients with congenital cyanotic cardiac disease (i.e., single ventricle states, transposition of the great vessels, tetralogy of Fallot) also have higher incidence rates of IE, estimated at 100–200/ 100,000 patient-years; this represents a rate approximately 50-fold higher than that of the general population [42]. The increased incidence of disease in this group is likely related to turbulent, high-velocity flow and stagnant eddies from right-to-left shunts. It should be noted that stratification of cardiac conditions is also determined not only by risk of developing IE, but on the attendant morbidity or mortality should IE develop. High- and moderate-risk categories are provided in Table 5.1.

Non-cyanotic congential heart disease includes conditions such as bicuspid aortic valve and coarctation of the aorta, as well as atrial septal defect (ASD), ventricular septal defect (VSD), and patent ductus arteriosus (PDA). Surgical repair of the latter three conditions has been reported to be associated with a negligible risk for IE (i.e., no greater risk than the general population). It should be noted, however, that the risk becomes negligible typically six months after surgical correction, provided that no other abnormality exists and no residual shunt is found by Doppler echocardiography, during which time endothelialisation of the material is complete [13,43].

Acquired valvular dysfunction includes aortic sclerosis, aortic stenosis (AS), aortic insufficiency (AI), mitral stenosis (MS), and mitral regurgitation (MR). The prevalence of these valvulopathies increases with age. Of these, AS,

Table 5.1. Cardiac Conditions Associated with Increased Risk for IE

High-risk:
1. Prosthetic cardiac valves (includes metallic, bioprosthetic, and homograft valves)
2. Previous endocarditis
3. Complex cyanotic congenital heart disease, e.g., single ventricle states, transposition of the great arteries, tetralogy of Fallot, double-outlet right ventricle
4. Surgically constructed systemic-to-pulmonic shunts/conduits

Moderate-risk
1. Most other congenital cardiac malformations, excluding atrial septal defect secundum and repaired atrial or ventricular septal defects
2. Acquired valvular dysfunction (e.g., rheumatic heart disease)
3. Hypertrophic obstructive cardiomyopathy
4. Mitral valve prolapse with mitral regurgitation or thickened leaflets on echocardiography

AI, MS, and MR result in abnormal high-velocity jet streams which can damage the endothelial lining and predispose to platelet aggregation and fibrin deposition on the valves, forming a nonbacterial thrombotic endocardial lesion. These vegetations can act as a nidus for infection when seeded by circulating bacteremia. Therefore, the ACC/AHA Guidelines for the management of patients with valvular heart disease [44] recommends that such patients, identified by physical examination or by echocardiography demonstrating at least moderate AS or MS or mild AI, receive IE prophylaxis.

Mitral valve prolapse (MVP), defined as a systolic displacement of all or part of a mitral valve leaflet at least 2 mm into the left atrium in a long-axis view on echocardiography, occurs in <5% of the general population [45]. MVP, however, is not uniformly associated with increased risk for IE. In fact, if auscultation reveals only the characteristic mid-systolic click and the valves are normal on echocardiography, the risk of IE in patients in this situation is negligible. However, if the valves are insufficient, such that the characteristic murmur of MR is produced, or there is echoradiographically demonstrable MR, prophylaxis is warranted [46]. If echocardiography demonstrates thickened, redundant mitral valve leaflets [45], such patients are also at increased risk for IE and prophylaxis should be administered [46]. In addition, male sex and age >45 years have been identified as predictors of increased risk for development of IE [45].

Procedures Producing Bacteremia

High-risk procedures, in this context, are those procedures associated with a high incidence of bacteremia, with "bacteremia" acting as a surrogate marker for IE risk. There is much controversy, however, about the role of invasive procedures, especially dental procedures, as the causative event leading to IE. The evidence for causality of odontogenic bacteremia is circumstantial, based on a temporal relation between dental procedures and subsequent manifestation of disease, and the identification of oral microflora (predominantly VGS, occasionally bacteria of the HACEK group) as the major pathogens. However, the mere presence of a temporal relation does not constitute proof of causation, particularly because of the influence of reporting bias: dental procedures are extremely common (e.g., 62.8% of adults aged 18–64 reported ≥1 dental visit within the last year in 2002 [47]), whereas IE is relatively uncommon (e.g., 3.3 cases/100,000 population/year in the United Kingdom, with similar figures for the United States [48] and France [41]). Furthermore, identification of the same type of bacteria in the mouth and in cardiac vegetations supports the hypothesis that the offending pathogens derive from a mucosally lined source, but it again may be unfairly blaming dental procedures. There is no doubt that certain odontogenic procedures may occasionally cause transient bacteremias that lead to IE. However, it has been estimated that dental treatment causes no more than 4% of all cases of IE [49]. A population-based, case-control study by Strom and colleagues comparing 273 hospitalized adults with IE and 273 matched outpatient controls found that the calculated risk for IE was no higher in the first month after the dental treatment than after 2 or 3 months, demonstrating the absence of an association between the two events [50]. Pallasch, using a mathematical model, has estimated that the absolute risk rate for IE from a single dental treatment in the general population to be 1/14,258,714 dental visits [51]. Therefore, although it is convenient to think that gingival instrumentation with bleeding permits oral microflora to access the circulation and establish IE, the evidence that dental manipulation causes IE is weak. How then do the oral bacteria end up on the vegetation? The history of a "recent" dental procedure may, in fact, be a surrogate marker of poor oral hygiene. Patients with poor oral hygiene are at increased risk for bacteremia in the absence of dental procedures, with the size of the inocula likely related to the degree of gingival inflammation [38,39]. Such transient bacteremia occurs with daily, trivial activities, such as chewing or tooth brushing. Guntheroth [49] devised a mathematical model to determine the cumulative exposure to bacteremia (CEB) resulting from "physiologic" activities (e.g., mastication, brushing teeth), and compared it to that from a "single dental extraction." It was estimated that over a period of one hypothetical month, the physiologic CEB was 5,370 minutes, in contrast to 6 minutes for surgical CEB. The CEB method was modified by Roberts [38] to include the percentage prevalence of bacteremia related to the dentogingival manipulative procedure (p), the intensity of bacteremia (i, in colony-forming

units (CFU)/mL), the length of the bacteremia (t), and the frequency of bacteremia-inducing events estimated for a one-year period (f). The modified CEB (in CFU min/mL/year) for various activities were as follows: toothbrushing, 6,323; flossing, 3,285; chewing, 3,285; single extraction of a permanent tooth, 0.014. To estimate the relative bacteremic challenge produced by one procedure versus another, the cumulative exposure index (CEI) was calculated, using the single deciduous molar extraction as the standard procedure, as it is widely recognized as causing a "significant bacteremia" [38]. Roberts demonstrated that the CEI for toothbrushing twice a day is 154,219 times greater than that of an extraction. He concludes that dental surgical procedures pose a low risk for IE. Rather, everyday procedures are much more likely (e.g., 8,000-fold higher risk) to cause transient episodes of low-grade bacteremias, that with time, results in a cumulative risk sufficient to cause IE. The mechanism by which this occurs is proposed to be via small movements of the tooth within the alveola, producing intermittent positive and negative pressures that cause microscopic gingival vascular damage, with subsequent aspiration of organisms into the circulation [38].

Further supporting the refutation of dental procedures as a major cause of IE are studies which raise doubt about the efficacy of pre-dental treatment antibiotic prophylaxis. In a nationwide, case-control study in the Netherlands, van der Meer and colleagues [52] estimated that the protective efficacy of chemoprophylaxis was 49% for first-ever IE occurring within 30 days of a procedure. The same group, in a prospective, population-based case study, demonstrated that medical and dental procedures cause only a small fraction of IE cases; furthermore, full compliance with prophylaxis might have prevented IE in 47 (17.1%) of 275 patients with late prosthetic or native valve IE involving a previously known cardiac lesion who underwent a procedure with an indication for prophylaxis. For an incubation period of 30 days, prophylaxis might have prevented IE in 23 (8.4%) of these 275 patients, or 5.3% of all patients with endocarditis (i.e., total of 427 cases) [53]. The case-control study by Strom et al. [50] also challenges the usefulness of IE prophylaxis, concluding that even if prophylaxis was 100% effective, it would reduce the incidence of IE by only 2.0 cases per 1 million person-years. A case-control study in France by Lacassin and colleagues [54] demonstrated that dental procedures were not associated with an increased risk for IE, and that antibiotic prophylaxis provided a protective efficacy of only 46%, which was not statistically significant. These studies provide evidence suggesting that from a public health perspective, the routine use of antibiotic prophylaxis will only prevent a limited number of cases and is thus not justified. However, three points need to be emphasized: Firstly, some of the studies [50,54] still demonstrated an association between procedures in at-risk patients and the subsequent development of IE. Secondly, the studies were population-based, case- or case-control study design, raising the possibility of ecological fallacy in analysis interpretation, where the effect of antibiotic prophylaxis at the population level may be negligible, but may continue to be worthwhile for the individual patient [55]. Indeed, the study by van der Meer [52] admits that the small number of cases entered into the trial resulted in a small power that may have failed to detect a significant protective effect, and that there was the possibility that some subgroups may benefit from the use of prophylaxis. Lastly, case-control studies, with all their merits, are not the strongest level of evidence on which current medical decision making is based. These studies do, however, emphasize the importance of carefully identifying at-risk patients that will most benefit from prophylaxis. Furthermore, they underscore the need for more robust studies.

In the absence of a conclusive, prospective, randomized study, expert committees currently believe that prophylaxis should continue as recommended [39–41,56], despite the fact that it is an uncommon cause of IE, due to the high morbidity and mortality associated with this disease. Although anaerobic bacteria are the principal components of the oral microflora and are released into the circulation after dental/oral procedures [21,57], they rarely cause IE. The predominant organisms of concern are the VGS, which are the targets for prophylaxis. A fundamental component of prophylaxis is good oral hygiene through daily, proper self-care and regular professional care. Antiseptic mouth rinses, either chlorhexidine- or povidone-iodine-based, may reduce the incidence and/or magnitude of bacteremia prior to dental procedures [58] and are recommended by the current AHA [39] and French [41] guidelines prior to invasive oral procedures to reduce the risk of IE. However, antimicrobial rinses do not permeate beyond 3 mm into the gingival sulcus and thus do not eradicate bacteria at the entrance into the

systemic circulation [59], raising the need by some for more supportive evidence of benefit. Systemic antibiotic prophylaxis is recommended for at-risk patients (see Table 5.2). Prophylaxis is recommended for procedures associated with significant bleeding [3,13,39]. As well, it is recognized that unanticipated bleeding may occur on occasion in patients who did not receive prophylaxis prior to the procedure; in these cases, experimental data suggests that the appropriate pre-procedure regimen can still be administered within two hours of the procedure with similar efficacy [13,39]. Interestingly, however, visible bleeding may not be a clinically relevant tool, as a previous study has demonstrated that bleeding is a poor predictor of odontogenic bacteremia [38]. In cases where multiple consecutive dental interventions are required, repeated prophylaxis is also required. Because repeated single-dose antibiotic administration may select for resistant organisms which persist in the mouth, multiple procedures are recommended to be carried out in one sitting (if possible) or separated by 9–14 days [39,41].

Streptococcal bacteremia can also occur via manipulation of other mucosal surfaces lining the upper respiratory tract (e.g., tonsillectomy [60–62], mastoidectomy [63], septoplasty [64]). Although the use of a rigid bronchoscope is suggested to be a potential bacteremic-inducing procedure via mucosal damage and for which prophylaxis is recommended [39,40,56,65], there is no literature to support this opinion. In fact, one prospective nonrandomized clinical

Table 5.2. Procedures Associated with Increased Risk for IE and Recommended Prophylaxis Regimens for Adults

Category of procedures	Specific at-risk procedures for which prophylaxis is recommended	Prophylaxis regimen for adults	
		1st line	2nd line
Dental	1. Dental extractions 2. Periodontal procedures / gingival surgery Note: other dental procedures previously recommended include— a. Dental implant placement and replantation of avulsed teeth b. Root canal or surgery only beyond the apex c. Subgingival placement of antibiotic fibres or strips d. Initial placement of orthodontic bands (not brackets) e. Intraligamentous local anesthetic injections f. Prophylactic cleaning of teeth or implants where bleeding is anticipated	1. Amoxicillin 2 g po 1 h before procedure 2. If patient unable to take orally: Ampicillin 2 g IM/IV within 30 min before procedure	Allergic to penicillin— 1. Clindamycin 600 mg po 1hr before procedure OR 2. Cephalexin* or cefadroxil* 2 g po 1 h before procedure OR 3. Clarithromycin (or azithromycin) 500 mg po 1 h before procedure Allergic to penicillin and unable to take orally— 1. Clindamycin 600 mg IV within 30 min before procedure OR 2. Cefazolin* 1 g IV within 30 min before procedure
Respiratory	1. Tonsillectomy or adenoidectomy 2. Bronchoscopy with a rigid bronchoscope 3. Surgery involving the respiratory mucosa		
Esophagus	1. Sclerotherapy of esophageal varices 2. Esophageal stricture dilatation		
Gastrointestinal	1. Endoscopic retrograde cholangiography with biliary obstruction 2. Biliary tract surgery 3. Surgery involving the intestinal mucosa	High-risk—Ampicillin 2 g IM/IV + gentamicin 1.5 mg/kg (max: 120 mg) within 30 min before procedure THEN Ampicillin 1 g IM/IV (OR amoxicillin 1 g po) 6 h later	High-risk and allergic to β-lactams—Vancomycin 1 g IV over 1-2 h + gentamicin 1.5 mg/kg (max: 120 mg); complete infusion within 30 min before procedure
Genito-urinary	1. Cystoscopy 2. Urethral dilatation 3. Prostatic surgery	Moderate-risk— 1. Amoxicillin 2 g po 1 h before procedure 2. If patient unable to take orally—Ampicillin 2 g IM/IV within 30 min before procedure	Moderate-risk & allergic to β-lactams— Vancomycin 1 g IV over 1–2 h; complete infusion within 30 min before

*Cephalosporins should not be used in patients with type 1/immediate-type hypersensitivity to b-lactams.
Routes of administration: po = orally; IM = intramuscularly; IV = intravenously.

study in 25 children undergoing diagnostic rigid tracheobronchoscopy for airway assessment demonstrated no cases of bacterial growth in blood cultures [66]. Fiberoptic bronchoscopy, previously thought to be benign with five studies (291 patients) demonstrating a procedure-induced bacteremia rate <1% [67] and for which prophylaxis is not recommended [39,56,65], may actually be associated with higher rates. Yigla and colleagues [67] demonstrated a bacteremia rate of 6.5% in a prospective study of 200 consecutive patients that underwent fibre-optic bronchoscopy without either pulmonary infection or an unusually high rate of invasive procedures. If additional studies can support this finding, it may have implications in future revisions of IE prophylaxis guidelines.

The esophageal procedures with the highest associated bacteremia rates are sclerotherapy of esophageal varices and esophageal dilation of a stricture [68,69]. Earlier studies have demonstrated rates of 31% for sclerotherapy (61 patients) and 45% for dilation (59 patients), in which the majority of organisms were VGS [68]. More recent prospective studies support these rates. Zuccaro and colleagues [70] performed blood cultures before and after stricture dilation in 103 patients without valvular heart disease and in a control group of 50 patients undergoing upper endoscopy without dilation. They demonstrated that 21% (22/103) of patients undergoing dilation had positive blood cultures, with VGS as the predominant isolate. Among 100 procedures in 86 patients undergoing esophageal dilation by Nelson et al. [71], 22 (22%) were associated with a positive post-dilation blood culture. Although these episodes of bacteremia post-endoscopy are short lived (i.e., typically <30 minutes), their clinical significance is unclear (as it is with other post-procedure bacteremias). One prospective comparative study randomizing 39 patients to prophylaxis (i.e., cefotaxime, 19 patients) or no antibiotic (20 patients) revealed a significant reduction in post-procedure bacteremic episodes in the group receiving antibiotic (5.3% vs. 31.6%, respectively; $P = .04$)) [72]. However, a recent review of the infectious disease complications of GI endoscopy has revealed only two cases of IE after sclerotherapy have been reported, one involving a prosthetic valve (despite prophylactic administration of appropriate antibiotics) and another on a native valve [69]. Nonetheless, current guidelines continue to recommend prophylaxis for these procedures [39,41,73]. Endoscopic variceal ligation (EVL, "banding") has replaced sclerotherapy as the procedure of choice in the management of varices because of its greater efficacy and fewer associated complications. In a historical cohort study comparing the rates of transient bacteremia between the two procedures, positive blood cultures occurred more frequently in the sclerotherapy group (17.2%) than in the ligation group (3.3%, $P < 0.03$) [74]. A review of seven studies addressing this issue, including the one mentioned, reports bacteremia rates associated with EVL ranging from 0% to 25%, with a mean frequency of 8.8% [69]. The attributable risk of IE to endoscopic variceal ligation is unknown, as no cases have currently been reported in the English literature.

Endoscopic retrograde cholangiopancreatography (ERCP) has become a commonly performed procedure. The diagnostic and therapeutic utility of ERCP has been well demonstrated for a variety of disorders, including the management of biliary obstruction, predominantly due to choledocholithiasis or biliary malignancies. The rate of bacteremia after contrast injection or instrumentation of unobstructed pancreatic or bile ducts ranges from 0% to 15% (mean frequency of 6.4%) [69]. Biliary obstruction, however, may lead to infection of the biliary system with a variety of organisms. Although the predominant organisms are Gram-negative bacillary enterics (e.g., *E. coli*, *Klebsiella* spp.) [75,76], which are common causes of cholangitis/biliary sepsis, they are uncommon causes of IE, although they may cause disease in high-risk patients (e.g., those with prosthetic valves). The major organisms from an infected biliary tree that can cause bacteremia with the potential for IE are *Enterococcus* spp. and VGS [75]. The enterococci are particularly more common among patients with previous biliary endoprosthesis [76]. Instrumentation of an obstructed biliary system has resulted in bacteremia rates as high as 26.5% (mean 18.0%) [69], hence the rationale for prophylaxis. Although earlier studies provided some evidence that prophylaxis may reduce the incidence of post-ERCP bacteremia [77,78], a meta-analysis by Harris and colleagues [79] that reviewed five prospective, randomized placebo-controlled trials failed to show such a benefit among patients who received prophylaxis, arguing against the routine prophylactic use of antibiotics prior to ERCP to reduce bacteremia.

This is not to say, however, that antibiotics should not be used in patients with known cholangitis. As well, because the meta-analysis excluded two studies where patients received antibiotics before and after the ERCP, it is possible that continuation of the prophylaxis after the procedure may reduce bacteremia. Therefore, such a regimen continues to be recommended for patients with biliary obstruction and high-risk for IE [39–41,73]. A similar rationale exists for surgery on the biliary and gastrointestinal tracts [39–41].

Endoscopic ultrasound (EUS) is a relatively new procedure. One of its greatest benefits is the ability to perform fine-needle aspiration (FNA), the two procedures referred to as EUS-FNA. EUS-FNA has been used to aspirate fluid from cystic lesions, pseudocysts, and fluid collections for both diagnostic and therapeutic purposes [80]. The frequency of bacteremia as a complication of EUS and EUS-FNA has been prospectively studied in 3 separate trials, which included approximately 250 patients [81–83]. These studies did not find a statistically significant increase in the rate of bacteremia when compared with that seen at upper endoscopy. Based on these data, prophylactic antibiotics are not recommended for FNA of solid masses and lymph nodes [80]. Some experts recommend prophylactic antibiotics as well as 48 hours of antibiotics after the procedure for EUS-FNA of the perirectal space [80]. EUS-FNA of cystic lesions appears to carry an increased risk of febrile episodes and possibly sepsis and, therefore, warrants prophylactic antibiotics, as well as a short postprocedure course [80].

Colonoscopy has a surprisingly low rate of bacteremia (2–5%) [10,69,84], most commonly with organisms that are not typically causes of IE. Therefore, antibiotic prophylaxis is not recommended for this procedure, including when it involves biopsy or polypectomy [85].

Genitourinary (GU) instrumentation is necessary for the diagnosis and treatment of benign and malignant urological diseases. However, instrumentation and catheterization of the GU tract is also the leading cause of nosocomial urinary tract infections (UTIs) [86]. Less frequently, bacteremia can result from these interventions, the rates varying with different procedures. Development of bacteremia directly attributable to the GU procedure typically occurs after colonization of the urine. As such, the majority of studies on the use of prophylactic antibiotic regimens prior to GU interventions have assessed the efficacy in preventing UTIs. There have been only a few studies that have assessed the efficacy in preventing bacteremia, reflecting the infrequent occurrence of this complication. When bacteremia occurs, the clinical manifestations range from asymptomatic, to transient fever, to septicemia/urosepsis. IE due to manipulation of the GU tract is extremely uncommon, but has been reported [87–89]. As such, the evidence for IE prophylaxis in GU procedures is scant and is based largely on the efficacy in preventing bacteremia, as well as on expert opinion.

As with lower gastrointestinal procedures, GU procedures will mostly produce bacteremia with Gram-negative organisms (e.g., *E. coli*, *Klebsiella* spp. [90–92]), which are common causes of urosepsis but are uncommon causes of NVE. These organisms may, however, cause IE in high-risk patients (e.g., those with prosthetic valves). Of the organisms arising from the native GU tract, the predominant ones that may cause NVE are *Enterococcus* spp. and the VGS [92]. Although the risk that any particular patient will develop endocarditis is low, the rate of bacteremia following invasive urinary tract instrumentation is high in the presence of bacteriuria. For example, cystoscopy, urethral dilation, and transurethral resection of the prostate (TURP) in the presence of bacteriuria precipitated bacteremia at rates of 25% [93], 40% [92], and 52% [92], respectively. This perioperative bacteremia is usually transient and symptomless—in as many as ~6% of cases in one study [94]—though it may progress to perioperative septicemia. With this in mind, sterilization of the urinary tract with antimicrobial therapy in patients with bacteriuria should be attempted prior to elective procedures [93,95]. Such intervention has been shown to reduce the risk of septicemia [96]. Whether it also reduces the risk of IE is unknown. However, in a study of 15 non-catheterized patients with sterile urine, cystoscopy resulted in post-procedure bacteremia in 13% of patients [97], which can theoretically result in IE in at-risk patients. As well, the incidence of post-procedure bacteremia after transurethral procedures (i.e., TURP, transurethral resection of bladder tumour/TURBT) ranged from 30% to 45% in three prospective, comparative studies [98–100], which was reduced by approximately 80–90% with appropriate antimicrobial prophylaxis

[93]. These studies were marked, however, by relatively high rates of bacteriuria in both comparison groups [93], which accounts for the high rates of bacteremia in the absence of prophylaxis. In a meta-analysis of ten randomized controlled trials of antibiotic prophylaxis for TURP in men with sterile urine (i.e., preoperative urine specimen containing $< 1 \times 10^5$ CFU/mL), a significant decrease in the frequency of postoperative bacteremia was noted with the intervention, albeit with lower baseline rates (4% vs. 1%, risk difference of –0.02, 95% confidence interval of –0.04–0.00) [101]. The rate of bacteremia after combined cystoscopy and transrectal biopsy of the prostate was 73% in one study [97]. Hence, mono-antimicrobial prophylaxis (e.g., aminopenicillins or glycopeptides) is recommended for moderate-risk patients prior to these urological procedures to target the above mentioned Gram-positive organisms. For high-risk patients, combination therapy targeting Gram-positive and Gram-negative flora is recommended.

Antimicrobial Prophylaxis

Because VGS are felt to be the predominant pathogens potentially to cause IE after dental/oral, respiratory, and esophageal procedures, aminopenicillins are the recommended prophylaxis. In the past, VGS were nearly uniformly susceptible to penicillin and other β-lactams, as well as to lincosamides and macrolides [102]. Therefore, the current AHA guidelines on IE prophylaxis, which were published in 1997 [39], recommend the use of amoxicillin (ampicillin if the patient is unable to tolerate oral intake). Amoxicillin was recommended over penicillin because it is better absorbed from the GI tract and because it provides higher and more sustained levels [39]. In humans, the elimination half-life of amoxicillin is 50–60 minutes [103]. Clindamycin or macrolides are alternatives in those unable to tolerate β-lactams. A contemporary review of the antimicrobial susceptibility of VGS demonstrated that amoxicillin at a concentration of ≤ 0.5 μg/mL inhibited 87%, 64%, and 100% of isolates in the *S. sanguis*, *S. mitis*, and *S. milleri* groups, respectively, as well as two of the three isolates in the *S. salivarius* group [104]. Hence, the use of amoxicillin as a prophylactic regimen was justified. However, several studies have since demonstrated increasing rates of VGS isolates from oropharyngeal specimens [105] and bloodstream infections [102,106–109] that are not susceptible to penicillin, macrolides, or lincosamides. Furthermore, resistance to these antibiotics can occur with repeated prophylaxis doses for serial procedures distributed closely in time [39,41]. Therefore, continued monitoring of such resistance patterns is mandatory, and modifications of future guidelines may be necessary. Until such time, amoxicillin remains the recommended prophylaxis regimen for the above-mentioned procedures. When comparing the AHA guidelines from those of Europe (BSC, French), differences in amoxicillin dose is seen. The latter recommend a single 3-g oral dose, which produces serum levels above the MIC of most oral streptococci for a period of 6–14 hours [110]. The AHA proposes 2-g, instead of 3-g, because the serum kinetics produced by the two different doses are very similar, although the lower dose is associated with fewer side effects [111]. For patients with a history of penicillin allergy, clindamycin remains appropriate. Alternatives include macrolides, such as clarithromycin or azithromycin, which have demonstrated efficacy in experimental models and have convenient dosing regimens, although they are more expensive. Cephalosporins also have demonstrated efficacy, but should not be used in patients with a history of type 1 (immediate-type/anaphylaxis) hypersensitivity reaction to β-lactams. For patients unable to take medication orally, intravenous regimens are recommended, and administration of the full dose should be completed within 30 minutes of the procedure.

For procedures involving the biliary system or the gastrointestinal or genitourinary tracts, the predominant pathogen of concern is *Enterococcus* spp. Previous studies have reported that among cases of enterococcal IE, ~40% were associated with a recent gastrointestinal or genitourinary procedure (i.e., within 2–6 weeks) [28]. Enterococci however, are notoriously more resistant than VGS, with typically higher MICs to β-lactams [112]. Thus, after administration of amoxicillin, the corresponding serum levels fall below the MIC of enterococci sooner than for VGS, resulting in a decreased period of bacterial growth inhibition. To overcome this issue in high-risk patients, a second dose of the β-lactam is currently recommended six hours after the first dose to ensure prolongation of adequate serum levels and to enhance protective efficacy. The rationale for the combination of amoxicillin and gentamicin is based on the rat model of

Enterococcus IE, in which administration of both agents was necessary for successful prophylaxis against inocula >ID_{90} [32]. Alternatively, administration of a single dose of vancomycin (in conjunction with gentamicin) can be used in high-risk patients unable to tolerate β-lactams. The evidence for this recommendation derives from experimental studies in which vancomycin demonstrated prolonged serum half-life, producing serum levels greater than MIC for a longer period of time (compared to ampicillin-based regimens), which resulted in significantly greater area under the curve (AUC) and serum inhibitory activity, and more consistent protective effect [28]. Because of vancomycin's pharmacokinetics, a second dose is not considered necessary. For moderate-risk patients, the second dose of aminopenicillins is optional.

Reasons Against Prophylaxis

Since IE is potentially fatal, prophylaxis seems reasonable. The benefit of giving antibiotic prophylaxis to otherwise healthy people, however, should outweigh its risks. The major complications associated with administration of prophylaxis include allergic reactions, toxic side effects of antimicrobials, adverse interactions with other drugs, and development of resistant organisms.

The most significant adverse event associated with the penicillins is hypersensitivity reactions, which can range from a troublesome rash to life-threatening anaphylaxis. Previous studies that have compared the rates of IE-associated deaths to the rates of deaths from antibiotic-induced anaphylaxis have questioned the benefit of prophylaxis. In a quantitative analysis of published data on prophylaxis in patients with mitral valve prolapse (MVP), Bor and Himmelstein [113] calculate that among 10 million patients with MVP undergoing a dental procedure, an estimated 47 nonfatal cases and 2 fatal cases of IE would occur if no prophylaxis were given, compared to 5 cases of IE and 175 deaths due to drug reactions if all patients were given prophylaxis with a penicillin. Similarly, Tzukert and colleagues [114] demonstrated that patients receiving penicillin/amoxicillin propylaxis to prevent IE are five times more likely to die from anaphylaxis to the drug than from IE, with estimated rates of 1.36 deaths versus 0.26 deaths per million population, respectively. These studies were conducted in the mid-1980s, and national guidelines have since been revised to tailor prophylaxis to at-risk patients. No study has since demonstrated whether the risk–benefit ratio has been modified by the latest recommendations. Nonetheless, the potential for adverse drug reactions must always be borne in mind. Such a consideration should also include non-allergic toxicities (e.g., aminoglycoside-induced nephrotoxicity), as well as potential drug–drug interactions.

An emerging problem resulting from inappropriate use of antimicrobial agents is the development of *C. difficile*-associated disease (CDAD). *C. difficile* is the most common cause of infectious diarrhea among hospitalized patients. It is well-documented that recent antibiotic use (e.g., within 42 days [115]) predisposes to acquisition of *C. difficile*. Essentially all antibiotics have been associated with risk for CDAD, including those recommended for IE prophylaxis. In a meta-analysis by Bignardi [116], use of ampicillin or amoxicillin was associated with a pooled odds ratio of 3.7 for acquiring disease (95% CI: 2.6–5.5), while the rates for clindamycin, 1st-generation cephalosporins, and vancomycin were 9 (6.3–12.9), 2.6 (1.8–3.7), 3.1 (1.8–5.2), respectively. Development of CDAD leads to prolonged hospitalizations [117,118]. It can also be associated with severe disease (i.e., megacolon, perforation, colectomy, shock requiring vasopressor therapy, or death within 30 days after diagnosis) [119]. In certain geographic areas, CDAD is associated with increased mortality rates, with a one-year cumulative attributable mortality of 17% [117]. Development of CDAD following antibiotic prophylaxis for dental procedures has been reported [120], as it has after single doses of antibiotics for other procedures [121,122]. Emergence of CDAD emphasizes the need to weigh the risks versus the benefits of antibiotic prophylaxis.

An additional concern from the large-scale use of IE prophylaxis is the development of antimicrobial resistance. In healthy human volunteers, administration of repeated doses of amoxicillin was followed by emergence of resistant VGS from the oral flora [123]. A case of *S. mitis* IE developing despite seemingly-appropriate prophylaxis has been reported in a patient who received two recent courses of amoxicillin for dental procedures [124]. In the neutropenic cancer patients, exposure to previous β-lactams was associated with an increased risk of bloodstream infection (non-endocarditis) with

β-lactam-resistant VGS [125,126]. Previous exposure to antibiotics has also permitted the emergence of resistant enterococci [127] and *S. aureus* [128,129]. Consequently, judicious use of antibiotics, in general, is advocated, and administration of antimicrobial prophylaxis should not be done indiscriminately, but tailored to those specifically at-risk for disease.

Emerging Issues

The current recommendations for IE prophylaxis are based on an epidemiology in which VGS were the predominant pathogens. Recent studies have demonstrated that *S. aureus* has become the major cause of IE [130]. An increasing proportion of cases of *S. aureus* bloodstream infection and IE is acquired nosocomially or nosohusially (i.e., health-care-associated) [130–132], due to increasing use of intravascular devices (e.g., central venous catheters, dialysis catheters, prosthetic vascular grafts, pacemakers/ defibrillators). These devices can also permit coagulase-negative staphylococci (CoNS, e.g., *S. epidermidis*) to establish endovascular infections. Indeed, the incidence of CoNS IE is also increasing [133]. The existing aminopenicillin-based prophylaxis recommendations are not likely to be effective in preventing *S. aureus* IE, based on in vitro susceptibility testing in which <5% of clinical isolates are inhibited by penicillin [134–136]. Similarly, they are not expected to be effective against CoNS. There are currently no national guidelines regarding IE prophylaxis for the above-mentioned procedures. The recommendations that exist recommend prophylaxis to minimize the risks of intraoperative contamination and surgical site infection [137]. Typically a first-generation cephalosporin directed primarily against staphylococci is administered in the peri-implantation time period for clean-contaminated procedures, and only for a short duration (e.g., a few doses) [137]. This approach, however, may not be adequate to prevent bacteremia. For devices in which a portion remains external to the patient, and thus provides a persistent portal of entry, the brief administration of the peri-procedure prophylaxis is certainly not sufficient to prevent bacteremic episodes that may occur during the lifespan of the implanted device. In particular, the use of central venous catheters (CVCs) has emerged as a major risk factor for bacteremia and IE [132]. Consequently, health-care-associated IE (HA-IE), defined as acute IE occurring 48–72 hours or more post-admission to hospital and/or IE directly relating to a hospital-based procedure performed during a previous hospital stay within eight weeks of admission, currently accounts for approximately 7.5–29% of all cases of IE seen in tertiary hospitals [138]. As such, modification of IE prophylaxis recommendations is required to address this changing epidemiology. One intervention which may be particularly useful for preventing CVC colonization, and therefore may minimize the risk of bacteremia and IE, is the antibiotic lock technique. This technique consists of filling and closing of the catheter lumen with a high-concentration antibiotic solution that acts locally to eradicate catheter-associated bacteremia, but that allows the side effects and toxicity associated with systemic administration of antibiotic to be avoided. Future studies are required before such intervention can be recommended.

Conclusion

Guidelines exist to assist clinicians in stratifying their patients' risk of IE with regard to various procedures. Unfortunately, most of the recommendations are not based on robust, scientific evidence, but, instead, are consensus expert opinion. In addition, emergence of antimicrobial resistance and a changing epidemiology of IE will likely necessitate revision of current guidelines.

Key Points

1. Guidelines exist for antibiotic prophylaxis against infective endocarditis (IE). There is little robust clinical evidence supporting proof that antibiotic prophylaxis decreases the immediate subsequent risk for IE. The strength of the evidence rests on animal studies, which may or may not accurately reflect human disease, as well as on expert opinion. Nonetheless, a priori algorithms have been proposed for the health-care practitioner, based on patient risk factors for disease as well as the likelihood of bacteremia from a given procedure.
2. The mechanism(s) by which antibiotics affect prophylaxis remain unclear, but may involve

interfering with bacterial adherence to a fibrinous valvular vegetation and/or clearance of pathogen after such adherence.

3. Current recommendations provide both oral and intravenous regimens, the latter for patients unable to take medication orally. There is no evidence for superiority of one regimen over the other. The recommendations also provide alternatives for patients with a history of allergy to β-lactams. The suggested regimens may decrease but will not eliminate the risk of IE.
4. Given that the microbiology and the antimicrobial resistance patterns of the most common pathogens causing IE are evolving, guidelines will need to be regularly revised.

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6

Diagnostic Approach to Endocarditis

James W. Tam, Rizwan A. S. Manji, Nasir Shaikh and Andrew Morris

Case Study

A 37-year-old man was seen in the emergency department with a fever of ten days' duration associated with chills, rigors, sweats, headache, lethargy, and weakness. A Medtronic-Hall mechanical aortic valve prosthesis had been implanted 18 years previously. He had been asymptomatic until his present illness. At the time of appearance of fever (with temperatures to 103.9 °F.), he noted the sudden onset of pleuritic left upper quadrant pain and severe pain in the left posterior thigh. He had recently traveled to the Punjab without antimalarial prophylaxis. Coumadin was his only medication, and the anticoagulation level was in the therapeutic range. He had not been treated with antibiotics. The patient had a blood pressure of 90/71 with a regular heart rate of 98 beats per minute. There was no evidence of heart failure or pneumonia on examination or chest x-ray. He had no other symptoms to suggest a urinary or abdominal source of sepsis. Does this patient have endocarditis and what should be done for him?

The diagnosis of infective endocarditis (IE) can be a difficult one to make. Since the late 1970s attempts have been made to develop diagnostic criteria and algorithms to predict the presence of IE. Making the correct diagnosis is important for a number of reasons, including ensuring that antibiotic treatment is adequately prolonged, determining whether there is a need for surgical intervention, and confirming that another source of infection has not been missed.

In this chapter, we briefly review the history of IE leading to the current diagnostic approach, the existing stratagems for case definitions, and the utility of echocardiography in assisting with diagnosis. We also examine specific scenarios in which the diagnosis of IE may be particularly challenging.

Historical Perspective

Endocarditis, an inflammatory disorder of the endocardium, has been recognized by the anatomical pathologists for some time. Prior to the bacteriological era, however, the various types of endocarditic lesions could not be categorized as infectious or non-infectious. Austin Flint's chapter on endocarditis likely referred to rheumatic valvular heart disease rather than to infectious endocarditis [1]. However, he utilized the terms "acute," "subacute," and "chronic" in his description, and this classification was subsequently adopted as standard nomenclature.

The diagnosis of IE remained challenging and continued to be dependent on a constellation of infectious symptoms and signs in association with bacteremia, auscultatory evidence of valvular involvement, and signs of large-and/or small-vessel peripheral arterial embolization. This dependence on both clinical skills and the bacteriological laboratory was, in the latter part of the 20th century,

supplemented by the addition of echocardiographic visualization of the lesion and of the assessment of its hemodynamic and structural consequences.

In 1945, R. H. Major, in a comprehensive review, *The History of Endocarditis,* mentions Laennec's attribution of the first mention of this disorder to Lazare Riviere in 1707: "In the left ventricle of the heart round caruncles were found like the substance of the lungs, the larger of which resembled a cluster of hazelnuts and filled up the opening of the aorta" [2]. Major notes that Morgagni, in 1761, while observing a ruptured aortic valve cusp observes that "from the very lips of their rupture other excrescences were protuberant." Virchow, the great anatomical pathologist, noted in 1856 that IE was associated with emboli and that he had seen "innumerable vibrions" in a thrombus [2]. Klebs, in 1875, had become convinced that all cases of IE were infectious in origin [2]. In 1878, Rosenbach demonstrated in experimental studies that IE was associated with bacteremia and damaged cardiac valves and he recommended that the diagnosis be dependent on the presence of positive blood cultures in association with specific signs and symptoms [2].

It is instructive to view the understanding of infectious IE through the eyes of a single individual, Sir William Osler, as revealed in successive editions of his textbook *The Principles and Practice of Medicine*. The first edition, in 1892, divides endocarditis into "acute" and "chronic" forms. Acute endocarditis was further divided into contained "simple" and "malignant" forms [3]. In simple endocarditis there were small vegetations with microorganisms in association with systemic symptoms, fever, and a heart murmur [3]. In malignant endocarditis, there was acute IE with "a malignant character" [3]. Symptoms were varied and diverse and might include fever, sweats, weakness, delirium, and emboli. Malignant endocarditis was subdivided into a Septic type, a typhoid type, and a "cardiac group, the latter being associated with chronic valvular heart disease, fever, and "evidence of recent IE" [3]. Osler noted that the diagnosis of IE was often "difficult" but was easy when there were "marked embolic symptoms." To the modern reader, although his classification may be difficult to interpret, his conclusion about the difficulty in diagnosing the disorder continues to be appreciated.

In his 1909 article, "Chronic Infectious Endocarditis:", Osler reported ten cases he had accumulated between 1888 and 1908—all of whom had died [4]. He noted that "endocarditis with fever as its only symptom may be prolonged for weeks or months" and mentioned that some patients had had fever for 4–12 months. He clearly understood the infectious nature of the disease and commented that "it has long been recognized that malignant endocarditis is really an acute septicemia with localization in the endocardium." He then noted that, "as a rule the valves involved are already the seat of a sclerotic change" and that "the source of infection is only rarely to be determined." [4]

The diagnosis of IE in these ten cases was dependent on the presence of fever or chills, purpura, or "painful nodular erythema" (subsequently given the eponym of Osler's nodes—see Figure 6.1), mitral or aortic murmurs, and embolism (the latter appearing in four of the ten cases). Osler noted that the most suggestive features of IE were (a) a previous valve lesion, (b) embolic features, (c) skin lesions (see Figures 6.2 and 6.3), and (d) progressive cardiac changes. As a final note he added, "with...blood cultures one should now be able to determine the presence of septicemia" [4].

In Osler's 8th edition of his textbook, the disorder became classified as acute or chronic IE with the usual culprits being streptococci, staphylococci, pneumococci, and gonococci [5]. In this 1912 edition he highlighted the difficulty of diagnosing infectious IE and remarked that it "rests upon physical signs which are notoriously uncertain." In the 10th edition in 1926 he divided IE into acute, subacute, and chronic forms and emphasized that "blood cultures aid greatly and are necessary for an etiological diagnosis" [6]. By the 14th edition in 1942 he had identified "acute non-bacterial endocarditis," in addition to "acute," "subacute," and "chronic bacterial endocarditis" [7]. The diagnosis of bacterial IE was still dependent on a constellation of signs and symptoms: fever, sweats, weight loss, large- and small-vessel emboli, clubbing, leukocytosis, heart murmurs, splenomegaly, hematuria, and positive blood cultures.

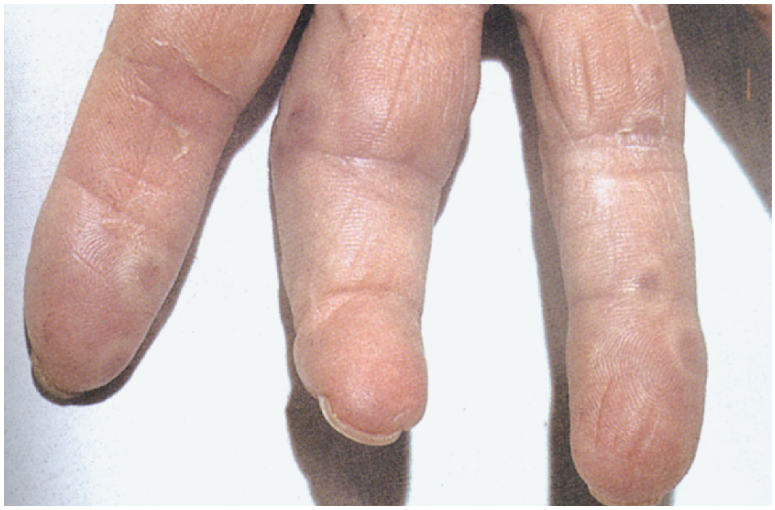

Figure 6.1. Osler's node—Violaceous, tender nodules on the volar surfaces of the fingers (associated with minute infective emboli or immune complex deposition). (*Color Atlas & Synopsis of Clinical Dermatology*, Fitzpatrick, TB, et al. McGraw-Hill, © 2001, with permission of the McGraw-Hill Companies).

Diagnostic Approach

History and Physical Examination

In the tradition of Osler, the diagnosis of IE is apparent when patients present with the classical clinical findings. Unfortunately, most patients do not present in this classic manner and the diagnosis of IE is often difficult to establish. The main components—history, physical exam, lab investigations, chest x-ray, electrocardiogram and blood cultures—are the mainstays of clinical diagnosis and have led to diagnostic algorithms proposed by Pelletier, von Reyn, and the group from Duke University.

On history-taking, careful attention should be paid to predisposing cardiac lesions (prosthetic heart valve, underlying valvular heart disease, intracardiac shunts, etc.). A history of previous coronary artery bypass surgery is not a risk factor for IE. A source for potential bacteremia should also be sought (recent dental surgery,

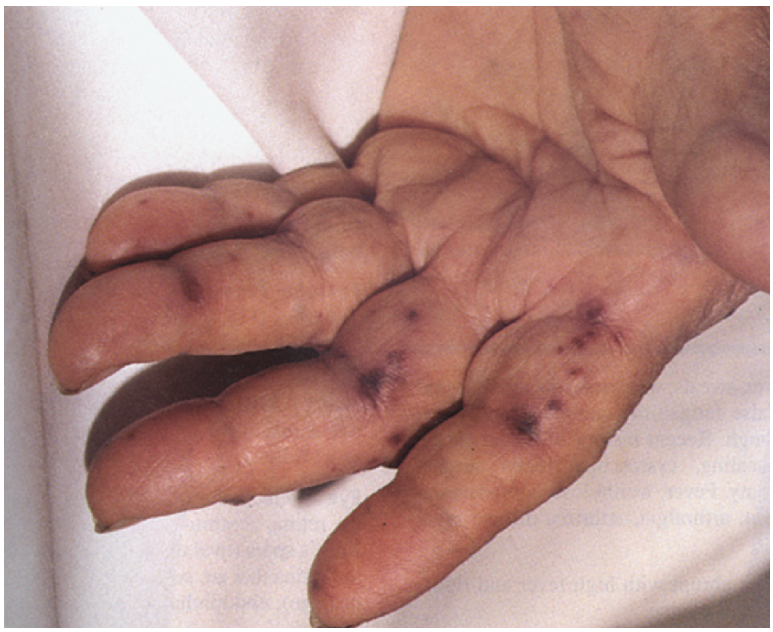

Figure 6.2. Janeway lesions—Hemorrhagic, infarcted macules and papules on the volar surfaces of the fingers (in a patient with *S. aureus* endocarditis). (*Color Atlas & Synopsis of Clinical Dermatology*, Fitzpatrick, TB, et al. McGraw-Hill, © 2001, with permission of the McGraw-Hill Companies).

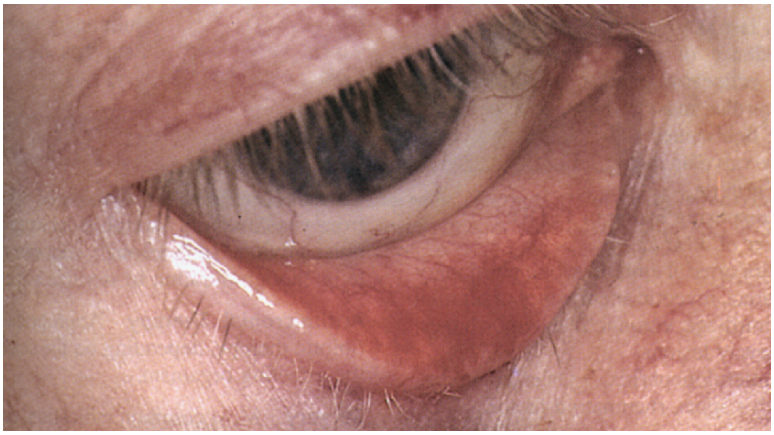

Figure 6.3. Submucosal hemorrhage of the lower eyelid in an elderly diabetic patient with enterococcal endocarditis. Splinter hemorrhages of the nail bed and Janeway lesions were also present. (*Color Atlas & Synopsis of Clinical Dermatology,* Fitzpatrick, TB, et al. McGraw-Hill, © 2001, with permission of the McGraw-Hill Companies).

intravenous drug use, indwelling intravascular catheter, etc.).

On physical examination, fever is almost always present. One should look for evidence of hemodynamic compromise (shock or congestive heart failure), new regurgitant murmur, and evidence of septic emboli. Emboli may involve the mucocutaneous surfaces, the skin of the extremities and/or other major organs such as the brain (producing stroke), the kidneys (producing renal dysfunction), the abdominal viscera (such as the spleen producing infarction and pain), the retina (Roth spots—exudative, hemorrhagic, edematous areas in the retina—see Figure 6.4), and in the setting of right-sided IE, the lungs (producing septic pulmonary infarcts). Cutaneous manifestations such as petechiae (usually on the extremities) are the most common manifestation but are nonspecific. Mucous membrane petechiae can be seen on the palate or conjunctivae (often seen with eversion of the eyelids). Janeway lesions (macular, blanching, nonpainful, erythematous lesions on the palms and soles—see Figures 6.2 and 6.3), Osler's nodes (painful, violaceous nodules found in the pulp of fingers and toes—see Figure 6.1), and Roth spots (Figure 6.4) are more specific for IE but are not diagnostic [8]. The relative frequencies of the various symptoms and signs are provided in Table 6.1 [8].

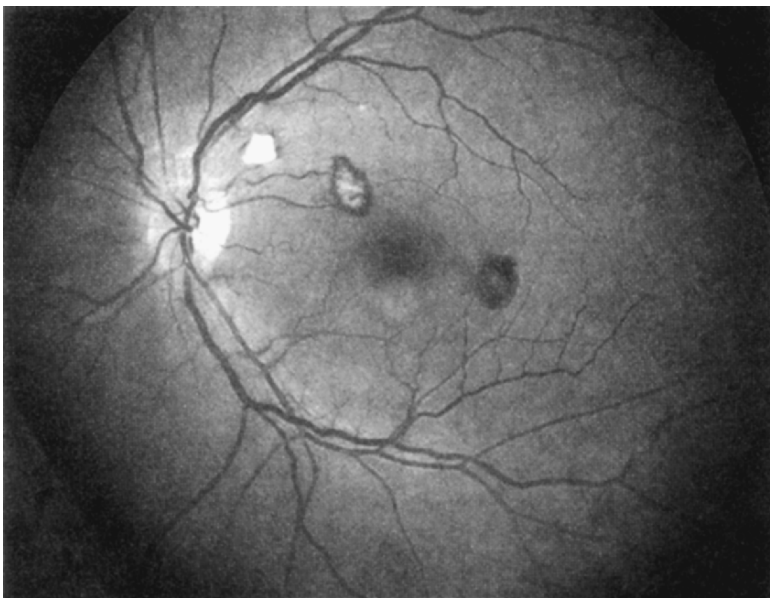

Figure 6.4. Roth spots—A 40-year-old woman with rheumatic valvular heart disease and Strept. viridans endocarditis. Three lesions, from left to right, demonstrate the evolution of a Roth spot (*Circulation* 1999;99:1271, with permission from Lippincott Williams Wilkins).

Table 6.1. Frequency of Symptoms and Signs in Infective Endocarditis

Most common—80-90% of patients Fever (80%) and heart murmur (90%)
Fairly common—30–50% of patients Chills (40%), weakness (40%), dyspnea (40%), embolic phenomenon (>50%), skin manifestations (20–50%), splenomegaly (20–60%), petechiae (20–40%), clubbing (15–50%)
Common—15–25% of patients Sweats (25%), anorexia (25%), weight loss (25%), malaise (25%), cough (25%), stroke (20%), nausea/ vomiting (20%), headache (20%), septic complications such as pneumonia/meningitis (20%), myalgia/arthalgias (15%), edema/chest pain (15%), abdominal pain (15%), splinter hemorrhages (15%), Osler's nodes (10–25%), signs of renal failure (10–25%)
Uncommon—≤ 10% of patients Janeway lesions (< 10%), delirium/coma (10–15%), hemoptysis (10%), back pain (10%), changing murmur (5–10%), new murmur (3–5%)

Source: Adapted from Mandel GL, Bennett JE, Dolan R. *Principles and Practice of Infectious Diseases*. 6th edition. Philadelphia: Elsevier Churchill Livingstone, 2005. With data from [24, 52–54].

Investigations

General Investigations

Laboratory investigations may reveal anemia, leukocytosis with a left shift, elevated erythrocyte sedimentation rate, and glomerulonephritis (with hematuria or active urinary sediment). Immunologic perturbation may also occur in subacute or chronic cases leading to high titers of rheumatoid factor.

The chest x-ray may show evidence of preexisting valvular disease (valvular calcification or cardiomegaly) or a complication arising from the infection (congestive heart failure or septic pulmonary emboli). Rarely, suppurative pericardial effusion from periannular abscess formation may produce a globular heart on x-ray.

A careful examination of the electrocardiogram should be made to rule out heart block (as this is one of the complications of IE as the infectious process involves the aortic valve annulus and membranous interventricular septum).

Bacteriologic Investigations

Three aerobic blood cultures (with a minimum of 10mL per bottle), from separate venipuncture sites, should be obtained over at least an hour before beginning therapy. Blood cultures inoculated with at least 5 mL of blood had a 92% detection rate for bacteremia compared to only 67% for bottles inoculated with less than 5 mL in one study [9]. The estimated yield from blood cultures increased approximately 3% per mL of blood cultured. Anaerobic cultures may be performed, but only rarely will the organism be anaerobic. If a patient has not been treated with antibiotics prior to obtaining the blood cultures there is minimal benefit beyond three cultures [10]. However, there may be additional diagnostic yield if antibiotics had been administered or if the initial blood cultures were negative.

Not all bacteremias imply the presence of IE. Certain species are more commonly associated with the disease. For example, bacteremias caused by group A or C streptococci are unlikely to be associated with IE. However, bacteremias caused by group G streptococci are often associated with IE [11]. Similarly, infection with *Enterococcus faecalis* is associated with IE more often than are other enterococcal species [12]. Most Gram-negative rods such as *Escherichia coli* and *Proteus* are unlikely to cause IE [13]. Organisms such as *Propionibacterium, Corynebacterium, Bacillus*, and coagulase-negative staphylococci recovered from blood cultures likely represent skin contamination and are unlikely to cause IE. In such cases, blood cultures should be repeated (using sterile technique) to ensure that the organisms were contaminants.

Special mention should be made about *Staphylococcus aureus*. *Staphylococcus aureus* bacteremia, regardless of source, carries a high risk of IE. All patients with *S. aureus* bacteremia should be clinically evaluated for IE.

There are a small percentage of number of patients with a high clinical suspicion for IE who do not have positive blood cultures. The most common reason is partial sterilization due to prior administration of antibiotic therapy. Another possible reason for negative cultures is IE due to atypical organisms which are more

difficult to isolate in culture such as *Coxiella burnetii* (Q fever), *Tropheryma whipplei, Brucella, Mycoplasma, Chlamydia, Histoplasma, Legionella* and *Bartonella*, and HACEK organisms (*Haemophilus aphrophilus, Actinobacillus actinomycetemcomitan, Cardiobacterium homini, Eikenella corroden, and Kingella kingae*). Blood cultures may need to be incubated longer (up to 21 days) for some of these organisms (e.g., HACEK group). Other tests, such as polymerase chain reaction on valve tissue, may need to be performed for *C. burnetii* and *Bartonella*. In other instances special media may need to be used. Antibody titers for *C. burnetti* can also be helpful. Local microbiology expertise should be sought when an atypical organism is suspected to be the cause of IE.

Echocardiographic Investigations

Prior to the availability of echocardiography the only way to visualize a vegetation was by surgery or autopsy. The development of echocardiography and the identification of criteria for the diagnosis of IE have significantly improved our ability to diagnose and treat this disease. Echocardiography has become one of the major diagnostic procedures available today.

The echocardiographic hallmark of IE is an endocardial mass lesion usually referred to as a "vegetation" (as mentioned earlier). This is usually defined as an oscillating mass attached to an endocardial surface, such as a valve or supporting structure, or a structure in the path of regurgitant jets [13]. Additionally, echolucency, suggesting the presence of abscess formation, and doppler evidence of valvular dysfunction should be sought. Further details on the diagnostic and prognostic information provided by echocardiography are provided in the next chapter of this book.

Both transthoracic echocardiography (TTE) and transesophageal echocardiography (TEE) have proven to be extremely useful in the diagnosis of IE. Transthoracic echocardiography is generally believed to have a lower sensitivity than TEE in diagnosing IE. A negative TTE study (i.e., no vegetation) does not preclude the diagnosis of IE, but the finding of normal valves (both morphologically and functionally) substantially reduces its probability. In one study, 96% of patients with normal valves on TTE also had a normal examination by TEE [14]. In addition, TTE has a specificity approaching 100%, and has therefore very few false-positive results [15].

TEE, although more invasive, is more sensitive and has a better spatial resolution than TTE for the detection of IE (94–100% sensitivity for TEE vs. 44–63% for TTE) [15,16]. TEE is especially useful for the detection of smaller vegetations, the diagnosis of prosthetic valve endocarditis, the detection of paravalvular abscess formation (87% sensitivity for valve abscess with TEE versus 28% for TTE) [17], and for the assessment of embolic risk [18]. The negative predictive value of TEE is nearly 100% for patients with native valves, but patients with prosthetic valves may have a negative TEE and still have IE [19]. In the latter patients, clinical assessment is especially important.

Roe et al. compared TTE and TEE in 114 cases of suspected IE assessed retrospectively over a six-year period [20]. Concordant results occurred in 55% of cases. A change in diagnostic category occurred in 25% of cases when the results of TEE were added to those of TTE (11% for patients with native valves and 34% for those with prosthetic valves). Twenty-two patients were reclassified as having definite IE rather than possible based upon TEE findings. Nineteen of these patients had an intermediate probability of IE, positive blood cultures and a negative or inconclusive TTE.

More recently, the advent of high-frame-rate imaging particularly with harmonic imaging has led to improvements in transthoracic imaging quality. Two studies have evaluated the role of modern day TTE in the diagnosis of IE. Reynolds et al. performed a retrospective review of 55 patients with proven native valve IE at a single center between 1998 and 2001 [21]. The studies were selected and interpreted blindly by an experienced echocardiographer. Despite good or excellent TTE quality, with the addition of second harmonic imaging, the sensitivity of TTE for the detection of native valve vegetation was only 55%. There were five missed vegetations in cases in which the corresponding TEE images revealed masses greater than 10 mm in size.

Aminbakhsh et al., at our institution, examined the prospective role of TTE and TEE in consecutive patients with an intermediate clinical likelihood of native valve IE [22]. We found that TTE was able to make a firm diagnosis in 25 of 36 (70%) of patients. There was 100% concordance with TEE in these patients (11 positive, 14 negative). Indeterminate TTE results occurred

in the remaining 11 patients (30%) due to limited image quality or complex underlying native valve disease. TEE results were clearly positive in eight and clearly negative in two cases. The lone remaining case remained equivocal despite TEE. Thus, the value of TEE in patients with suspected native valve IE and intermediate clinical likelihood may be limited to those with recognized suboptimal TTE images or underlying complex valvular abnormality. This is consistent with the findings of Humpl et al., who showed that there was excellent concordance between TTE and TEE in children with suspected IE in whom the potential adverse effects of sedation and esophageal intubation associated with TEE could be avoided [23].

Table 6.2. Diagnostic Criteria by Pelletier and Petersdorf

Definite: Histologic evidence of endocarditis on autopsy or surgery
Probable
Uniformly positive blood cultures AND all of—
Underlying valve disease
Evidence of skin or visceral emboli
OR
Negative blood cultures AND all of—
Fever > 38 °C
New regurgitant murmur
Evidence of skin or visceral emboli
Possible
Uniformly positive blood cultures AND—
Underlying valve disease OR evidence of skin or visceral emboli
OR
Negative blood cultures AND all of—
Fever > 38 °C
Underlying valve disease
Evidence of skin or visceral emboli

Source: Adapted from [24].

Case Definitions and Validation Studies

Case Definitions

A series of diagnostic criteria have been developed by Pelletier and Petersdorf (1977), von Reyn (1981), and the Duke group (1994). The Pelletier and Petersdorf criteria required pathological confirmation of the diagnosis of IE and thus, were not very useful for prospective clinical diagnosis [24]. Von Reyn and colleagues improved the case definitions to make them more clinically relevant [25]. In 1994, investigators from Duke University modified the von Reyn criteria to include echocardiographic findings in the diagnosis of IE [13]. In addition, they expanded the category of predisposing heart conditions to include intravenous drug use.

(i) Pelletier and Petersdorf criteria (see Table 6.2): Their classification scheme consisted of three diagnostic categories: definite, probable, and possible. These diagnostic criteria were quite specific but were not very sensitive. Many patients with clinically suspected IE failed to meet diagnostic criteria.

(ii) von Reyn criteria (see Table 6.3): The von Reyn system was designed to make the diagnostic criteria more clinically applicable. The classification scheme consisted of four categories: definite, probable, possible, and rejected. Pathological confirmation of vegetations, or of an abscess, was still required to define a case as definite. Thus many cases were classified as probable or possible since many patients did not have pathological confirmation (i.e., by surgery or autopsy) of their disorder. Although the von Reyn criteria lacked prospective validation, the specificity of their classification system was superior to that of Pelletier and Petersdorf.

(iii) Duke criteria: Investigators at Duke University further refined the diagnostic criteria to make the case definitions more clinically applicable to patients suspected of having acute IE. This group has since published modifications of their original criteria after the validation studies (see below) were completed [26]. The new criteria include the addition of the presence of *Coxiella burnetii* as a major criterion and the elimination of echocardiographic minor criterion. Possible IE has been redefined to include one major plus one minor criterion or three minor criteria (see Table 6.4). In addition, the role for transesophageal echocardiography for the diagnosis of IE has been made more explicit to include patients with prosthetic valves and those suspected of having complicated IE (such as a paravalvular abscess) [26].

Validation Studies

After the Duke criteria were published, a number of studies appeared that compared the von Reyn criteria to the Duke criteria for the diagnosis of IE [13,27–29]. These studies utilized pathologically confirmed cases of IE and retrospectively assessed the ability of the von Reyn and the Duke criteria to categorize the probability of IE. In general, the Duke criteria

Table 6.3. von Reyn Criteria for Diagnosis of Infective Endocarditis

Definite
Direct histologic evidence of infective endocarditis from surgery or autopsy
OR
Bacteriology (Gram stain or culture) of valvular vegetation or peripheral embolus
Probable
Persistently positive blood cultures plus ONE of the following:
New regurgitant murmur
Predisposing heart disease AND vascular phenomena
OR
Negative or intermittently positive blood culture plus ALL of the following:
Fever
New regurgitant murmur
Vascular phenomena (petechiae, splinter hemorrhages, conjunctival hemorrhages, Roth spots, Osler's nodes, Janeway lesions, aseptic meningitis, glomerulonephritis, peripheral emboli, central nervous system emboli, coronary emboli, peripheral emboli)
Possible
Persistently positive blood culture plus ONE of the following:
Predisposing heart disease (definite valvular or congenital disease or cardiac Prosthesis excluding permanent pacemakers)
Vascular phenomena
OR
Negative or intermittently positive blood culture plus ALL of the following:
Fever
Predisposing heart disease
Vascular phenomena
Rejected
Endocarditis unlikely, alternative diagnosis generally apparent
Endocarditis likely, empiric antibiotic therapy warranted
Culture negative endocarditis diagnosed clinically but excluded by postmortem

Source: Adapted from [25].

were more likely to have diagnosed cases as definite IE (80–100%) and would not have rejected any of the cases of proven endocarditis. On the other hand, the von Reyn criteria defined 50% of these cases as probable. More importantly, the von Reyn criteria would have rejected 20–50% of the cases proven pathologically to be IE. The Duke criteria also classified 75% of confirmed prosthetic valve endocarditis (PVE) cases as definite and rejected no cases of PVE. The von Reyn criteria, however, rejected 20% of these confirmed cases of PVE [30]. Dodds et al. assessed the clinical cases rejected by the Duke criteria and determined the negative predictive value to be at least 92% [31]. Therefore, at the present time, the Duke criteria are the standard diagnostic criteria for patients with suspected IE.

Appropriate Use of Echo and Suggested Approach to a Patient Suspected of Having Endocarditis

The meaning and significance of the term "clinically suspected IE" will vary between observers. The range may include patients with unexplained isolated fever as well as those with the classic findings of fever, new regurgitant murmur, embolic phenomenon, and persistent bacteremia. Jassal et al., at our institution, found significant variation between the assessment of probability of IE between the attending team and the research team [32]. The latter employed a standardized scoring system to determine pre-test likelihood of IE. The determination of probability or likelihood of disease may have a bearing on the selection and timing of echocardioaphic evaluation [33]. Various studies have demonstrated no to very minimal utility of echocardiography in patients with low pretest likelihood of the disease [32–34].

In practice, we propose that the selection and timing of echocardiographic evaluation (TTE, TEE, both) be based on an assessment of the clinical likelihood of IE as well as the clinical risk of an adverse event (see Figure 6.5) [20,35]. Although systematic prospective evaluation of the utility of echocardiography in different patient subsets has not been well defined, we operationally define high clinical risk as any one of a number of high-risk features which include any of the following:

Table 6.4. Modified Duke Criteria for Diagnosis of Infective Endocarditis

Major Criteria
- Positive blood cultures for infective endocarditis
  - In the absence of a primary focus, positive cultures from two separate blood cultures of one of the following typical organism:
    - *Streptococci viridans*
    - *Streptococcus bovis*
    - HACEK group (*Haemophilus* species, *Actinobacillus actinomycetes comitants*, *Cardiobacterium hominis, Eikenlla* species, *Kingella kingae*)
    - Community-acquired *Staphylococcus aureus* or entercocci

OR
- Persistently positive blood cultures of a microorganism consistent with IE

OR
- Single blood culture for *Coxiella burnetii* or antiphase I IgG antibody titre > 1:800.

Evidence of endocardial involvement
- New valvular regurgitation

OR
- Positive echocardiogram (oscillating intracardiac mass in the absence of an alternative anatomic explanation OR abscess OR new partial dehiscence of prosthetic valve)

Minor criteria
- Predisposing heart condition OR intravenous drug use
- Fever (at least 38.0 °C)
- Vascular phenomena (major arterial emboli, septic pulmonary infarcts, mycotic aneurysm, intracranial hemorrhage, conjunctival hemorrhage, Janeway lesions)
- Immunologic phenomena (glomerulonephritis, Osler's nodes, Roth spots, rheumatoid factor)
- Microbiologic evidence of positive blood culture not meeting major criterion but excluding single positive culture for coagulase negative *Staphylococci* and organisms that do not cause endocarditis OR serologic evidence of active infection with organism consistent with IE.

Definite
- Two major criteria

OR
- One major and three minor criteria

OR
- Five minor criteria

OR
- Microorganism demonstrated by culture or histology of a vegetation, embolized vegetation or in an intracardiac abscess

OR
- Histologic evidence of active endocarditis (vegetation or intracardiac abscess)

Possible
- One major and one minor critieria

OR
- Three minor criteria

Rejected
- Firm alternative diagnosis

OR
- Resolution of manifestations of endocarditis with 4 or less days of antibiotics

OR
- No pathologic evidence of infective endocarditis at surgery or autopsy after 4 or less days of antibiotics

OR
- Does not meet criteria for possible infective endocarditis (above)

Source: Adapted from [26].

1) hemodynamic compromise from suspected significant valvular abnormality (e.g., shock, CHF, clinical evidence of prosthetic valve dysfunction)
2) overwhelming infection (persistent fever despite treatment, new heart block or suppurative pericarditis suggesting periannular abscess, persistent *S. aureus* bacteremia)
3) underlying valvular abnormality known to be poorly responsive to medical treatment (e.g., prosthetic valve, AV shunt)
4) multiple embolic phenomenon.

The patients with evidence of high clinical risk features deserve prompt echocardiographic evaluation that may lead to important and

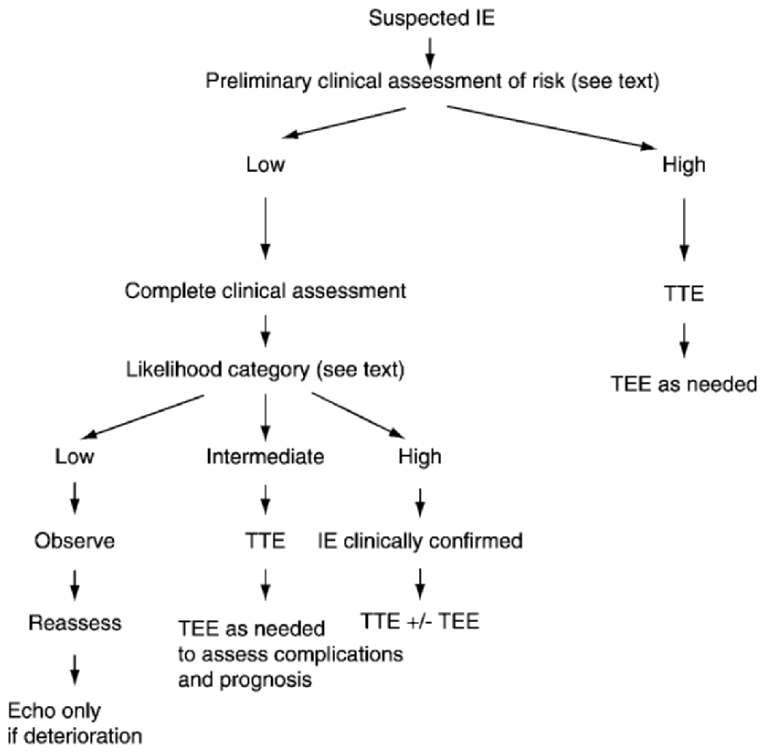

Figure 6.5. Suggested diagnostic algorithm for a patient with suspected infective endocarditis.

timely medical or surgical intervention. Although we still recommend baseline TTE in all patients, there should be a very low threshold to proceed to TEE in this high-risk group, especially in the setting of persistent *S. aureus* bacteremia or suspected prosthetic valve endocarditis. These special circumstances will be discussed later in this chapter.

In patients with more stable status (low clinical risk), we recommend waiting for the results of initial blood culture and full evaluation of the clinical criteria before embarking on the use of echocardiography. Often, the results of blood cultures and other tests are available within the first few days. This will allow stratification of patients into high-likelihood (confirmed diagnosis), intermediate-likelihood, and low-likelihood groups prior to echocardiography [32]. It must be remembered that any low-risk patient may deteriorate to high-risk over time; serial careful clinical assessment is therefore required. In addition, although the diagnostic yield of echocardiography is generally felt to be very low in patients with objectively derived low clinical likelihood, diagnostic tests may still be requested on occasion by physicians for the purpose of reassurance to themselves or their patients [32]. A diagnostic algorithm is presented (see flow chart, Figure 6.5).

Low-likelihood patients (no major Duke criteria, 0–2 minor criteria) should be observed only [32]. In those patients who are found to have an alternative source of infection, treatment should be directed to that source and echocardiography (TTE and TEE) safely deferred unless there is a clinical change [33,34].

A high-likelihood patient—based upon the constellation of clinical and bacteriologic criteria (two major Duke criteria or 1 major and 3 minor)—should be treated as a confirmed case of IE with a prolonged course of antibiotics [32]. Echocardiography (TTE) should be performed promptly to help determine prognostic information that may help with timing of surgery. Routine TEE in this population remains unevaluated, and should be at the discretion of the clinical team in consultation with the echocardiologist.

The intermediate likelihood subgroup where the diagnosis of IE is suspected but not confirmed on clinical and bacteriologic grounds is a sample in whom the addition of a positive

Table 6.5. High-Risk Features for Presence of Endocarditis in Patients with *S. aureus* Bacteremia

Community-acquired infection
Absence of apparent source of infection
Presence of metastatic infectious foci
Presence of hematuria
Underlying native valvular disease or known prosthetic valves
Previous endocarditis
Intravenous drug use
Persistent fever at 72 hours.
Persistent bacteremia, usually 3 days after initiation of therapy

echo finding would greatly assist in establishing a firm diagnosis of IE. We define intermediate likelihood as one major criterion or three minor criteria prior to echocardiography [32]. There is some controversy in determining the best initial echocardiographic strategy in this population. The American College of Cardiology/American Heart Association guidelines recommend that such patients be evaluated initially with TTE [36]. In those who have indeterminate studies, TEE should be pursued. This is supported by our experience [22]. Heidenreich et al. suggest initial use of TEE for the population with pretest likelihood between 4% and 60% [37]. In practice, the choice of modality depends on the anticipated image quality in the individual patient and the practical setup of the individual laboratory. TEE requires additional personnel and training and has small but finite risk of procedural complication as well as failed esophageal intubation [38]. Further larger prospective comparative evaluations using modern-day TTE equipment are required [21,22]. In the intermediate likelihood subgroup, a negative TTE or TEE does not necessarily exclude the diagnosis of IE [21,35]. A subset of these patients with negative echo findings (TTE, TEE) may still manifest positive findings with time [19]. Occasionally, a firm alternative diagnosis is subsequently discovered by other means [35].

Special Populations and Endocarditis

There are a number of patient populations that deserve special mention in regard to the diagnosis of IE. These are patients with prosthetic heart valves, patients with *S. aureus* bacteremia, and patients with HIV. Diagnostic issues related to these three groups will be covered below.

Prosthetic Valve Endocarditis

More than 60,000 prosthetic heart valves are implanted in United States annually. Prosthetic valve endocarditis is classified as early (up to 60 days after valve replacement), intermediate (2 months to 12 months), and late (> 12 months). IE is a rare complication occurring in 0.5% to 1% of cases per year, and its late occurrence is even less common [39]. In patients with prosthetic valves and nosocomial bacteremia, 43% may have IE [40]. This risk is similar for mechanical and bioprosthetic valves. In mechanical valves, infection is usually located at sewing ring, in bioprosthetic valves it can also involve the cusps, while in composite graft it may even affect distal anastomosis or coronary reimplantation site [41].

El-Ahdab et al. evaluated the incidence and outcome of IE in patients with prosthetic valves with *S. aureus* bacteremia [42]. The overall rate of definite IE was 51%. The incidence was not different between mechanical versus bioprosthetic valves, mitral versus aortic prostheses, and early (< 12 months after prosthetic valve implantation) versus late (> 12 months after implantation) presentation. There was a higher incidence of definite endocarditis in patients with persistent fever and persistent bacteremia.

In prosthetic valves, the sensitivity of TTE is only 17% to 36% and for TEE is 82% to 96% [40]. TEE should be the test of choice in suspected prosthetic valve endocarditis, especially in the mitral position, because of its increased sensitivity for the detection of complications (abscesses, paravalvular leaks, dehiscence of the valves) and because of the limitation of TTE in the diagnosis (reverberations artifact from metallic structures). TTE should be repeated in high-risk patients for IE (persistent fever, persistent bacteremia, unknown source of infection), if the initial study is negative [42].

Staphylococcus aureus Bacteremia and Endocarditis

Staphylococcus aureus is fast becoming a leading cause of bacteremia, both as a hospital-acquired infection as well as a community-acquired infection. It is currently the second most common blood culture isolate. In the recent era, the number of cases of *S. aureus* bacteremia due to methicillin-resistant *S. aureus* (MRSA) has been

steadily increasing [43]. Although not all cases of *S. aureus* bacteremia imply the diagnosis of IE, the incidence of proven *S. aureus* IE is also increasing and represents the most common bacteriologic cause of native valve IE amongst patients with intravenous drug use and second leading cause of IE overall.

In the setting of the *S. aureus* bacteremia, it is critical to consider the diagnosis of IE because of the therapeutic and prognostic implications. The reported prevalence of IE varies in different studies, depending on the population studied and the likelihood of IE. The incidence of IE among prospectively identified adults in the general population with *S aureus* bacteremia is ~12–25%, depending on the selection criteria [44,45]. In a multicenter trial, Chang et al. found that in presence of *S. aureus* bacteremia, the prevalence of endocarditis was 21% in community-acquired infections, 35% in intravenous drug users, 5% in hospital acquired infections, and 12% in the hemodialysis population [43]. Sixty-nine percent of cases were secondary to methicillin-susceptible *S. aureus* (MSSA) and 31% were secondary to MRSA. Methicillin-susceptible *S. aureus* was more common in community-acquired infections, in patients with intravenous drug use, and in patients with previous endocarditis. MRSA was more likely to be hospital-acquired and to be found in patients on hemodialysis. MRSA was also more likely in patients with persistent bacteremia and prolonged fevers.

Certain features, such as those listed in Table 6.4, have been noted to be associated with higher risk for the presence of IE and presence of these features should prompt echocardiography.

All patients with *S. aureus* bacteremia should have repeat blood cultures performed three days after initiating antibiotics [44]. If persistent bacteremia is noted, then endocarditis should be highly suspected; and echocardiography, if needed TEE, should be strongly considered. Also, investigation for metastatic foci of infection should also be performed. Usually echocardiography is not recommended in patients with nosocomial *S. aureus* bacteremia and low-risk features for endocarditis (absence of factors identified in Table 6.4).

Recently performed studies evaluating the role of transesophageal echocardiography in *S. aureus* bacteremia have raised some concerns [45,46]. These studies found that neither assessment of clinical features nor transthoracic echocardiography was able to predict the risk of IE. In another study, Roder et al. identified a significant number of patients with IE at autopsy when it was not suspected clinically in patients with *S. aureus* bacteremia [47]. Also, the low risk of endocarditis in a patient with nosocomial infection as well as with an intravascular catheter has also been questioned in recent studies. Despite low clinical likelihood, Thangaroopan found TEE evidence of vegetations in 2 of 87 in his series, with both patients displaying the triad of *S. aureus* bacteremia, immunosoppression, and persistent fever [33]. The cost-effectiveness of TEE to determine the duration of antibiotic therapy in patients with clinically uncomplicated intravascular catheter associated *S. aureus* bacteremia has also been established [48]. These studies suggest a low threshold for consideration for TEE for IE with *S. aureus* bacteremia.

In spite of the above studies, the role of empiric initial TEE in risk stratification in every patient with persistent *S. aureus* bacteremia may be limited by factors including cost, limited resources because of the requirement of specialized physicians and equipment, time, and occasionally the presence of other indications for prolonged antibiotic therapy. Also, patients with endocarditis identified only by TEE compared to TTE generally have a better prognosis and outcome [49], likely because of the smaller size of the vegetation and fewer complications. Also the question has been raised whether endocarditis identified by TEE only may represent early diagnosis, which may require only a short course of antibiotics, as well as the possibility of a false-positive result when small masses are identified on valves, leading to overtreatment [45].

HIV and Endocarditis

Seropositivity for human immunodeficiency virus (HIV), per se, does not appear to increase the risk of IE. The incidence of IE is rare in HIV-positive patients without intravenous drug abuse (IVDA). Abraham et al. showed that in HIV-positive patients, the identification of bacteremia is associated with less IE risk than in HIV-negative patients with bacteremia, even with typical IE organisms [50].

The prevalence of IE varies from 6.3% to 34% in HIV patients actively using intravenous drugs, and is independent of treatment with

anti-HIV medications [51]. Overall, it seems that the incidence of IE in HIV-positive patients has decreased with modern HIV therapy [51].

The clinical presentation IE in HIV patients is similar to those without HIV. *Staphylococcus aureus* is the most frequent organism and accounts for approximately 70% of cases [51]. HIV-positive patients with IE tend to be younger and less likely to have underlying predisposing cardiac disease as compared to HIV-negative patients with endocarditis [50]. HIV-positive intravenous drug abusers (IVDAs) have a higher rate of right-sided involvement and of *S. aureus* infection than HIV-negative IVDAs. Mortality rates are similar in both groups, indicating that the presence of HIV does not affect mortality unless CD4 counts are low (< 200/μL). With acquired immunodeficiency syndrome (AIDS), there is a 30% higher mortality rate with IE than non-AIDS HIV patients. The survival rate of HIV patients with IE is similar to patients that found in patients without HIV (85% vs. 93%) [51].

Nonbacterial thrombotic endocarditis, also known as marantic endocarditis, occurs in 3–5% of AIDS patients, especially in patients with HIV wasting syndrome. It predominantly involves left-sided valves with friable endocardial vegetations, consisting of platelets within a fibrin mesh with few inflammatory cells. The lesions are often clinically silent [51].

Case Study—Follow-Up

Laboratory data revealed leukocytosis, normal hematocrit, and mildly elevated liver enzymes. Urinalysis showed 6–10 RBCs per high-power field and no active urinary sediment. Three of six blood cultures grew Gram-positive cocci. The organism was difficult to identify and the culture was referred to the Federal Reference Laboratory for characterization.

The chest x-ray was normal. The electrocardiogram revealed sinus rhythm with a normal PR interval. A CT scan of the abdomen revealed splenic infarcts and possible renal infarcts. TTE revealed mechanical aortic valve stenosis a mean aortic systolic gradient was 46 mm Hg and the calculated valve area was 0.9 cm^2. The left ventricular ejection fraction was normal at 67%. A large mass was suspected on the mechanical aortic valve and was confirmed by TEE, which revealed a mobile mass measuring 4 x 5 mm consistent with a vegetation. There was no evidence of perianular abscess formation.

The patient was treated with vancomycin for six weeks and gentamicin for two weeks. A cardiac surgical consultant recommended completion of antiobiotic therapy and subsequent replacement of the aortic valve prosthesis.

Conclusion

Infective endocarditis can be a difficult diagnosis to make. However, a thorough history, careful physical exam, and application of validated diagnostic criteria can improve diagnostic accuracy. Echocardiography (TTE and TEE) is an extremely useful tool in the diagnosis and prognosis of IE, but it needs to be used appropriately. In general, TEE is more sensitive and specific compare to TTE but is also more invasive and associated with a small but definite complication risk. Patient selection for and timing of echocardiography should be based on stratifying patients into clinical risk categories (high vs. low) and assessing the likelihood of IE (high, intermediate, and low). Patients with high clinical risk should undergo echo on a high-priority basis. Patients with low clinical risk but a high likelihood of IE should be empirically treated and an echo performed not for diagnostic purposes but to guide prognosis and treatment. Patients with low clinical risk and low clinical likelihood need not routinely undergo echocardiography, whereas those with low clinical risk and intermediate clinical likelihood should undergo echocardiography to help clarify the diagnosis. We should be particularly vigilant about the diagnosis of IE in patients with persistent *S. aureus* bacteremia and patients with prosthetic heart valves. In these patients, we recommend a low threshold for echocardiography (TTE and TEE). TEE has proven to be very useful and should be performed in the majority of these patients.

Key Points

1. Perform a thorough history, physical exam, routine investigations (including blood cultures), and apply the Duke criteria to establish the diagnosis of IE.
2. Certain organisms can be very difficult to culture and may give rise to "culture-negative"

IE. If these organisms are suspected, discussion and consultation with the microbiology laboratory is recommended.

3. When appropriately used, echocardiography (TTE and TEE) is extremely useful in defining both the diagnosis and prognosis of IE.
4. Categorization of patients into strata of clinical probability of disease and into strata of clinical risk for morbidity and mortality may help to determine the most appropriate timing of the echocardiographic examination and the choice of the initial echocardiographic modality.
5. In patients with persistent *S. aureus* bacteremia or patients with prosthetic heart valves, we recommend a low threshold for echocardiography and a reduced threshold for the performance of TEE, in particular.

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7

Role of Transthoracic and Transesophageal Echocardiography in the Management of Endocarditis

Chris Johnson and Kwan-Leung Chan

Case Study

An 80-year-old woman with a bioprosthetic aortic valve was hospitalized for chest pain and heart failure. Fever was documented during the hospitalization and blood cultures grew *Staphylococcus epidermidis*. She underwent transthoracic echocardiography (TTE) which showed that the aortic prosthetic valve was functionally normal with no stenosis or regurgitation, but the prosthetic leaflets were not well seen. Transesophageal echocardiography (TEE) was subsequently performed, showing nodular thickening of the aortic prosthetic leaflets but no valvular or perivalvular regurgitation. There was no evidence of vegetation or abscess.

She was continued on antibiotic treatment for infective endocarditis (IE). Ten days later, she developed cardiac arrest and could not be successfully resuscitated. Autopsy showed severe coronary artery disease, and a vegetation of 1 cm in diameter on one of the prosthetic aortic leaflets.

Although TEE has a high sensitivity and specificity in the detection of vegetation, false-negative studies such as this case do occur. A negative TEE study reduces the likelihood, but does not exclude the diagnosis of, IE. When there is a high clinical suspicion for IE, repeat TEE should be performed to look for evolving echocardiographic findings.

Introduction

Infective endocarditis has protean manifestations and clinical diagnosis is frequently difficult, leading to a delay in making the diagnosis. As vegetation is the hallmark of IE, prompt diagnosis can be facilitated if there is a reliable noninvasive means to detect vegetation.

Echocardiography has been intimately involved in the detection of vegetation since its introduction into clinical practice. Technological advances in the last three decades have dramatically improved the ability of echocardiography to detect vegetation, valvular damage, and perivalvular complications, such that echocardiographic findings are now an accepted diagnostic criterion for IE. Furthermore, echocardiography can provide important prognostic information, especially in complex cases such as patients with virulent organisms and patients with persistent fever or bacteremia despite treatment. Echocardiography may be overused in patients with low likelihood of IE, but it is clearly indicated when the findings have a direct impact on diagnosis or management (Table 7.1).

Native Valve Endocarditis

Detection of Vegetation

Vegetation is the hallmark of the disease and most frequently is attached to the upstream side of the cardiac valves. Unusual locations such as

Table 7.1. Indications for Echocardiography in Infective Endocarditis

Diagnosis in patients with medium to high likelihood of endocarditis
Strong suspicion for culture negative endocarditis
Persistent bacteremia with virulent organism and no known cause
High-risk patients including patients with prior endocarditis, congenital heart disease or prosthetic heart valve
Prognosis and management issues
Identify underlying valvular and non-valvular lesions and associated abnormalities
Assess hemodynamic severity and ventricular function
Reassessment in complicated cases including clinical change and symptomatic deterioration

the myocardium or aorta have been recognized. Left atrial mural vegetations have been found at the site of impingement of a jet of mitral regurgitation due to infectious endocarditis. The finding of a mural vegetation on the left atrial wall should prompt a careful search for evidence of mitral valve endocarditis and mitral regurgitation. The ability of ultrasound to produce images of the heart offers clinicians the opportunity to identify valvular vegetations, which previously required direct inspection at surgery or autopsy.

Transthoracic Echo

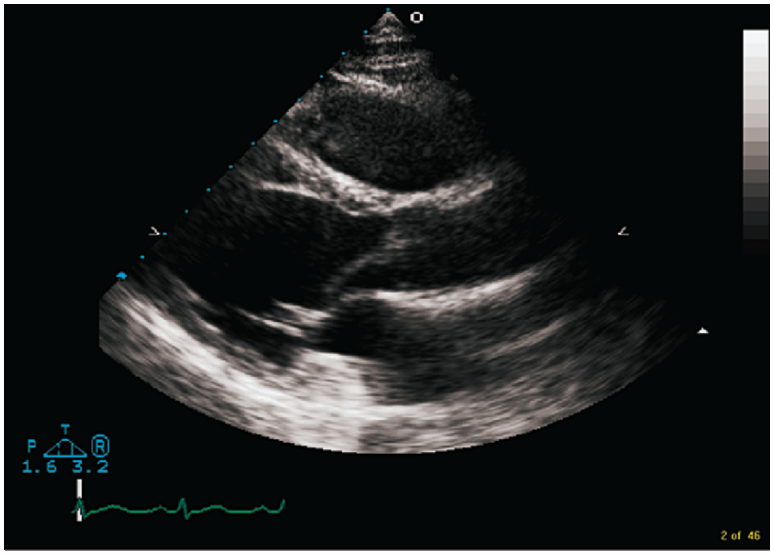
The first series describing vegetations detected by echocardiography with pathological correlation was in 1973 using M-mode transthoracic echocardiography (TTE). The M-mode criteria for diagnosis of a valvular vegetation are a nonuniform, shaggy echogenic mass attached to a valve leaflet but not interfering with its motion [1–4]. When compared to autopsy or surgical findings, this definition of vegetation is specific but insensitive [3]. False-positive findings include old vegetations from remote episodes of endocarditis, thickened leaflets of myxomatous mitral valves, sclerotic aortic valves and mitral valve fluttering related to aortic insufficiency [3]. Important prognostic information can be derived from findings such as ruptured mitral valve chordae, torn and flail aortic cusps, and premature closure of the mitral valve due to severe aortic insufficiency, all of which may require surgical intervention [5].

Two-dimensional echocardiography provides spatial orientation superior to M-mode and has rapidly replaced M-mode in the detection of vegetation, which is defined as an irregularly shaped echogenic mass adherent to valves, endothelial surfaces, or intracardiac prosthetic devices often with high-frequency motion independent of the underlying cardiac structure. Usually it can be imaged throughout the cardiac cycle in multiple views [6–8]. Vegetations can be characterized by morphologic features including size, location, number, shape, mobility, and consistency (Figure 7.1) [8]. The size of a vegetation that can be detected by TTE depends on the image quality. With fundamental imaging, 90% of vegetations diagnosed on TTE are greater than 5 mm in maximum dimension [8]. Harmonic imaging may be more able to detect smaller vegetations particularly in patients with suboptimal images [9]. However, TTE (with and without harmonics) underestimates vegetation size by up to 50% compared to TEE [9], and TTE is not sensitive enough to detect small vegetations particularly in patients with preexisting valvular abnormalities (Table 7.2) [10,11]. The causes of false-negative and false-positive findings for vegetations are listed in Table 7.3.

The overall sensitivity and specificity of TTE for detecting valvular vegetations are 48% and 94%, respectively (Table 7.4). These are average values from a number of series published over the past two decades using a variety of ultrasound machines in patients with varying pre-test likelihoods of endocarditis [10–15]. For many series, the pre-test likelihood of endocarditis was high, which may contribute to an overestimation of the specificity of transthoracic echo findings for vegetations.

Transesophageal Echo

Transesophageal echo (TEE) involves the insertion of an ultrasound transducer mounted on a gastroscope into the esophagus and stomach to image the heart. The close proximity of the heart to the esophagus and the lack of intervening structures such as chest wall and lungs ensure higher image quality using TEE compared to TTE. Transesophageal echo has higher sensitivity and specificity in the detection of vegetations in patients with suspected endocarditis (Table 7.5) [10,12–15]. The superior image quality of TEE permits the visualization of small vegetations



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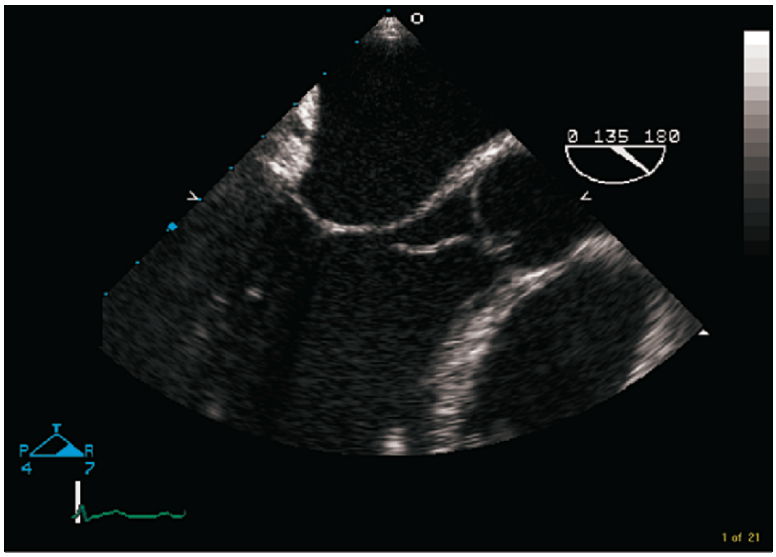

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Figure 7.1. A long filamentous vegetation attaching to the aortic valve and protruding into the left ventricular outflow tract during diastole. This is detected by both transthoracic (**A**) and transesophageal (**B**) echocardiography.

Table 7.2. Relationship Between Vegetation Size and Sensitivity of Transthoracic Echocardiography*

Vegetation size (mm)	Sensitivity (%)
<5	0–25
5–10	50–69
>10	84–100

*Based on studies by Erbel et al., 1988, and Reynolds et al., 2003, with transesophageal echocardiographic findings used as the reference standard.

(2–5 mm) on native heart valves that are commonly missed by TTE (Figure 7.2) [10,11]. Despite the superior image quality, TEE faces similar limitations in terms of false-positive and false-negative studies (Table 7.3). Libman–Sacks endocarditis refers to the case of vegetations that occur on the valves of patients with systemic lupus erythematosus (SLE) in the absence of infection [16]. Pathologically these vegetations

Table 7.3. Pitfalls in the Detection of Vegetations by Echocardiography

Mimics of vegetation (false positives)
Preexisting valvular abnormalities
Sequelae of prior valve surgery
Components of prosthetic valves
Normal structures
Thrombi
Tumor
Extrinsic mediastinal masses
Artifacts
Vegetation not detected (false negatives)
Preexisting valvular abnormalities
Prior endocarditis
Prosthetic material
Suboptimal images
Early disease with small vegetation

are made up of inflammatory cells associated with fibrous tissue and fibrin. They appear as small protrusions usually 2 to 4 mm in diameter adherent to endocardium, more frequently at valve commisures [16]. Echo studies of patients with SLE have documented these non-infectious vegetations in up to 18% of patients [17]. They are indistinguishable from vegetations due to IE; therefore the clinical context is essential to avoid misdiagnosis of infectious endocarditis. Antiphospholipid antibody syndrome can be seen as an isolated clinical entity or in association with SLE and also causes Limans-Sachs vegetations [18]. Nonbacterial thrombotic endocarditis refers to the occurrence of noninfective valvular vegetations in the setting of metastatic cancer, and their echocardiographic appearance is indistinguishable from infectious vegetations [19]. In the setting of preexisting valvular disease such as severe myxomatous changes, detection of vegetation can be difficult. False–negative TEE studies can occur in the early stage of endocarditis which has not resulted in a vegetation large enough to permit visualization by TEE. In such situations, a repeat TEE in 7–14 days can increase the sensitivity for detecting valvular vegetations [9,20]. The overall sensitivity of TEE for valvular vegetations is 92% and specificity is 94% (Table 7.5). Again, this is derived from series where the pre-test likelihood of endocarditis was high, which may result in an overestimate of the accuracy of TEE for diagnosis of vegetations.

Summary

1. A vegetation is an irregularly shaped echogenic mass adherent to valves, endothelial surfaces, or intracardiac prosthetic

Table 7.4. Transthoracic Echocardiography in the Diagnosis of Valvular Vegetation

Reference	Sensitivity %	Specificity %	PPV %	NPV %	Proportrion with IE (%)	Proportion with Prostheses (%)
Erbel et al., 1988 [10]	63	98	92	91	96/176 (55)	ND
Shivley et al., 1991 [12]	44	98	88	84	16/24 (24)	3/66 (5)
Birmingham et al., 1992 [13]	30	100	100	57	33/63 (52)	2/64 (3)
Shapiro et al., 1994 [14]	60	91	86	72	30/64 (47)	0/64 (0)
Lowry et al., 1994 [15]	36	83	ND	ND	28/85 (33)	29/85 (34)
Reynolds et al., 2003 [11]	55	ND	ND	ND	51/101 (50)	ND
Average	48	94	91.5	76	254/513 (50)	34/269 (13)

IE = infective endocarditis, ND = not determined, NPV = negative predictive value, PPV = positive predictive value.

Table 7.5. Transesophageal Echocardiography in the Diagnosis of Valvular Vegetation

Reference	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Proportrion with SBE (%)	Proportion with Prostheses (%)
Erbel et al., 1988 [10]	100	98	95	100	96/176 (55)	ND
Shivley et al., 1991 [12]	94	100	100	98	16/24 (24)	3/66 (5)
Birmingham et al., 1992 [13]	88	97	97	88	33/63 (52)	2/64 (3)
Shapiro et al., 1994 [14]	87	91	90	88	30/64 (47)	0/64 (0)
Lowry et al., 1994 [15]	93	91	ND	ND	28/85 (33)	29/85 (34)
Average	92	95	96	94	254/513 (50)	34/269 (13)

IE = infective endocarditis, ND = not determined, NPV = negative predictive value, PPV = positive predictive value.

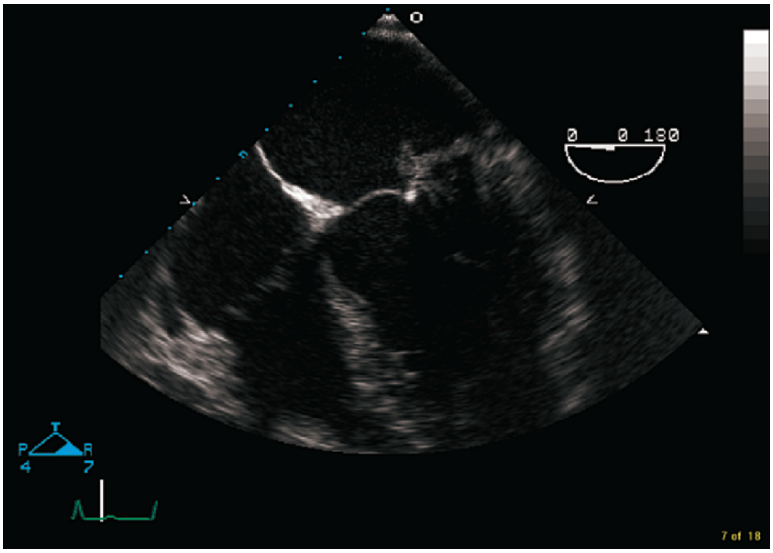


Figure 7.2. A small vegetation on the posterior mitral leaflet on transesophageal echocardiography. This is not detected by transthoracic echocardiography.

devices with high-frequency motion independent of the associated valve or prosthesis which is apparent throughout the cardiac cycle in multiple views.

2. Important causes of false-negative TTE images for endocarditis are small vegetations (< 5 mm), prosthetic valves, and poor image quality.
3. TEE is more sensitive and specific than TTE for detecting vegetations.
4. Echo findings specific for endocarditis should be used in conjunction with clinical findings to avoid misdiagnosis of endocarditis.
5. Mural vegetation can be seen on the left atrial wall in the path of mitral regurgitation jet.

Valvular Abnormalities

Perforation of left-sided valves is a complication of endocarditis that may have important implications for clinical management. The echo definition of perforation is an interruption of leaflet continuity at a site removed from the commisures and color Doppler shows a high velocity eccentric jet traversing the defect at the leaflet (Figure 7.3) [21,22]. Valvular perforation should not be diagnosed when a regurgitant jet originates from the coaptation area and there is no evidence of interruption of leaflet continuity. Mitral and aortic regurgitation that results from valve perforation is usually eccentric.

Almost all mitral valve perforations and some aortic valve perforations occur within aneurysms arising from the infected valve. An aneurysm or diverticulum of the mitral valve is a saccular outpouching bulging into the left atrium during systole and collapsing during diastole (Figure 7.4) [22]. Frequently mitral valve aneurysms and perforations are associated with aortic valve vegetations and aortic regurgitation, likely a result of satellite vegetation on the mitral valve caused by the aortic regurgitant jet. Therefore, finding a mitral valve aneurysm and/or perforation in a patient with endocarditis should prompt a careful assessment of the aortic valve for vegetations and regurgitation.

The diagnosis of perforation is a predictor of the need for surgery and early mortality, because patients with perforation frequently have hemodynamically significant valvular regurgitation. Patients with valvular insufficiency due to perforation may be amenable to patch repair which is preferable in these patients [22]. Despite good response to medical therapy, patients with a valvular perforation should have clinical and imaging follow-up for progression of valvular regurgitation.

Endocarditis is the most common cause of mitral valve aneurysm and perforation. There

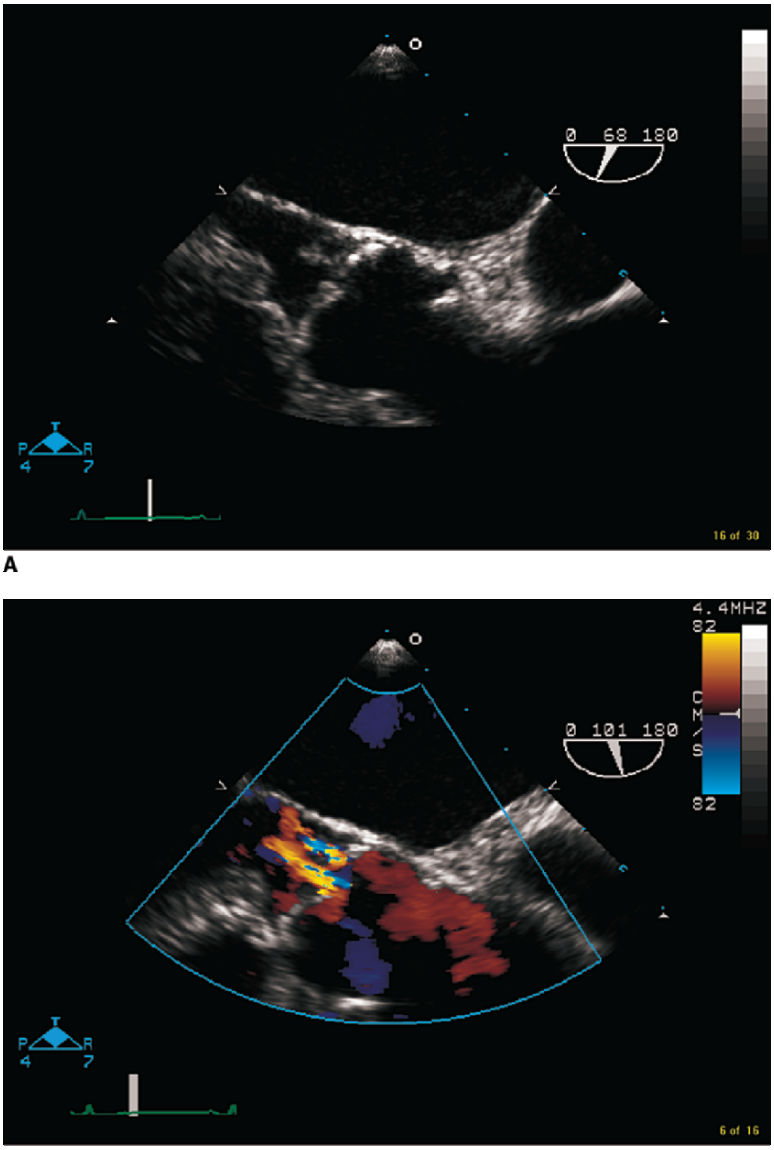


Figure 7.3. A small aneurysm with perforation on the aortic non-coronary cusp on transesophageal echocardiography (**A**). Aortic regurgitation traversing the perforated aneurysm is shown by color flow imaging (**B**).

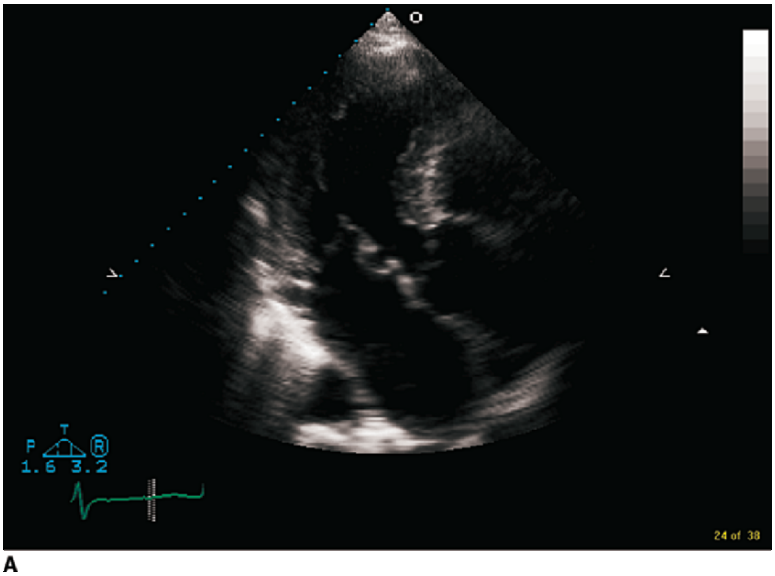
are very few non-endocarditis-related causes of mitral valve aneurysm such as osteogenesis imperfecta, Marfan's syndrome, Ehlers–Danlos, and pseudo xanthoma elasticum [23–25].

Transthoracic Echo

To image leaflet discontinuity directly by TTE requires high-quality images not usually obtained in most patients. The sensitivity of TTE for the diagnosis of valvular perforation is low and varies from 30% to 70% (Table 7.6) [21,22,26].

Transesophageal Echo

TEE is more sensitive for detecting valvular perforation than TTE (Table 7.6). In addition most



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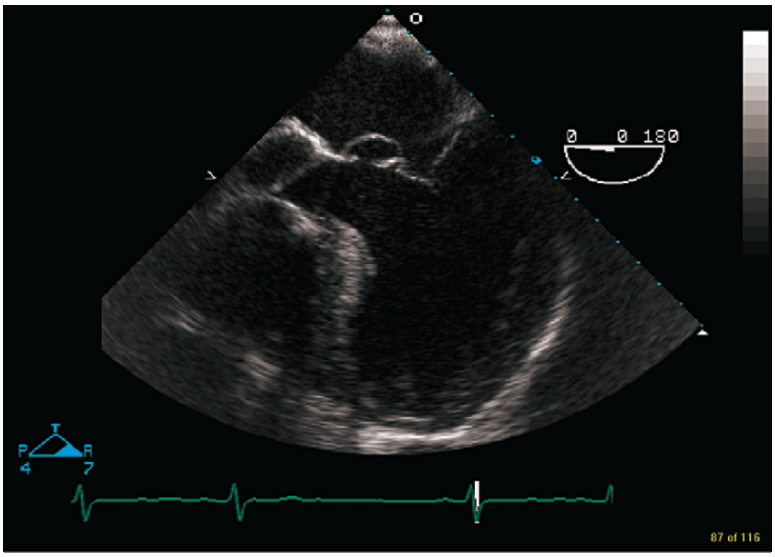

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Figure 7.4. An aneurysm without perforation involving of the anterior mitral leaflet on both transthoracic (**A**) and transesophageal (**B**) echocardiography.

perforations can be directly visualized rather than relying on the color flow jet traversing the valve leaflet. This direct visualization of a perforated leaflet increases diagnostic certainty (Figure 7.5). The size of perforations visualized on TEE agrees closely with pathologic examination and range from 2 to 7 mm [22]. The higher sensitivity of TEE for detecting vegetations is important in excluding aortic valvular IE as the cause for mitral valve perforation or aneurysm.

Table 7.6. Comparison of Transthoracic with Transesophageal Echocardiography in the Diagnosis of Valvular Perforation

Reference	Sample Size	Sensitivity of TTE (%)	Sensitivity of TEE (%)
Cziner et al., 1992 [21]	10	30	90
DeCastro et al., 1997 [22]	20	70	100
Vilacosta et al., 1999 [26]	13	38	100

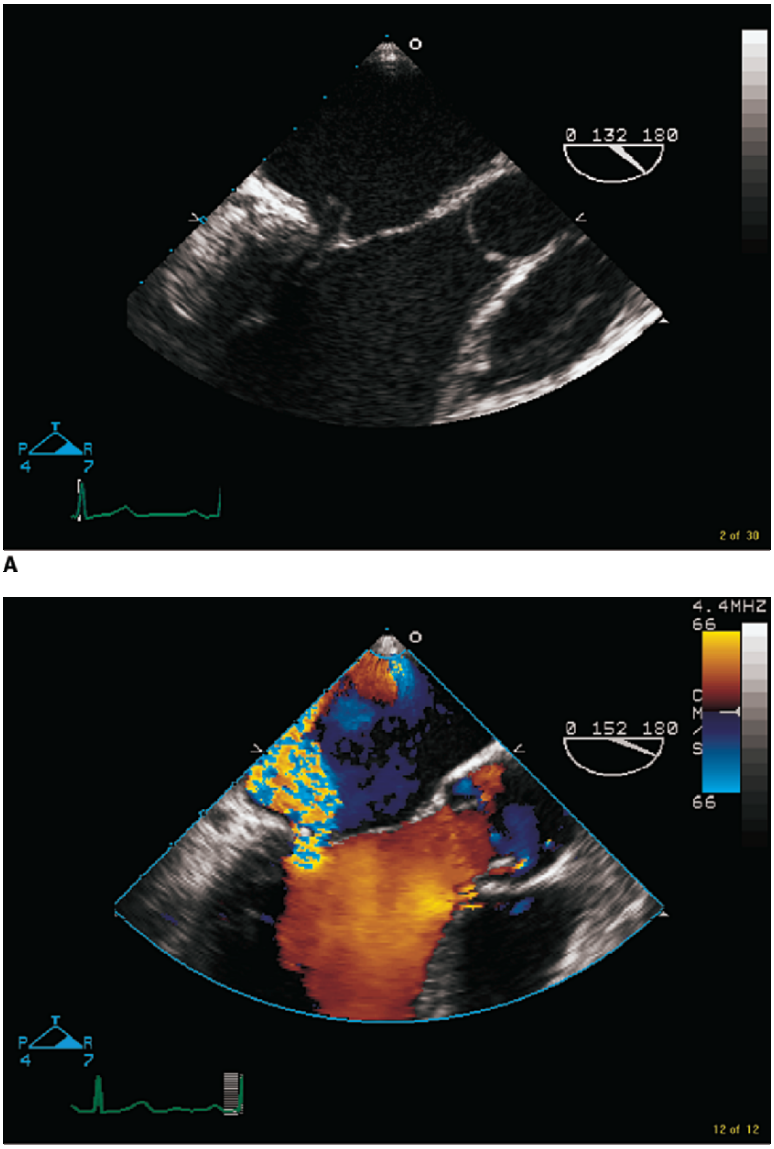


Figure 7.5. A perforated aneurysm located close to the tip of the anterior mitral leaflet on transesophageal echocardiography (**A**). Mitral regurgitation traversing the defect is detected by color flow imaging (**B**).

Summary

1. IE is the most common cause of valvular perforations or aneurysms in adult patients.
2. Valvular perforation should be suspected when the origin of the regurgitant jet is remote from the area of leaflet coaptation.
3. Perforations are often seen in the presence of valve aneurysms.
4. TEE is more sensitive and specific for diagnosing valvular perforations by direct visualization of leaflet discontinuity.

Perivalvular Abscess and Related Complications

The natural history of perivalvular abscess has become better understood, largely because of serial echocardiographic studies in these patients who undergo surgical intervention as well in those who only receive medical treatment [27,28]. These studies have showed that perivalvular abscess is a dynamic process and is the precursor of all other perivalvular complications, including perivalvular dehiscence, pseudoaneurysm, and fistula. Furthermore,

perivalvular abscess has a predilection to the aortic root.

The pathological definition of a paravalvular abscess is a region of necrosis with purulent material that does not communicate with a cardiac chamber or great vessel lumen [29]. This is mirrored by the echocardiographic definition of abscess which is a localized abnormal echolucent area within the perivalvular tissue that does not communicate with the circulation (Figure 7.6) [28]. In addition to identifying the presence of an abscess, there are a number of surgically relevant features that can be delineated using echo. These include the maximum thickness of the abscess cavity, the circumferential extent of the abscess, and involvement of surrounding structures. Long axis views of the aortic root and ascending aorta can be used to define the maximum thickness of the abscess cavity.

As the perivalvular abscess evolves, other features become evident. Echolucent space develops indicative of cavitation and communication with contiguous structures. Serial

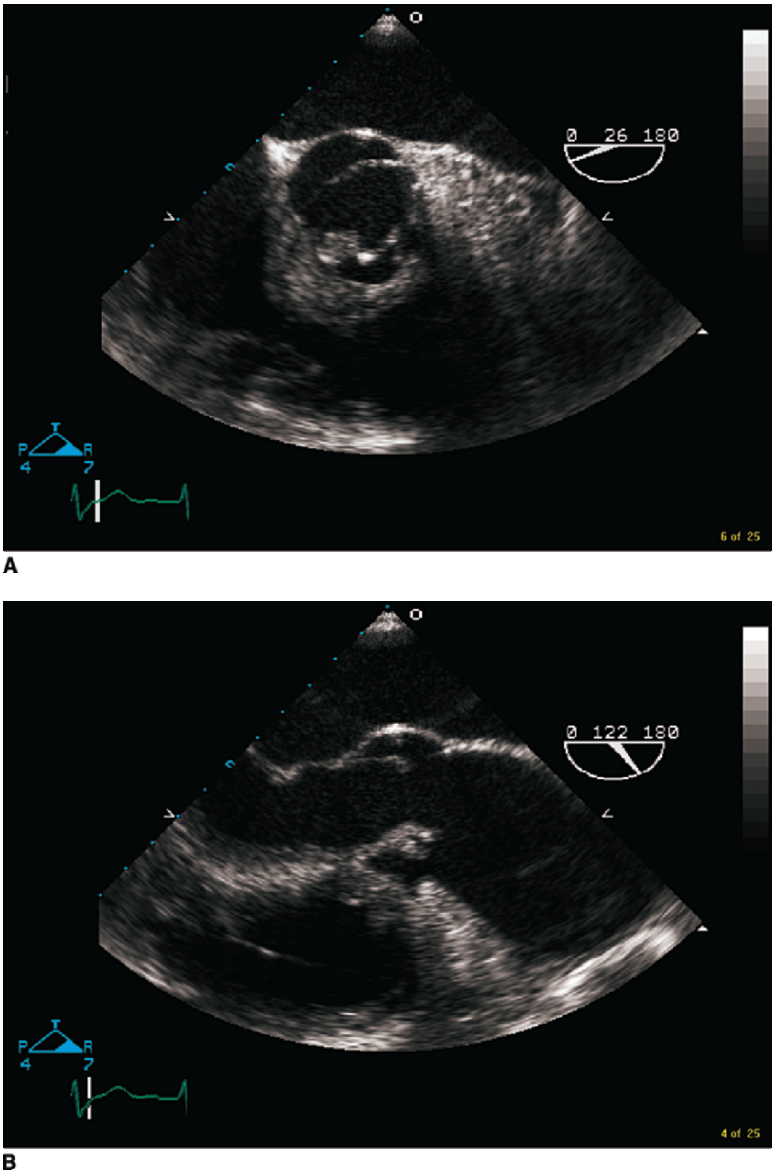
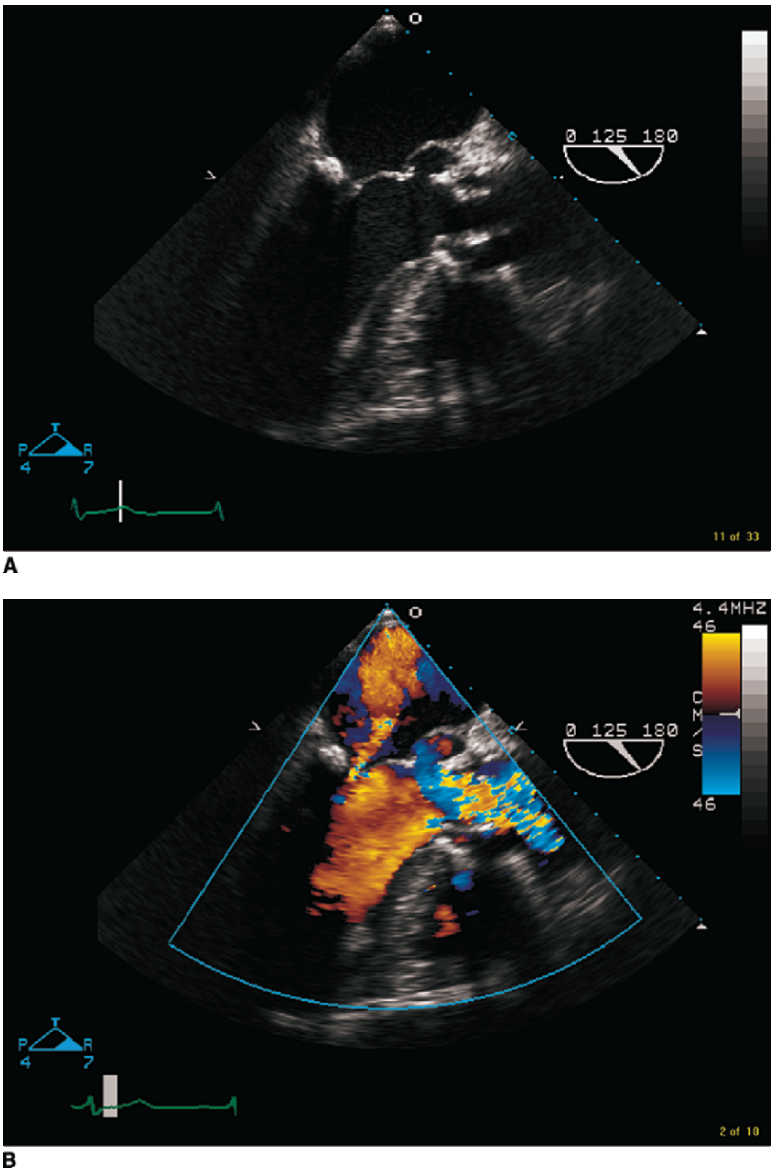


Figure 7.6. A large abscess anterior to the aortic root in the transesophageal aortic short-axis (**A**) and long-axis (**B**) views. A large vegetation is present on the aortic valve which is bicuspid.

echo evaluation of abscesses in the setting of endocarditis has documented the development of pseudoaneurysm from abscess cavities [27,28]. Most of these pseudoaneurysms arise as a result of a connection between the aorta and the abscess cavity [28]. A pseudoaneurysm is an echolucent space with flow originating from either the left ventricle (LV) or aorta. This appears as a pulsatile echolucent pouch anatomically related to the valve annulus [29]. When the pseudoaneurysm originates below the aortic annulus, the connection is between LV and the pseudoaneurysm cavity and color flow imaging shows flow entering the cavity in systole from the LV (Figure 7.7) [30]. Using the color flow jet as a guide may help to image the LV to pseudoaneurysm connection. The maximum dimension of LV to Aortic discontinuity on 2-D imaging can vary from 1 to 24 mm [30].

A fistula develops as a result of abscess drainage into and communication with two vascular structures. For instance, aneurysm of the mitral aortic intervalvular fibrosa may develop a



A

B

Figure 7.7. A pseudoaneurysm at the mitral annular intervalvular fibrosa on transesophageal echocardiography (**A**). Color flow imaging shows low velocity flow within the pseudoaneurysm communicating with the left ventricular outflow tract (**B**).

communication to the left atrium (LA) in addition to its communication with the left ventricular outflow tract, resulting in a fistula connecting the left ventricle with the left atrium. In other cases there may be LV to LA connection with no aneurysm of the interventricular fibrosa. Hemodynamically, the result of this LV to LA connection can be thought of as "supranular mitral regurgitation" (Figure 7.8) [31]. Even in patients who have had surgery for perivalvular abscess, perivalvular complications are common and should be looked for in the follow-up of these patients.

The clinical factors predictive of periannular complications are listed in Table 7.7 [29,32,33].

The presence of periannular complications of infective endocarditis has implications for the prognosis and may be an indication for surgical management, although most patients with periannular complications who have surgery do so for clinical indications such as persistent infection or

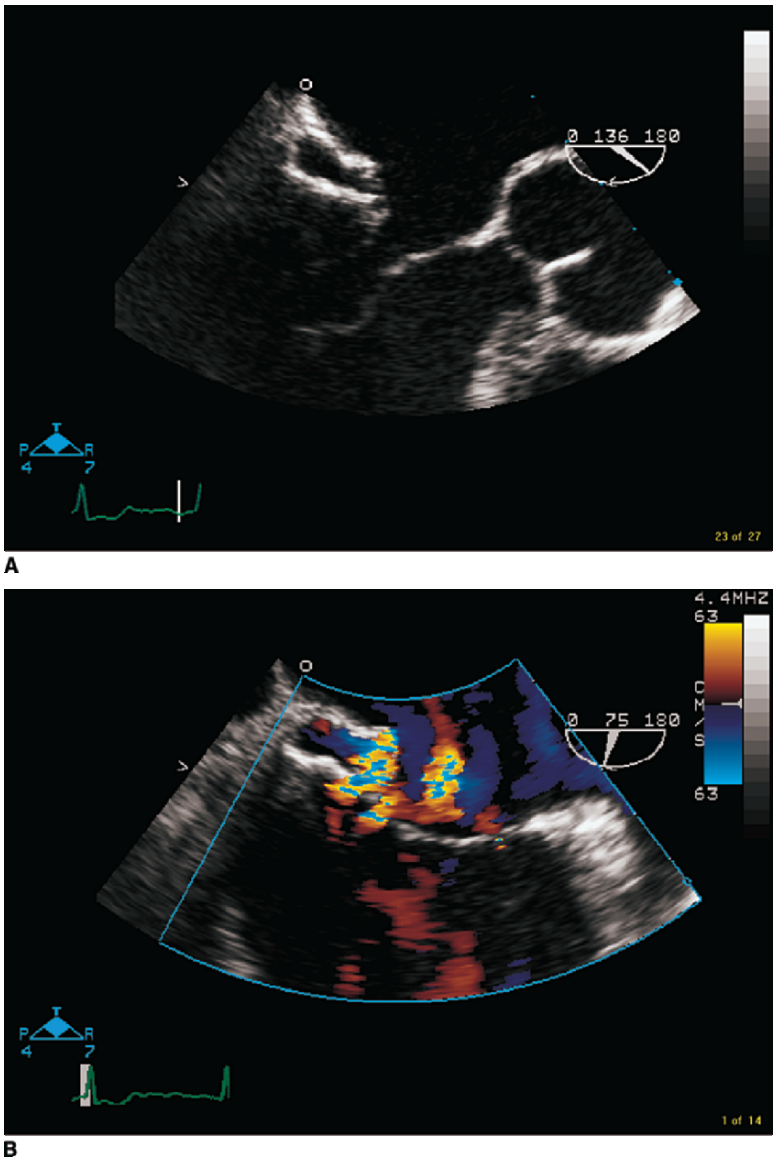
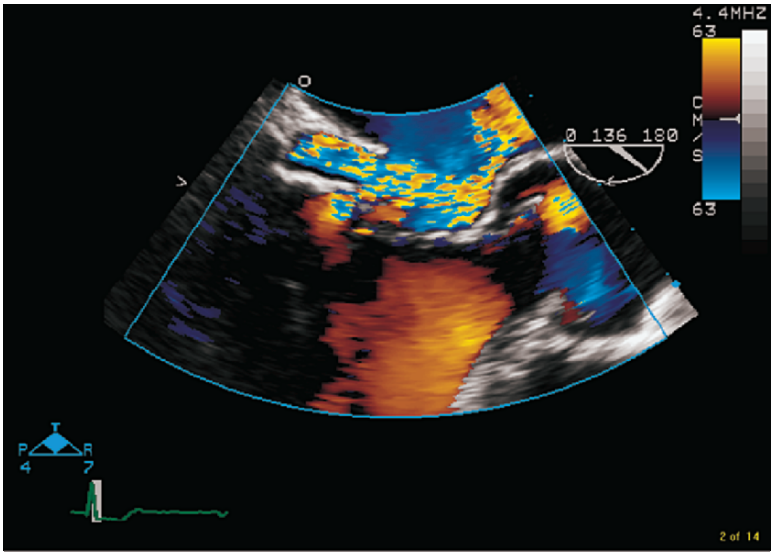


Figure 7.8. Left ventricle to left atrium fistula at the mitral annulus on transesophageal echocardiography (**A**). Color flow imaging shows the direction of the fistula flow from the left ventricle into the fistula (**B**)

(*Continued*)



C

Figure 7.8.—(*Continued*) and from the fistula into the left atrium (**C**).

Table 7.7. Risk Factors in the Development of Perivalvular Complications in Infective Endocarditis*

Risk factor	Relative risk	*P*-value
Prosthetic valve	1.88	< 0.01
Aortic position	1.81	< 0.01
Coagulase negative staphylococci	1.77	< 0.05
Atrioventricular block	2.66	< 0.01
Intravenous drug use	2.5	< 0.01

*From Omani et al., 1989 [33]; San Roman et al., 1999 [32]; and Graupner et al., 2002 [29].

heart failure due to dysfunction of the infected valve. Patients with periannular abscess have a high mortality whether or not they undergo surgery (Tables 7.8 and 7.9) [27–29,34–36]. In patients referred for surgical intervention, preoperative echo is vital to plan the surgical intervention and provide guidance for operative risk. The range of operative procedures used to surgically manage periannular complications in patients with IE is discussed in details in Chapter 7.

The circumferential extent of abscess and the presence of a fistula have been shown to predict increased operative risk [35]. Hemodynamically significant aortic or mitral regurgitation increases operative risk in the setting of abscess [36]. Patients who survive surgery for perrianular complications of endocarditis are at continued risk for cardiovascular morbidity. Perivalvular regurgitation is present in the majority of patients who have surgery for periannular complications of endocarditis. Patients operated on in the setting of aortic root abscess had a 78% rate of postoperative aortic regurgitation versus 26% in postoperative patients with endocarditis and no abscess [37]. Perivalvular leaks causing symptoms or impaired LV function may necessitate redo valve surgery [28]. Finally, recurrent or persistent infection can occur post operatively which in some cases requires further surgical intervention.

Transthoracic Echo

Abnormal thickness of the aortic root (>10 mm) without a cavity can be a sign of perivalvular

Table 7.8. Short- and Long-Term Mortality in Patients with Perivalvular Abscess who Received Medical Treatment Only

Reference	Sample size	Early mortality	Late mortality	Late surgery	Mean follow-up
Byrd et al., 1990 [27]	5	0	3	0	3 years
Aguado et al., 1993 [34]	10	9	ND	ND	30 days
Choussat et al., 1999 [35]	20	ND	8	ND	6 months
Chan, 2002 [28]	12	0	8	3	4.5 years

TEE = transesophageal echocardiography, TTE = transthoracic echocardiography, ND = not determined.

Table 7.9. Short- and Long-Term Mortality in Patients with Perivalvular Abscess who Were Treated Surgically

Reference	Sample size	Early mortality	Late mortality	Late surgery	Mean F/U
Byrd et al., 1990 [27]	5	2	1	0	26 months
Aguado et a., 1993 [34]	30	8	1	4	78 months
Choussat et al., 1999 [35]	213	35/213	87	0	6 months
Chan, 2002 [28]	31	6	10	8	4.5 yrs
Cosmi et al., 2004 [36]	24	ND	9	0	ND

TEE = transesophageal echocardiography, TTE = transthoracic echocardiography, ND = not determined.

Table 7.10. Comparison of Transthoracic with Transesophageal Echocardiography in the Diagnosis of Perivalvular Abscess

	TTE		TEE		Proportion of abscesses infecting
References	Sensitivity (%)	Specificity (%)	Sensitivity (%)	Specificity (%)	prosthetic valves (%)
Ellis et al., 1985 [38]	86	88	ND	ND	17/22 (77)
Daniel et al., 1991 [40]	28	ND	87	ND	16/46 (35)
Aguado et al., 1993 [34]	80	85	ND	ND	13/36 (36)
Tingleff, 1995 [39]	ND	ND	100	ND	18/36 (50)
Blumberg, 1995 [41]	28	90	78	100	12/24 (50)
San Roman, 1999 [32]	ND	ND	90	100	46/46 (100)
Choussat, 1999 [35]	36	ND	80	ND	77/233 (33)
Graupner, 2002 [29]	ND	ND	80	92	36/78 (46)

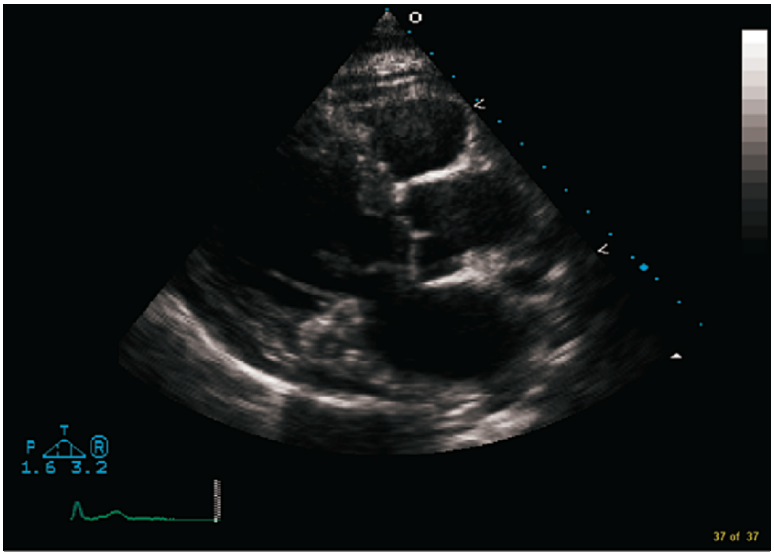
TEE = transesophageal echocardiography, TTE = transthoracic echocardiography, ND = not determined.

abscess [38]. At surgery, such thickening has been shown to correspond to a perivalvular abscess cavity containing purulent material [39]. Abscess cavities can be located at any point on the aortic annulus [39]. TTE may be particularly helpful for aortic root abscesses, especially anterior aortic root abscesses. Short-axis views of the aortic root and ascending aorta can determine the circumferential extent of the abscess cavity and its anatomic relation to the valve annulus. On color flow imaging of both short and long axis images, an abscess cavity will have no Doppler evidence of communication between the abscess cavity and a great vessel or cardiac chamber. The accuracy of echo in the diagnosis of abscess is summarized in Table 7.10 [29,32,34,35,38,41]. While TTE is specific for diagnosing abscess, a wide range of sensitivities have been reported. This wide range in sensitivity for TTE in detecting abscess likely reflects the highly variable pretest probability of abscess in patients making up the populations studied. The sensitivity of TTE in detecting abscess remains limited even with harmonic imaging [9]. If abscess is suspected clinically and not identified on TTE, then a TEE should be performed. The main reasons for false-negative TTEs for abscess are poor image quality and the lack of specificity of the echo features. Compared to periaortic abscess, mitral annular abscesses are even more difficult to diagnose by TTE due to the far field nature of the mitral annulus resulting in suboptimal images.

Non-infectious causes of aortic root thickening include inflammatory aortitis, severe atheroma (unusual in the aortic root and ascending aorta), aortic dissection, and recent cardiac surgery [38]. A thorough knowledge of the normal anatomy and echocardiographic appearance of the atrioventricular groove is required to avoid misdiagnosing the presence of a mitral valve abscess (Table 7.11). The main cause of false-positive TTE diagnosis of abscess in the mitral position is degenerative changes of the mitral annulus such as mitral annular calcification and in its more severe form caseous calcification of the mitral annulus (Figure 7.9). The typical appearance of caseous calcification of the mitral annulus on echo is a large echodense mass with smooth borders, which on short axis images can have a semilunar shape within the

Table 7.11. Normal Structures and Conditions Involving the Atrioventricular Groove that May Mimic Mitral Annular Abscess

Loculated pericardial effusion
Prominent epicardial fat
Descending thoracic aorta
Dilated coronary sinus
Shadowing from mitral annular calcification
Dilated left circumflex coronary artery



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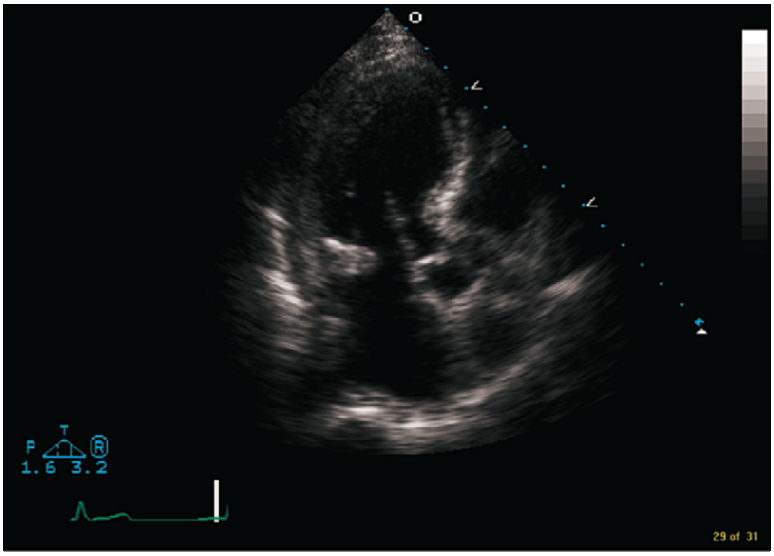


B

Figure 7.9. Caseous calcification at the mitral annulus can mimic annular calcification. The large, circular, echodense mass with echolucent centre is shown in the transthoracic parasternal long axis (**A**) and apical long-axis (**B**) views.

atrioventricular groove [42]. Surgical and pathological inspection reveals the contents to be a pastelike material which microscopically contains calcium and lymphocytes but no infectious organisms [42]. Clinical correlation is essential when confronted with this entity.

Aortic pseudoaneurysm has a propensity to affect the posterior aortic root and can be identified as an echo lucent space (Figure 7.10). Color flow imaging shows only low velocity to-and-fro flow within the pseudoaneurysm. A fistula is a communication with flow between two cardiac chambers or great vessels [29,32]. Fistulas can result from the development of connections within cardiac chambers and great vessels in the setting of a preexisting abscess or pseudoaneurysm. In fact, the majority of fistulas are found in the setting of other periannular complications such as abscess or pseudoaneurysm [43]. Another cause of fistula involves the progression of infection of the mitral annular intervalvular fibrosa. A fistula should be suspected when color flow imaging shows turbulent flow originating in one cardiac chamber or great vessel and terminating in a second great vessel or chamber (Figure 7.11). Patients suspected to

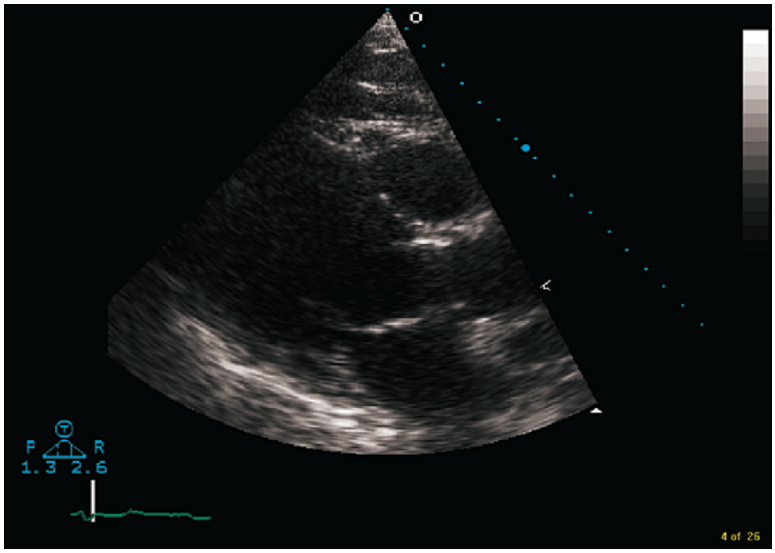


Figure 7.10. A large echofree cavity posterior to the aortic root in the transthoracic parasternal long axis view. Aortic pseudoaneurysm is usually not well seen on transthoracic echocardiography.

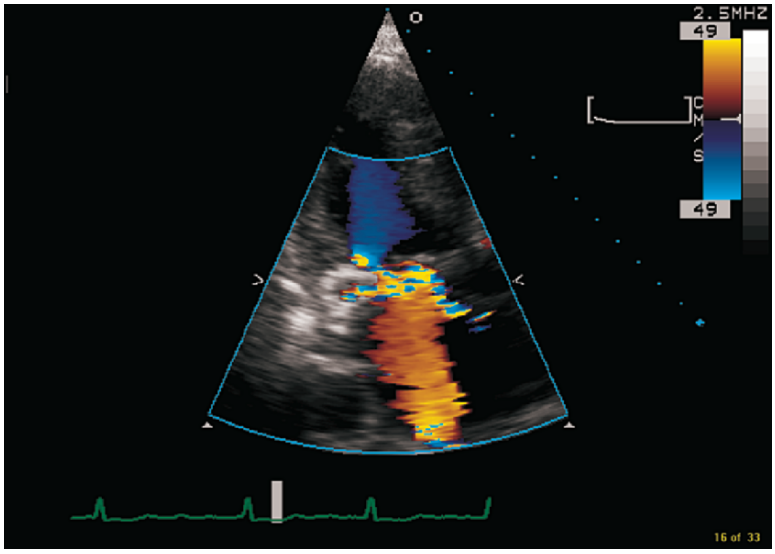


Figure 7.11. Turbulent flow within an echolucent structure at the mitral annulus suggestive of a fistula on transthoracic echocardiography.

have perivalvular complications should undergo TEE to assess the extent and anatomic relationship of the abnormalities in relation to the adjacent cardiac structures.

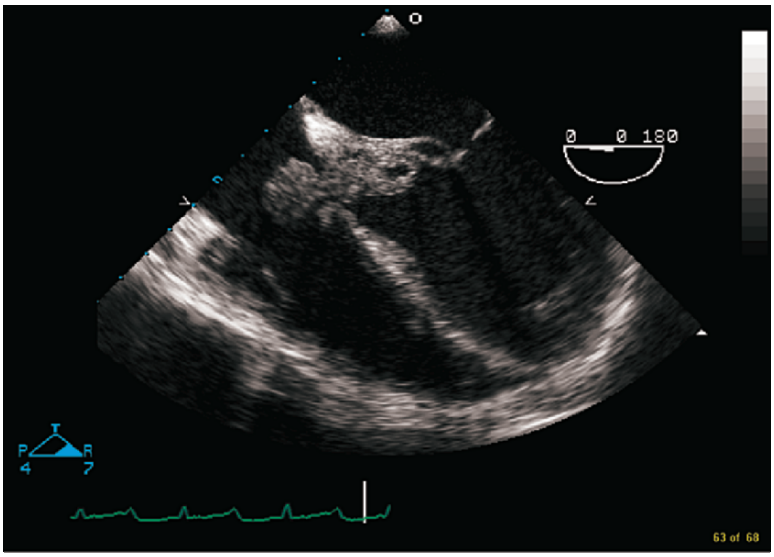
Transesophageal Echo

TEE is more sensitive and specific for the detection of abscess in both the aortic and mitral positions (Table 7.10). The sensitivity of TEE ranges from 78% to 90% with a specificity from 92% to 100%. Adhering to the requirement for echolucency to define abscess can result in false negatives, particularly in the early stage of periannular infection [29]. Serial TEE evaluation of periannular infection in patients managed medically has shown that early abscesses appear as abnormal thickening of the aortic root which subsequently cavitates (Figure 7.6). Therefore echolucency is a specific sign for abscess but may not be present in the earliest stages of abscess formation. In situations where abscess is suspected but the only finding is abnormal wall thickness, repeat imag-

ing with TEE may document the development of an echolucent cavity, thus increasing sensitivity to detect this complication while avoiding false positives due to non-infectious causes of increased aortic root thickness.

On TEE an aneurysm of the mitral aortic intervalvular fibrosa demonstrates systolic expansion and diastolic collapse of the interannular zone between the anterior mitral leaflet and the aortic valve [31] (Figure 7.7). Color flow imaging allows the identification and localization of holes and fistulae that may be present within the aneurysm and result in connection between LV and LA. In some cases such fistulas or holes can occur without an aneurysm, typically as a complication of aortic valve IE (Figure 7.12). In the series by Karalis et al., these complications and fistulas were correctly identified by TEE in all seven cases but by TTE in only one case [31].

Compared to TTE, TEE is more sensitive and specific for the diagnosis of pseudoaneurysm and fistula. In addition, the circumferential extent, anatomic relationship and site of communication are better delineated by TEE. As



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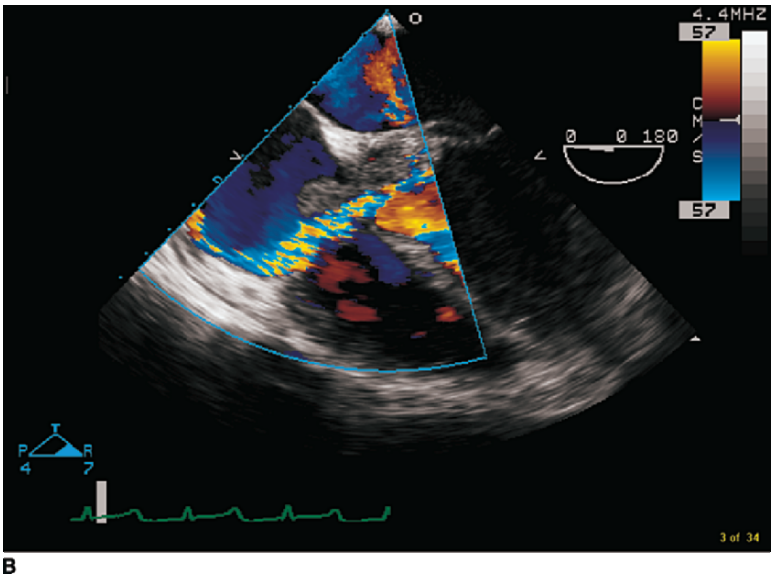


B

Figure 7.12. Large vegetations involving the mitral and tricuspid valves on transesophageal echocardiography (**A**). Color flow imaging shows the left ventricle to right atrium fistula.

with periannular abscess, TEE offers higher accuracy and more detailed imaging and is therefore recommended in all cases of known or suspected perivalvular complications.

Summary

1. Perivalvular abscess is a dynamic process and is the precursor of perivalvular abnormalities such as pseudoaneurysm and fistula.
2. TTE can diagnose aortic root abscess but rarely diagnoses mitral abscess.
3. TEE is more sensitive and specific in detecting periannular abscess, aneurysms, and fistulas.
4. Patients with periannular abscess have high short- and long-term morbidity and mortality despite surgical treatment.

Right-Sided Endocarditis

Right-sided IE is a particularly common problem in injection drug users. The majority of vegetations in right-sided endocarditis are found on the tricuspid valve, usually on the atrial side. Occasionally vegetations can encase the entire leaflet or be on the ventricular side of the tricuspid valve. Right-sided vegetations tend to be large (10 to 20 mm or more) regardless of the causative organism. Tricuspid valve regurgitation can be present and can range in severity from mild to severe [44–46].

Transthoracic Echo

Vegetations in right-sided IE in injection drug users were initially described on M-mode and 2 D echo in 1980 [44]. Most cases of right-sided endocarditis are readily diagnosed by TTE, because the vegetations are usually large (Figure 7.13). Rarely right-sided vegetations can involve the Eustachian valve. In a large series of endocarditis, five cases of Eustachian valve endocarditis were identified, representing 3.3% of all cases of right-sided endocarditis [47]. In four of the five cases, there were also vegetations on the tricuspid valve. In only one case IE was isolated to the Eustachian valve. The diagnosis was readily made by TTE. The key to distinguishing vegetation from the normal Eustachian valve was abnormal thickness (> 5) mm and chaotic, independent motion unrelated to the cardiac cycle [47].

Right-sided endocarditis can involve the pulmonic valve. The majority of pulmonic valve endocarditis occurs in patients with prior intervention for congenital heart disease. In the absence of prior cardiac intervention, the usual setting of pulmonic valve endocarditis is either injection drug use or indwelling central lines [48]. The majority of cases are readily diagnosed

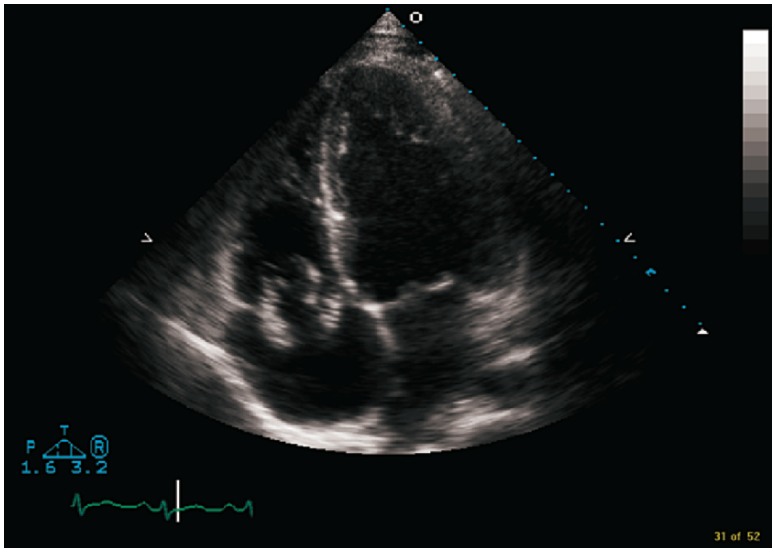


Figure 7.13. Multiple large vegetations involving the tricuspid valve on transthoracic echocardiography.

by TTE, with a sensitivity for detecting pulmonic vegetations of 91% [48]. In addition to the standard parasternal short axis view, a subcostal view can be useful.

Transesophageal Echo

Transthoracic echo is usually adequate to diagnose right-sided IE and assess the severity of tricuspid valve regurgitation. Although TEE can provide better delineation of the anatomic relationship between vegetation and valve leaflets, the information rarely alters the diagnosis or management [46]. Nevertheless, TEE can be useful in selected patients with suspected right-sided IE as defined in Table 7.12 [49].

Summary

1. Right-sided endocarditis is accurately diagnosed using TTE.
2. Vegetations in right-sided endocarditis are frequently large (5–20 mm) regardless of causative organism.
3. TEE is reserved for specific situations in suspected right-sided IE.

Prosthetic Valve Endocarditis

Detection of Vegetation

Endocarditis can affect bioprosthetic or mechanical heart valves as well as indwelling central lines and pacemaker wires. Vegetations have a predilection to affect the sewing ring of both the bioprosthetic and mechanical valves, although the leaflets of the bioprosthetic valve can also be involved. The presence of new perivalvular regurgitation is generally indicative of IE. Echocardiographic evaluation of endocarditis in the setting of prosthetic valves can be more challenging due to the reverberations created by prosthetic material.

Table 7.12. Indications for Transesophageal Echocardiography in Injection Drug Users with Suspected Right-Sided Endocarditis.

Poor transthoracic images
History of prior endocarditis
Preexisting valve abnormalities
Suspected left-sided endocarditis
Suspected pulmonic valve endocarditis
Patients considered to have possible endocarditis and negative TTE

TTE = transthoracic echocardiogram.
Reproduced from Chan, KL, Echocardiography in right sided endocarditis (Editorial) Clin Invest Med. 2002 Aug; 25(4): 134–6, with permission from the Canadian Society for Clinical Investigation.

Transthoracic Echo

The sensitivity of TTE for diagnosing endocarditis is lower for prosthetic valves than for native valves (Table 7.13) [50–52]. Transthoracic echo detects evidence of prosthetic valve endocarditis in only about a third of the cases. Therefore TEE should be performed if prosthetic valve endocarditis is suspected even though TTE shows no evidence to support the diagnosis. False-positive echocardiographic findings for IE in the setting of prosthetic valves include echogenic masses of non-infectious origin such as sutures, pannus, and thrombus. Correlation with clinical and microbiological data is required to avoid misdiagnosis. For bioprostheses, the main cause of false positives is non-infectious degeneration of bioprosthetic valve leaflets [52]. Typically degenerated bioprosthetic valve cusp has bright and echodense nodules which can therefore be distinguished from the soft, shaggy, mobile echodensity more typical of a vegetation.

Transesophageal Echo

Transesophageal echo is more sensitive and specific for evidence of prosthetic valve endocarditis compared to TTE (Figure 7.14). While TTE detects prosthetic valve endocarditis in about a third of the cases, the sensitivity of TEE for detecting prosthetic valve IE is 77% to 100% (Table 7.13). The most common situation where

Table 7.13. Comparison of Transthoracic with Transesophageal Echocardiography in the Diagnosis of Prosthetic Valve Endocarditis

References	Sample size	Sensitivity of TTE (%)	Sensitivity of TEE (%)
Mugge et al., 1989 [50]	22	27	77
Taams et al., 1990 [51]	12	25	100
Daniel at al., 1993 [52]	33	36	82

TEE = transesophageal echocardiography, TTE = transthoracic echocardiography.

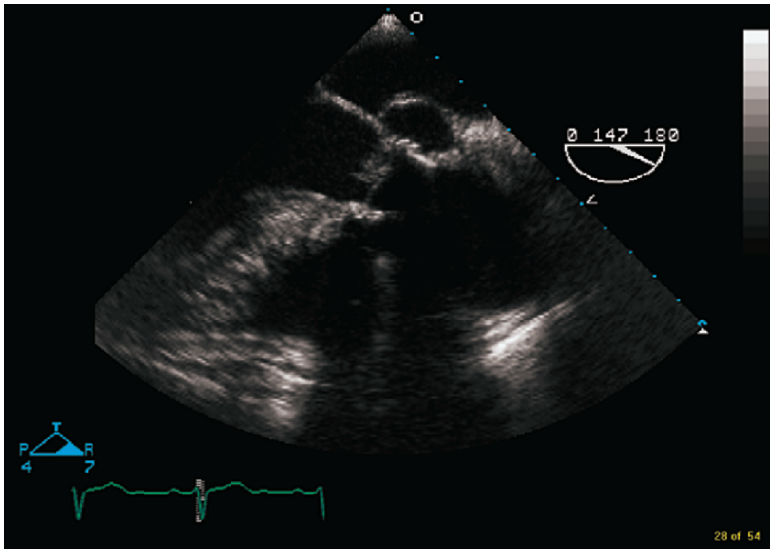


Figure 7.14. A vegetation involving a leaflet of a bioprosthetic aortic valve on transesophageal echocardiography. Also present is an aortic root pseudoaneurysm.

TEE misses evidence of IE is in patients with aortic prosthetic valves [52]. This problem is magnified in the setting of aortic prosthetic valve infection when there is also a mitral prosthesis, as reverberations from the mitral prosthesis can mask the aortic prosthesis. For bioprostheses, the enhanced image quality of TEE often allows visualization of degenerative leaflets in greater detail than TTE. The bright echogenic appearance of degenerating bioprosthetic valve cusps can usually be distinguished from valvular vegetation (Figure 7.15). The high image quality of TEE images often reveals bright filaments on the sewing rings, which are generally non-infectious in origin and are readily distinguished from vegetation. Prosthetic valve strands are thin (< 1 mm) mobile echodensities of variable length, and pathological examination suggests that these strands are composed of collagen rather than vegetation [53]. Prosthetic valve thrombosis appears indistinguishable from vegetation on TEE. It is important to combine TEE imaging data with clinical and laboratory evidence of infection to distinguish thrombus from vegetation due to endocarditis.

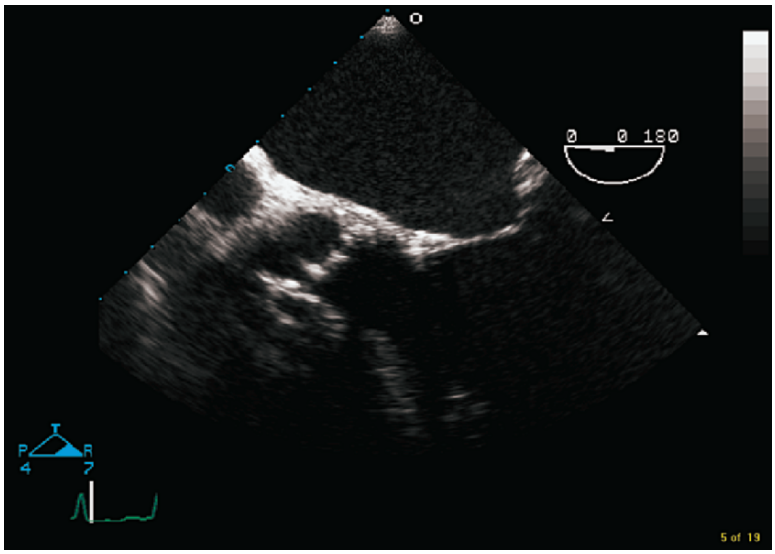
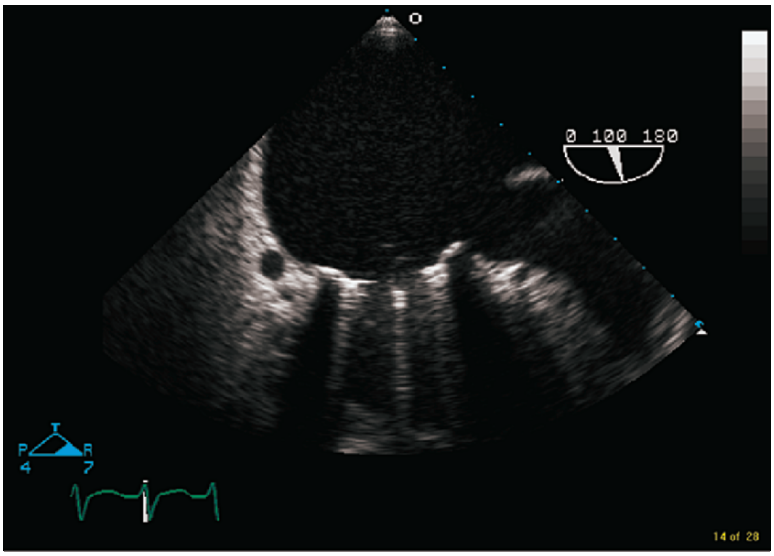


Figure 7.15. Degenerative changes of an aortic homograft mimicking vegetations on transesophageal echocardiography.

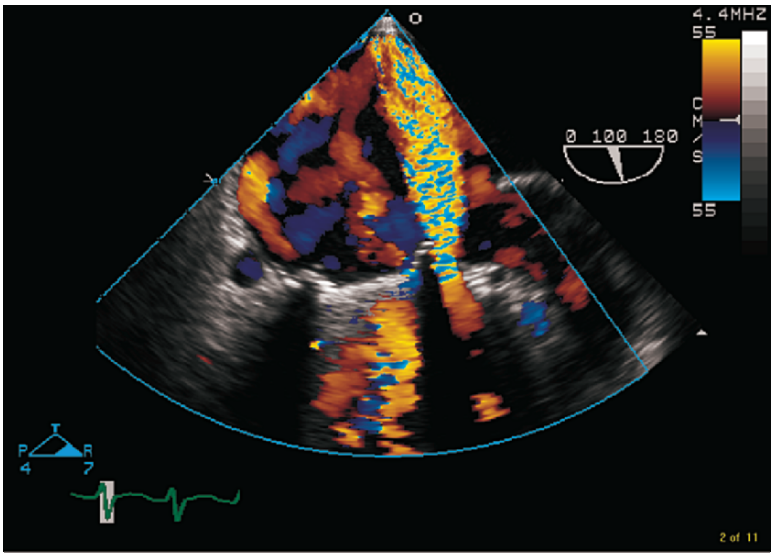
The presence of a periprosthetic regurgitation, if it is a new finding, raises the possibility of IE, underscoring the importance of baseline echo study in patients with prosthetic valves (Figure 7.16). Trace to mild perivalvular regurgitation is not uncommon in patients with prosthetic valves and no IE. The finding of an isolated, tiny perivalvular leak with no other echo findings of endocarditis in the setting of a prosthesis should be interpreted with caution [54]. In bileaflet mechanical valves, normal prosthetic regurgitation is eccentric and should not be confused with perivalvular leak.

Summary

1. TTE is specific but insensitive for the diagnosis of prosthetic valve endocarditis.
2. TEE is more sensitive and specific for prosthetic valve endocarditis than TTE. Most patients with prosthetic valves and suspected IE should have TEE.
3. Important false positive TEE findings include echodensities of non-infectious origin such as prosthetic valve strands, thrombi, and degenerating changes on bioprosthetic leaflets.



A



B

Figure 7.16. Localized dehiscence of a mechanical mitral valve on transesophageal echocardiography (**A**). Color flow imaging shows the perivalvular mitral regurgitation traversing the defect (**B**).

Perivalvular Abscess and Related Complications

The diagnosis of perivalvular abscess is more difficult in patients with prosthetic IE, because increased perivalvular thickness is a common finding in these patients even in the absence of IE. A previous study for comparison is useful in the assessment of these patients, and repeat studies in seven to ten days to look for evolutional changes as previously discussed with native valve IE remains very pertinent. Perivalvular abnormalities are common even in patients who have had early cardiac surgery to treat perivalvular abscess, and a recent study showed that these complications were present in about a third of these patients [28].

Transthoracic Echo

Perivalvular complications are more difficult to diagnose because the reverberation artifact from the prosthetic valve can mask surrounding structures (Table 7.10). This is particularly a problem with the posterior aortic root, which is obscured in patients with mechanical aortic prostheses. As infection disrupts the sewing ring annulus, part of the ring can dehisce leading to abnormal excessive rocking of a prosthesis. A rocking motion in excess of 15 degrees out of concordance with the supporting structures of the valve has been proposed as a criteria for perivalvular abscess [38]. The degree of rocking is proportional to the circumferential extent of LV-aortic discontinuity. This can vary from as little as one-quarter to as much as three-quarters of the circumference of the annulus [30]. When examined at autopsy and surgery, valves with excessive rocking have been shown to have dehiscence between 40% to 95% of the circumference of the sewing ring. The main false-positive sign of abnormal valve rocking relates to mitral and tricuspid prostheses in patients with very large mitral and tricuspid annuli and usually large atria [38]. In such patients, abnormal valve rocking can be seen without periannular abscess.

Transesophageal Echo

TEE can overcome many limitations of TTE in assessing the perivalvular region in patients with prosthetic valve IE [19,28,35]. Thus most patients with prosthetic valve IE should have TEE even if the image quality of TTE is adequate. An abscess on the anterior surface of the aortic root in the setting of a prosthetic aortic valve can be difficult to detect by TEE since the aortic prosthesis can shadow the anterior aortic root which is in the far field of the TEE image plane. In such cases images from TTE compliment the TEE images, by showing the anterior aspect of the aortic root and ascending aorta.

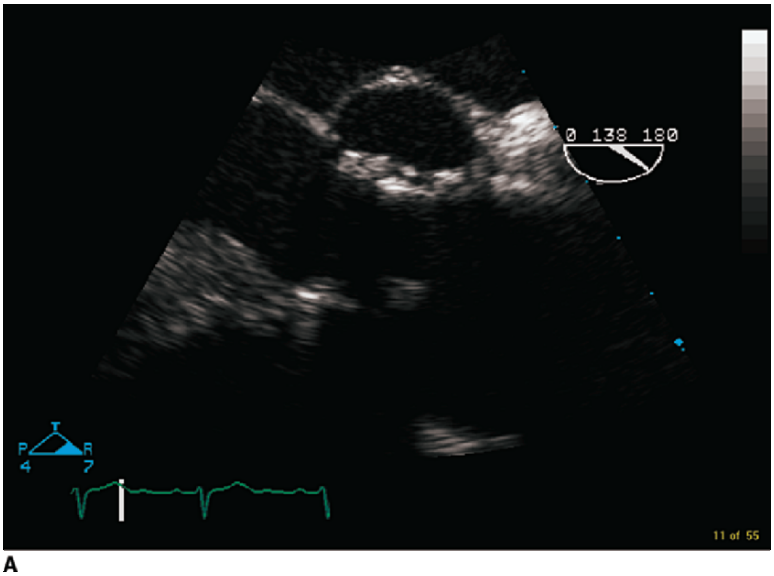
Perivalvular regurgitation in the setting of mitral valve prosthesis is optimally assessed by TEE, which provides detailed information regarding number, size, and location of the regurgitation jets (Figure 7.16). This information can be useful in the selection of patient for device closure of the perivalvular leak after the infection has been adequately treated. Other perivalvular complications including pseudoaneurysm and fistula are also better imaged with TEE which should be performed in most patients suspected to have these perivalvular complications particularly if surgical intervention is contemplated (Figure 7.17).

Summary

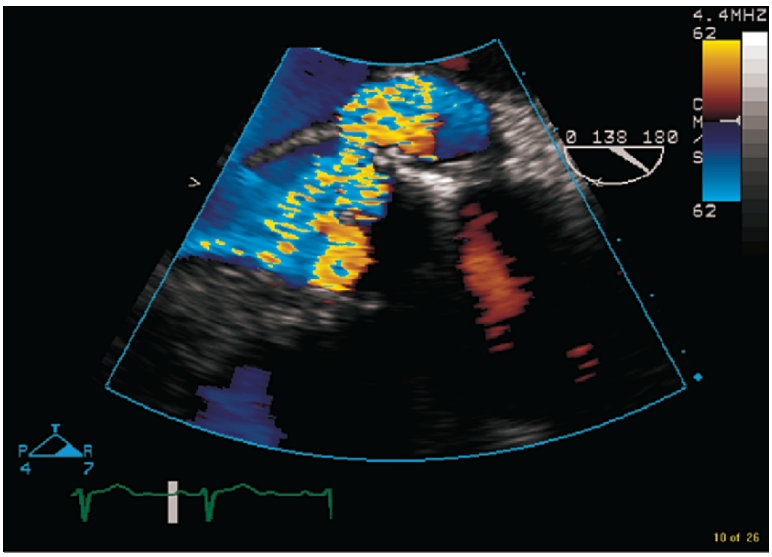
1. Increased aortic wall thickness and excessive prosthetic valve rocking are signs of perivalvular abscess.
2. TEE should be performed in all patients with prosthetic valves and suspected perivalvular complications.
3. TEE may not adequately assess prosthetic valves in the aortic position.

Endocarditis Associated with Pacemaker Leads and Central Venous Catheters

Masses adherent to intracardiac catheters and leads are common even in the absence of IE. Thus, the diagnosis of IE in this clinical setting requires clinical correlation such as the use of the Duke criteria. Vegetations associated with pacemaker leads can occur either in the atrium or ventricle, ranging in size from less than 5 mm to over 20 mm [56]. Echo evidence of vegetation is present in the majority of patients with pacemaker lead IE. In addition to the typical shaggy, mobile, soft echodensity characteristic of



A



B

Figure 7.17. A large pseudoaneurysm at the posterior aortic root on transesophageal echocardiography (**A**). This serves as a fistula connecting the left ventricle with the aorta. Color flow imaging shows flow from the pseudoaneurysm into the left ventricular outflow tract during diastole (**B**). This is the same patient as in Figure 11.

vegetations, infected pacemaker leads can have a sleeve-like appearance on the sheath [57]. In rare cases of pacemaker lead IE, this sleeve-like appearance on the pacemaker lead may be the only abnormality with no echo evidence of mobile masses. Vegetations attached to the tricuspid valve are found in the minority of patients [56]. In contrast to IE affecting native right-sided valves, pacemaker-lead-related endocarditis is much more likely to be detected using TEE. Overall, TEE is more sensitive for detecting pacemaker-related vegetations than TTE [57]. Therefore if pacemaker lead endocarditis is suspected but not detected by TTE, TEE should be performed.

Endocarditis can also arise in the setting of indwelling central venous catheters. As is the case for pacemaker-lead-associated IE, TEE is more sensitive for the detection of vegetations in the setting of indwelling catheters than TTE [57].

Summary

1. TEE is more sensitive than TTE for the diagnosis of pacemaker-lead-associated IE.

2. Both mobile masses and a sleeve-like echodensity on the intracardiac leads are echo findings of pacemaker associated vegetations.

Conclusions

The relative value of TEE versus TTE in establishing the diagnosis of IE depends on the clinical pretest probability of IE. In patients with a low pre-test probability, in whom there are few minor and often no major clinical features of IE, TTE is generally adequate and TEE seldom gives additional information [58]. The exceptions may be patients with high-risk features and in whom TTE is known to have a low sensitivity for detecting evidence of IE (Table 7.1). Patients with prosthetic valves and technically inadequate TTE images are one example. In patients with an intermediate pre-test probability of IE, TEE often adds diagnostic information even when TTE image quality is high. These patients are frequently categorized to have possible IE based on clinical and TTE findings alone. In many of these patients diagnostic certainty can be increased with TEE, and IE can either be excluded or confirmed with obvious implications for clinical management [59,60]. TEE is especially important in patients suspected to have culture-negative IE, because many of these patients would be classified as possible endocarditis based on TTE findings, but with the TEE findings about 25% of these patients can be diagnosed to have definite endocarditis [61]. In patients with a high probability of IE, TEE is not needed for diagnosis but may be required to provide additional information to evaluate prognosis and to guide management. It may be more cost effective to perform TEE without TTE in patients with intermediate or high probability of IE, but this approach has not been properly evaluated in a clinical trial. In patients with suspected IE our practice is to always proceed first with TTE and to add TEE in specific groups of patients. This approach allows a goal-oriented TEE based on TTE findings and limits the risks of TEE to those patients who would benefit from the procedure.

Key Points

1. TEE is not necessary in patients with low likelihood of IE and good TTE images.
2. Despite good TTE images, TEE is recommended in the setting of suspected prosthetic valve IE, suspected culture negative IE, and bacteremia with virulent organisms such as *Staphylococcus aureus*.
3. TEE is indicated in the assessment of perivalvular abscess and related complications in both native valve IE and prosthetic valve IE.
4. Perivalvular abscess is a dynamic process, and TEE can provide useful prognostic information during the follow-up including in patients who have undergone cardiac surgery for perivalvular abscess.

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8

Surgical Management: Indications and Technical Issues

Thierry G. Mesana and Bijan Jahangiri

Case Study

A 48-year-old man, diagnosed with infective endocarditis (IE), had been in hospital for five days. Blood cultures had been consistently positive for *Staphylococcus aureus*. Intravenous antibiotic treatment had been administered since hospitalization and modified as per culture results. Transesophageal echocardiography (TEE) on the second day in hospital revealed vegetations on the ventricular aspect of the coronary aortic cusps, the largest measuring 8 mm in length with moderate aortic regurgitation, a large perforation of the anterior mitral leaflet with moderately severe mitral regurgitation, and suspicious presence of a small abscess in the aortomitral curtain in the form of a very small area with minimal echolucency. Cardiac surgery was consulted, and the decision was made to continue medical therapy and repeat TEE in two days. On day 7 after admission, a repeat TEE confirmed the presence of an abscess in the previously suspected location in the aortomitral curtain, significantly increased in size compared to the previous TEE images. Cultures were negative, but leukocytosis and fever persisted. The patient was taken to the operative room the following day for urgent surgery. The operation involved removal of the infected and insufficient aortic valve together with the infected aortic root and removal of the aortomitral curtain containing the abscess. An aortic homograft was used to replace the removed aortic root and valve, and the anterior mitral leaflet accompanying the homograft was used to construct a new aortomitral curtain. The edges of the perforation in the anterior leaflet of the native mitral valve were first debrided of small vegetations, and an autologous pericardial patch was used to repair the defect. Surgery was then concluded and the patient was sent in a stable condition to the intensive care unit for postoperative care and completion of an antibiotic course.

This case illustrates the importance of early involvement of cardiac surgery in the care of an IE patient and the significance of treating present, or preventing imminent, hemodynamic instability, even in the face of active infection. It also underscores the role of TEE as a valuable means for diagnosis and follow-up.

General Principles

Infective endocarditis is not a common disease. A French survey in 2002 estimated the incidence of IE at 31 per one million adults [1], and a large European multicenter survey showed that only 159 (3.2%) of 5001 patients with valvular disease had a history of IE [2]. Thus, surgical treatment of IE constitutes a relatively small portion of all cardiac surgery procedures. Yet, during their admission for IE, about a third of all patients required cardiac surgery [3]. Not surprisingly, the absolute number of IE operations is large enough for these procedures to be considered a significant entity in cardiac surgery. Of 1,262 patients undergoing valve surgeries at our institute over a period of 39 months, 51 (4%) were operated on to treat IE.

Surgical procedures for "active" or "acute" IE are technically more demanding than operations for acquired non-infected valvular lesions. The main challenge in acute IE is to address the two coexisting aspects of the disease: (1) the infectious process that requires removal of all infected tissues to prevent recurrence of IE, and (2) the altered valvular anatomy and function that should be corrected or restored. This may require extremely complex and high-risk surgical procedures, although operations in "healed" IE with no residual infection or perivalvular involvement can be handled similar to conventional valve operations.

The decision-making process is key to the final surgical outcome, underlining the critical need for each individual case to be carefully assessed for the infectious process and evaluated for valvular dysfunction in order to decide on when and how to operate.

Assessing the Infectious Process

This step is critical in achieving optimal control of an active infection. Failure of infection control and active infection at the time of surgery is a risk factor in all surgery. It may result in residual infected tissue after surgery and increased risk of recurrence. First, any predisposing local factors such as anatomic or functional valve abnormalities, or factors related to general patient condition (immunosuppression, history of cancer, etc.) should be identified and managed to evaluate risks and prevent recurrence. Next, a possible primary source of infection, either obvious or latent, such as soft tissue abscess or poor dental hygiene, must be identified and eradicated prior to heart surgery. Septic dissemination may also result in non-cardiac infectious localization, including metastatic abscesses (e.g., splenic abscess), mycotic aneurysms, and cerebral emboli, which should be addressed, as they may significantly complicate the surgical strategy.

Finally, the causative microorganism should be identified and treated as per culture results. In culture-negative IE, the most probable organisms should be determined based on epidemiological and demographic characteristics of the individual case. The identified or probable causative organism determines the specific or empiric antibiotic therapy pre- and perioperatively. Determining the causative microorganism is significant in decision-making, in that it has a direct impact on the course, pathophysiology, and complications of IE, and hence on its management. *Staphylococcus aureus* IE, for instance, causes more serious valvular damage and is associated with a higher embolization and mortality rates [4]. Fungal IE generally does not respond well to medical therapy, and surgery is eventually needed; thus earlier intervention is usually warranted. In streptococcal IE, vegetation size is an independent risk factor for embolic events [5]. Q Fever IE is a leading cause of negative blood-culture IE and should be investigated through specific immunological testing [6,7].

Evaluating the Severity of Valvular Involvement

In the first place, the type of *IE* should be considered as to whether it is native valve endocarditis (NVE) or prosthetic valve endocarditis (PVE). The latter is associated with more severe complications, operative technical difficulties, and less favorable results compared to NVE. Surgical results are also better for an initial IE episode than for recurrent IE.

All valves and related structures should be assessed to determine the involved valves, extent of disease (e.g., annular involvement), and presence of intracardiac complications (i.e., abscesses, aneurysm/pseudo-aneurysm, fistula, aortoventricular/atrioventricular discontinuity, etc.). Such complications constitute independent risk factors with adverse impact on operative outcomes and survival.

Deciding on When and How To Operate

The role of timing in the surgical management of IE cannot be overemphasized. Operating too soon carries a higher risk due to the unstable condition of the patient, excessive cardiac tissue friability (resulting in early postoperative periprosthetic leakage), and greater possibility for recurrence (due to residual, minimally diseased foci that might go unnoticed during surgery). An undue delay in operation, on the other hand, may result in life-threatening sepsis or extensive structural destruction with irreversible damage

to cardiac function. Timing in active IE can often be no less challenging than determining the type of the operation.

The choice of whether to repair the native valve or to replace it with a prosthetic valve—and in cases of replacement, whether to implant a bioprosthetic or mechanical valve—is ultimately verified intra-operatively. In multiple valve involvement, a proper combination of repair and replacement procedures may be used as appropriate for the individual case. Surgical techniques can vary along a wide spectrum of complexity, from the simple stitching repair of a well-defined leaflet perforation to an extensive aortic root replacement, and from an isolated mitral valve replacement to a complex valve and annulus reconstruction, including the correction of septal defects, fistula, aneurysm/pseudoaneurysm, or atrioventricular discontinuity. Plans will occasionally require modification or refinement based on the findings in the operating room or due to technical issues encountered intraoperatively.

Indications and Evaluation for Surgery

Generally speaking, major absolute indications for surgical intervention in IE include—

1. hemodynamic compromise,
2. persistent and/or uncontrolled infection despite aggressive medical therapy, and
3. embolization [2,3,8–11].

Significant anatomical changes and complications caused by IE, such as aneurysm, fistula, and atrioventricular discontinuity, may also be considered an indication, as they usually indicate the imminent occurrence of hemodynamic compromise. Some authors have advocated other relative indications for surgery (Table 8.1) [2,5,11]. The most common indication for surgery is usually heart failure, followed by persistent sepsis [2,9,12].

Surgical outcomes are better in healed IE operations than in acute IE surgeries. However, in the presence of a major indication, or when clinical judgment strongly suggests that surgical indication is imminent, there should be no delay in carrying out the operation, even with active IE. Hemodynamic stability takes priority over infection control by medical treatment.

Table 8.1. Indications for Surgery in IE

Absolute indications
Hemodynamic compromise due to valvular dysfunction
Uncontrolled infection despite appropriate antimicrobial treatment
Fungal endocarditis with vegetations
Embolic event (cerebral or peripheral)
Recurrent embolization
Emboli after adequate antibiotic therapy
Anatomical complications/deformities
Abscess
Fistula
Aneurysm/pseudoaneurysm
Aortoventricular/atrioventricular discontinuity
Valve dehiscence and paravalvular leak (in PVE)
Relative indications
Echocardiographic detection of—
Large vegetations (>10 mm in diameter)
Vegetations increasing in size after 4 weeks of antimicrobial therapy
New conduction blocks

When to operate for IE remains a controversial issue and is often addressed on a case by case basis. Surgical timing strategies have evolved considerably over the recent years, owing to the developments in the medical management of infectious diseases and in diagnostic tools, echocardiography in particular. The more routine use of TEE, beginning in the 1990s, has especially led to earlier and more accurate identification of surgical indications and more optimal timing of operation.

Early diagnosis by echocardiography and blood cultures, identification of the causative microorganisms, detection of localized foci of infection by advanced imaging techniques, and availability of more effective antimicrobials have all definitely changed the decision-making process and timing for surgery. Such improvements have even enhanced the frequency of successful medical management without the immediate need for cardiac surgery. On the other hand, improvements in operative techniques, postoperative care, availability and quality of prosthetic valves, and the accuracy in early prediction of inevitable surgery are all in favor of earlier surgical intervention. Many situations that were once considered high-risk for surgery have demonstrated better outcomes with surgical intervention than with conservative medical management.

Significant acute aortic or mitral regurgitation with heart failure in the setting of NVE is an obvious indication for surgery. Some authors have also advocated the following findings as

indications for surgery: large vegetations [2,11], especially those that are >10 mm in diameter [13]; increase in the size of vegetations after adequate antimicrobial therapy [5]; and the presence of vegetations in the setting of a fungal IE [5], since antifungal penetration into vegetations is not adequate for cure. Detection of vegetations following an embolic event may require urgent surgery, if further embolic episodes are deemed imminent.

In the absence of severe valvular dysfunction, surgical timing will be influenced by TEE information demonstrating the anatomy and function of the valves, perivalvular structures, and possible extension of the infectious process to the annular and/or muscular structures. Although some cases of perivalvular abscess can be successfully treated medically, the presence of annular/perivalvular abscesses indicates surgery [14]. Even with controlled infection and stable hemodynamic situation, perivalvular abscess constitutes a risk factor for more serious complications and recurrent IE, and perivalvular abnormalities are common despite early surgical intervention [14,15]. Abscesses are commonly associated with pseudoaneurysm and/or fistula formation. If echocardiography is not conclusive with regard to abscess presence or extension, the patient should be followed closely with serial echocardiographic studies. Abscesses are found more often in aortic IE, but have a higher incidence of pseudoaneurysm/fistula formation in the mitral position [16]. Septal abscesses associated with aortic IE may cause conduction abnormalities. Indeed, a new conduction block on ECG in the setting of IE has a high positive predictive value for the presence of perivalvular abscess [17].

In cases of PVE, surgical indications would include all of the aforementioned plus prosthesis dehiscence and new/dynamic paravalvular leak as documented by serial echocardiography. Increasing paravalvular leak is an ominous sign of circumferential extension of dehiscence and should lead to consideration of more aggressive treatment including surgery.

A complication of the infectious process that mandates careful evaluation is systemic embolization, a cardinal determinant of mortality and morbidity in IE patients. Embolic events are reported in up to half of IE cases [5]. Of these, up to 71% are cerebral embolic events [18]. Most embolic events occur within two weeks of onset of symptoms [18] or initiating antibiotic therapy [19]. Therefore, the greatest impact of surgical intervention on the incidence of emboli is within these time limits. An embolic event during the first two weeks of antimicrobial therapy or recurrent embolism at any time should indicate surgery [8]. A detailed discussion on strategies to prevent embolism is presented in Chapter 13.

A major issue in the timing of surgery is the presence of a cerebral infarct. Because of the risks imposed by anticoagulation and the potential risk of cerebral edema due to cardiopulmonary bypass, it is generally agreed that hemorrhagic cerebral infarct is a contraindication to surgery, at least temporarily. The main controversy arises on the timing of surgery with non-hemorrhagic infarcts due to their potential for hemorrhagic transformation. Some investigators have demonstrated better outcomes when surgery is performed at least 11 days after ischemic and 23 days after hemorrhagic cerebrovascular accident [20]. Others have reported considerably more favorable outcomes even when cardiac surgery is performed within 72 hours of cerebrovascular accidents as opposed to deferring operation after eight days [18]. Our practice and recommendation is to defer the operation for at least two weeks after a non-hemorrhagic stroke and four weeks after a hemorrhagic episode [21].

In some patients, symptomatic embolic CVAs may be followed by the detection of intracranial mycotic aneurysms, the rupture of which can cause catastrophic results [5]. Although uncommon, these aneurysms can sometimes leak slowly, and anticoagulation for cardiopulmonary bypass can predispose these patients to a potentially fatal hemorrhage. Careful imaging studies prior to cardiac surgery should therefore be undertaken if there is any clinical suggestion of a possible intracranial mycotic aneurysms.

Splenic abscess (or abscess located elsewhere) is another complication of the infectious process in IE that may cause persistent bacteremia/sepsis. It does not usually respond well to antibiotic therapy and should be treated surgically, by splenectomy (or surgical drainage and debridement in other locations), or drained percutaneously before valve surgery is performed. In general, every attempt is made to eradicate any identified source of infection before cardiac surgery for IE is performed to prevent recurrence.

Both cranial and abdominal computed tomography should be considered in all patients with IE to assess for the presence of any abscess, infarct, hemorrhage, or aneurysm.

Finally, like any other open-heart surgery, the patient should also be evaluated from other cardiac and non-cardiac standpoints. Hepatic and renal functions are of particular importance, as they have a great impact on the surgical outcomes. Unjustified delay of the operation, when surgery is indicated, may cause deterioration in renal and/or hepatic function due to both the disease itself and the toxicity of medications, antibiotics in particular.

This underscores, once again, the significance of the right timing for surgery. Comorbidities (diabetes, etc.) should be considered and properly addressed. In patients with a high risk of coronary artery disease, preoperative angiography should be performed to assess for the possible need of coronary artery bypass grafting at the same operative session.

In view of the fact that cardiac surgery is an integral part of IE management, early consultation with the cardiac surgery team is strongly recommended following the diagnosis of IE. This will allow the surgical team to be fully familiar with the patient, in case surgery is eventually needed. It will also enable medical and surgical teams to join forces in determining the need and optimum timing for surgery. The American College of Cardiology/American Heart Association Guidelines for the Management of Patients with Valvular Heart Disease also support early surgical consultation in IE cases [22].

Operative Techniques

Accessing and Preserving the Heart

Partial or total median sternotomy is used for IE operations. In cases with previous coronary bypass surgery, right thoracotomy may be preferred to access the mitral valve, avoiding possible damage to patent grafts. Access to the mitral valve is excellent through right thoracotomy, although it does not allow easy access to the aortic root. For aortic IE complicated by an aortic root aneurysm or pseudo-aneurysms, particularly in redo operations, cardiopulmonary bypass is preferably established through the femoral vessels. Deep hypothermia may also be necessary and safer prior to repeat sternotomy. Myocardial protection is very important considering that surgery may involve long durations of cross-clamping and myocardial ischemia. With retrograde blood cardioplegia, excellent myocardial protection can be achieved by repeat injections (every 20 minutes) through the coronary sinus without interrupting the surgeon's work on the valve reconstruction. This technique avoids the manipulation of catheters and the need for direct antegrade root perfusion, which can cause migration of infected material into the coronary circulation in infected aortic root with severe aortic insufficiency. It also eliminates the need for cannulating possibly friable coronary ostia that might further complicate the operation.

Valves are accessed through usual approaches, such as left atriotomy for mitral valve or ascending aortotomy for aortic valve. However, more complex approaches may be required to evaluate all deformities and achieve optimal debridement of all infected tissues, including biatrial combined with aortic approach. More extensive cardiac incisions will require more time to repair and pose a higher intraoperative risk of bleeding, although they may occasionally be inevitable.

Choosing To Repair or To Replace

When valve repair is an option, it is preferred over replacement. Advanced technical skills and sufficient experience in complex repair procedures are crucial to achieve a high success rate of repair procedures. Valve reconstruction (repair) surgeries are more often feasible in the mitral or tricuspid position than in aortic valve. This is mainly due to larger leaflet sizes of the mitral and tricuspid valves (better tolerating partial tissue resection and suturing). The greater prevalence of extensive tissue destruction in the aortic IE also reduces the feasibility of aortic valve repair.

There are no randomized clinical trials to evaluate the outcomes of valve repair versus replacement in patients with IE. The views provided are, therefore, observational. Native valve preservation has been associated with significantly lower perioperative morbidity and shorter hospital recovery time than replacement [23,24]. Mortality also tends to be lower with valve repair, even though the difference is not statistically significant. The benefits of valve

repair also include eliminating the need for aggressive anticoagulation therapy, thus reducing the immediate risk of bleeding complications as well as the need for lifetime anticoagulation.

There is no significant difference in mortality between mechanical and bioprosthetic valves. Therefore, the choice is based on balancing the advantages and disadvantages of each in the individual patient. Mechanical valves are very reliable and durable, but they require lifelong oral anticoagulation. On the other hand, bioprostheses do not need anticoagulation, but they degenerate after 10–15 years and require reoperation and replacement with another prosthetic valve. Thus, in younger patients with a long life expectancy and in whom there is no significant risk of hemorrhage, mechanical valves are preferred. In patients with shorter life expectancy where durability is not an issue, in patients with high risk of hemorrhage, in young women with an intention of childbearing who should not be exposed to the teratogenic effects of warfarin, and in patients who choose not to receive a mechanical valve, bioprosthetic (porcine or bovine) valves are a valuable substitute for mechanical valves. It should be mentioned that in the case of women with childbearing intentions, an option is to implant a mechanical valve with oral anticoagulation, and then switch to heparin preconception and during pregnancy. However, the required close monitoring of heparin injections and anticoagulation renders this choice less practical and unadvisable for most patients.

When the aortic root is extensively damaged, a composite graft incorporating a prosthetic valve and a vascular graft can be used. The other option is the use of homografts, which usually have very good results in experienced hands [25]. Although no conclusive data is available comparing homografts and prosthetic valves in terms of durability and risk of recurrent IE, current data from surgical series indicate satisfactory results with the use of homografts [25]. However, the limited availability of homografts precludes the widespread use of this treatment modality.

In any instance, the final choice to repair or replace the valve can only be made after thorough anatomical and functional assessment by the surgeon intraoperatively.

Assessing the Valves and Adjacent Structures

Structural cardiac lesions in IE include (a) lesions that existed prior to the onset of the disease and (b) new lesions caused by IE (Table 8.2). Preexisting lesions may include mitral valve prolapse, any valvular stenosis or insufficiency, congenital defects such as bicuspid aortic valve and residual lesions from previous IE, including those related to prosthetic valve implantations. Lesions caused by the current IE include vegetations (most frequent IE lesions), leaflet/cusp perforation, rupture of chordae tendinae, annular dilatation, abscesses, aneurysm/pseudoaneurysm, and annular or septal fistulae. The type and extent of lesions determine the surgical technique; and hence, the operation can be anywhere along a spectrum of technical difficulty, from simple suturing of a leaflet/cusp perforation to complex reconstruction and replacement techniques including homograft implantation.

Table 8.2. Structural Lesions in Infective Endocarditis

Lesion	Remarks
Common Lesions	
Vegetations	On ventricular aspect of aortic valve, atrial aspect of mitral valve
Leaflet Perforation	Usually in the anterior mitral leaflet; anterior mitral leaflet involvement also caused by vegetative aortic IE
Abscesses	Mostly seen in *S. aureus* IE; more common in PVE; in NVE, up to 50% in aortic valve and 5% in mitral valve IE
Aneurysm/Pseudoaneurysm/Fistula	Usually develops from abscess
Uncommon Lesions	
Stenosis	More common in mitral and tricuspid valves, PVE and fungal IE
Suppurative pericarditis	Seen in myocardial perforation
Myocardial infarction/Ruptured chordae rendinae	Due to coronary emboli or vegetations on subvalvular structures
Preexisting valvular lesions	Especially mitral valve prolapse and degenerative aortic valve changes

The most common lesions in IE and technical considerations in their surgical management are the following:

1. Vegetations: These are the most common lesions in IE. They are usually found on the ventricular aspect of the aortic valve and on the atrial side in the mitral valve. The size and site of the attachment of the vegetation and the relation to the leaflet/cusp size are important. Removal of large or multiple vegetations leaves a large defect in the leaflet that is more difficult to repair and valve replacement might be the proper or only choice in extensive vegetative IE. Due to smaller surface areas of aortic cusps compared to mitral leaflets, the size of a lesion that could be readily repaired in the mitral leaflet may be too large for aortic cusp repair. This is one main reason why mitral valve repairs are more commonly performed than aortic valve repairs. Vegetations should be removed in one piece to avoid fragmentation, and cardiac manipulation should be minimized to prevent dislodging potential embolic material. The location of vegetation attachment is also important. Repair of lesions in the middle of a leaflet is more feasible compared to vegetations with a base involving two leaflets/cusps and/or the annulus. Discrete lesions in the free margin of the anterior mitral leaflet can be removed with a triangular resection, and for posterior leaflet lesions, a quadrangular resection is usually used (Figure 8.1). Infection involving both mitral leaflets at or near the commissures dictates leaflet resection and debridement of the annulus. In such cases, it may be feasible to perform direct suturing to reconstitute the commissure and to plicate the annulus with pledgetted sutures (Figure 8.2).
2. Perforation: Not infrequently, IE leaves behind a perforation in the leaflet/cusp, causing valvular insufficiency. Perforations are more common in the anterior leaflet of the mitral valve, and they may be caused by satellite vegetation due to aortic valve IE. Thus, the anterior mitral leaflet should always be carefully examined for the presence of erosions and perforations in patients with aortic IE. Small perforations with smooth, regular margins may be closed by direct suturing of the edges. Prolene sutures are preferred for their lack of spaces between interwoven threads and probably lower risk of recurrent IE. Larger perforations, and defects left behind from partial leaflet resection, can be repaired using autologous or bovine pericardial patches (Figure 8.1B,C). Autologous pericardium is harvested and stripped of fat and connective tissue. Pericardial patches may be used fresh or preserved intraoperatively in a glutaraldehyde-buffered solution and rinsed in saline prior to use [26]. Separate sutures are preferred to continuous sutures, and reinforcing pledgets should be considered with caution, due to the fact that

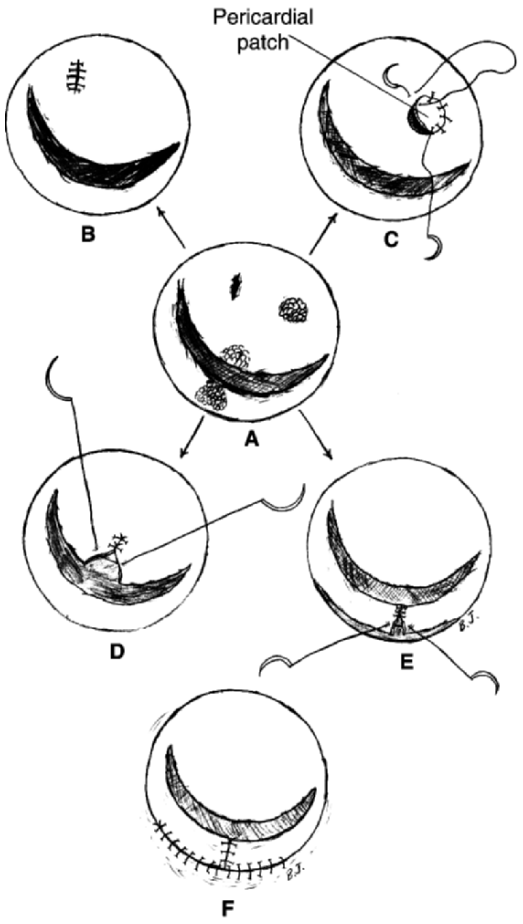

Figure 8.1. **A:** Surgical approach to repair the mitral valve in the setting of vegetations or perforations. **B:** Small perforations with regular margins may be repaired by directly suturing the edges. **C:** The defect in the anterior mitral leaflet caused by the removal of vegetation can be repaired using a pericardial patch. **D:** Triangular resection for the removal of a lesion in the free margin of anterior mitral leaflet. **E, F:** Quadrangular resection and sliding plasty for discrete lesions in the posterior mitral leaflet.

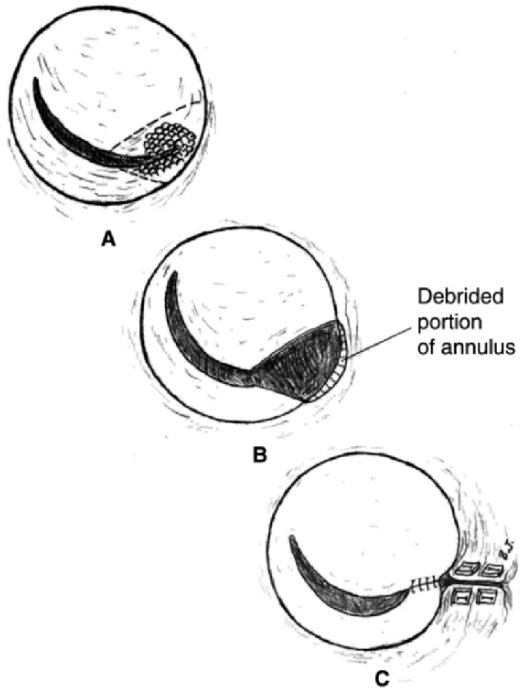

Figure 8.2. **A:** Lesions involving both anterior and posterior mitral leaflets at the posteromedial commissure. The dashed lines outline where the leaflets will be resected. **B:** Diseased portions of both anterior and posterior leaflets are resected. The affected annulus is also debrided. **C:** Reconstruction is performed by directly suturing the edges of the anterior and posterior leaflets and plicating the annulus with pledgetted sutures.

they add more foreign material exposed to recurrent infection. Debridement of the perforation prior to patch repair is of utmost importance.

3. Perivalvular abscesses: They must be carefully searched, evaluated, and treated. Extensive debridement of abscesses is the key to immediate and long-term surgical success. Abscesses are predominantly associated with IE caused by *Staphylococcus aureus* and are much more common in aortic IE than in mitral IE (25–50% in aortic vs. 1–5% in mitral IE) [27]. However, they have more severe adverse impacts in the mitral position. In aortic IE, abscesses mostly form at the weakest location of the annulus, near the membranous portion of the interventricular septum, in the vicinity of the atrioventricular node [8]. This anatomical predilection of abscesses explains the development of new conduction blocks resulting from abscess formation. Abscesses below left coronary cusp, between posterior wall of the left ventricle (LV) and left coronary ostium, are also not uncommon and tend to extend toward the anterior mitral leaflet and the non-coronary cusp section of the annulus.

Mitral annular abscesses usually occur in the posteroinferior portion, and this part should be carefully inspected for abscesses when mitral valve is being resected. A well-defined, small abscess can be drained, debrided, and the remaining defect can be corrected with a pericardial patch. When discontinuity is present between LV and left atrium (LA), a modified technique for valve replacement can be used, which consists of interrupted horizontal mattress sutures with pledgets placed on the LV side of mitral annulus, carried up through the LA side of the debrided annulus, and then through the sewing ring of the prosthetic valve. However, the distance between the edge of LV and LA after debridement and the fragility of the infected tissue poses a failure risk on such a technique either immediately in the operating room or during postoperative period. To avoid excessive tension on weakened ventricular or atrial structure, a good alternative is to reconstruct the annulus with pericardium, attached first to the LV with running 4-0 or 3-0 prolene suture, and then attached to the atrium. Prosthetic valve will then be placed with pledgetted sutures in the upper portion (atrial side) of the pericardial patch (Figure 8.3). Thus, the prosthesis will be more atrially positioned rather than in the ventricular cavity. Biological glue can be used as a good adjunct to such a reconstructive procedure. Glue can be spread posteriorly to the pericardial patch after completion of ventricular suture and before completion of atrial sutures of the patch. The risk of postoperative AV discontinuity is considerably reduced with this procedure.

In aortic valve IE repair is also preferred to replacement, although repair is less frequently feasible with the aortic valve compared to the mitral valve, as previously discussed. Lesions limited to one cusp, sparing the annulus (Figure 8.4A) can be removed and reconstructed with tailored pericardium. When the annulus is also involved (Figure 8.4B), annuloplasty accompanies cusp reconstruction. Extensive disease of the noncoronary sinus involving the annulus and the anterior mitral leaflet (Figure 8.4C) requires a more complicated procedure involving removal of the lesion, reconstruction of the

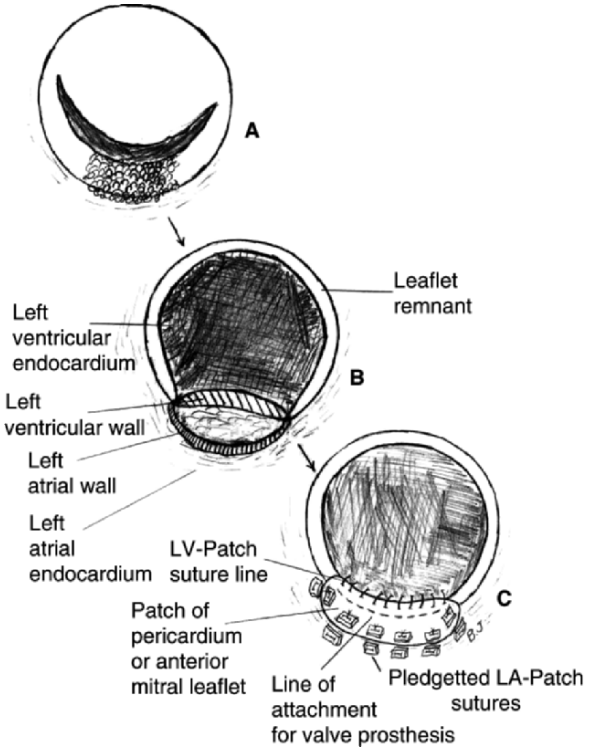

Figure 8.3. **A:** Surgical approach to treat abscess involving the mitral annulus. **B:** The infection is extensively debrided, leaving behind a defect at the atrioventricular junction. The anterior and posterior mitral leaflets are also resected, leaving a narrow rim of leaflet remnant. **C:** The atrioventricular defect is repaired with a patch tailored from the pericardium or, occasionally when the anterior leaflet is not diseased, from the anterior mitral leaflet. The patch then serves as a part of the anchorage for the prosthetic mitral valve.

resulting structural defect with a pericardial patch, reconstruction of the noncoronary cusp using a piece of pericardium, and annuloplasty.

If the abscess or other structural damage involves the aortic structures extensively, aortic root replacement will be the procedure of choice. Root replacement is done in the usual fashion following debridement of the infected tissue. Extra care is taken to place the proximal suture line low (proximally) enough in the LV outflow tract that any discontinuity between the LV and proximal aorta is eliminated. Homograft aortic roots provide a good means for this type of operation. The anterior mitral leaflet is involved when there is extensive aortic root destruction and extension to the aortomitral curtain. Involvement of this critical intersection of aortic and mitral valves requires complicated surgical approach through both LA and ascending aorta. Homografts which often include the anterior mitral leaflets offer the optimal material to repair such defects. This may involve extensive debridement and reconstruction of LA roof and atrial septum with pericardial patch which also serves as anchor for suturing in place the aortic homograft (Figure 8.5). Alternatively, the aortomitral curtain of the aortic homograft can be used to repair the defect resulting from the debridement (Figure 8.6)

Surgical Outcomes and Complications

Excellent surgical results can be achieved in situations where infection has been brought under control, IE is confined to a native valve, valve damage is amenable to repair or simple replacement, and the patient is relatively young without comorbidities. Table 8.3 summarizes factors that negatively affect morbidity and/or mortality after surgical management of IE.

Both short- and long-term results are less favorable following surgery for PVE as compared

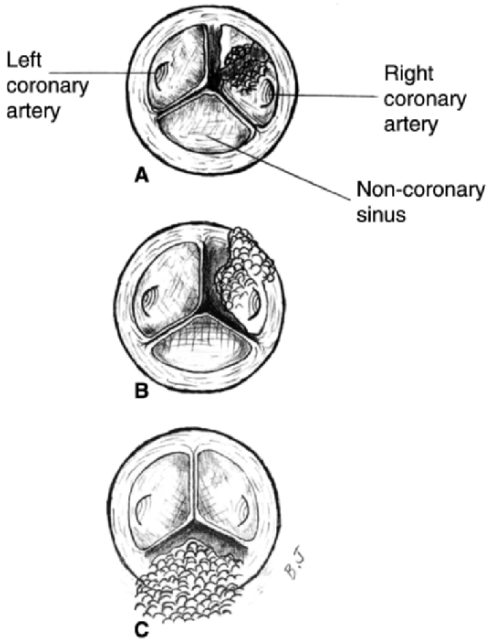

Figure 8.4. Various locations and extents of infection on the aortic valve. **A:** Lesion limited to the right coronary cusp, sparing the annulus. The lesion has eroded the cusp, resulting in a tear in the cusp. **B:** Lesion involving the right coronary cusp and extending to the annulus. **C:** A diseased noncoronary sinus with extension of the lesion to the annulus and the anterior mitral leaflet.

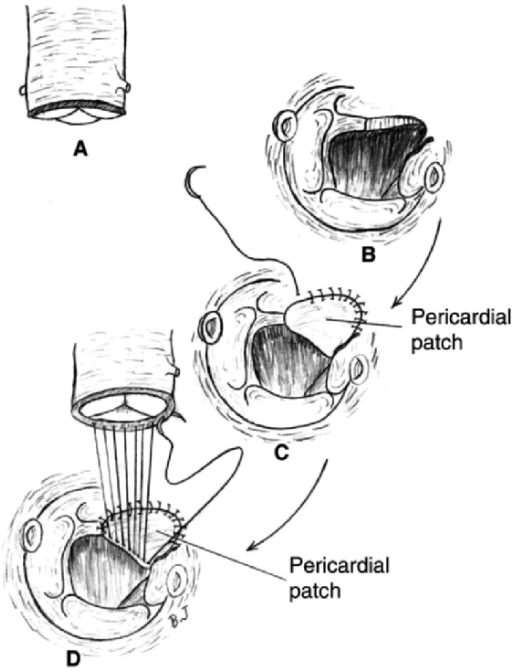

Figure 8.5. A: An aortic homograft without the aortomitral curtain. **B:** The defect left from the removal of the aortic root and the diseased aortomitral curtain. **C:** A pericardial patch is first used to repair the defect at the aortomitral location. **D:** The aortic homograft is then anchored in place with part of the homograft sutured onto the pericardial patch.

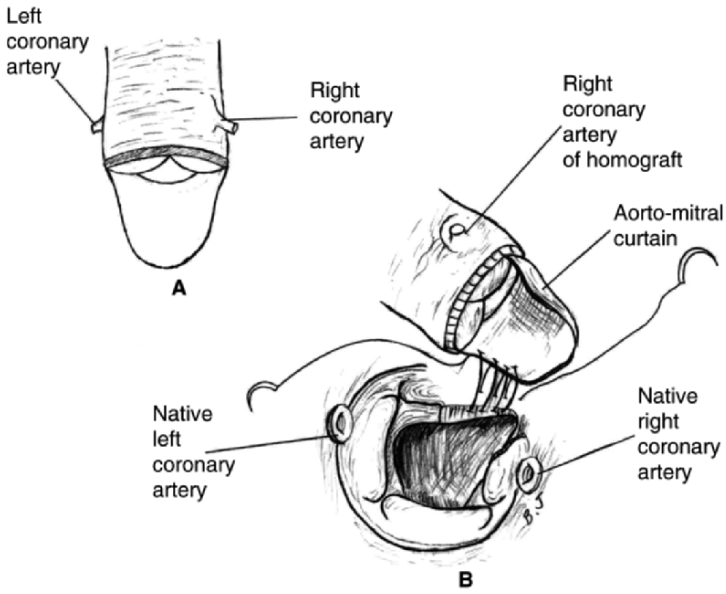

Figure 8.6. Homografts can be used in the reconstruction of extensively diseased aortic root. **A:** An aortic homograft with the accompanying aortomitral curtain. **B:** The aortomitral curtain of the aortic homograft can be used to repair the defect caused by the removal of aortic root lesions extending to the aortomitral location.

Table 8.3. Factors Adversely Affecting Surgical Outcomes (Mortality and Morbidity)

PVE (versus NVE)
Intracardiac abscess
Left-sided (versus right-sided) IE
Aortic (versus mitral) IE
Extensive disease/destruction, multiple valve involvement
Staphylococcal or culture-negative infection
Advanced age
Increasing cardiopulmonary bypass and aortic cross-clamp time
Valve replacement versus repair (affects morbidity only)
Delay in surgery in face of worsening cardiac function
Early PVE (associated with higher rate of late death)
Emergent /urgent surgery due to progressive heart failure
Poor LV function (whether or not due to IE)
Postoperative sepsis (most commonly pneumonia)
Postoperative renal failure
Liver failure

Table 8.4. Hospital (or 30-Day) Mortality in NVE and PVE

Study	NVE (%)	PVE(%)	*P*-value
Murashitaet al., 2004 [28][a]	15.5	33.3	0.0123
Romano et al., 2004 [29]	6.6	24.2	<0.0001
d'Udekem et al., 1997 [5]	4	13	0.062
Wilhelm et al., 2004[b] [23]	3.2		
Amrani et al., 1995[c] [30]	8.5		
Akowuah et al., 2003[d] [31]		24	

[a] Numbers in brackets [ ] indicate reference numbers.
[b] Native mitral valve endocarditis.
[c] Native aortic valve endocarditis.
[d] Aortic and/or mitral PVE.

to NVE (Tables 8.4 and 8.5). The reasons for relatively poor outcomes in PVE are higher rates of staphylococcal infection and perivalvular abscess, the presence of less healthy perivalvular tissue, risks of reoperation, and a generally older population compared to NVE patients. Multiple valve disease is associated with more extensive tissue destruction, longer duration of operation, and less favorable results (Table 8.5).

The infecting microorganism directly affects mortality and morbidity. Staphylococcal infections, especially those caused by *Staphylococcus aureus*, as well as culture-negative IE are associated with poor outcomes (Tables 8.6 and 8.7). *Staphylococcus aureus* infections cause more extensive destruction, more frequent abscess formation, and greater hemodynamic derangement.

Valve repair procedures, especially in the mitral position, are associated with significantly lower postoperative morbidity than valve replacement. However, there is no significant difference between repair and replacement procedures in terms of mortality (Table 8.8).

The first postoperative year is of crucial importance, as most of the adverse events occur during this period. Patients who have an event-free first postoperative year are likely to have a favorable long-term survival. Table 8.9 summarizes surgical complications. Recurrent IE is a serious postoperative complication and is associated with poor prognosis, especially when it occurs in the replaced prosthetic (versus repaired native) valves. Early recurrent IE is usually due to residual infected tissue, and the recurrence risk can be minimized by complete debridement of the infected tissue and proper surgical technique. Late recurrent IE is more frequent in patients who have abscess at the

Table 8.5. Survival in NVE and PVE

	Survival in NVE (%)					
Study	1-year	5-year	10-year	15-year	20-year	*P*-value
Romano et al., 2004 [29][a]	91	82	67.5	48.8		0.0016 (vs. PVE)
Wilhelm et al., 2004 [23]	93	81	61			
Amrani et al., 1995 [30]						
Non-complex operations[b]		93.5	93.5			0.042
Complex operations[c]		79.9	76.1			
Moon et al., 2001[32]			54		44	<0.003 (vs. PVE)
	Survival in PVE (%)					
	1-year	5-year	10-year	15-year	20-year	*P*-value
Romano et al., 2004 [29]	79.7	64.2	33.5	33.5		0.0016 (vs. NVE)
Moon et al., 2001[32]			41		16	<0.003 (vs. NVE)
Akowuah et al., 2003 [31]			58			

[a] Numbers in brackets [ ] indicate reference numbers.
[b] Single aortic valve replacement.
[c] Aortic valve replacement plus another valve procedure.

Table 8.6. Effect of Infecting Microorganism on Survival

Study	Infecting Microorganism	Early Postoperative Mortality (%)			*P*-value
Murashita et al., 2004 [28][a]	*Staphylococcus aureus*, *Staphylococcus epidermidis*, or culture-negative	17.8			0.158
	Other pathogens	0			
Amrani et al., 1995 [30]	*Staphylococcus aureus*	8.5			
	Other pathogens	0			
d'Udekem et al., 1996 [8]	Staphylococci	22			0.020
	Other pathogens	3			
		Survival (%)			
		1-year	5-year	10-year	*P*-value
Wilhelm et al., 2004 [23]	*Staphylococcus aureus*	76.5	65	44	0.008
	Other pathogens	98.9	84.9	67	

[a] Numbers in brackets [ ] indicate reference numbers.

time of the initial operation [9]. Recurrent IE rates are given in Table 8.10.

There is no significant difference in either short- or long-term survival between mechanical and bioprosthetic valves. A recent study suggests superiority of mechanical valves in the mitral position in terms of mortality for patients 51–70 years of age [33]. However, further studies are required to support this finding. Due to the need for lifetime anticoagulation in mechanical valves, this group has a higher risk of hemorrhage. Reoperation, on the other hand, is more common in bioprosthetic valves due to propensity for degeneration over time. Bioprostheses are also associated with a higher rate of recurrent endocarditis [33–35]. Table 8.11 gives a brief comparison of mechanical versus bioprosthetic valves.

Table 8.7. Effect of Infecting Microorganisms on Event-Free Survival (Murashita et al., 2004 [28])

Infecting Microorganism	Three-Year Freedom from Events (%)
Staphylococcus aureus	55.6
Culture-negative	47.6
Streptococcus	100

Table 8.8. Valve Replacement Versus Repair

Study	Operative/In-Hospital Mortality			
	Mortality with Repair (%)	Mortality with Replacement (%)		*P*-value
Wilhelm et al., 2004 [23][a]	1.7	4		0.67
Mihaljevic et al., 2004 [24]	0	13		0.14
	Survival (%)			
	1-year	5-year	10-year	*P*-value
Wilhelm et al., 2004 [23]				
Valve replacement	96.5	92.5	79	0.1
Valve repair	98	95.4	95.4	
Mihaljevic et al., 2004 [24]				
Valve replacement	78	73		Not significant
Valve repair	85	85		
	Morbidity			
	Variable	Valve Replacement	Valve Repair	*P*-value
Wilhelm et al., 2004 [23]	Perioperative Morbidity (<30 days after surgery)	62%	5%	< 0.001
Mihaljevic et al., 2004 [24]	Median of Hospital Stay	21 days	9.5 days	< 0.01

[a] Numbers in brackets [ ] indicate reference numbers.

Table 8.9. Postoperative Complications

Early Complications	Late Complications
Failure of repair procedure	Deterioration of repair
Prosthetic dehiscence with/ without significant paravalvular leakage	Prosthetic dehiscence with/ without significant paravalvular leakage
Sepsis (most commonly pneumonia)	Anticoagulation-related events (in mechanical valves)
Renal failure	
Hemorrhage	Recurrent IE, including PVE
Need for reoperation	Bioprosthesis degeneration
Atrioventricular block and/or arrhythmia (with/without need for permanent pacemaker)	
Recurrent IE, including PVE	

Table 8.10. Risk of Recurrence of Infective Endocarditis Following Surgical Intervention for Endocarditis

Study	Type of IE in the Study	Rate of Recurrent IE (%)	
		At 5 years	At 10 years
d'Udekem et al., 1997 [8][a]	NVE and PVE	9	21
Mihaljevic et al., 2004 [24]	NVE	5.7[b]	
Akowuah et al., 2003 [31]	PVE	40	

[a] Numbers in brackets [ ] indicate reference numbers.
[b] All reinfections occurred within 5 months of surgery.

Table 8.11. Comparison of Outcomes in Mechanical and Bioprosthetic Valves

Operative Mortality: No significant difference
Bleeding: More frequent in mechanical valves (Associated with anticoagulation)
Reoperation: Higher rate with bioprostheses in younger (< 60 years) patients (Degeneration)
Recurrent Endocarditis: More frequent in bioprostheses
Long-Term Survival: No significant difference

Right-Sided Infective Endocarditis

Isolated tricuspid valve (TV) endocarditis is rare, except in the setting of intravenous drug abuse. Valve surgery is infrequent in isolated TV endocarditis, because of less pronounced impact on hemodynamics compared to the involvement of aortic or mitral valve. Involvement of the TV, however, does often accompany left-sided IE. In any case, surgical procedures on the TV mostly involve repair, and not replacement, owing to the anatomic and hemodynamic characteristics of the TV and the right heart. The principles and techniques of TV surgical procedures are similar to those for the mitral valve.

Summary

Despite advances in diagnosis and medical management, the need for valve surgery remains high in patients with IE and more so in those with aggressive infecting organisms. The primary consideration for surgical intervention is the hemodynamic derangement resulting from IE. Recent studies have shown that surgery can be successfully performed to restore hemodynamic stability and to help eradicate refractory infection, even in the setting of active IE before the completion of antibiotic treatment.

Valve surgery in IE carries high risks of short- and long-term complications, but the surgical results have steadily improved. Valve repair is preferable to valve replacement, if it is technically feasible. Aortic homografts are ideal in patients with aortic root destruction who requires extensive reconstruction of the aortic root and surrounding structures.

Optimal management of patients with IE requires a multidisciplinary approach, with surgical input an integral part of the management. Cardiac surgery team should be consulted soon after the diagnosis of IE is made, so that the surgical team is fully aware of the clinical course. This will provide the opportunity to develop a more comprehensive strategy and to avoid delay if and when surgery is required.

Key Points

1. Surgical consultation early in the course of the disease should be considered in all patients with IE, as about a third of IE patients require surgery during their hospitalization.
2. A thorough pre-operative workup from infectious and hemodynamic standpoints is crucial.
3. The main indications for surgery are hemodynamic instability, persistent sepsis, and recurrent embolization.
4. Hemodynamic stability must be prioritized over medical control of infection.
5. Native valve reconstruction (repair) is superior to replacement in terms of morbidity and tends to be associated with better survival.

6. PVE, intracardiac abscesses, poor LV function, and staphylococcal or culture-negative IE are associated with less favorable postoperative outcomes.
7. Outcome in the first postoperative year predicts the long-term course.
8. In properly selected surgical candidates, excellent results can be expected.

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9

Treatment of Native Valve Endocarditis: General Principles and Therapy for Specific Organisms

Donald C. Vinh and John M. Embil

Case Study

An otherwise well 53-year-old man had mitral valve prolapse diagnosed 20 years prior, and had been clinically stable. He presented with an eight-week history of night sweats and a 5-kg weight loss. Approximately one month prior to the onset of symptoms, the patient underwent a dental cleaning and took amoxicillin 2 g, 1 h prior to the procedure. The physical examination revealed a man who appeared well and whose blood pressure in the right arm in the sitting position was 118/64 mm Hg with a heart rate of 84 beats per minute (regular). His chest was clear to auscultation and his heart sounds were normal with the exception of a grade 3/6 systolic murmur radiating to the axilla. The peripheral pulses were all palpable and peripheral edema was absent. A blood culture yielded *Streptococcus mutans*.

A transthoracic echocardiogram revealed significant myxomatous mitral valve disease; marked thickening of the posterior leaflet with a shaggy appearance and flail segment involving predominantly the middle scallop were seen. Severe eccentric mitral regurgitation was present. The left atrium was significantly enlarged. This study was followed up with a transesophageal echocardiogram, which demonstrated that the posterior mitral valve leaflet was diffusely thickened and very redundant. There was severe prolapse of this leaflet. There was at least one small mobile mass at the leaflet tip, but the entire posterior leaflet was thickened and somewhat shaggy. The findings were consistent with endocarditis.

The *S. mutans* had a minimal inhibitory concentration (MIC) to penicillin of 0.008 g/mL. Since the patient was stable, it was elected to initiate home parenteral antimicrobial therapy with penicillin G, 18 million units per day administered by continuous infusion pump for 4 weeks. The patient had an uneventful course of therapy and underwent an elective mitral valve replacement one year later.

Introduction

Infective endocarditis (IE), if inadequately treated, is fatal. Even with appropriate management, overall mortality rates range from 10% to 25% [1–3]. Clinical outcome is influenced by multiple factors, including valve characteristics, host factors, causative organism, development of intracardiac or systemic complications, and management options available.

The therapeutic modality initially used in the treatment of IE is medical. The role of surgery, however, continues to expand; aggressive surgical intervention, particularly in the early stages of developing complications, can be associated with a reduction in mortality. This chapter will focus on the role of medical, and where appropriate, surgical, management in native valve endocarditis. Discussion regarding newer antibiotics is provided. Endocarditis involving prosthetic valve/intravascular devices, as well as endocarditis in special patient subpopulations, such as in intravenous drug users and in immunocompromised hosts, are discussed in other chapters.

Principles of Medical Therapy

Infective endocarditis remains a relatively rare disease, with annual incidences ranging from 15 to 60 cases per million]. Due to this low rate, good, prospective, randomized controlled trials assessing the benefits of various antibiotic regimens in the treatment of IE have been difficult to perform. Therefore, the principles of antimicrobial selection for IE are based on the understanding of the behavior of the causative pathogen, proper interpretation of antibiotic susceptibility testing, an understanding of vegetation characteristics, and proper application of antimicrobial pharmacokinetic and pharmacodynamic data. These considerations are complemented by animal experimental models and by clinical outcomes of published observational studies to form consensus-based guidelines for the optimal management of IE.

Fundamental to the management of IE is early diagnosis and prompt initiation of effective antimicrobial therapy. Therefore, proper laboratory identification of the pathogen to the species level is essential, with subsequent antimicrobial susceptibility testing using standardized protocols to determine the minimal inhibitory concentration (MIC). Testing for synergistic combinations of antibiotics (e.g., high-level aminoglycoside resistance for *Enterococcus* spp.) using standardized protocols should also be done where appropriate.

The MIC of an antimicrobial agent is defined as the lowest concentration which results in maintenance or reduction of inoculum viability; it is the lowest concentration of the drug needed to prevent microbial growth in vitro [6]. The MIC can then be compared to a reference standard database, such as that from the Clinical and Laboratory Standards Institute (formerly the National Commmittee for Clinical Laboratory Standards (NCCLS)), to interpret whether the pathogen is "susceptible," "intermediate," or "resistant" to the tested antimicrobial. Definitions of these terms are provided Table 9.1. It is important to note that the MIC represents a unique relation between a particular bacterial species and the tested antimicrobial agent. Because different antibiotics are tested at different concentrations, the MIC numbers cannot be directly compared.

The minimum bactericidal concentration (MBC) is the lowest concentration of an antibiotic, expressed in mg/L, that under defined in vitro conditions reduces by ≥99.9% (3 $\log_{10}$) the number of organisms in a medium containing a defined inoculum of bacteria, within a defined period of time [7]. Although the MBC is an in vitro microbiological method to determine the killing efficacy of antibacterial agents, its routine use in clinical practice is precluded by inaccuracy of measurement, as well as technical limitations (e.g., suboptimal inocula, difficulties with interpretation of a 99.9% bactericidal endpoint) that produce varying and thus invalid results [8–10]. As such, various working groups for endocarditis, including the British Society for Antimicrobial Chemotherapy (BSAC) and the American Heart Association committee (AHA), do not recommend its routine determination [11,12]. The value of the MBC, however, allows for the definition of antimicrobial agents as bactericidal, bacteriostatic, or tolerant.

Bactericidal antibiotics, generally speaking, are those that kill bacteria, whereas bacteriostatic agents are those that prevent the growth of bacteria (i.e., keeps them in the stationary phase of growth). In IE, a bactericidal regimen (either monotherapy or combination therapy) is considered necessary for cure [2,3,10,13]. The actual microbiological definition of "bactericidal" is a ≥99.9% reduction in viable bacterial density in an 18–24-hour period, producing an MBC to MIC ratio ≤4, whereas "bacteriostatic" is defined as a ratio of MBC:MIC > 4 [10]. Tolerance occurs among bacterial strains when a bactericidal antibiotic loses its killing efficacy but retains its bacteriostatic activity (i.e., MIC unchanged) and is defined as a ratio of MBC:MIC > 32 [7,14].

Although conceptualizing antibiotics as being either bactericidal or bacteriostatic may be use-

Table 9.1. Definitions of Terms Used in Antimicrobial Susceptibility Testing [520]

Susceptible (S)—implies that infections may be treated appropriately with the dosage of antibiotic recommended for the type of infection and infecting species, unless otherwise indicated.
Intermediate (I)—implies that infections may be treated if the antibiotic is able to reach specific tissues where the drug will be concentrated (for example, quinolones in the urine) or when the drug can be used in higher than usual doses without adverse effects. This category also includes a "buffer zone," which should prevent small, uncontrolled technical factors from causing major discrepancies in interpretation.
Resistant (R)—isolates are not inhibited by the usually achievable systemic concentrations of the drug in normal dosage and/or fall in the range where specific microbial resistance mechanisms are likely (for example, β-lactamases) and clinical efficacy has not been reliable in treatment studies.

ful, these categories are not mutually exclusive, but rather represent a continuum of antimicrobial activity. Bactericidal activity is not an invariable property of an antibiotic; it is also influenced by the organism, inoculum burden, as well as growth conditions [9,10,15]. For example, cell wall active agents such as β-lactams and glycopeptides are quite effective in vitro in killing *S. aureus*, and would thus be considered "bactericidal." Yet these same agents do not produce the ≥ 99.9% in vitro kill of enterococci within the 24-hour incubation period, and are therefore "bacteriostatic" for this organism. Inoculum burden critically affects antibiotic activity [16,17] : within cardiac vegetations, bacteria may reach very high concentrations (10^8–10^{10} organisms per gram of tissue) [10,16]. Fixed-dose concentrations of antibiotics against standard bacterial inocula in vitro (e.g., 10^5 $\log_{10}$ CFU/g) may not reflect this situation of high bacterial burden in vivo; as such, it may lead to clinical failure. Growth conditions also influence the activity of antibiotics. β-lactams and glycopeptides require bacterial cells to be actively dividing to exert their bactericidal activity. In endocarditis, bacteria within vegetations are in a steady-state growth phase; this slow growth impairs the bactericidal action of cell wall active agents [10,15]. Therefore, an understanding of bacterial dynamics and pathogen-drug relations is crucial to correct antimicrobial selection.

To enhance the bactericidal activity of a selected antibiotic regimen further requires an understanding of pharmacokinetics and pharmacodynamics, with subsequent optimization of these parameters. Pharmacokinetics (PK) refers to the factors that determine the drug concentrations at the site of infection after a dose of an antimicrobial drug is given; it is affected by the absorption, distribution, and elimination of the drug [18]. For example, the oral formulation of certain antibiotics, in combination with the severity of illness of the host, would lead to slow, erratic, or poor absorption of the drug. This, in turn, would produce variable antibiotic serum levels, which would be disastrous in IE. Hence, the intravenous route is considered the best route of administration because it provides maximal bioavailability [15,18]. However, with newer antibiotics in which the oral formulation has high (near 100%) bioavailability, this dogma in the management of IE may change. The concentration of an antibiotic in the serum is also affected by its volume of distribution, its metabolism, and its elimination. With IE, the site of infection is an intravascular vegetation enclosed in a layer of biofilm that renders penetration of antibiotics difficult. This phenomenon may explain the superiority of some antibiotics over others in the management of IE, depending on their degree of vegetation penetration. It also provides the rationale for using high doses of antibiotics and a prolonged duration of treatment. Another factor that determines efficacy of antibiotic at the site of infection is protein binding. All drugs bind to some extent to serum proteins; however, it is the free (unbound) drug that is active [18]. Antibiotics that are highly protein bound in vivo may actually be clinically ineffective, even though they demonstrate significant in vitro killing activity. Such was the case with cefonicid, a second-generation cephalosporin that was clinically inadequate for the treatment of IE due to *S. aureus* [19]. Lastly, an understanding of how a certain antibiotic is metabolized or excreted, and whether this clearing system is impaired in the host, will allow for optimal dosing while minimizing toxicity.

Pharmacodynamics relates drug exposure (i.e., pharmacokinetics) to the antimicrobial effect of the drug, to provide a more rational basis for determination of optimal dosing regimens in terms of the dose and the dosing interval [20,21]. The two major components of antibiotic activity are its pattern of kill and its post-antibiotic effect (PAE). The pattern of bactericidal activity can be concentration-dependent, in which the rate of kill is directly dependent on the amount of drug (peak serum concentration) relative to the MIC, or time-dependent, in which the bactericidal efficacy is dependent on the amount of time the serum antibiotic concentration exceeds the MIC. For time-dependent antibiotics such as β-lactams and glycopeptides, further increasing antibacterial concentrations above the MIC does not result in proportional increases in killing. The PAE refers to a variety of persistent effects that last after antimicrobial exposure. Examples include the in vitro PAE, which is the extent of growth retardation of bacteria that occurs when drug levels are suddenly eliminated, as well as the post-antibiotic leukocyte effect, in which organisms in the postantibiotic state of growth are more susceptible to the antimicrobial activity of white blood cells [20]. As the vegetations in IE are composed of fibrin, platelets, and bacteria, with few

phagocytes [15], the post-antibiotic leukocyte effect would be intuitively negligible in IE. The clinical significance of other PAE in IE remains to be elucidated.

Based on the pattern of bactericidal activity and the PAE, antibiotics can then be divided into three categories [20,21] : (1) concentration-dependent killing and moderate to prolonged persistent effects (examples include aminoglycosides, quinolones, and daptomycin); (2) time-dependent killing and minimal to no persistent effects, such as β-lactams; and (3) time-dependent killing and moderate to prolonged persistent effects, including glycopeptides, oxazolidinones, clindamycin, macrolides, and tetracyclines. This framework will determine subsequent modifications of dosing regimens to optimize bactericidal efficacy [20]. For the first group, enhancing peak serum concentration (while avoiding or minimizing toxicity) would be the preferred intervention. For β-lactams, adjusting the interval between infusions or using agents with longer half-lives would be undertaken to increase the duration of exposure. For the third group, enhancing the amount of drug is predicted to be an important determinant of clinical efficacy.

As mentioned previously, in addition to bactericidal and bacteriostatic activity, antibiotics can also be tolerant (i.e., inhibit bacterial growth but without killing activity). Although the clinical relevance of tolerance in endocarditis is unknown (as MBC is not routinely tested), retrospective microbiological studies have demonstrated this phenomenon among clinical isolates in treatment failures of β-lactams and glycopeptides [22–24]. It may also provide additional rationale for the use of synergistic combination therapy in certain cases of IE.

Selecting the appropriate antibiotic regimen at the start of therapy is but the first step. Reassessment of antmicrobial performance is continuously required. The only reliable measure of clinical efficacy is ultimate cure without relapse. In the interim, it is important to monitor for evidence of improvement, including defervescence, sterilization of blood cultures, and normalization of inflammatory markers [15,25,26]. Failure to demonstrate such features, in the presence of correct clinical and laboratory diagnosis, may reflect pharmacological error (e.g., insufficient dose, dosing interval, or antibiotic serum levels) or the development of IE complications. To ensure pharmacological optimization, consultation with a pharmacist with experience in antimicrobial therapy should be considered. As well, therapeutic drug level monitoring, especially for aminoglycosides and glycopeptides, is recommended [11,12,15,27].

Recognition of syndromes indicating the presence of IE complications is crucial in patient management. These complications can be classified into cardiac and extra-cardiac. The cardiac manifestations include congestive heart failure (CHF), periannular extension of infection (with subsequent abscess or fistula formation, or rupture), valve obstruction, or prosthesis instability. The extra-cardiac manifestations result from embolic phenomena; the major sequelae include neurological compromise (e.g., stroke with or without hemorrhage, mycotic aneurysm) and metastatic infections. The presence of these complications can assist in determining the need and timing for surgical intervention.

In summary, the appropriate treatment of IE requires early diagnosis, as well as prompt effective antmicrobial therapy, and is best managed via a multidisciplinary team approach, involving at least specialists in infectious disease, cardiologists, pharmacists, and cardiac surgeons.

Native Valve Endocardits (NVE)

The major pathogens causing NVE are the streptococci, enterococci, and staphylococci. Emerging pathogens include fungi. Members of the HACEK group are discussed in the chapter along with pathogens causing culture-negative endocarditis.

Streptococal NVE

The nomenclature of the streptococci is complex. However, with respect to NVE, it is clinically useful to divide streptococci into the following categories [11,12,27,28] : (1) oral (or viridans group) streptococci; (2) *S. bovis* complex; (3) nutritionally variant streptococci; (4) *S. pneumoniae*; and (5) beta-hemolytic streptococci.

Oral (or Viridans Group) Streptococci

The oral (or viridans group) streptococci are a heterogeneous group of streptococci that constitute a vital part of the normal flora of the human

upper respiratory tract, gastrointestinal tract, and female genital tract. Previously, when rheumatic heart disease was prevalent, viridans streptococci were the most common cause of NVE, accounting for as much as 60–80% of all cases of IE; their incidence over the last 20 years has since decreased [2,29,30]. Currently, viridans group streptococci are divided into the following groups [31] : *S. mutans* group, *S. salivarius* group, *S anginosus* group (previously *S. milleri* group [32]), *S. sanguinis* group, and *S. mitis* group. Although the taxonomy of these organisms will change, what is important for the clinician to understand is the diversity of pathogens that clinically and therapeutically behave as "viridans streptococci" and that there are species-specific variation in antibiotic sensitivities.

Antimicrobial susceptibility testing of the viridans streptococci by CLSI (NCCLS) criteria categorize these pathogens as penicillin-susceptible (MIC ≤ 0.12 mg/L), or penicillin non-susceptible, which are further classified as either intermediate (MIC 0.25–2 mg/L) or high resistance (MIC ≥ 4 mg/L) [33]. These microbiological laboratory criteria, however, are different than those used by the AHA, BSAC, and the European Society of Cardiology (ESC), which define penicillin-susceptible as a MIC ≤ 0.1 mg/L, intermediate as MIC 0.1–0.5 mg/L, or high resistance as MIC > 0.5 mg/L [8,11,12,27]. The rationale for this discrepancy is unclear [34], but establishing lower MIC thresholds to label a viridans streptococci as "intermediate" or "resistance" presumably errs on the side of clinical caution and ensures more aggressive antimicrobial intervention. The clinical criteria are used in the recommendations of antibiotic therapy.

Previously, it was felt that all oral streptococci were fully sensitive to penicillin [35]. Since the 1990s, however, these *Streptococcus* spp. have been displaying increasing resistance to penicillin and other β-lactam antimicrobial agents. In particular, the *S. mitis* group is commonly implicated, especially (although not exclusively) among neutropenic cancer patients, who are exposed to various therapeutic and prophylactic antibiotic regimens [36–41]. Frequently, these penicillin non-susceptible viridans group streptococci also show reduced susceptibility to ceftriaxone, erythromycin, and clindamycin [35,42–44]. Glycopeptide resistance, however, is uncommon [35,42,44,45]. As well, high-level aminoglycoside resistance among the viridans streptococci is uncommon, although if present, it is more commonly reported with streptomycin than with gentamicin [8,45,46]. Streptomycin-resistant isolates, however, can still demonstrate in vitro synergistic susceptibility to the combination of penicillin and gentamicin; conversely, gentamicin-resistant isolates do not always demonstrate high-level streptomycin resistance [46]. As such, testing for resistance to these aminoglycosides for each viridans streptococcal isolate should be performed.

Antimicrobial susceptibility testing dictates not only which antibiotics may be used, but also assists in determining the duration of therapy. Early clinical studies found that when a total dose of 14–16 million units of penicillin was given alone for up to 2 weeks, the relapse rate was 15%; this rate decreased to < 1.5% with four weeks of therapy [47]. Experimental evidence of the combination of penicillin with an aminoglycoside demonstrated more rapid eradication of streptococci from IE vegetations, as assessed by bacterial counts and relapse in animal models after termination of therapy [46]. Clinical studies of the two-week combination regimen demonstrated a relapse rate of 2% [48]. However, the patient population in these studies excluded those with shock or metastatic septic foci. Therefore, for viridans streptococci that are penicillin- and aminoglycoside-sensitive, a two-week treatment regimen may be considered, provided that appropriate conditions for short-course therapy are fulfilled. These conditions are outlined in Table 9.2.

The *S. anginosus* (or "*S. milleri*") group has a propensity to form abscesses, as well as to cause hematogenously disseminated infection [49,50]. More specifically, however, it appears that *S. constellatus* and *S. intermedius* of this group are more commonly associated with abscess

Table 9.2. Conditions for Two-Week Combination Therapy for Penicillin-Sensitive and Aminoglycoside-Sensitive Streptococcal Endocarditis [8,11,28]

1. Penicillin-sensitive oral (or viridans group) streptococcus or *S. bovis* (penicillin MIC ≤0.1 μg/mL)
2. Native valve IE
3. No cardiac complications (e.g., intra-cardiac abscess, heart failure, aortic insufficiency, conduction abnormalities)
4. No extra-cardiac complications (e.g., septic embolic foci)
5. No vegetation >5 mm in diameter on echocardiography
6. Clinical response within 7 days: there should be resolution of fever, the patient should feel well, and the appetite should return

formation, whereas *S. anginosus* is more commonly associated with IE [51]. Furthermore, it appears that IE due to the *S. anginosus* group, and *S. anginosus* in particular, may be associated with a higher mortality rate than IE due to other viridans streptococci [51]. As such, the duration of antimicrobial therapy for NVE caused by the *S. anginosus* group may need to be longer than that for NVE caused by other viridans streptococci [52].

The prevalence of penicillin non-susceptible viridans group streptococci has been increasing worldwide, with rates as high as 30–45% reported [36,40,43,53]. The mechanism of action appears to be alterations in penicillin-binding proteins [54]. The clinical significance is as expected, with increased morbidity and mortality reported among patients infected by these pathogens [37,55,56]. The degree of penicillin resistance (i.e., intermediate versus high) affects the antibiotic regimen selected, as well as the duration of therapy. The antibiotic regimens for the treatment of viridans streptococcal IE are provided in Table 9.3.

Table 9.3. Antibiotic Treatment for IE Due to Viridans Group Streptococci and *S. bovis* complex

Category	First-line	Duration	Second-line	Duration	Comments
Penicillin-sensitive (MIC ≤0.1 mg/L)	Penicillin G12–18 million units/day IV	4 weeks			Continuous infusion or q4h; BSAC recommends 10–20 million units/day IV (i.e., $2–3 \times 10^5$ U/kg)
	Ceftriaxone 2 g / day IV	4 weeks			
	Penicillin G (above dose) + gentamicin 3 mg/kg/day IV	2 weeks			See Table 9.2 for indications for 2-week therapy. Gentamicin can be given as once daily dosing; when 3 divided daily dosing is used, aim for peak concentration of 3–4 μg/mL and trough concentration <1 μg/mL
	Ceftriaxone (above dose) + gentamicin 3 mg/kg/day IV	2 weeks			
			Vancomycin 30 mg/kg/day IV q12h	4 weeks	Recommended only for β-lactam intolerance; aim for peak concentration of 30–45 μg/mL 1-h post infusion and trough concentration of 10–15 μg/mL.
			Vancomycin (above dose) + gentamicin 3 mg/kg/day IV	2 weeks	Recommended by BSAC, not by AHA
Relatively penicillin-resistant (MIC >0.12 but ≤0.5 μg/mL)	Penicillin G 24 million units/day IV + gentamicin 3 mg/kg/day IV	2 weeks combined therapy, then 2 weeks β-lactam alone			Continuous infusion or q4h; BSAC recommends up to 30 million units/day IV (i.e,. 3–400,000 U/kg). In situations where the risk of aminoglycoside use is high, 4 weeks of β-lactam alone may be considered; consultation with infectious disease specialist should be considered.
	Ceftriaxone 2 g/day IV + gentamicin 3 mg/kg/day IV	2 weeks combined therapy, then 2 weeks β-lactam alone			
			Vancomycin 30 mg/kg/day IV q12h	4 weeks	Recommended only for β-lactam intolerance; aim for peak concentration of 30–45 μg/mL 1-h post infusion and trough concentration of 10–15 μg/mL
			Vancomycin 30 mg/kg/day IV q12h + gentamicin 3 mg/kg/day IV	2 weeks combined therapy, then 2 weeks Vancomycin alone	Recommended by BSAC, but not by AHA
Penicillin-resistant (MIC > 0.5 μg/mL)	See Table 9.4				

S. bovis Complex

"*S. bovis*" is the common name used to designate the group D non-enterococcal streptococci, which are common inhabitants of the intestinal flora of humans. The taxonomy of the *S. bovis/S. equinus* complex (herein referred to as "*S. bovis* complex") is evolving and currently consists of the following species: *S. bovis*, *S. equinus*, *S. gallolyticus*, *S. infantarius*, *S. pasteurianus*, and *S. lutetiensis* [31,57]. The significance to the clinician of knowing this nomenclature derives from the association of "*S. bovis*" with certain co-morbidities. Lack of awareness of the species that constitute the complex can lead to underdiagnosis of these serious underlying conditions [58]. Recent epidemiologic data from the International Collaboration on Endocarditis (ICE) has demonstrated that the proportion of IE due to *S. bovis* complex is increasing, accounting for 10.9% of cases before 1989, with a dramatic rise to 23.3% of cases after 1989 [59]. Therefore, an understanding of the clinical features of *S. bovis* complex IE is necessary.

The *S. bovis* complex is very similar to the viridans streptococci in terms of virulence and antimicrobial susceptibility, with the possible exception of increasing clindamycin resistance [60], a bacteriostatic antibiotic not routinely used in the treatment of IE. As such, therapeutic guidelines for these groups of pathogens are identical [2,11, 12,15,27], shown in Table 9.3.

There are, however, subtle but significant differences in the IE due to *S. bovis* complex. These differences can be divided into two categories: IE features and associated co-morbidities.

With respect to IE features, studies have demonstrated that patients with this disease are typically of older age, male predominance, higher rates of co-morbid illnesses, with no previously known valve disease [4,59,61–63]. Furthermore, this syndrome has a predilection for the mitral valve, although it can commonly involve multiple valves [59,62,64,65]. Recently, *S. bovis* complex IE has also been found to account for a higher proportion of cases among patients with prosthetic valves [59]. The data on whether *S. bovis* complex IE is associated with more frequent embolic and neurologic complications is conflicting [59,62–65]. The rates, however, of early surgical treatment and of mortality did not differ significantly when comparing *S. bovis* complex IE to viridans streptococcal IE [59,63,65,66].

The major associated comorbidity of *S. bovis* complex bacteremia is colonic neoplasm, mainly with *S. bovis* biotype I (*S. gallolyticus* subsp. *gallolyticus* as per new nomenclature) [58,59,65]. Various studies have demonstrated that 25–80% of patients with *S. bovis* complex bacteremia harbor a colorectal tumor [67,68]. The mechanism by which this complex of bacteria is related to neoplasia remains to be elucidated, but bacterial proteins with the potential to induce a chronic infectious or inflammatory process has been proposed [67]. Nonetheless, the association is well described enough that all patients with *S. bovis* complex bacteremia, including IE, need aggressive evaluation of the gastrointestinal tract, especially the colon, when clinically feasible [12,66,68,69]. Other conditions possibly associated with these pathogens include chronic liver disease [65,70] and various extra-intestinal neoplasms [68,71].

Nutritionally Variant Streptococci

The nutritionally variant streptococci (NVS) were originally identified in 1961 as a novel strain that exhibited satellitism around colonies of other bacteria [72]. These bacteria have fastidious growth characteristics, requiring complex media enriched with vitamin B6 or L-cysteine, as well as pleomorphism and variable Gram-stain reactions [73]. Recent 16S rRNA gene sequencing studies have demonstrated that the NVS are two new genera: *Abiotrophia* (consisting currently of only one species, *A. defectiva*), and *Granulicatella* (composed of *G. adiacens*, *G. balaenopterae*, and *G. elegans*) [74]. Here, they will be collectively referred to as "NVS." These bacteria are members of the normal flora of the oral cavity, as well as the gastrointestinal and genitourinary tracts [75] and account for approximately 5% of all cases of streptococcal IE [72,75]. However, because they are fastidious, it is possible that most previous cases were misdiagnosed as culture-negative IE, thus underestimating their prevalence. Routine modern blood cultures can detect the NVS, usually in 2–3 days [72,76,77], although the sensitivity of this method is unknown. Subsequent microbiologic identification and antimicrobial susceptibility testing should be performed. Although there are no specific CLSI (NCCLS) interpretive criteria for *Abiotrophia* or *Granulicatella* spp., current

practice is to use the criteria for "*Streptococcus* spp. other than *S. pneumoniae*" [73,78,79].

NVS IE usually occurs as a result of bacteremia in patients with underlying valve injury [72]. Although it is generally characterized by a slow and indolent course, it is usually more severe, and associated with higher morbidity and mortality, than IE due to viridans streptococci or enterococci [72,80,81]. In a review of 30 cases of NVS IE, the bacteriological failure rate was 41%, despite the in vitro bactericidal effects of antibiotics in two-thirds of cases; approximately 27% of patients required replacement with a prosthetic valve and approximately 20% of patients developed fatal CHF or major systemic emboli [72,81]. The slow growth rate of the bacteria and the production of large amounts of exopolysaccharide in vivo may account for the difficulties encountered in treatment [80]. Another contributing factor is antimicrobial susceptibility. When using CLSI (NCCLS) laboratory criteria, almost 50% of NVS may not be susceptible to penicillin, although there are species-specific variations in sensitivities, with *A. defectiva* being more commonly non-susceptible [72,73,78,82]. Susceptibility testing with aminoglycosides has demonstrated variable sensitivities [83]. Lack of susceptibility has also been demonstrated with other β-lactams (e.g., cefazolin, cefotaxime) [73,78] as well as macrolides (e.g., azithromycin) [73]. Most strains have, however, remained susceptible to clindamycin, rifampin, quinolones, and vancomycin [78,82,83]. As such, IE due to NVS is treated according to the recommendations for treating enterococci (see Table 9.4) [12,52].

S. pneumoniae

In the pre-antibiotic era, *S. pneumoniae* was responsible for approximately 15% of all cases of IE [84]. Since the advent of penicillin, pneumococcal IE has become a rare illness, causing 1–3% of all cases of NVE [84,85]. Despite the availability of penicillin, the mortality rate associated with this disease remains high, with case-fatality rates ranging from 28–60% [84].

Pneumococcal IE is usually preceded by pneumonia and is most commonly seen in alcoholic patients [84,85]. Underlying valvular heart disease is not a prerequisite for pneumococcal endocarditis [85]. Once IE is established, the course is typically aggressive, with rapid destruction of valvular tissue and subsequent CHF [84,86]. As well, this disease has a predilection to form large vegetations on the aortic valve, predisposing to embolization that can lead to pneumococcal meningitis [84,86]. In fact, the triad of pneumococcal pneumonia, complicated by endocarditis and meningitis, is referred to as Osler's triad as well as Austrian syndrome [84,85,87].

Patients with pneumococcal IE may be treated medically or with combined medical-surgical therapy. Evidence suggests, though, that persons with this disease be considered for early surgical intervention, as the mortality rate among patients who received medical therapy alone (63–80%) was much higher compared to the mortality rate of patients who received combination therapy (32%) [86]. This phenomenon was first noticed prior to the high prevalence of penicillin non-susceptibility among *S. pneumoniae* that is widely appreciated today.

In the early 1990s, *S. pneumoniae* strains that had a high level of resistance to penicillin appeared in the United States [88]. Since then, rates worldwide have generally demonstrated an increase in penicillin non-susceptible strains (PNSP) [89–92]. By the end of the 1990s, approximately 25% of *S. pneumoniae* stains in the U.S. demonstrated intermediate (MIC 0.1–1 μg/mL) or high-level (MIC >2 μg/mL) resistance to penicillin, with similar trends described globally [93–96]. Furthermore, PNSP isolates have also demonstrated increasing resistance to other agents, most notably to macrolides, trimethoprim-sulfamethoxazole (TMP-SMX), clindamycin, tetracyclines, and chloramphenicol [90,91,97,98]. Fortunately, these latter antibiotics are not routinely used in the management of IE. Third-generation parenteral cephalosporins (e.g., cefotaxime, ceftriaxone) and glycopeptides (e.g., vancomycin) currently possess significant activity against these multi-drug-resistant pneumococci [95,99–102]. Thus, these agents remain the recommended mainstay of empiric therapy for *S. pneumoniae* endocarditis as well as definitive therapy for IE due to intermediate- or high-level penicillin resistance [12,84] (see Table 9.5). If vancomycin monotherapy is selected for the management of pneumococcal IE, it is important that the possibility of meningitis be excluded, as there is concern about the penetration of vancomycin into cerebrospinal fluid in adults [103]. In patients with

Table 9.4. Antibiotic Treatment for NVE Due to Penicillin-Resistant (MIC >0.5 μg/mL) *Streptococcus* spp. (Non-Pneumococcus), Nutritionally Variant Streptococci (NVS), and *Enterococcus* spp.

Category	First-line	Duration	Second-line	Duration	Comments
Penicillin-resistant (MIC >0.5 μg/mL) *Streptococcus* spp. (viridans group streptococci and *S. bovis* complex)	Ampicillin 2 g IV q4h + gentamicin 3 mg/kg/day IV	4–6 weeks of combined therapy			AHA recommends: 4 weeks if patient is symptomatic ≤ 3 months; 6 weeks if symptomatic > 3 months.
	High-dose Penicillin G (e.g. 18–30 million units/day) IV + gentamicin 3 mg/kg/day IV	4–6 weeks of combined therapy			High-dose penicillin G: 3–4 × 10^5 U/kg
			Vancomycin 30 mg/kg/day IV q12h + gentamicin 3 mg/kg/day IV	6 weeks	
Nutritionally variant streptococci (NVS): *Abiotrophia* spp. *Granulicatella* spp.	Ampicillin 2 g IV q4h + gentamicin 3 mg/kg/day IV	4–6 weeks of combined therapy			AHA recommends: 4 weeks if patient is symptomatic ≤3 months; 6 weeks if symptomatic >3 months
	High-dose penicillin G (e.g., 18–30 million units/day) IV + gentamicin 3 mg/kg/day IV	4–6 weeks of combined therapy			High-dose penicillin G: 3–4 × 10^5 U/kg
			Vancomycin 30 mg/kg/day IV q12h + gentamicin 3 mg/kg/day IV	4–6 weeks of combined therapy	BSAC recommends 6 weeks, because of the high rate of relapse, as well as blood cultures weekly during therapy and after completion of therapy.
					Vancomycin alone is as effective as penicillin G + gentamicin in an experimental rabbit model, and thus may be considered if the risks of gentamicin toxicity are high
<u>*Enterococcus* spp.</u>					
Penicillin S Gentamicin S Vancomycin S	Ampicillin 2 g IV q4h + gentamicin 3 mg/kg/day IV	4–6 weeks of combined therapy			
	High-dose penicillin G (e.g., 18–30 million units/day) IV + gentamicin 3 mg/kg/day IV	4–6 weeks of combined therapy			
			Vancomycin 30 mg/kg/day IV q12h + gentamicin 3 mg/kg/day IV	≥ 4 weeks of combined therapy (BSAC); 6 weeks of combined therapy (AHA)	Indicated only for patients unable to tolerate β-lactams
Penicillin S Gentamicin R Streptomycin S Vancomycin S	Ampicillin 2 g IV q4h + Streptomycin 7.5 mg/kg IV q12h	4–6 weeks of combined therapy			For streptomycin, aim for peak serum concentration of 20–35 μg/mL and trough <10 μg/mL
	Penicillin G 24 million units/day) IV + Streptomycin 7.5 mg/kg IV q12h	4–6 weeks of ombined therapy			
			Vancomycin 30 mg/kg/day IV q12h + Streptomycin 7.5 mg/kg IV q12h	≥ 4 weeks of combined therapy (BSAC) 6 weeks of combined therapy (AHA)	Vancomycin indicated only for patients unable to tolerate β-lactams

(*Continued*)

Table 9.4.—*Continued*

Category	First-line	Duration	Second-line	Duration	Comments
Penicillin S Gentamicin R (MIC > 500 μg/mL) Streptomycin R (MIC >2000 μg/mL) (i.e., high-level aminoglycoside resistance) Vancomycin S	Ampicillin 2 g IV q4h High-dose penicillin G (e.g., 24–30 million units/day) IV	8 weeks (BSAC); ≥ 6 weeks (AHA)	Vancomycin 30 mg/kg/day IV q12h	8 weeks (BSAC); ≥ 6 weeks (AHA)	Surgical intervention may be necessary
Penicillin R (β-lactamase +) Gentamicin S Vancomycin S	Ampicillin-sulbactam 2 g IV q4h + gentamicin 3 mg/kg/day IV	6 weeks	Vancomycin 30 mg/kg/day IV q12h + gentamicin 3 mg/kg/day IV	≥ 4 weeks of combined therapy (BSAC); 6 weeks of combined therapy (AHA)	Usually gentamicin resistant, in which case >6 weeks of ampicillin-sulbactam is needed
Penicillin R (intrinsic resistance) Gentamicin S Vancomycin S	Vancomycin 30 mg/kg/day IV q12h + Gentamicin 3 mg/kg/day IV	≥ 4 weeks of combined therapy (BSAC); 6 weeks of combined therapy (AHA)			
Penicillin R Gentamicin R Vancomycin S	Vancomycin 30 mg/kg/day IV q12h	8 weeks (BSAC) ≥ 6 weeks (AHA)			Surgical intervention may be necessary for cure
Penicillin variable Gentamicin R Vancomycin R	*E. faecalis*— Ampicillin 2 g IV q4h + Ceftriaxone 2 g IV q12h OR Ampicillin 2 g IV q4h + Imipenem/cilastatin 500 mg IV q6h	≥ 8 weeks			Strongly consider consultation with an Infectious Disease specialist. Surgical intervention may be necessary for cure. Prolonged (>2 weeks) therapy with Linezolid may be associated with thrombocytopenia (see text)
	E. faecium— Linezolid 600 mg po/IV q12h OR Quinupristin/Dalfopristin 7.5 mg/kg IV q8h	≥ 8 weeks			

S = susceptible; R = resistant

S. pneumoniae IE and meningitis, high-doses of a third-generation cephalosporin should be used [52]. If the isolate is resistant to third-generation cephalosporins (e.g., cefotaxime MIC ≥ 2 μg/mL), then vancomycin and rifampin should be added [52].

Given the aggressive nature of this disease, including the associated risk of meningitis and the high mortality rates with medical therapy alone, the preferable treatment of patients with pneumococcal IE may be a combined medical–surgical approach. This recommendation is largely based on a meta-analysis of 197 cases reported in the English literature of this disease among adult patients in the penicillin era [84]. The mortality rate among 91 patients treated with antibiotics alone was 62%, compared to 32% among 37 patients managed with a com-

Table 9.5. Antibiotic Treatment for NVE Due to *S. pneumoniae* and β-Hemolytic Streptococci

Category	First-line	Duration	Second-line	Duration	Comments
Penicillin-sensitive *S. pneumoniae* (MIC <0.1 μg/mL)	Penicillin G 24 million units/day IV	4 weeks			**Note:** *S. pneumoniae* IE may require combined medical–surgical therapy for cure
	Ampicillin 2 g IV q4h	4 weeks			
	Third-generation cephalosporins: ceftriaxone 2 g IV q12h OR Cefotaxime 2 g IV q4 to 6h	4 weeks			
	Cefazolin 2 g IV q8h	4 weeks			Recommended by AHA, but not by BSAC
			Vancomycin 30 mg/kg/day IV q12h	4 weeks	Vancomycin indicated only for patients unable to tolerate β-lactams
Penicillin-non-susceptible *S. pneumoniae* (PNSP):					
Intermediate resistance (MIC 0.1–1 μg/mL) with NO meningitis	Penicillin G 24 million units/day IV	4 weeks			Recommended by AHA, but not by BSAC; data derived from animal model, with concern about its clinical significance [84]
	Third-generation cephalosporins: ceftriaxone 2 g IV q12h OR Cefotaxime 2 g IV q4 to 6h	4 weeks			
			Vancomycin 30 mg/kg/day IV q12h	4–6 weeks [521]	Vancomycin indicated only for patients unable to tolerate β-lactams or if isolate is resistant to third-generation cephalosporins
Intermediate resistance (MIC 0.1–1 μg/mL) WITH meningitis	Third-generation cephalosporins: ceftriaxone 2 g IV q12h OR Cefotaxime 2 g IV q4 to 6h	4 weeks			
			Vancomycin 30 mg/kg/day IV q12h + Rifampin [522]	4–6 weeks	Vancomycin indicated only for patients unable to tolerate β-lactams or if isolate is resistant to third-generation
High-level (MIC > 2 μg/mL)	Vancomycin 30 mg/kg/day IV q12h + rifampin [522]	4–6 weeks			Fluoroquinolones as combination therapy may be of use [86]
β-hemolytic streptococci:					Surgical intervention may be necessary for cure
Group A streptococci (*S. pyogenes*)	High-dose penicillin G (e.g., 24 million units/day IV)	4 weeks			
			Cefazolin 2 g IV q8h	4 weeks	
			Ceftriaxone 2 g IV q12h	4 weeks	
			Vancomycin 30 mg/kg/day IV q12h	4 weeks	
Groups B, C, G	High-dose penicillin G (e.g., 24 million units/day IV) + gentamicin 3 mg/kg/day IV	Combination therapy for ≥ 2 weeks, then penicillin G for 2–4 weeks [107]			
			Vancomycin 30 mg/kg/day IV q12h + gentamicin 3 mg/kg/day IV	Combination therapy for ≥2 weeks, then vancomycin for 2–4 weeks	

bined modality approach. Similar studies with smaller samples sizes of patients with definite pneumococcal IE support this suggestion [104,105]. The optimal timing of surgical intervention in this disease remains unknown; perhaps trans-esophageal echocardiography (TEE) may play a role. The optimal duration of antimicrobial therapy, either alone or after surgical intervention, also remains unclear, but four to six weeks is recommended [12,84].

The role of pneumococcal vaccination in providing primary protection against pneumococcal IE is unknown. In one study, *S. pneumoniae* IE developed in two patients who had been previously immunized: one patient developed disease due to a serotype that was represented in the vaccine, whereas the second patient had a history of alcoholism and chronic obstructive pulmonary disease and developed IE due to a strain that was not serotyped (105]. Although no conclusion can be made regarding the efficacy of immunization in primary prevention, it is important to note the possibility of developing pneumococcal disease (endocarditis or otherwise) despite a history of vaccination, as most people develop a humoral response to only ~75% of the antigens in the vaccine [84]. Recurrence of disease is extremely rare [106] and so the role of immunization for secondary prevention is unknown.

β-Hemolytic Streptococci

IE due to β-hemolytic streptococci (BHS) is extremely uncommon, accounting for ≤ 5% of cases [107]. The major pathogens are groups A (*S. pyogenes*), B (*S. agalactiae*), C, and G, with group B being the most common cause of BHS IE [107,108].

The typical clinical characteristics is one of an acute infection, often occurring on normal heart valves, producing large valvular vegetations, and frequently complicated by embolic phenomena [107,108]. Most patients have underlying conditions, including diabetes mellitus, malignancy, chronic alcoholism/cirrhosis, varicella, and HIV [107–109].

Few studies have been published regarding the optimal treatment of this uncommon condition. Because penicillin resistance by the BHS remains uncommon, it remains the cornerstone of therapy, and is recommended as monotherapy in group A streptococcal IE in patients that do not have allergy to this antibiotic [11,12]. For the remaining BHS (Lancefield groups B, C, and G), for which the penicillin MICs can be higher than for *Streptococcus* pyogenes, there is some evidence regarding the benefit of combined therapy (i.e., penicillin with an aminoglycoside), and is therefore recommended [11,12]. The antibiotic regimens for the treatment of BHS IE are provided in Table 9.5. The duration of antimicrobial therapy remains ill-defined. Recommendations of four weeks for group A streptococcus and four to six weeks for groups B, C, and G streptococci have been made, in the absence of any complications [52]. Microbiological evidence of sterilization of excised cardiac valves after four weeks of a ß-lactam, with or without aminoglycoside for the first two weeks, supports this recommendation [110].

A significant proportion (50–60%) of patients have required adjunctive surgical intervention [107,108]. The most frequent indication for cardiac surgery was acute valve insufficiency. The authors of the two largest series to date on BHS IE believe that a more aggressive surgical intervention is associated with diminished mortality rates, although the benefit of surgery could not be clearly demonstrated [107,108]. Nonetheless, consultation with a cardiac surgeon should be considered early in the course of management.

Enterococcal NVE

Enterococci account for 5–15% of cases of NVE and is usually due to *E. faecalis* or *E. faecium* [4,12,111]. Treatment of enterococcal infections in general, and NVE in particular, is made difficult due to the mechanisms of resistance possessed by these pathogens, which can be divided into three categories: inherent (or intrinsic) resistance, tolerance, and acquired resistance. The inherent mechanisms of resistance are, by definition, species characteristics present in all or most of the strains of that species and are encoded on the chromosome [112]. Tolerance is defined as delayed or decreased bactericidal killing by growth-inhibiting concentrations of bactericidal compounds [113]. As mentioned before, a strain is defined as "tolerant" when the MBC/MIC ratio is ≥ 32. Acquired resistance occurs either from a mutation in the existing DNA or, more clinically relevant, from acquisition of new DNA.

Enterococci are inherently resistant to certain β-lactams, specifically the semi-synthetic penicillinase-resistant penicillins (e.g., oxacillin, nafcillin) and cephalosporins, as well as to lincosamides (e.g., clindamycin), traditional antimicrobial agents used for Gram-positive cocci [112,114]. Furthermore, enterococci are intrinsically resistant to trimethoprim-sulfamethoxazole (TMP/SMX) in vivo, aminoglycosides (low level), and aztreonam [112,115]. The mechanisms responsible for this natural resistance are diverse and have permitted the emergence of the enterococci as major pathogens.

Intrinsic resistance to the aforementioned β-lactams is due to the presence of specific penicillin-binding proteins (PBPs) with poor affinity to these antibiotics [112]. Low-affinity PBPs are multifunctional enzymes that can catalyze complete peptidoglycan synthesis under conditions in which all the other normal PBPs are inhibited by β-lactams [116]. In the enterococci, PBP-5 is the predominant low-affinity PBP. It is a normal component of the enterococcal PBP repertoire and is constitutively expressed, thereby allowing bacterial cell survival in the presence of semi-synthetic penicillins and cephems.

Lincosamide antibiotics include lincomycin, naturally produced by actinomycetes, and clindamycin, a semi-synthetic derivative of lincomycin. The enterococci are inherently resistant to clindamycin [112,115], although there are several mechanisms by which this occurs. For example, *E. faecalis*, the predominant clinical species, is characterized by the LSA phenotype, defined as resistance to not only the lincosamides, but also to streptogramins A (dalfopristin, pristinamycin II, virginiamycin M) [117]. This phenotype is mediated by the *lsa* gene, which encodes for a protein that has structural homology to antibiotic efflux pumps of other Gram-positive organisms [118]. There are two other major mechanisms by which the enterococci have developed lincosamide resistance. One method is by a ribosomal methylase encoded by an *ermAM*-like gene. This enzyme leads to N6 dimethylation of a specific adenine in the 23S rRNA, which confers resistance to lincosamides, but also to macrolides and to streptogramin B antibiotics; this phenotype is designated MLSb [119,120]. Acquired resistance can also occur via the dissemination of the *linB* gene, which encodes for lincosamide nucleotidyltransferase that leads to inactivation of such antibiotics [119].

TMP/SMX is considered to not be an effective antibiotic for the treatment of enterococcal infections, even though it demonstrates in vitro activity [121]. Treatment failures have been demonstrated in both animal models of endocarditis and in the clinical setting of urinary tract infections [122,123]. The proposed explanation as to why this combination is not effective is related to the ability of the enterococci to incorporate pre-formed folic acid, which enables them to bypass the inhibition of folate synthesis imposed by TMP/SMX [112].

Low-level aminoglycoside resistance (LLAR) is an inherent property of enterococci. High-level aminoglycoside resistance (HLAR) is an acquired characteristic and is discussed below. There are two major mechanisms conferring LLAR: First is decreased bacterial cellular uptake, seen in all enterococci [112]. The means by which enterococci are able to limit aminoglycoside uptake relate to the biochemical characteristics of the aminoglycosides, as well as to bacterial metabolism [124]. As aminoglycosides are charged, hydrophilic molecules, they are unable efficiently to cross the lipid-containing cell membrane of enterococci to reach their ribosomal target. Additionally, the anaerobic metabolism of enterococci results in poor active transport of these antibiotics into the cells.

The other method of LLAR is seen only in *E. faecium* and occurs via inactivation of certain aminoglycoside antibiotics (tobramycin, netilmicin, kanamycin, and sismicin) by a chromosomally encoded enzyme [112]. This additional method explains the differences in MICs of these aminoglycosides seen for *E. faecalis* when compared to *E. faecium*. The typical MIC of tobramycin for *E. faecalis* is in the range of 8–64 mg/L; that of kanamycin is in the range of 250 mg/L [112]. The MICs of tobramycin and kanamycin for *E. faecium*, however, are higher [112]. This resistance pattern is attributed to the production of an aminoglycoside 6′-acetyltransferase (AAC-6′) enzyme [124]. The clinical consequence of this enzyme is that combinations of a cell wall active agent with one of these aminoglycosides (tobramycin or kanamycin) will fail to demonstrate synergism against *E. faecium*. Synergism, or enhanced killing, for the enterococci is defined as a $\geq 2\text{-log}_{10}$ increase in killing versus the effect of the cell-wall active agent alone when the aminoglycoside is used in a subinhibitory concentration [112]. However,

synergy is maintained if the aminoglycoside that is used is either gentamicin or streptomycin.

As a consequence of these inherent mechanisms of resistance, the above-mentioned antibiotics possess no bactericidal or bacteriostatic activity against the enterococci. In addition, the majority of *Enterococcus* spp. demonstrate "tolerance" to various cell-wall active agents, whereby cell growth is inhibited at clinically achievable concentrations, but not cell death. The major antibiotics with such properties are penicillin, aminopenicillins (amoxicillin, ampicillin), and glycopeptides (teicoplanin, vancomycin). Ampicillin generally has lower MICs than penicillin, and thus may be the preferred agent [115,125]. Ampicillin MICs for *E. faecalis* generally are 0.5–4.0 μg/mL, whereas for *E. faecium*, the MICs are typically 4–8 μg/mL [115]. The ureidopenicillins (azlocillin, mezlocillin, piperacillin) have approximately the same activity against enterococci as penicillin and ampicillin [125]. This bacteriostatic effect is suboptimal in the management of infective endocarditis, which classically requires a bactericidal regimen. Such an effect can be achieved by the combination of gentamicin or streptomycin to one of these cell-wall active agents.

The mechanism of tolerance of enterococci to β-lactams remains unclear, but is clearly distinct from resistance, demonstrated by the fact that each feature can be elicited independently among *E. faecalis* strains exposed in vitro to penicillin [126]. It has been suggested that tolerance may be associated with changes in the autolysis system [127]. β-Lactam-induced lysis of bacteria is the consequence of inhibition of biosynthesis of peptidoglycan, as well as to hydrolysis of cell walls by bacterial autolytic enzymes. It has been shown that an increase in autolytic activity among clinical enterococcal isolates correlated with increased penicillin-induced lysis and killing [127]. Conversely, *E. faecalis* strains with reduced or absent autolytic activity were less susceptible to penicillin [128]. However, neither modification of one enterococcal autolysin gene, nor alteration of its expression, resulted in any significant change in MIC or in tolerance to β-lactams [129]. As such, tolerance to β-lactam remains a poorly understood phenomenon.

Because of the limited antimicrobial options, optimal management of ampicillin-susceptible enterococcal NVE should involve the addition of an aminoglycoside (i.e., gentamicin or streptomycin) to a cell-wall active agent (i.e., ampicillin or glycopeptides). This combination results in a synergistic bactericidal activity related to the fact that cell-wall active agents markedly increase the penetration of aminoglycosides into the bacterial cell, allowing binding to its ribosomal target [130]. Alternatively, if aminoglycoside therapy is contraindicated (e.g., potential worsening of renal insufficiency), prolonged treatment with a β-lactam, classically ampicillin, while maintaining the serum antibiotic concentration above the MIC of the isolate, may be sufficient (see Table 9.4).

Unfortunately, acquired antimicrobial resistance to aminoglycosides and to cell-wall active agents has complicated the management of this disease. High-level aminoglycoside resistance, currently defined by CLSI (NCCLS) as an MIC of streptomycin ≥ 2,000 μg/mL or an MIC of gentamicin ≥ 500 μg/mL, was first described in 1979 [131]. Rates have increased worldwide, with prevalence as high as ~75% [132], and it is particularly common among strains of *E. faecium* [133]. The mechanism of this resistance is related to the presence of aminoglycoside-modifying enzymes, some of which are located on transferable plasmids [134,135]. A bifunctional enzyme (2″-phosphotransferase-6′-acetyltransferase) mediates high-level gentamicin resistance, as well as resistance to tobramycin, amikacin, netilmicin, and kanamycin [114,125]. Streptomycin resistance, however, is mediated by completely different mechanisms. It occurs as a result of ribosomal resistance, in which there is alteration of ribosomal target sites, or by streptomycin adenyltransferase, which modifies and inactivates aminoglycosides [136]. Because gentamicin and streptomycin resistance may differ among *Enterococcus* spp., aminoglycoside screening should include tests for high-level resistance to both of these aminoglycosides. If one of these antimicrobials demonstrates lack of HLAR, it should be used, if the clinical situation permits. If NVE is due to an *Enterococcus* spp. with HLAR to both aminoglycosides, absence of synergism with a cell-wall active agent can be predicted. As there is no clinical efficacy to using such agent in these situations, and with the inherent risks of aminoglycosides, monotherapy with a cell-wall active agent should be employed.

Acquired ampicillin resistance has compromised the management of enterococcal infec-

tions. The two clinically major species each have their own mechanism mediating such resistance. β-lactamase production is exclusively described in *E. faecalis*; this enzyme is felt to have been acquired from *S. aureus* via a transferable plasmid [112,115]. β-Lactamase production occurs at low levels and produces an "inoculum effect," such that at low to moderate inocula (10^3–10^5 CFU/mL), there is only a minor increase in MIC and such penicillinase-producing enterococci usually appear no more resistant than other enterococci [114]. However, at high inocula ($\geq 10^7$ CFU/mL), when sufficient enzymes are produced, such strains are highly resistant to penicillin, aminopenicillins, and ureidopenicillins [114]. As a result of this inoculum effect, β-lactamase-mediated penicillin resistance is not detected by routine disk susceptibility testing [112]. In the clinical laboratory, hydrolysis of the chromogenic cephalosporin, nitrocefin, is the definitive test for β-lactamase production [125]. The activity of the penicillinase is inhibited by β-lactamase inhibitors (i.e., clavulanic acid, tazobactam, sulbactam) [114]. Although there have been reports of clinical infection with β-lactamase-producing *E. faecalis* [133], it does not appear that this mechanism of resistance is a major virulence factor among enterococci [137,138].

Non-β-lactamase producing, ampicillin-resistant enterococci is usually *E. faecium*. The mechanisms of this resistance appear to be overproduction of the naturally present PBP5, as well as amino acid substitutions in PBP5 resulting in a further decrease in affinity to β-lactams [114,115,137,138]. Acquisition of this form of β-lactam resistance accounts for the majority of clinically relevant isolates.

In the face of β-lactam resistance, the only therapeutic options, until recently, were the glycopeptides (vancomycin, teicoplanin). These antibiotics function by binding to the terminal D-alanyl-D-alanine present on the pentapeptide side chains of the peptidoglycan precursors, inhibiting peptidoglycan synthesis. In North America, vancomycin is the only glycopeptide currently commercially available and it is recommended as the drug of choice for serious enterococcal infection only in cases of significant penicillin allergy or in the treatment of ampicillin-resistant strains. Vancomycin, when combined with gentamicin or streptomycin, does demonstrate synergism against *Enterococcus* spp. in vitro and in vivo [125]. Vancomycin should not, however, be used for ampicillin-susceptible strains, as it usually has higher MICs against enterococci than ampicillin [139]. As well, there is concern that careless overuse of vancomycin contributes to the emergence of vancomycin-resistant pathogens.

Glycopeptide resistance is an emerging problem. First described in the 1980s, vancomycin-resistant enterococci (VRE) have become an important nosocomial pathogen globally. The most common phenotype of resistance, *vanA*, is associated with acquired, inducible, high-level resistance to vancomycin (MIC ≥ 64 μg/mL) and to teicoplanin (MIC ≥16 μg/mL) [121]. The *vanA* phenotype is mediated by genetic elements that are carried on a transposon (Tn*1546*) and is transferable to other susceptible enterococci by conjugation [115]. Other acquired glycopeptide-resistant phenotypes have been also been characterized, including *vanB*, as well as *vanD*, *vanE,* and *vanG*, which are much less common. The *vanB* phenotype, which is chromosomally mediated, inducible, and transferable by conjugation, mediates inducible resistance to vancomycin, but not to teicoplanin [121]. However, the development of teicoplanin resistance occurs rapidly during antibiotic exposure. Bloodstream infection with VRE can be very difficult to treat because there may be concomitant ampicillin resistance, as seen with virtually all *E. faecium* [115]. Vancomycin-resistant *E. faecalis*, however, usually remains susceptible to ampicillin. Furthermore, a recent retrospective case-control study demonstrated that patients with bacteremia caused by VRE were more likely to die than were those with vancomycin-susceptible enterococcal bacteremia, with a summary odds ratio for death of 2.52, and a 95% confidence interval of 1.9–3.4 [140].

In face of glycopeptide resistance, treatment of VRE poses significant challenge. Fortunately, VRE endocarditis remains relatively uncommon, with no local, national, or international incidence rates reported in the English literature. For VRE infections in general, two classes of antibiotics have been approved: the streptogramins and the oxazolidnones.

Among the approved streptogramin class of antibiotics is quinupristin/dalfopristin (Q/D, Synercid®, Aventis Pharmaceuticals, Inc.). It is a parenteral antibiotic that is structurally related to the macrolides and lincosamides. Its mechanism of action is inhibition of early (peptide

chain elongation) and late stages of bacterial protein synthesis [141]. Interestingly, Q/D demonstrates good in vitroactivity against *E. faecium*, with MIC_{90} of 1–2 μg/mL, but very poor activity against *E. faecalis*, the predominant enterococcal pathogen, with MIC_{90} of 8–16 μg/mL [141]. The reason for this difference in activity is likely due to decreased 50S bacterial ribosomal binding of Q/D in *E. faecalis* [141]. In in vitro studies, Q/D is bactericidal for VRE [141]. However, in time-kill studies, Q/D demonstrates only bacteriostatic activity; this difference in effect is due to the expression of the MLS_b phenotype (described previously), which encodes for the methylation of the 23S ribosomal binding site [141,142]. Q/D-resistance has been reported among clinical VRE isolates, ranging from <10% to 22% [142]. Furthermore, emergence of Q/D-resistance while on therapy has also been described. Clinical failure with Q/D has been reported with VRE endocarditis [143,144].

Linezolid (LZL, Zyvox™, Pfizer, Inc.) is the only currently available oxazolidinone. It is prepared as a parenteral or as an oral formulation, with the latter having 100% bioavailability [145]. LZL functions by binding to the 23S ribosomal RNA of the 50S subunit on the bacterial ribosome, thus inhibiting protein synthesis [145]. By virtue of its unique action, cross-resistance to LZL has not been reported among enterococci that have developed resistance to other antibiotics [146]. LZL has shown consistent bacteriostatic activity against vancomycin-susceptible and vancomycin-resistant *E. faecium* and *E. faecalis*. In murine models [147] and in clinical reports [148], LZL was effective in the treatment of VRE bacteremia. It has also been reported to be effective for VRE endocarditis [149–152], although not consistently [153]. Furthermore, resistance to LZL has developed among VRE in patients receiving the drug for an extended period of time, typically >3 weeks [154–156]. This issue raises some concerns about its use as monotherapy in VRE endcarditis, which typically requires a prolonged course of antimicrobial therapy. Ideally, synergism can be achieved when combined with other antimicrobials. However, using the standard checkerboard assay to determine the fractional inhibitor concentrations (FIC) indices, LZL primarily demonstrated in vitro indifference (i.e., no synergy) against *Enterococcus* spp. when assessed in combination with other antimicrobials [157]. Consequently, the role of LZL in VRE endocarditis remains unestablished.

Staphylococcal NVE

Staphylococcal NVE may be caused by *S. aureus* or by coagulase-negative staphylococci (CoNS, e.g., *S. epidermidis*). It had been previously believed that *S. aureus* caused primarily NVE, while CoNS caused primarily prosthetic-valve endocarditis [52]. Recent, large-scale epidemiologic studies, however, have demonstrated the changing epidemiology of staphylococcal NVE.

S. aureus

S. aureus endocarditis occurs in four clinically distinct populations [158] : intravenous drug users (IVDUs); patients with prosthetic valves; patients with health-care-acquired (nosocomial or nosohusial) endocarditis; and non-IVDU patients with community-acquired endocarditis. This chapter will focus on the latter group, as the former groups are discussed in other chapters.

Recent studies have demonstrated that *S. aureus* has become the leading cause of endocarditis, accounting for approximately 30% of cases [158,159]. Of these, approximately 87% are NVE [158]. Although a large proportion of cases of *S. aureus* IE are community-acquired [160,161], there is an increasing prevalence of health-care-associated disease, owing in part to the growing use of interventional procedures and implantable devices [159]. Community-acquired *S. aureus* NVE may involve right-sided and/or left-sided cardiac structures. Right-sided disease typically has high cure rates with relatively short-course medical therapy alone [52]. In non-IVDUs, *S. aureus* predominantly involves the left-side and is associated with mortality rates ranging from 25–50% [2,52]. *S. aureus* NVE is also associated with higher rates of embolization (cerebrovascular and systemic) and persistent bacteremia when compared to NVE due to other pathogens [159,162].

The management of *S. aureus* infections in general, and NVE in particular, has become increasingly difficult owing to evolving mechanisms of antibiotic resistance. Penicillin was introduced into clinical practice in 1941 and it was demonstrated to be an effective anti-staphy-

lococcal agent. Within one to two years of its introduction, however, highly penicillin-resistant isolates of *S. aureus* were found [163]. The mechanism of resistance is due to acquisition of a plasmid-mediated penicillinase. Penicillin resistance propagated rapidly, and currently, > 95% of *S. aureus* strains are resistant to penicillin [164]. However, in the rare instance where an isolate responsible for IE is susceptible to penicillin, it should be used in high doses (e.g., penicillin G 24 million units/day IV).

The emergence of penicillin-resistant *S. aureus* during the 1940s prompted the development of a new class of penicillins that were specifically targeted against these penicillin-resistant strains. The first representative of this class, methicillin, was introduced in 1951. By the mid-1950s, however, methicillin-resistant strains of *S. aureus* (MRSA) were prevalent. This resistance is mediated by the production of an alternate penicillin-binding protein, termed PBP-2a, which is encoded by the *mecA* gene [165]. PBP-2a has low affinity for β-lactams, thus allowing synthesis of the bacterial cell wall despite the presence of normally lethal β-lactam concentrations [166]. In addition to mediating resistance to methicillin (and other semi-synthetic penicillinase-resistant penicillin), it also provides resistance to cephalosporins, cephamycins, and carbapenems [166]. The *mecA* gene is encoded on a mobile genetic element, the staphylococcal chromosomal cassette *mec* (SCC*mec*), which also contains insertion sites for plasmids and transposons that facilitate acquisition of resistance to other antibiotics. Consequently, cross-resistance to other classes of antibiotics, such as erythromycin, clindamycin, gentamicin, trimethoprim-sulfamethoxazole (TMP/SMX), and ciprofloxacin may occur [166]. Although MRSA was typically considered a nosocomial pathogen, typing of SCC*mec* has identified community-associated MRSA strains (CA-MRSA) that are distinct from the hospital strains in pathogenicity and antimicrobial susceptibility [167]. Although the majority of MRSA strains causing IE are healthcare-associated [159], IE due to CA-MRSA has also been reported [168]. There is some evidence to suggest that infections with MRSA are associated with increased morbidity and mortality, when compared to infections with methicillin-susceptible *S. aureus* (MSSA) [169,170]; this association has also been demonstrated in endocarditis [158,160,171]. There is some concern, however, that the increased mortality associated with MRSA infections may be biased by confounding variables, such as length of hospitalization [172] or severity of illness [173]; in other words, the colonization/infection with MRSA represents a surrogate marker of increased length of hospitalization, which, in turn, is a reflection of multiple or severe comorbidities. This latter factor may, in fact, be the principle reason for the higher mortality rates.

The treatment of choice for MRSA, both nosocomial and community-acquired, is the glycopeptide class of antimicrobials. In North America, vancomycin is the glycopeptide commercially available. Teicoplanin has been used in other parts of the world. At appropriate doses, the efficacy of these glycopeptides in the management of *S. aureus* IE is comparable [174]. However, the efficacy of the glycopeptides is inferior to that of the β-lactams for the management of IE with *S. aureus* isolates that demonstrate in vitro susceptibility to both classes of antimicrobials [173,175,176]. This inferiority is reflected in a delayed clearance of bacteremia (i.e., > 6 days), higher rates of treatment failure, and higher rates of relapse [177–179]. These effects are due to vancomycin's suboptimal pharmacokinetics (i.e., poor vegetation penetration) and pharmacodynamics (i.e., slower in vitro bactericidal effect [180]) when compared to β-lactams. Thus, in IE with MSSA, β-lactams are the drug of choice.

More recently, strains of *S. aureus* with decreased susceptibility to vancomycin have been recognized. These isolates are inhibited by vancomycin concentrations of 8–16 μg/mL, which is interpreted as "intermediate susceptibility" by CLSI (formerly NCCLS) criteria [181]. Despite this in vitro classification, infections caused by these vancomycin-intermediate *S. aureus* (VISA) strains have not responded well clinically when treated with vancomycin, including cases of endocarditis [182–185]. These strains appear to develop from preexisting MRSA strains under the selective pressure of prolonged and/or suboptimal administration of vancomycin [186,187]. In addition to VISA, there has also been increased recognition of heterogeneously vancomycin-intermediate *S. aureus* (h-VISA) strains; these are strains of *S. aureus* containing subpopulations of vancomycin-resistant daughter cells, typically at a rate of one organism per 10^5–10^6 organisms, for which the apparent

vancomycin MICs of the parent strain are only 1–4 mg/L (i.e., susceptible) [188]. These subpopulations typically have MICs that are two- to eightfold higher than that for the original clinical isolate. The clinical significance of h-VISA isolates remains to be fully elucidated. It has been reported in association with IE [182,189]. As well, evidence suggests that infections with such strains are associated with clinical evidence of vancomycin treatment failure (defined as persistent fever and bacteremia for >7 days after commencement of vancomycin therapy) with high bacterial load infection [190], although another study found that heteroresistance is not a common cause of persistent or recurrent bacteremia [191]. Therefore, further studies are required to determine the frequency of h-VISA in endocarditis, as well as the significance of heterogeneity in its management.

In addition to VISA and h-VISA, there have been reports of infections with strains of *S. aureus* that demonstrate complete resistance to vancomycin, defined as an MIC of vancomycin ≥32 μg/mL [181]. These vancomycin-resistant *S. aureus* (VRSA) strains remain, thankfully, relatively uncommon in the clinical setting. VRSA strains appear to differ from VISA strains with respect to their mechanisms of resistance. VISA strains undergo changes in peptidoglycan synthesis after prolonged vancomycin exposure, resulting in an irregularly shaped, thickened extracellular matrix on electron microscopy [192]. There is also decreased cross-linking of the peptidoglycan strands, which allows increased exposure of D-Ala-D-Ala residues [185]. These residues bind and sequester vancomycin outside the cell wall, blocking its effect within the cytoplasmic membrane. VRSA strains, on ther other hand, develop vancomycin resistance via the acquisition of the *vanA* operon, presumably from surrounding vancomycin-resistant *E. faecalis* [185,193]. These isolates produce cell wall precursors with D-Ala-D-Lac, instead of D-Ala-D-Ala, that have low affinity for vancomycin, conferring resistance.

Isolated right-sided NVE accounts for only 5–10% of cases of infective endocarditis [194]. The majority of cases occur in patients with IVDU, but 5–10% of cases occur in nonusers [195–197]. The major pathogen is *S. aureus* [194,197,198]. A previous major cause was rheumatic tricuspid valve disease. With medical progress, it is predominantly occurring as a complication of other cardiac anomalies, as well as from central venous/intracardiac catheterization [194,199]. Of course, it can also occur as a component of multi-valvular IE [200]. The majority of the clinical literature on the management and prognosis of isolated right-sided *S. aureus* NVE has been extrapolated from the experience in patients with IVDU, which is discussed in chapter 3.

The symptoms of isolated right-sided *S. aureus* NVE are predominantly nonspecific constitutional symptoms, i.e., fever, chills, night sweats, and malaise, which may contribute to a delay in diagnosis. The major reason for seeking medical attention is the deveopment of respiratory symptoms (e.g., dypnea, pleuritic chest pain, productive cough, hemoptysis), usually the result of septic pulmonary emboli [197]. One study suggests that the triad of recurrent pulmonary events, anemia, and microscopic hematuria (termed "the tricuspid syndrome") should raise clinical suspicion of tricuspid valve endocarditis [194]. Typically, there is a paucity of cardiac signs and symptoms, although right-sided congestive heart failure may occur.

Isolated right-sided *S. aureus* NVE has a low mortality. Relatively abbreviated courses of medical therapy alone produces cure rates >90% [201]. In the absence of any intracardiac or extra-pulmonary metastatic disease, right-sided NVE with MSSA may be successfully treated with as little as two weeks of a variety of intravenous anti-staphyloccocal therapies, typically a penicillinase-resistant penicillin with or without an aminoglycoside (e.g., nafcillin plus tobramycin) [202–204]. An alternative successful regimen has been ciprofloxacin (IV then oral) plus oral rifampin for four weeks [205,206]. It should be remembered, however, that this literature is based on the experience in patients with IVDU, where such regimens produced a relapse rate of ~6% [180,207], necessitating prolongation of treatment (e.g., to four weeks) for cure. Furthermore, such short-course regimens may not be appropriate in patients with cardiac or extra-cardiac complications, fever lasting ≥7 days, or advanced HIV infection (i.e., CD4 count < 200 cells/mm^3) [208].

In right-sided NVE due to MRSA, vancomycin is currently the standard treatment, typically at doses of 30 mg/kg/24 hours in divided doses, with monitoring of serum levels [180,208]. The efficacy of vancomycin treatment for MRSA IE, however, is less than that for β-

lactams for MSSA IE, even in the management of right-sided disease [180]. As such, when vancomycin needs to be used, a more prolonged course of intravenous therapy is required. In a retrospective review of 300 cases of *S. aureus* right-sided NVE, chiefly composed of IVDUs, a 28-day course of vancomycin was adequate for most patients, producing a cure rate of ~70–80% [180]. However, when compared to treatment with β-lactams, the use of vancomycin was associated with delayed clearance of bacteremia and higher rates of complications.

Most of the experience with *S. aureus* right-sided NVE is based on patients with IVDU and suggests that valve replacement is rarely indicated. Surgery should, however, be considered in patients with vegetations >1.0 cm, as these patients are at increased risk for developing new-onset and recurrent emboli [199] and right-sided heart failure [209]. Vegetations >2.0 cm are associated with increased risk of death [210]. Persistent fever, clinically evident right-sided heart failure [198], or increased right ventricular end-diastolic dimension by echocardiography [209] have also defined subgroups of patients who subsequently required valvular surgery. The occurrence of septic pulmonary emboli, despite antimicrobial therapy, is not considered an indication for surgery if the patient is clinically improving [208,211,212]. It should be noted, however, that the experience with surgical intervention in non-IVDU patients with this infection is limited.

In general, tricuspid valve replacement has been avoided in patients with right-sided IE because of the high likelihood of contamination of the prosthetic valve with ongoing IVDU. In patients without drug use, this fear should not preclude such intervention. Alternatively, vegetectomy (i.e., excision of the vegetation only) or tricuspid valvuloplasty can be performed. However, the preferred type of surgery remains to be determined.

Left-sided *S. aureus* NVE is by far more common than right-sided infection. Furthermore, it is a more virulent disease. The overall mortality rate for this infection ranges from 20–65% [201]. Even when diagnosed correctly and managed with appropriate antimicrobial therapy, the complication rate ranges from 20% to 50% [201]. Congestive heart failure is the most common complication, and it portends a poor prognosis. Neurologic manifestations occur in 20–35% of patients [158,213]. These typically occur early in the disease, either before or shortly after the administration of antibiotics [214]. Recurrent emboli are infrequent if the infection is adequately controlled with antimicrobial therapy [213,214]. Neurological complications are accompanied by high mortality rates. Therefore, rapid diagnosis and initiation of antimicrobial therapy may still be the most effective means to prevent neurologic complications.

Antimicrobial therapy, for reasons discussed previously, should include a β-lactam when possible. For the uncommon situation caused by penicillin-susceptible *S. aureus,* benzyl penicillin at maximal doses is the preferred agent. The treatment of choice for MSSA NVE is a penicillinase-resistant semi-synthetic penicillin (e.g., cloxacillin 2 gm intravenously every four hours). Although for other types of *S. aureus* infections, such as cellulitis, first-generation cephalosporins have proven useful as alternatives, the use of such agents (e.g., cefazolin) in the treatment of MSSA NVE is with caution. There have been three previously reported cases of cefazolin failure in patients with such infection. The infecting strain isolated produced β-lactamase type A, which has very high rates of cefazolin hydrolysis. Furthermore, these strains produced high amounts of the enzyme. As such, these isolates demonstrated high MICs to cefazolin. In the context of a cardiac vegetation, where the number of residing organisms can be as high as 10^{10} CFU/gram of tissue, Nannini and colleagues propose that an inoculum effect mediated clinical failure. That is, the high quantity of bacteria results in the production of large amounts of enzyme with inherently augmented cefazolin hydrolysis rates, leading to inactivation of the drug and persistence of the infection. As such, the authors caution that cefazolin usage for treatment of MSSA NVE may be associated with clinical failure. It is unclear what the frequency of such isolates is in clinical practice. Therefore, semi-synthetic penicillins (or penicillin itself) should be used whenever possible. In the absence of any complications, four weeks of therapy is usually sufficient [12,52].

The addition of aminoglycosides to β-lactams produces an enhanced bactericidal effect in vitro, as well as in a rabbit experimental model of endocarditis. However, several clinical studies have failed to demonstrate a clinical benefit, as evidence by equivalent efficacy of cure rates when compared to β-lactam monotherapy, when the total length of therapy was four to six

weeks. There was demonstration, though, that combination therapy did result in significantly faster clearance of bacteremia, but this did not correlate with a more rapid clinical response, as both groups of patients were febrile for approximately the same length of time. There was, however, an increased incidence of nephrotoxicity in the group receiving the aminoglycoside. As such, the use of aminoglycosides (e.g., gentamicin) in the management of MSSA NVE should be limited. The BSAC does not recommend it use in this setting [12], whereas the AHA recommends that if it is used, it be done only for the first three to five days of therapy for left-sided disease [52]. Furthermore, the latter group recommends regular administration of gentamicin, such as two or three times daily, rather than once-daily therapy, with a total daily dose not to exceed 3 mg/kg in patients with normal renal function.

For MRSA NVE, vancomycin is the drug of choice. However, it may be associated with suboptimal outcomes [178,179]. Optimization of dosage to achieve a one-hour serum peak concentration of 30–45 μg/mL and trough concentration of 10–15 μg/mL may be beneficial [12,52]. The BSAC recommends the use of a second antibiotic, in addition to vancomycin, either rifampicin (300–600 mg 12 hourly by mouth), gentamicin (1 mg/kg body weight eight hourly, modified according to renal function), or sodium fusidate (500 mg eight-hourly by mouth), based on susceptibility testing [12]. This suggestion, though, is based on expert opinion. Although rifampin demonstrates potent activity against *S. aureus* in vitro, the in vitro effect when combined with semisynthetic penicillins, vancomycin, or aminglycosides is highly variable [173]. As well, one study of patients with MRSA IE comparing vancomycin monotherapy to vancomycin plus rifampin showed no statistically significant difference in clinical outcome [179]. Similarly, there is insufficient published evidence robustly to demonstrate a clinical benefit for fusidic acid-based combination therapy [215].

The other major indication to use vancomycin has traditionally been in patients who are unable to tolerate β-lactams. Because of the superior efficacy of this class of antimicrobials, for patients with a questionable history of type 1, immediate-type hypersensitivity reaction to penicillin (e.g., urticaria, angioedema), skin testing should be performed to penicillin [52]. If negative, β-lactams should be instituted. Alternatively, a cephalosporin may be considered [52]; first-generation cephalosporins should be used with caution.

Given the suboptimal efficacy of glycopeptides in the management of MRSA NVE, as well as the emergence of VISA/h-VISA/VRSA, alternative antimicrobial therapy is desired. The newer agents with the potential to address this need are the following: quinupristin/dalfopristin (Q/D), linezolid (LZL), daptomycin, and minocycline. Trimethoprim-sulfamethoxazole (TMP/SMX) may have activity as well, and thus antimicrobial susceptibility testing should be performed. The clinical experience with these agents in the management of MRSA or VISA/VRSA NVE, however, is limited. Q/D, a streptogramin antibiotic, demonstrates variable in vitro activity against MRSA isolates. Most MRSA strains possess the MLSb phenotype, rendering them cross-resistant to macrolides, lincosamides, and streptogramin B, mediated by methylation of the ribosomal target [216]. Expression of this phenotype may be constitutive or inducible; when it is constitutive, strains are resistant to quinupristin. The combination, Q/D, retains activity, although the bactericidal activity is reduced [216]. Furthermore, although quinupristin demonstrates homogeneous penetration into cardiac vegetations in an experimental endocarditis model, dalfopristin demonstrated a significantly decreased concentration gradient between the periphery and the core of the vegetation, implying poor penetration of the agent that maintains activity of the Q/D combination [217]. There have been few reported clinical cases in the English literature of Q/D in the treatment of MRSA NVE. It has been used successfully in 1 patient when used alone [218], and in another patient when used in combination with vancomycin and cardiac surgery [219]. However, when used in a worldwide emergency-use protocol for patients with MRSA infections intolerant of or failing prior therapy, the response rates among the few patients with endocardits was suboptimal. Only about half of the patients had a clinical response, but among patients that could be bacteriologically evaluated, both were clinical failures, suggesting that Q/D as monotherapy may not be able to consistently sterilize cardiac vegetations [220]. Further data is certainly needed.

The data supporting the use of LZL is conflicting. In a rabbit model of staphylococcal

endocarditis, LZL significantly reduced bacterial vegetation densities [221]. The antimicrobial activity of LZL is not affected by inoculum size [222]. As well, there have been several cases described in which LZL was successfully used to treat MRSA or VISA endocarditis (both native and prosthetic) in cases of glycopeptide failure or intolerance [182,183,185,189,223]. However, this enthusiasm is tempered by experimental data demonstrating suboptimal activity [224], and clinical data demonstrating clinical failure and LZL-non-susceptibility [225–229]. As such, LZL may represent a therapeutic option in the management of MRSA/VISA NVE in certain populations, but emergence of resistance with clinical failure may occur.

Daptomycin is the most effective and rapidly bactericidal of the novel anti-MRSA antimicrobial agents; it produces clearance of bacteremia faster than vancomycin and the other agents [230]. In a rat model of MRSA endocarditis, daptomycin produced significant decreases in the residual bacterial counts in cardiac vegetations [231]. Similar results were obtained using simulated endocardial vegetations [232]. One case report describes the successful use of daptomycin the treatment of MRSA prosthetic valve endocarditis complicated by perivalvular aortic abscess with persistent MRSA bacteremia unresponsive to vancomycin therapy; surgery was not required [233]. The clinical experience is, however, limited, and an experimental model suggests that daptomycin may have limited diffusion in fibrin clots [234]. Hence, it may be predicted to be associated with clinical failure; future studies are needed.

Owing to the aggressive nature of the disease, with its associated complications, a more aggressive treatment approach has been advocated. Therefore, valve replacement surery has become an important adjunct in the management of *S. aureus* NVE, allowing for a higher likelihood of successfully eradicating the infection. Indications for cardiac surgical intervention have emerged and are discussed in the section "The Role of Surgery" below. Briefly, these indications include congestive heart failure, persistent bacteremia, hemodynamically significant valvular dysfunction, perivalvular extension of infection (abscess or fistula), persistent (uncontrolled) infection (e.g., increase in vegetation size after four weeks of antimicrobial therapy), and lack of effective antimicrobial therapy available (or alternatively, difficult-to-treat pathogens). Several studies have demonstrated the beneficial role of surgery in these situations, with relatively low operative mortality rates when compared to in-hospital mortality rates with medical therapy alone, and good long-term results [158,235–238]. Although patient selection bias may contribute to the observed effect, large prospective randomized studies have not been performed, largely because they represent ethical and methodological challenges.

Coagulase-negative staphylococci (CoNS)

NVE caused by CoNS has become increasingly more common, with most recent estimates of approximately 5–7% of all cases [239]. However, it is likely that the incidence rate will increase, due to increasing dependence of medical progress on intravascular catheters, indwelling devices, and other invasive procedures.

CoNS are a heterogeneous group of Gram-positive coccal species with a clustered appearance on Gram stain and a negative reaction on tube coagulase test. In practical terms, however, the slide coagulase test is a more rapid surrogate marker of the tube coagulase test, demonstrating very good correlation, albeit with a few exceptions (see below). The CoNS are residents of the normal human skin microflora. CoNS have a propensity to cause foreign body infections because of their propensity to adhere to polymer surfaces and form biofilm [240]. Due to these properties, CoNS account for a significant portion of prosthetic valve endocarditis, discussed in chapter 11. However, in the native heart, particularly in the presence of preexisting valvular or congenital heart disease [241–243], the CoNS can cause endocarditis. In general, the clinical course and outcome of the CoNS-NVE is variable, ranging from a subacute, indolent infection with few complications to a fulminant, destructive infection, complicated by valve dysfunction, heart failure, and embolic phenomena. The difference in virulence appears to be species specific, although host factors likely contribute as well. Although *S. epidermidis* is the species most frequently associated with NVE, the clinical characteristics and management of certain other CoNS-NVE are also presented. It is important to note that although CoNS are considered to be low-virulence pathogens, a recent international study demonstrated that patients with CoNS-

NVE had rates of congestive heart failure and of mortality similar to, as well as rates of cardiac valvular surgery higher than, patients with NVE due to *S. aureus* [239]. This point emphasizes the virulent nature of these "skin flora" organisms.

S. epidermidis

The large majority of CoNS-NVE is caused by *S. epidermidis*, accounting for rates of 85–91% of cases [239,242]. *S. epidermidis* can cause a rapidly progressive and destructive endocarditis, and observational series suggest that successful management requires a combination of surgery and antibiotics [239,241,244,245]

The susceptibility of CoNS to antimicrobial agents is extremely variable. Although community-acquired isolates are frequently susceptible to a wide variety of agents, strains isolated from hospitalized patients are typically resistant to multiple antibiotics [241,242,246]. Such multiresistance makes management of serious infections with CoNS particularly difficult.

The optimal antimicrobial management of *S. epidermidis* NVE is extrapolated from experience with *S. aureus* [12,52]. If standardized antimicrobial susceptibility testing demonstrates susceptibility to β-lactams, then these agents are the drugs of choice, as they have been associated with improved survival [175]. Of the β-lactams, penicillin is rarely an option. An earlier report had suggested that among cases of CoNS-NVE, those that were community-acquired were usually sensitive to penicillin [242]. However, determination of penicillin susceptibility among CoNS has since been refined. Resistance to penicillin among CoNS is mediated by a plasmid-borne, inducible β-lactamase [247]. This resistance phenotype is not detected by routine microdilution techniques and is best identified by pre-exposing the isolate to an appropriate inducing agent, such as oxacillin [246]. Such a technique has demonstrated that only a very low percentage of *S. epidermidis* appear susceptible to penicillin in vitro; of these "penicillin susceptible" isolates, a significant percentage were β-lactamase producers [247]. As such, these isolates were considered resistant. A different study had identified β-lactamase activity in 75% of *S. epidermidis* isolates [248]. These studies demonstrate that resistance to penicillin via an easily transferable plasmid carrying an inducible β-lactamase enzyme is highly prevalent.

More problematic, however, is the development of methicillin resistance among CoNS. Although there is geographic variation, methicillin-resistant *S. epidermidis* (MRSE) is very common, particularly among nosocomially acquired isolates, with prevalence rates as high as 60–70% [249]. Methicillin resistance is mediated by the inducible *mecA* gene, which encodes an altered penicillin-binding protein (PBP 2a) that has reduced affinity for β-lactams [250]. As such, it confers resistance to all penicillins, including the semi-synthetic penicillinase-resistant penicillins, as well as to cephalosporins and carbapenems [246,251].

Detection of methicillin resistance is hampered by the fact that MRSE isolates are phenotypically heteroresistant. As such, only a small fraction of organisms (~10^{-8}–10^{-4} [246,252]) actually express the resistant phenotype under in vitro testing conditions. Consequently, these isolates may be missed during antimicrobial susceptibility testing. Currently, most clinical laboratories use phenotypic methods to detect MRSE [251]. For all screening methods, oxacillin was preferred, as it was the most sensitive member of the semi-synthetic pencillinase-resistant β-lactams for the detection of resistance [251]. Currently, cefoxitin is recommended [33]. These generally produce reliable and satisfactory results. However, there is the possibility that some resistant strains may not be detected by this method, which could lead to suboptimal therapy. The most accurate method of detecting methicillin resistance is by detection of the *mecA* gene [253]. However, a practical clue on the antibiogram to the presence of MRSE is the presence of resistance to multiple other antibiotics, including erythromycin, clindamycin, tetracycline, chloramphenicol, and gentamicin [246].

S. epidermidis also may possess plasmid-mediated aminoglycoside-modifying enzymes, particularly AAC(6′)/APH(2″) [251,254]. This latter enzyme has the capacity to inactivate various clinically useful aminoglycosides, including gentamicin, tobramycin, netilmicin, and amikacin. As a result, isolates possessing such enzymes may be resistant to these aminoglycosides. Concomitant methicillin and aminoglycoside resistance has been reported in approximately 50% of isolates surveyed in one study [255].

S. epidermidis may also possess the MLS_b phenotype, encoded by various *erm* genes (predominantly *ermC* [251]), and conferring resistance to macrolides, lincosamides, and streptogramin B.

Rifampin, a bacterial DNA-dependent RNA-polymerase inhibitor, possesses significant anti-staphylococcal activity. Monotherapy with rifampin, however, is strongly discouraged, as it consistently selects for the development of resistant mutants. Resistance to rifampin often develops by mutations in the *rpoB* gene that encodes the β-subunit of DNA-dependent RNA polymerase [256]. Evidence of clinical benefit with the use of rifampin against MRSE has been predominantly in patients with prosthetic valve endocarditis who were being concomitantly treated with glycopeptides and aminoglycosides [257] and is thus indicated in these situations [12,52]. The use of rifampin (along with teicoplanin) in CoNS-NVE was associated with emergence of rifampin resistance (and teicoplanin resistance) while on therapy in 1 patient [244]. A contributing factor may have been the simultaneous use of teicoplanin, an alternate glycopeptide, which has been associated with treatment failure when used in the management of staphylococcal endocarditis [12]. Therefore, the use of rifampin for CoNS-NVE remains debatable, with the British guidelines recommending it as a second agent when vancomycin is used for MRSE [12], while the American guidelines do not refer to it as an option [52].

The glycopeptide, vancomycin, remains a cornerstone of therapy for CoNS-related infections. Teicoplanin has also been used, although as mentioned previously, it is not available for use in North America. Furthermore, teicoplanin resistance seems to be particularly common among CoNS [258–260], and has emerged while on therapy in associaton with clinical failure [244,261]. As with *S. aureus*, there is concern that the efficacy of vancomycin in CoNS NVE may not be as good as expected. There are two major reasons that contribute to the suboptimal efficacy of vancomycin in the treatment of CoNS NVE. Firstly, as extrapolated from the literature on *S. aureus* IE, the pharmacology of vancomycin may be inadequate, with poor penetration into cardiac vegetations and altered bactericidal activity due to the high bacterial inoculum inherent in such vegetations (i.e., inoculum effect) [222,262,263].

The second factor relates to the microbiology of *S. epidermidis*, which possesses the capacity to produce a surrounding biofilm, as well as inherent resistance mechanisms to glycopeptides that can provide a survival advantage. Under in vitro testing conditions (e.g., time-kill studies), both vancomycin and teicoplanin exhibit good bactericidal activity against CoNS [264]. However, such testing is done on planktonic (i.e., free floating) organisms. One of the major virulence factors of *S. epidermidis* is biofilm formation, whereby the bacteria adhere to various surfaces and produce glycocalyx, resulting in colonies of bacteria embedded in a biofilm. *S. epidermidis* bacteria existing in this state demonstrate altered metabolism, with a remarkable ability to tolerate significantly higher levels of antibiotics when compared to their planktonic form [240]. As such, the killing efficacy of achievable peak serum concentration of various antibiotics, including vancomycin, is drastically decreased [263,265]. Although biofilm formation is a well-known explanation for failure of antibiotics to cure *S. epidermidis* infections associated with prostheses, it likely also contributes to the unsatisfactory results seen in CoNS NVE treated with antimicrobial therapy alone, as evidenced by the high rates of cardiac surgery required [239].

The resistance of *S. epidermidis* to glycopeptides, however, is not mediated solely through biofilm formation. CoNS, including *S. epidermidis*, inherently possess chromosomally encoded mechanisms of resistance, consisting of overproduction of an abnormally thick cell wall and increased capacity to bind and sequester glycopeptides in the cytoplasm [265,266]. Furthermore, there is altered peptidoglycan cross-linkage, which may further inhibit vancomycin binding to target sites [193,266]. This glycopeptide resistance is heterogeneously present among populations of CoNS. Complete resistance to glycopeptides at the population phenotype level can be easily selected under laboratory conditions by serial or prolonged exposure of isolates to such antibiotics [267,268]. It has been hypothesized that extensive use of vancomycin in hospitals may also lead to such selection in vivo, allowing for the emergence of CoNS with increased MICs to vancomycin, with subsequent clinical failure [265,268]. This feature is alarming, in view of the fact that decreased susceptibility to glycopeptides is correlated with resistance to other antibiotics, including β-lactams, leaving little room for antimicrobial therapy [193,269].

Due to the emergence of glycopeptide resistance among CoNS, novel classes of antibiotics with alternate mechanisms of action are desirable.

Of these, Q/D, LZL, daptomycin, and telavancin are potentially the most promising, based on the following preliminary data. Conclusive clinical efficacy data on these agents, however, is currently limited.

As discussed previously, Q/D (quinupristin/daltopristin) is a combination of two semisynthetic derivatives of pristinamycin. This combination antimicrobial binds to the 50S bacterial ribosome, resulting in irreversible inhibition of protein synthesis, with subsequent bactericidal effects [141]. Its spectrum of activity is limited to Gram-positive bacteria; however, it has good activity against MRSE. In one study analyzing Q/D activity against 658 isolates of CoNS, >97% of tested isolated had Q/D MICs of < 4 g/L [270]. Of the 186 clinical isolates of *S. epidermidis* specifically, resistance rates to Q/D were <1% [270]; such rates have been confirmed in other studies [271]. As well, clindamycin susceptibility appears to be predictive of Q/D susceptibility [270], which may allow for clinical laboratories to use clindamcyin as a surrogate antibiotic for Q/D during antimicrobial susceptibility testing. Animal models of endocarditis to determine the efficacy of Q/D have focused on *S. aureus* (see above); based on this data, Q/D displays homogeneous distribution throughout experimental vegetations with effective sterilization [272]. There is at this time, however, a paucity of clinical data. As such, there are no formal recommendations regarding the use of Q/D for the treatment of CoNS NVE with reduced vancomcyin susceptibility. However, Q/D therapy was effective in three critically ill (non-endocarditis) patients with MRSE infection unresponsive to vancomycin [273]. Thus, future studies are required for this promising antibiotic. The major limitations in the use of Q/D is incompatibility with several drugs, which is problematic because Q/D is given parenterally, and its numerous drug interactions [274]. Furthermore, there appears to be geographic differences in inherent Q/D resistance among CoNS. For example, 16% of such isolates were resistant in a study from Taiwan, suggesting that Q/D may not be appropriate empiric therapy in certain regions [275].

LZL (linezolid), an oxazolidinone, also possesses activity against MRSE. Among 186 clinical isolates of *S. epidermidis*, the MIC_{50} was 2.0 mg/L, the MIC_{90} was 4 mg/L, and there was 0% resistance to LZL [270]. As with Q/D, there is a paucity of clinical data on the use of LZL in CoNS NVE, although one case report describes the successful treatment of *S. epidermidis* NVE using an oral LZL regimen. Oral management was likely effective because of the 100% bioavailability of LZL. The major adverse events associated with the use of LZL include gastrointestinal disturbances, peripheral neuropathies, and hematologic abnormalities [276]. This latter complication, consisting of anemia and/or thrombocytopenia, is particularly problematic with prolonged use (≥2 weeks) of this agent [277]. Prolonged therapy, however, is necessary in the management of endocarditis. As such, it is recommended to monitor for the development of cytopenias with periodic complete blood counts (e.g., weekly [276]). There is some suggestion that supplementation with vitamin B6 may mitigate the cytopenias [278], although further evidence is required.

Daptomycin, a cyclic lipopeptide, also exhibits activity against MRSE. Its mechanism of action involves the calcium-dependent insertion of the compound into the bacterial cytoplasmic membrane, with subsequent alteration of membrane integrity and transmembrane potential [279]. The data on the use of daptomycin for endocarditis, though, is inconclusive. In a rabbit model of endocarditis, a single dose of daptomycin at 10 mg/kg IV produced an apparently effective response, resulting in a mean bacterial burden of 1.8 ± 1.9 $\log_{10}$ CFU per gram of vegetation, compared to 6.9 ± 1.0 $\log_{10}$ CFU per gram of vegetation among rabbits receving no treatment [280]. However, in another rabbit model using high doses of daptomycin (20 mg/kg or 50 mg/kg) [234], the authors demonstrated a significant antibiotic gradient from the periphery to the core of the fibrin clot, with associated increased survival of staphylococci in the core. For MRSE, differences between bacterial counts in the periphery and in the core of the same clots were approximately 2 to 3 $\log_{10}$ CFU/g. However, in an in vitro simulated endocardial vegetation pharmacodynamic model [232], >70% penetration was achieved by daptomycin, associated with large bacterial density reductions (>4 $\log_{10}$ CFU/g). Currently, there is no clinical experience with daptomycin in MRSE NVE. As such, more information is required before recommending the use of daptomycin the treatment of MRSE NVE.

Telavancin, a novel lipoglycopeptide, demonstrates bactericidal activity against staphylococci and exhibits substantial antimicrobial

activity against staphylococcal biofilms, producing a decrease in the number of bacteria eluted from in vitro biofilms [281]. Currently, there are no reports of the use of telavancin in the treatment of CoNS NVE.

Based on the most recent data from the International Collaboration of Endocarditis (ICE), CoNS NVE (85% of which were due to *S. epidermidis*) was frequently complicated by heart failure (49/99 patients, 49%) and intracardiac abscess (15/99, 15%). For these reasons, patients with *S. epidermidis* NVE more frequently required cardiac surgery when compared to *S. aureus* NVE (54% vs. 35%, respectively, $P < 0.001$) [239]. Furthermore, the rates of mortality with CoNS NVE were similar to those of *S. aureus* NVE (19% vs. 25%, respectively, $P = .21$), dispelling the belief that CoNS NVE is a benign disease. Given the high rates of cardiac complications associated with *S. epidermidis* NVE, early cardiac surgery consultation is suggested.

S. lugdunensis

S. lugdunensis NVE requires special mention because of its reputed aggressive nature. *S. lugdunensis* was first described by Freney et al. in 1988 [282], deriving its species name from Lyon (Latin adjective of *Lugdunum*), the French city where it was first isolated [283]. As with other CoNS, it is commonly found on the skin [283]. *S. lugdunensis*, however, is particularly common in the perineal area, which was felt to be the source of NVE in 10 of 21 cases where a portal of entry was known [284].

The identification of *S. lugdunensis* in the microbiology laboratory can be made difficult because some strains may test positive on the slide coagulase test (see above) [285]. As such, such isolates may be misidentified as *S. aureus*. This misidentification can be overcome by performing the tube coagulase test, which is negative for *S. lugdunensis*. Other features suggestive of *S. lugdunensis* include the production of ornithine decarboxylase and pyrrolidonyl arylamidase [282]. The correct identification of *S. lugdunensis* is critical because of the severe disease associated with it, which may be anticipated or preempted with early speciation.

S. lugdunensis NVE is uncommon, with a recent review of the English literature identifying 48 reported cases [284]. Of these, a fulminant course with symptoms < 3 weeks in duration was reported in 74% of cases. Cardiac complications were particularly common: intracardiac abscess formation (23%), perforation, and destruction of a valve (21%), and large vegetations (11%). Systemic emboli with metastatic foci of infection occurred in 32% of cases.

S. lugdunensis is generally susceptible in vitro to β-lactams [284,286]. In a study of 59 clinically significant isolates of *S. lugdunensis*, 76% were β-lactamase negative, and all strains were susceptible to oxacillin, cephalothin, gentamicin, rifampin, and vancomycin [287]. Therapy should be guided by susceptibility data, and in most instances, a β-lactam plus rifampin or gentamicin is adequate therapy [288]. Because the MICs of penicillin are usually ≥ 2 dilutions lower than that of oxacillin, penicllin intravenously may be the drug of choice once antimicrobial suscepbility testing confirms it as an option [284,289].

Unfortunately, because of the destructive nature of this pathogen, surgical intervention is almost always necessary, despite "adequate antimicrobial coverage." In particular, *S. lugdunensis* NVE is characterized by a shorter, more aggressive clinical history, perivalvular abscess formation, and a high mortality rate. In a review by Vandenesch et al. in 1993 [290], the mortality rate from this disease was 70%, and only 35% of the cases underwent surgery. After 1993, with early cardiac surgery occurring in 64% of cases, the mortality rate was 18% [284]. Although the numbers are small, it is felt that the decrease in mortality is attributed directly to early surgical intervention.

Other Coagulase-negative staphylococci

Case series have also reported CoNS NVE due to *S. warneri* [291–293], *S. capitis* [294], and *S. saprophyticus* [295,296].

S. warneri, a skin commensal but representing only 1% of the skin staphylococci in normal individuals [291], is associated with an acute and aggressive presentation of NVE. It appears to have a predilection for valve destruction or abscess formation [292,293]. As such, optimal management from cases reported suggests that a combined medical and surgical approach is warranted. Similarly, *S. saprophyticus*, a typical

pathogen for community-acquired urinary tract infections, can also have a virulent presentation [295].

S. capitis, a member of the normal flora of the human scalp, face, neck, and ears [297], is reportedly associated with a more benign course, in which a four-week course of antimicrobial therapy is usually sufficient, provided that the patient has a sustained clinical response [294].

Gram-negative bacilli

Non-fastidious Gram-negative bacilli are rare causes of bacterial endocarditis, accounting for 5–10 % of cases [298,299]. Within this category, the major categories of the pathogens of NVE are the Enterobacteriaceae and the non-fermentative Gram-negative bacilli.

The family Enterobacteriaceae are defined as facultatively anaerobic Gram-negative bacilli, characterized by a negative oxidase reaction and the ability to metabolize nitrites to nitrates. The major pathogens within this family with the ability to cause NVE are the following: *E. coli*, *Klebsiella* spp., and *Salmonella* spp., although reports of cases due to other Gram-negative enteric pathogens have been described.

E. coli NVE is rare, with only 39 cases (both definite and probable) identified in a review of case series from the English literature [300]. The major risk factors identified were diabetes mellitus and previous heart disease. The most likely source of for *E. coli* NVE was urinary tract infection. Based on the reported cases, the most common site of infection was the mitral valve [300,301]. Valvular vegetations were typically large, and intra-cardiac complications such as perforation and abscess were reported. Arterial embolization was also common [301]. Various antibiotic regimens were used, based on antimicrobial susceptibility testing, and included third-generation cephalosporis and fluoroquinolones, as well as combination therapy with aminopenicillins, and aminoglycosides. Surgery appears to play an important role, as evidenced by trends in mortality rates: Prior to 1960, the mortality rate was 100%, whereas after 1960, the mortality rate was 57% ($P < 0.05$ by χ^2-test). Correspondingly, none of the patients prior to 1960 underwent surgery, whereas 52% of patients had undergone surgical intervention after 1960. This fact would suggest the need for a low threshold for surgical consultation in cases of *E. coli* NVE that does not respond promptly to antimicrobial therapy.

Klebsiella spp. are very rare causes of NVE, accounting for approximately 1.5% of reported cases in a comprehensive review of this condition by Anderson and Janoff [299]. Among the 23 cases of *Klebsiella* endocarditis in which the affected valve was specified, the majority (17/23 cases, 74%) involved the aortic valve, followed by the mitral valve. The most common source was the urinary tract. Of the cases in which antibiotic usage was reported, aminoglycosides and cephalosporins were most commonly administered (86% and 67% of cases, respectively). However, a wide variety of antimicrobial agents were administered, including combination therapy. The selection of antibiotics used was influenced by the time period in which these sporadic episodes occurred; as such, it is not possible to conclude superiority of one antibiotic regimen over others. Of the 31 patients with *Klebsiella* NVE, 10 were cured, 10 died, and no outcome was reported for 11 subjects. Of the 10 who were cured, medical therapy alone was effective in 5 cases, whereas surgery was a component of management in 4. In the remaining 1 survivor, the use of surgery was not specified. Of the 10 patients who died, 4 received only medical therapy, whereas surgery was used in 2 cases; in the remaining 4 cases, the use of surgery was not specified. The mortality, however, appeared to decrease over time. The mortality rate for *Klebsiella* NVE was 73% in cases reported prior to 1980, but only 22% in those published after 1980. Furthermore, the mortality rate tended to be lower for patients who underwent valve replacement during the course of their infection, when compared to those who did not. In conclusion, based on this literature review, bactericidal antimicrobial agents with the greatest in vitro activity against *Klebsiella* spp. should be used, and strong consideration should be given to combination synergistic therapy (e.g., third-generation cephalosporins and aminoglycosides). The optimal duration of therapy is unknown, but a minimum of six weeks seems prudent. However, because many patients fail to respond to medical treatment alone, early consultation with a cardiac surgeon is appropriate.

Salmonella spp. are well-recognized causes of endovascular infections such as endocardi-

tis, but can also cause infectious endarteritis (also referred to as infectious aortitis and mycotic aneurysms), and vascular graft infections [72,302]. The exact incidence of the different species as causative agents for NVE is difficult to estimate, largely because of the unresolved nomenclature of the *Salmonella* genus [303]. Nonetheless, frequently observed species include *Salmonella enterica* serovar *enteritidis*, *S. enterica* serovar *choleraesuis*, and *S. enterica* serovar *typhi* [72,304]. In approximately 30% of cases, diarrhea preceded the onset of endocarditis from three weeks to five months, or occurred concomitantly with the symptoms of endocarditis [302]. *Salmonella* spp. have a predilection for previously diseased cardiac valves. As such, the tricuspid valve is frequently involved in *Salmonella* endocarditis among intravenous drug users (IVDUs) [72,305]. In cases of *Salmonella* NVE among non-IVDUs, the mitral valve was involved in 36.6%, followed by the aortic valve in 16.6% [302], likely related to known risk factors, such as rheumatic heart disease and mitral valve prolapse [72]. Another major risk factor is advanced HIV/AIDS, likely related to the increased risk for non-typhi *Salmonella* bacteremia in this population [72]. *Salmonella* endocarditis is characterized by a destructive process, characterized by valve perforation, valve ring abscess, atrio-ventricular wall perforation, and/or valvular cusp rupture [302]. Other frequent complications include atrial thrombus formation/mural endocarditis, myocarditis, and pericarditis [306]. As a result of this destructive capacity, previously reported mortality rates are ~70% [307].

The optimal antibiotic treatment for *Salmonella* endocarditis is unknown, largely because of the paucity of clinical data and the general limitations associated with an animal model of this disease. The issue of antimicrobial selection has been further complicated by the emergence of resistance to various antibiotics, including those used for treatment of NVE, such as ampicillin. Ampicillin resistance is mediated by TEM-type β-lactamase-encoding plasmids [308]. Because of the emergence of ampicillin-resistant *Salmonella* and the dogma that bactericidal antibiotics are obligatory in the management of endocarditis to achieve cure, third-generation cephalosporins and fluoroquinolones have become the treatment of choice for *Salmonella* NVE [302].

Using a rabbit model of endocarditis caused by *S. enteritidis* (*S. enterica* subsp. *enteritidis*), the efficacies of different antibiotic regimens in sterilization of valvular vegetations has been estimated [309]. The efficacies varied with the *S. enteritidis* isolate used. For ampicillin-susceptible *S. enteritidis*, both ampicillin and cefotaxime produced the greatest reduction in the number of organisms isolated from the vegetations at the completion of therapy (ampicillin: 2.20 ± 1.1 $\log_{10}$ CFU/g of vegetation; cefotaxime: 1.36 ± 0.7; control: 8.32 ± 1.2); there was no significant difference in effect between these two agents. Ofloxacin also decreased the number of organisms recovered from the vegetations (3.17 ± 1.5), but appeared to be less active than cefotaxime. For vegetations seeded with ampicillin-resistant isolates, cefotaxime and ofloxacin were both equally effective (3.59 ± 1.6 and 3.99 ± 1.08, respectively). Interestingly, the efficacy of cefotaxime was reduced against ampicillin-resistant isolates (3.59 ± 1.6) compared to ampicillin-susceptible isolates (1.36 ± 0.7). The maintained bactericidal effect of cefotaxime and other broad-spectrum cephalosporins against ampicillin-resistant isolates is thought to be related to the stability of the antimicrobial agents to the plasmid-mediated β-lactamase [310]. Based on this animal model, the following antimicrobial regimens may be used for *Salmonella* endocarditis: For ampicillin-susceptible isolates, ampicillin should be used. Cefotaxime may also be used, and should be used for ampicillin-resistant isolates. For patients unable to tolerate cephalosporins, fluoroquinolones may be an alternative, if the isolate is susceptible. For life-threatening infections, empiric combination therapy with a third-generation cephalosporin and a fluoroquinolone has been recommended until susceptibility results are available [311]. There is some clinical evidence to support the use of these antibiotics [304,306,312–314]. There is no clinical data that suggests that combination therapy (i.e., third-generation cephalosporin plus a fluoroquinolone) is more effective than monotherapy.

Resistance to the extended-spectrum cephalosporins and fluoroquinolones, however, is emerging, mostly as a result of agricultural use of antibiotics [315]. The exact resistance rate, however, varies with different serovars and different antibiotics [316]. Resistance to fluoroquinolones is predominantly due to mutations in the DNA gyrase genes and can be predicted by

resistance to nalidixic acid by disk diffusion method during antimicrobial susceptibility testing [316,317]. Resistance to extended-spectrum cephalosporins is due to the production of β-lactamases, both extended-spectrum β-lactamases (ESBLs, particularly the CTX-M types) and AmpC β-lactamases (particularly the CMY-2 type) [316]. The increasing MICs of the salmonellae to these antibiotics are occurring in isolates with established resistance to chloramphenicol, ampicillin, and trimethoprim-sulfamethoazole. Consequently, the antimicrobial armementarium for the treatment of multi-resistant *Salmonella* endocarditis is frighteningly limited. Alternative agents that may demonstrate in vitro activity include imipenem, azithromycin, and aztreonam [311,317]. However, their roles in the management of *Salmonella* endocarditis are unproven. Some antimicrobial agents may demonstrate good in vitro activity (e.g., first- and second-generation cephalosporins [311], aminoglycosides [302,309]), but are not clinically effective.

Based on the above rabbit model, however, medical management alone of *Salmonella* endocarditis is not likely to be effective. After three days of antimicrobial therapy with agents demonstrating in vitro bactericidal activity, the cardiac vegetations remained infected and complete sterilization was never achieved [309]. Clinical experience also supports the essential role of surgery in reducing the mortality of *Salmonella* endocarditis [302,307,311]. The most common indications for surgery have been cardiac failure, relapsing bacteremia, and myocardial abscesses [302,304]. In the patients who survived, valve replacement was necessary. Thus, physicians should have a low threshold for surgical intervention. If surgical intervention is successful, antimicrobial therapy should be continued for a minimum of six weeks; many consultants would subsequently follow with several months of suppressive therapy, even for patients who are well [311,317].

A special form of endovascular infection associated with *Salmonella* spp. is the mural (non-valvular) endocarditis, including infection of ventricular post-infarction aneurysms. This manifestation is related to the organism's unique ability to adhere to the damaged endothelium of the heart and arterial walls. Patients with this type of infection have extensive disease from the endocardium to the pericardium, with pseudo-aneurysm formation, abscess formation, fibrosis, and hemorrhage [302]. If involvement of the pericardium (i.e., *Salmonella* pericarditis) develops, it may be complicated by tamponade [302,307]. Diagnosis of mural endocarditis can be confirmed by cross-sectional echocardiography, revealing ventricular aneurysm, thrombus, and/or pericardial effusion with thickening [302]. Left-ventricular angiography by follow-through from a pulmonary artery injection, to minimize the risk of thrombus dislodgment, can also be performed [302]. Antibiotic therapy should be initiated, but alone, does not eradicate the infection. If there is tamponade, pericardiocentesis or pericardiectomy is required [307]. Resection of ventricular aneurysm must also be performed [302].

Salmonella spp. also have the capacity to establish non-cardiac, endovascular infection (i.e., mycotic aneurysm, or endarteritis or infectious aortitis). The most commonly isolated serotypes are *Typhimurium*, *Enteritidis*, and *Choleraesuis* (in decreasing order) [317]. Most of the patients with mycotic aneurysm due to *Salmonella* spp. have preexisting atherosclerotic disease at the site of subsequently infected aneurysm [302,311,317]. One study demonstrated that the attack rate among adults >50 years of age with Salmonella spp. bacteremia was 25% [318]. The most common site of infection is the abdominal aorta, particularly the infra-renal portion [319]. The most common presentation included fever, abdominal pain, and/or back pain [319]. The diagnostic modality of choice is computed tomography (CT) of the abdomen with contrast, because of its ability to detect changes in the arterial wall and the periaortic tissue [319].

The management of *Salmonella* endarteritis has changed significantly. In previous times, the disease was uniformly fatal [317]. Early surgical intervention, however, has greatly increased survival. In a review of 148 cases from 1948 to 1999, patients who underwent combined medical/surgical therapy had a 62% survival rate [320]. The survival rate was further increased to 77% among 30 patients who specifically underwent excision of the infected vessel with extra-anatomical bypass via construction of an axillo-bifemoral graft [320]. However, anatomic in situ grafting may be acceptable if the infected area is limited and debridement is complete [321]. It may be the only option for supra-renal or thoraco-abdominal mycotic

aneurysms. In addition to surgical management, a prolonged course (≥6 weeks) of parenteral antibiotics is recommended [311,317], with the agent selected based on antimicrobial susceptibility testing of cultures obtained intraoperatively.

Pseudomonas aeruginosa

Pseudomonas aeruginosa NVE is a rare disease which usually affects right-sided heart valves in IVDUs [52,322] and is further discussed in chapter 3. Left-sided *P. aeruginosa* NVE in non-IVDUs has also been described [323]. The major risk factors identified were underlying valvular heart disease, hemodialysis, cardiac catheterization/ surgery, gastrointestinal and genitourinary tract procedures. Left-sided disease is characterized by an aggressive infection poorly responsive to antimicrobial therapy and is associated with mortality rates higher than isolated right-sided involvement [52]. Treatment failure may be attributed to the lack of correlation between in vitro and in vivo susceptibilities (e.g., as a result of biofilm formation), extremely large numbers of organisms present in infected vegetations, the phenotypic heterogeneity of the pathogen, and the frequent development of resistance on therapy [324–326]. In the absence of randomized controlled studies, but on the basis of clinical experience, the suggested management of left-sided *P. aeruginosa* endocarditis consists of immediate valve replacement, accompanied by a six-week course of high-dose, combined (β-lactam plus aminoglycoside) antimicrobial therapy [327]. The AHA recommends high-dose tobramycin (8 mg/kg/day IV in once-daily doses), with maintenance of peak and trough concentrations of 15–20 μg/mL and ≤2 μg/mL, respectively, in combination with either an extended-spectrum penicillin (e.g., ticarcillin, piperacillin) or ceftazidime or cefepime in full doses [52]. Carbapenems, however, have rapid bactericidal action against *P. aeruginosa* [326], with low intrinsic resistance rates [328]. Thus, they may be potentially considered in place of an extended-spectrum penicillin, in combination with an aminoglycoside. It should be mentioned, however, that the use of combination anti-pseudomonal therapy remains controversial. In the setting of suspected infection by *P. aeruginosa,* the use of more than one drug empirically is desirable to assure susceptibility to at least one antimicrobial agent. However, once susceptibility-testing results are available, it is unclear if combination therapy remains necessary, provided that pharmacokinetic parameters are optimized. Although there is no adequately powered, direct study of the effect of combination therapy on *P. aeruginosa* endocarditis, a recent meta-analysis favored the use of combination therapy for *P. aeruginosa* bacteremia, with an approximately 50% mortality reduction [329]. The authors caution, however, that the studies in the systematic review varied considerably in the types of antimicrobial used and there was considerable clinical heterogeneity.

NVE Due to Anaerobic Bacteria

NVE due to anaerobic bacteria is rare, with studies performed in the 1970s reporting them as the etiologic agent in 2–5% of cases [330]. Most cases of anaerobic NVE are caused by Gram-negative bacilli (predominantly *Bacteroides fragilis* group, other *Bacteroides* spp., and *Fusobacterium* spp.). Anaerobic Gram-positive rods (predominantly *Propionibacterium* spp.) have also been reported.

Among the 53 cases of endocarditis due to anaerobic Gram-negative bacilli (GNB) reviewed in the English literature [330], the majority (20/53, 38%) are due to *B. fragilis* group. This group of bacteria includes *B. fragilis* (sensu stricto), which is the most common isolate, and other species, such as *B. distasonis, B. ovatus, B. thetaiotaomicron,* and *B. vulgatus* [331] These bacteria are part of the normal GI flora. As such, the most common sources for *B. fragilis* group NVE were the gastrointestinal and the genital tracts [330,332]. NVE with this group of bacteria is frequently complicated by systemic embolization, occurring in 60–70% of cases [330]. In case studies published prior to 1974, *B. fragilis* group endocarditis was associated with a high mortality rate (14/17 cases, 81%) [330]. This dismal prognosis was most likely due to the lack of an effective antimicrobial agent with anaerobic coverage at that time. Of note, members of the *B. fragilis* group are resistant to penicillins, mostly through the production of β-lactamase [331]. With the introduction of metronidazole in the 1970s, there has been a significant reduction in death rates among patients infected with *Bacteroides* spp. in general [330]. This decline is

related to the high prevalence (>99%) of clinical isolates that are susceptible to metronidazole [331]. Other agents that retain this level of efficacy against clinical isolates include chloramphenicol and the carbapenems; β-lactam/β-lactamase inhibitor combinations also demonstrate activity against the majority [95–99%) of isolates [331]. The development of antibiotics with effective anti-*Bacteroides* activity has facilitated the medical management of this rare endocarditis.

Fusobacterium spp., also members of the *Bacteroidaceae* family, represent a rare cause of endocarditis. The two major clinical species of this genus are *F. necrophorum*, the etiologic agent of Lemierre's syndrome (septic internal jugular vein thrombosis) and *F. nucleatum*. Both organisms have been reported to cause NVE [333]. As with *B. fragilis* group NVE, arterial embolization was the most common complication [333]. In the pre-antibiotic era, the mortality rate from *Fusobacterium* bacteremia was approximately 80%; the rates of *Fusobacterium* NVE per se are unknown [333]. With the advent of antibiotics, the mortality rate has significantly diminished, owing to the general susceptibility of most *Fusobacterium* spp. to penicillin [330]. All reported cases of *Fusobacterium* endocarditis have had a favorable clinical course with antimicrobial therapy alone [330,333].

Propionibacterium acnes is an anaerobic, non-spore-forming, Gram-positive bacterium that demonstrates slow growth in vitro. It is part of the normal flora of the skin and mucous membranes [334]. Although frequently considered a contaminant, *P. acnes* has the capacity to cause serious infections. *P. acnes* has caused endocarditis involving prosthetic valves as well as native valves [335]. The capacity of this "benign" organism to do so relates to its ability to adhere to tissues with structural abnormality (e.g., rheumatic cardiac valves) or to foreign material (e.g., prosthetic valves) [334]. *P. acnes* endocarditis can be complicated by abscess formation, congestive heart failure, and arterial embolization [335]. The mortality rate for *P. acnes* NVE is unknown, but the mortality rate for prosthetic valve endocarditis is 21–46% [336]. Successful treatment of the few cases of NVE have used a combined modality approach [334,335]. *P. acnes* is usually susceptible to penicillin, ampicillin, vancomycin, and gentamicin [334,335,337].

Fungal Endocarditis

Fungi are uncommon but emerging causes of infective endocarditis, most recently accounting for 1–10% of organisms isolated, including ~10% of cases of prosthetic valve endocarditis [338].

Simplistically, fungi are classified as yeasts or moulds. Yeasts are facultatively anaerobic, unicellular, non-filamentous fungi that are typically spherical or oval in shape. The most common yeasts involved in fungal endocarditis (FE) are the *Candida* spp. [338,339], although FE with the other opportunistic yeasts (e.g., *Cryptococcus* spp. [340–342], *Saccharomyces* spp. [343], *Trichosporon* spp. [344–347], and *Rhodotorula* spp. [348,349]) have been sporadically reported. Moulds are aerobic, filamentous fungi. The predominant moulds involved in FE are the *Aspergillus s*pp. [339]. Dimorphic fungi are those organisms that exist as moulds (mycelial form) when incubated at room temperature under laboratory conditions and yeast phase, yeast-like cells, or spherule form when grown in human tissue or incubated at 37˚C on synthetic laboratory media. *Histoplasma capsulatum* is the most commonly reported dimorphic fungus involved in FE [339,350].

The development of antifungal therapies with diverse mechanisms of action is increasing. Currently, there are five classes of antimycotic agents that may be used for invasive fungal infections. These are the polyenes, the azoles, the allylamines, the fluoropyrimidines, and the echinocandins. To establish the spectrum of activity of these agents requires standardization of an antifungal susceptibility testing procedure. Such a procedure requires two components: a standardized method for in vitro testing, as well as criteria for the interpretation of such results that correlates with clinical outcome. Standardized methodologies for yeast [351,352] and for molds [353] have been adopted, and interpretive breakpoints for susceptibility testing for *Candida* spp. to azoles has been established [354]. This is an emerging field in diagnostic microbiology.

The main antifungal polyenes are natamycin, nystatin, and amphotericin B. Of these, amphotericin B (AmB) remains the drug of choice for the treatment of most invasive fungal infections [355,356]. AmB acts by hydrophobically binding to the ergosterol component of fungal membranes, creating aqueous pores consisting of an

annulus of eight AmB molecules [357]. These channels render the fungal cytoplasmic membrane permeable and allow the leakage of vital molecules from the cells, leading to cell death. As such, AmB exerts a fungicidal activity. Unfortunately, cross-reactivity to cholesterol in the mammalian cell membrane accounts for its toxic effects that often limits the dose of medication administered or requires premature termination of treatment.

Based on clinical experience and current interpretive criteria, the antimycotic spectrum of activity of AmB is extensive. It includes most commonly clinically encountered yeasts (e.g., *Candida* spp., *Saccharomyces* spp., *Trichosporon* spp.), molds (e.g., *Aspergillus* spp.) and dimorphic fungi (e.g., *Histoplasma capsulatum*, *Coccidioides* spp., *Blastomyces dermatitidis*) [356]. It should be remembered, however, that AmB does not reliably cover all fungal pathogens. Resistance to AmB may either be inherent or acquired. *C. lusitaniae*, for example, has been reported to be inherently resistant to AmB [355,358], although a review by Ellis [356] suggests that the data, in fact, may be contradictory and that most strains appear susceptible by current in vitro criteria. Furthermore, it is important to remember that despite appearing susceptible in vitro, invasive fungal infections may be frequently associated with clinical failure, possibly due to associated patient co-morbidities. Although acquired resistance to AmB has been sporadically reported, it does not appear to be a significant factor in the management of patients [356].

The major issues related to use of AmB are infusion-related adverse events and nephrotoxicity [359]. Of these, the most serious is the latter. In a study of patients with suspected or proven aspergillosis (non-endocarditis) [360], AmB was administered for a mean of 20 days and a median of 15 days to 239 patients; 53% developed nephrotoxicity (defined as doubling of baseline creatinine). Of these, about 15% required renal dialysis. To circumvent the problems of renal toxicity, various lipid formulations of AmB have been created: AmBisome (Astellas Pharma US, Inc.), a unilamellar liposomal preparation; Abelcet (Enzon, Inc.), a ribbonform lipid complex; and Amphocil or Amphotec (Intermune, Inc., Burlingame, Calif.), a discoidal complex of cholesteryl sulfate and AMB. These different formulations all contain AmB, but they differ with respect to reticuloendothelial clearance, volume of distribution, peak serum concentration (Cmax), and area under curve (AUC) [359,361]. Although these are major differences from a pharmacological perspective, the clinical significance of this difference is unclear. However, these formulations do represent significant improvement in terms of renal-sparing properties relative to the conventional preparation of AmB (i.e., AmB deoxycholate) [362–364]. In terms of efficacy, numerous trials demonstrated that the lipid formulations were consistently at least as effective as conventional AmB [361,363,365]. This equivalence (and potential superiority) may be related to the higher dosages permitted with these preparations. Certain preparations may also have more advantageous distribution to sites of infection. For example, administration of AmBisome in a rabbit pharmacokinetic model demonstrated sixfold more AmB in brain tissue than administration with other agents [366]. The clinical signficance remains to be established, but in the presence of endocarditis with embolic disease to the central nervous system, such property may favor its selection. Conventional AmB has poor penetration into cardiac vegetations [367,368]. The penetration of the various lipid-based formulations for AmB into cardiac vegetations has not been published.

Nystatin is an established antifungal agent but is restricted to topical use as it is ineffective orally and severely toxic when administered intravenously [369]. Because it has demonstrated broad in vitro antifungal activity against clinically relevant fungi, including those resistant to fluconazole and amphotericin B products, there has been renewed interest in its use via an altered preparation. Liposomal nystatin is one such formulation, and there is some evidence to suggest that it may be effective as salvage therapy for patients with invasive aspergillosis refractory to or intolerant of AmB [370]. Its role in the management of endocarditis remains speculative.

The azoles are divided into the older imidazoles, such as miconazole and ketoconazole, and the triazoles, which currently include fluconazole, itraconazole, voriconazole, posaconazole, and ravuconazole. These agents function by inhibiting the lanosterol 14α-demthylase enzyme, leading to decreased synthesis of ergosterol, the main sterol in the fungal cell membrane [357]. The depletion of ergosterol alters membrane fluidity, thereby reducing the activity of membrane-associated enzymes and leading

to increased permeability and inhibition of cell growth and replication [371]. Consequently, azoles exert a fungistatic effect. A major distinction between the imidazoles and the triazoles is the preferential affinity of the latter for fungal, as opposed to human, cytochrome P-450 enzymes, which subsequently accounts for its improved toxicity profile [372].

The spectrum of activity of the azoles expands with newer generations. The imidazoles are not used in the treatment of systemic fungal infections because of poor pharmacokinetics, unpredictable drug interactions, and/or adverse events profile [373]. Fluconazole is a highly water-soluble triazole, developed in both oral and parenteral preparations. The oral formulation has very good absorption, with ~90% bioavailability [374]. The spectrum of activity of fluconazole relative to fungal causes of endocarditis includes the majority of *Candida* spp., *Cryptococcus neoformans*, *Trichosporon* spp., and the dimorphic fungi [373,375]. Of note, fluconazole does not possess activity against all yeasts (e.g., *C. glabrata*, *C. krusei*) [376] and has no clinically meaningful activity against filamentous fungi (e.g., *Aspergillus* spp., *Fusarium* spp., *Scedosporium* spp., and the Zygomycetes, such as *Mucor* spp.) [373,377]. In a rabbit model of endocarditis, the ability of fluconazole to penetrate into cardiac vegetations appeared superior to that of AmB [378]. The distribution of fluconazole is excellent, including CSF penetration, with achieved CSF levels of approximately 80% of corresponding serum levels [379]. As such, it may be the drug of choice for endocarditis caused by susceptible yeasts complicated by septic emboli to the central nervous system. Fluconazole is safe, even at doses up to 1,600 mg daily [380]. In contrast to imidazoles, fluconazole has significantly less interaction with human cytochrome enzymes, and thus does not interefere with the synthesis of mammalian sterol-based hormones [373].

Itraconazole is a highly lipid soluble triazole with a broader spectrum of activity. In addition to *Candida* spp., *Cryptococcus neoformans*, and endemic dimorphic fungi, itraconazole also has activity against *Candida* non-albicans spp. and *Aspergillus* spp. [373,377]. As with fluconazole, itraconazole possesses no reliable activity against other filamentous fungi. The major limitation of itraconazole is its formulations. Initially introduced as a capsular form, which demonstrated erratic absorption, the preparation was modified to a novel, cyclodextrin-based oral solution, which demonstrated a bioavailability 60% greater than that of capsules [381]. Recently, an intravenous formulation has been developed. Clinical studies have demonstrated efficacy in prophylaxis against yeast and mold infections in patients at high-risk for disease (i.e allogeneic stem cell transplant recipients) [382,383]. The literature on the use of itraconazole in fungal endocarditis is limited. The major shortcomings of itraconazole are its lower rates of tolerability and increased potential for drug interactions, when compared with fluconazole [381].

Voriconazole, a second-generation triazole derivative of fluconazole, has a very wide spectrum of activity, including *Candida* spp. (albicans and non-albicans), *Cryptococcus neoformans*, *Aspergillus* spp., endemic dimorphic fungi, as well as other yeasts (e.g., *Trichosporon* spp.) and emerging molds (e.g., *Fusarium* spp., *Scedosporium* spp.) [384). Voriconazole, however, has no significant clinical activity against the zygomycetes [373,384]. In addition to demonstrating in vitro activity against these fungi, the magnitude of the activity is significantly higher; for example, voriconazole is several-fold more active than the predecessor triazoles against *Candida* spp. [373]. Furthermore, voriconazole has both an oral and parenteral formulation, with excellent bioavailability (98.99%, slightly decreased with concomitant food intake) [385]. As with fluconazole, voriconazole has good penetration into the CSF and brain parenchyma, and it has been used in the treatment of CNS aspergillosis (with improved, albeit unsatisfactory, survival rates) [384,386,387]. The major adverse events associated with voriconzole include the more-common, dose-related transient visual disturbances (up to 10% of patients), as well as the uncommon potential for hepatic dysfunction [384]. Unfortunately, cross-resistance to voriconazole, among isolates resistant to fluconazole and itraconazole, can occur [373]. Such a factor must be borne in mind when selecting empiric antifungal therapy.

Posaconazole is an analogue of itraconazole, and has potent activity against *Candida* spp. *Aspergillus* spp., as well as dematiaceous molds and zygomycetes [373]. Ravuconazole, another derivative of fluconazole, also has in vitro activity against a variety of yeasts and molds. These agents are currently undergoing clinical trials.

Their role in the management of endocarditis is undefined.

The allylamine antifungals inhibit squalene epoxidase, an enzyme involved in the synthesis of lanosterol, the precursor of ergosterol [388]. Among this class of agents, terbinafine is the most effective to date. Up to this point, terbinafine has been used principally in the management of dermatophytic infections. However, in vitro, terbinafine is highly active against a broad spectrum of pathogenic fungi, including *Candida* spp. (albicans and non-albicans), and filamentous fungi [388,389]. Among three patients with bronchopulmonary aspergillosis not responsive to the usual antimycotic therapies, systemic terbinafine resulted in eradication of *A. fumigatus* [390]. There is some evidence, however, that the anti-*Aspergillus* activity of terbinafine is greater for the non-fumigatus species [391]. Results from in vitro testing in combination with polyenes and azoles against *Candida* spp. and *Aspergillus* spp., suggests that the therapeutic potential of terbinafine may extend well beyond its current use and that further investigations are warranted [392,393].

The only fluoropyrimidine antimetabolite antifungal currently available is 5-fluorocytosine (5-FC, flucytosine), which exists in both oral and intravenous formulations [377]. 5-FC exerts its effect by being preferentially taken up within fungal cells, where it is converted to 5-fluorouracil (5-FU) [377,388]. 5-FU has two fates: It is converted to 5-fluorouridine triphosphate [5-FUTP], which is subsequently incorporated into fungal RNA, leading to inhibition of protein synthesis. 5-FU is also converted to fluorodeoxyuridine monophosphate (5-F-dUMP), which inhibits thymidylate synthetase and intereferes with DNA synthesis. Monotherapy with 5-FC is strongly discouraged because resistance occurs rapidly [377,388]. Combination therapy with amphotericin B and flucytosine is considered to be the treatment of choice for cryptococcal infections [394]. One case report describes the use of this combination in the management of a child with repaired congenital heart disease who developed *C. albicans* endocarditis [395]. The authors suggest that this antifungal combination should be considered an option, although their patient also underwent surgical intervention, and so the clinical benefit of the combination therapy per se is unclear. 5-FC / azole combination therapy has also been proposed, as it appeared more efficacious in an animal model of invasive candidal disease, when compared to azole monotherapy, with significant decrease in tissue fungal burden and prolonged survival [396]. Case reports in humans have also reported on the efficacy of such combinations [397,398]. Currently, there is no clinical data on the efficacy of this combination for fungal endocarditis.

The echinocandins are a novel class of semisynthetic lipopeptides that inhibit the synthesis of β-(1,3)-D glucan, a polysaccharide in the cell wall of many pathogenic fungi that is responsible for the cell wall's strength and shape [377]. Consequently, these agents render the fungal cell wall osmotically unstable. Caspofungin (Merck &Co., Inc.), the prototypical echinocandin, has broad-spectrum activity against *Candida* and *Aspergillus* spp. and is approved by the Food and Drug Administration (FDA) in the United States for treatment of aspergillosis in patients refractory to or intolerant of other therapies [399]. Caspofungin also has demonstrated potent in vitro and in vivo activity against *Candida* spp. and has approved indications for treatment of candidemia, intra-abdominal abscesses, peritonitis, pleural space infections, and esophageal candidiasis [399]. Cases in which Caspofungin has been successfully used as lone therapy for candidal endocarditis (i.e., without valvular replacement) have been reported [400–402]. Caspofungin, however, has poor CNS penetration in animal models [403,404], and there is concern that it may be inadequate as therapy for fungal endocarditis that is complicated by unrecognized embolic foci of infection [405].

Candida spp.

Candida spp. is the most common cause of FE and is responsible for 33–44% of all cases [339]. Approximately 50% of FE cases are caused by *C. albicans* [339]. *Candida* endocarditis occurs in the setting of particular risk factors, including structural cardiac valvular abnormalities, use of broad-spectrum antibiotics, central lines, parenteral nutrition, and surgery [339,406]. A previous review had reported intravenous drug abuse as a major risk factor for FE [407]. The epidemiology of risk factors, however, has since changed, and in a more recent review, only 4% of patients were reported as drug abusers [406].

With the increasing use of the above risk factors as a reflection of medical progress, it is probable that the incidence of candidal FE will increase.

The management of candidal FE remains poorly defined. An inherent difficulty in establishing treatment guidelines is the low incidence of this disease, thus precluding any appropriately powered, randomized, controlled clinical trials.

Prior to the advent of newer antifungal therapies, AmB was the only agent available. As such, the dogma in management of FE was to remove the infected tissue, replace the valve, and provide six to eight weeks of AmB therapy [408]. The importance of surgical intervention in the management of *Candida* endocarditis is exemplified by the differences in mortality rate without (~90% [395]) and with (~45% [407]) surgery. Surgical intervention should be performed as soon as possible, with removal of the valve and surrounding infected tissue. Current guidelines in North America recommend combined medical and surgical therapy, with medical therapy defined as AmB with or without flucytosine at maximal tolerated doses for a total duration of therapy of ≥6 weeks after surgery [376]. This recommendation is based on a non-statistically significant trend toward better outcome among patients who underwent surgery. It is also supported by a report that 160 days of AmB therapy did not sterilize a cardiac valve [409], emphasizing the need for surgical removal. This initial step of combined medical/surgical therapy, termed the "induction phase," is the first of a two-phase management plan. The purpose is to provide rapid control of infection. After a clinical response to the initial "induction phase," "prophylactic therapy" should be instituted. Typically, oral azoles have been used for this purpose.

The development of the azoles may now provide an alternative to AmB in the treatment of this condition. It has been shown that fluconazole is as effective as AmB for the treatment of candidemia (without endocarditis) [410]. Furthermore, in non-neutropenic, non-endocarditis patients, fluconazole in combination with AmB (0.7 mg/kg per day given only for the first five or six days) trended toward improved success and more rapid clearance of candidemia (excluding *C. krusei*) from the bloodstream, although it was not statistically significant [411]. It has also been used during the "prophylactic" stage (see below). Animal models, however, have suggested that fluconazole may be an effective agent for primary therapy of *Candida* endocarditis, as it demonstrates superior ability to penetrate cardiac vegetations than AmB [378]. The clinical data regarding the use of fluconazole for treatment of *Candida* NVE, however, is limited to a few successfully managed cases in the English literature [412–414]. Future studies are required.

Candida endocarditis has a propensity for relapse after valve replacement, and therefore requires careful follow-up for ≥1 year. This recommendation is based on small series of patients, in which typical follow-ups have ranged 6–12 months. However, relapse has been described in patients several years after treatment was discontinued [368,415]. Thus, it has been suggested that "cure" be defined as the absence of infection for ≥2 years after withdrawal of antifungal treatment [412]. Therefore, "prophylactic therapy" is used after a clinical response to the "induction phase" to minimize the risk of relapse and to attempt a cure. The duration of this phase is poorly defined, but given the potential disastrous complication of recurrence, lifelong suppressive therapy has been suggested [416]. In patients that are not deemed appropriate surgical candidates for valve replacement, or that refuse surgery, prophylactic therapy is used with the goal being lifelong suppression [376,406].

An alternative antimycotic is the echinocandin, caspofungin. The advantage of this agent is that it is fungicidal in vitro and in vivo against most isolates of *Candida* spp., including *C. krusei* and *C. glabrata* [376]. These two yeasts may demonstrate intrinsic (*C. krusei*) or acquired (*C. glabrata*) resistance to fluconazole, and they may also be less susceptible to AmB [376]. Furthermore, it has a benign toxicity profile and requires no modification of dose in patients with renal insufficiency. Case reports have described its successful use in the treatment of *Candida* endocarditis, both native [400,417] and prosthetic [401] valves. However, it may not be the agent of choice if cerebral septic emboli complicate the endocarditis, as it penetrates poorly across the CNS and may permit the development of candidal brain abscesses [405]. Further studies on its efficacy are required.

Aspergillus spp.

Aspergillus spp. are ubiquitous, filamentous fungi with hyaline, septated, branched hyphae.

These molds have the capacity to cause several diseases in both healthy and immunocompromised hosts. *Aspergillus* spp. are the second most common fungal organism, after *Candida* spp., causing endocarditis in patients with previous valvular surgery [339]; this condition is discussed in the chapter on prosthetic valve endocarditis. *Aspergillus* spp., albeit much less commonly, can also cause endocarditis in patients without prior cardiac surgery. The two major manifestations of cardiac aspergillosis in the native heart are *Aspergillus* NVE and *Aspergillus* mural (non-valvular) endocarditis.

Aspergillus NVE is much less common than endocarditis involving prosthetic valves, with a review by Gumbo et al. [418] identifiying 61 cases in the English literature. As with other forms of invasive aspergillosis, immunocompromised status (defined as presence of hematologic malignancy undergoing chemotherapy, adminstration of large or prolonged doses of corticosteroids, solid-organ transplant recipient receiving anti-lymphocyte therapy) was a major risk factor for *Aspergillus* NVE [418]. Advanced HIV, with marked CD4 T lymphocytopenia, also appears to be a risk factor [419].

The major clinical manifestations of *Aspergillus* NVE were fever (reported in 74% of cases), systemic embolization (69%), and a new regurgitant heart murmur (41%) [407,418]. Embolic phenomena frequently involved the central nervous system (brain, eyes), skin, and the aorta/large vessels [418,420]. Involvement of the brain can manifest with focal or general neurologic deficits. Ocular involvement manifests as endophthalmitis with sudden visual loss; this complication has been reported in 13% of cases [418]. As a corollary, it has been suggested that any patient with *Aspergillus* endophthalmitis should be evaluated for endocarditis, which has been associated in up to 40% of cases [421]. Skin involvement typically presents as subdermal nodules [418] or necrotic lesions [422]; either can serve as a substrate for biopsy that may allow for earlier presumptive diagnosis [418,420]. Vascular involvement can manifest as occlusive embolism, typically of large vessels (e.g., ilica, femoral, subclavian arteries) [418]. Alternatively, *Aspergillus* spp., as a result of their angioinvasive properties, can rapidly seed vascular walls and create focal areas of weakness that lead to aneurysmal disease. These aneurysms can occur in multiple vascular beds (e.g., ascending aorta, circle of Willis, peripheral) and can subsequently rupture [420]. Embolic disease to the kidney has been reported in 40% of cases [418]. Local complications can also develop, including pancarditis and cardiac rupture [423].

The major species reported as causing *Aspergillus* NVE include *A. fumigatus*, *A. flavus*, *A. terreus*, and *A. nidus* [418,420]. As with other forms of invasive aspergillosis, *A. fumigatus* was the most common cause of *Aspergillus* NVE. This frequency may relate to the fact that *A. fumigatus* has smaller conidia (2–3 μm), which allow for more efficient inhalation and bypass of the physical barriers of the respiratory system [419], from which they subsequently gain access to the bloodstream.

Aspergillus NVE most commonly affects the mitral valve and typically produces large vegetations, with the average size being approximately 40 mm [418]. Despite these large persistent endovascular vegetations, blood cultures are usually negative due to the facts that fungemia is intermittent and that *Aspergillus* spp. almost never grow in convential blood cultures media [418,420]. The sensitivity of blood culture for isolating *Aspergillus* spp. is 10–30% at most [408]. However, these large vegetations can usually be visualized by echocardiography, with transesophageal echocardiography (TEE) demonstrating higher sensitivity than trans-thoracic modality. Culture of embolic material, usually a cutaneous lesion, is a reliable means of establishing a rapid, presumptive diagnosis. Serologic diagnosis, by detecting host antibody response to the mold, has not proven an effective means of early diagnosis of infection with *Aspergillus* spp. [424]. One major reason is the fact that humoral immunity appears to play a minor role in providing host protection during invasive aspergillosis, although patients who recover from invasive aspergillosis develop detectable antibodies to *Aspergillus* spp. [425]. As well, the sensitivity and specificity of tests for detection of antibodies to *Aspergillus* spp. are low [425,426].

Promising tests for earlier and more reliable dectection of invasive aspergillosis, in general, include antigen detection tests and nucleic acid amplification. Galactomannan (GM) is a polysaccharide cell-wall component that is released by growing hyphae. The most recent test for detection of GM is an enzyme immunsorbent oassay (EIA), which has been shown in multiple studies to be a promising diagnostic tool for IA in neutropenic patients with cancer. However, the

reported sensitivity and specificity have been variable (57–100%, and 66–100%, respectively) [427]. β-D-glucan is a cell wall component of yeast and filamentous fungi. It has been found to be detectable in the blood in various invasive fungal infections, including those caused by *Candida* spp., *Aspergillus* spp., as well as *Fusarium* spp., *Trichosporon* spp., and *Saccharomyces* spp. [428]. The roles of these fungal antigen detection tests in early diagnosis of fungal endocarditis remain to be determined. Of the nucleic acid-based tests, the use of polymerase chain reaction (PCR) for early but robust confirmation of *Aspergillus* endocarditis is promising.

The optimum management in patients with *Aspergillus* NVE remains undefined. Most authors recommend a combination of medical and surgical therapy [418]. For medical treatment, in addition to managing the general complications of endocarditis, administration of antifungal therapy is crucial. AmB has traditionally been the mainstay of treatment for *Aspergillus* infection. However, the optimal dosage, total dose, and length of therapy have not been established. As mentioned previously, the nephrotoxic effect is the most common reason to limit dose or terminate therapy [359]. AmB also penetrates poorly into cardiac vegetations [367]. Nonetheless, based on retrospective data of few patients who survived *Aspergillus* endocarditis, the recommended total dosage of AmB is 2.5–3.0 g (or 50 mg/kg) [429]. It is important to remember that despite these high doses with a seemingly effective antifungal agent, clinical success is not guaranteed. The liposomal AmB, with its renal-sparing properties, has been used successfully to treat cases of *Aspergillus* endocarditis [430,431]; in a few cases, surgery was not required [432,433].

Because of the adverse events associated with AmB, other agents with activity against Aspergillus spp. have been used. 5-FC alone had no effect on survival in an experimental rabbit model of A. fumagatus endocarditis, but when used in combination with AmB (deoxycholate), valve sterilization was achieved in 30% of tested animals [434]. The combination has also proved effective in lowering mortality in neutropenic patients with pulmonary aspergillosis who did not receive a bone marrow transplant [435]. There is a paucity of data on this combination in *Aspergillus* endocarditis. Nonetheless, the adverse events profile of 5-FC necessitates regular monitoring of blood levels of the drug, as well as complete blood cell count and hepatic enzyme profile, to avoid the risk of toxicity.

Itraconazole, an azole with activity against *Aspergillus* spp., appears more efficacious than monotherapy with AmB in animal models [434]. However, its pharmacology (i.e., variable intestinal absorption, unpredictable drug interactions) has limited its use in primary treatment of *Aspergillus* endocarditis. It has been used successfully, however, as antifungal prophylaxis against recurrence once primary treatment was completed [431,433].

Voriconazole, a broad-spectrum triazole antifungal, is an appropriate agent for therapy for invasive aspergillosis [436]. Superior outcomes were obtained for hematological patients with aspergillosis who were treated with voriconazole, compared with conventional amphotericin B, in a large randomized trial [437]. It is now licensed for treatment of documented aspergillosis and other less common mold infections [436]. Given the superiority of voriconazole over AmB in the above trial, voriconazole could be considered the drug of choice for *Aspergillus* endocarditis, although no study currently exists to support this suggestion. One case report describes the successful use of oral voriconazole (in conjunction with aggressive surgical debridement) to treat *Aspergillus* prosthetic valve endocarditis with multiple embolic complications [438].

Caspofungin is an echinocandin with activity against *Aspergillus* spp. At this time, there have been no reports on the use of Caspofungin monotherapy for the management of *Aspergillus* endocarditis.

The optimal duration of antifungal therapy in the acute management of *Aspergillus* NVE remains undefined, although one study suggests that AmB deoxycholate at 1 mg/kg/day (or lipid-based equivalent) for ≥6 weeks is required [418]. This suggestion is based on the fact that embolic episodes with lesions that contain live *Aspergillus* spp. occurred in patients despite having received up to six weeks of AmB at 1 mg/kg/day. Furthermore, the mortality was high, despite a mean cumulative dose of 27 mg/kg of AmB. In certain cases, combination of AmB with 5-FC should be considered. The optimal duration of azoles in the management of acute disease is undefined, although this point may be moot as these are the agents most likely to be used for suppressive therapy (see below).

Surgery is an important adjunct to medical treatment and is recommended in all cases

[339,418,424,435]. Evidence supporting this suggestion derives from the dismal mortality rates among all patients with *Aspergillus* endocarditis treated with medical therapy alone (100%) versus the survival rates for those who undergo a combined medical/surgical approach (< 20%) [438]. However, one study found that surgical intervention with valve replacement did not improve moratlity rates, when compared with rates for patients who underwent antifungal therapy alone [406]. This discordance may be related to the antifungal therapies available that constitute medical therapy. Radical debridement of necrotic tissue with valve replacement using biomaterials (bioprosthesis or homografts) with or without aortic root replacement is the recommended procedure [420]. Lavage of the endocardium with an AmB solution is not efficacious and is no longer considered standard technique [420].

Despite the use of medical and surgical interventions, recurrence rate can be as high as 40% [420]. This high rate of relapse indicates the need for long-term antifungal maintenance therapy (sometimes referred to as "prophylaxis"), after treatment of the acute episode. Azoles have been used for this purpose, particularly itraconazole. Although voriconazole is not licenced for prophylaxis, a guinea pig model suggests that it is highly efficacious in the prevention and treatment of Aspergillus endocarditis and may be superior to itraconazole [439]. A minimum of two years of maintenance therapy is recommended using itraconazole, although given the potential disastrous complication of recurrence, lifelong therapy may be advocated for some patients [420].

Aspergillus mural endocarditis (ME) is a distinct clinical syndrome that differs from valvular endocarditis. Defined as growth or vegetations along the lining of the walls of the cardiac chambers with or without antecedent valvular lesions, it most commonly develops in patients with high levels of immunosuppression, particularly recipients of solid organ transplants [418,423]. ME is highly characteristic of *Aspergillus* spp. and it has been demonstrated in one-third of patients with *Aspergillus* endocarditis [423]. ME typically results from de novo seeding of an abnormal area of endocardium, or as a continguous extension of infection from underlying myocardial abscess [440]. On autopsy, it appears as white-yellow-gray excrescences typically several millimeters in diameter [423]. This diagnosis is difficult to confirm, even by echocardiography, although TEE is likely more sensitive [418,423,441]. The major complication associated with *Aspergillus* ME is embolic phenomena, typically producing micro-emboli leading to metastatic septic foci, rather than large occlusive emboli [423,440]. Fistulous tracts and cardiac rupture may also occur. The optimal management of this condition is poorly defined, but likely a combined medical and surgical approach, as for *Aspergillus* NVE, may be appropriate [418,442].

Endemic mycoses

The major endemic mycoses include histoplasmosis, coccidioidomycosis, blastomycosis, paracoccidioidomycosis, sporotrichosis, penicilliosis, chromoblastomycosis, lobomycosis, and mycetoma. These dimorphic fungi are found globally but each has a specific geographic niche. Most systemic infections with these pathogens occur after inhalation of conidia, while subcutaneous mycoses are caused by the inoculation with vegetable matter or soil. Of these organisms, *Histoplasma* spp. and *Coccidioides* spp. are the most common endemic mycoses associated with endocarditis.

The dimorphic fungus *Histoplasma capsulatum* causes histoplasmosis, which has a worldwide distribution but is especially more prevalent in certain parts of North and Central America. In the United States, it is endemic in the Ohio and Mississippi river valleys [443]. In Canada, endemic regions include Quebec, Nova Scotia, and eastern Ontario [444–446]. Bird and bat droppings enhance the growth of the organism in soil by accelerating sporulation [447]; these environmental factors also contribute to its geographic distribution. Infection occurs by means of inhalation of airborne mycelia, with conversion to yeast forms in the lung and subsequent hematogenous dissemination. Immunocompetent individuals with primary infection caused by low-level exposure are usually asymptomatic or experience minor respiratory illness, even though they have foci of microorganisms widely distributed throughout their bodies [447]. Symptomatic lesions at these sites of hematogenous spread define disseminated histoplasmosis. This latter condition is particularly more common among people with impaired cellular immunity, such as those with AIDS and those at the extremes of age [447].

In a systematic review of the English literature from 1965 to 1995, Ellis and colleagues identified 270 cases of FE, of which 15 (5.5%) were due to *H. capsulatum* [339], thus making it the fourth most common cause of FE in that time period. Unfortunately, certainty of the diagnosis remains unclear since the authors were not able to report on how such a diagnosis was made in each case. The general diagnostic modalities identified in the meta-analysis included blood culture, culture of cardiac vegetation, and histopathologic examination of the cardiac valve. Of these, the latter two are accepted methods for definitive diagnosis of histoplasmosis, with culture of tissue specimens typically requiring four to six weeks for growth [447]. Blood cultures may be helpful, depending on the methodology used. The Isolator lysis-centrifugation method is considered the optimal method because it has consistently proven to be more effective for overall recovery and earlier detection of *H. capsulatum* from blood specimens, when compared to broth systems, including commercially available radiometric ones [447,448]. Adjunctive tests which may be generally helpful for diagnosis of the various *Histoplasma*-related syndromes include the following [447]: (1) Serologic tests, of which the complement fixation test using both yeast and mycelial antigens, as well as the immunodiffusion assay which identifies the H and M precipitin bands, are the standard tests to detect antibodies to *H. capsulatum*. (2) Fungal stains, such as silver stain of tissue sections (e.g., bone marrow) or Wright's stain of peripheral blood smears. (3) Polysaccharide antigen detection can be used in sterile body fluids, such as the blood, urine, CSF, or bronchoalveolar lavage fluid. The high frequency of *H. capsulatum* FE from 1965 to 1995 was not subsequently seen in a retrospective systematic review of FE from 1995 to 2000 performed by Pierrotti and Baddour, in which a similar methodology identified only 2/150 (1.3%) of cases [406].

A literature review, however, focusing specifically on the diagnosis of *Histoplasma* endocarditis, identified a total of 43 cases in the English literature since 1943 [350]. In 42 of 43 cases in that series, the diagnosis was secured via histopathology and/or culture of valve material, along with adjunctive tests. Infection occurred on both native valves (36/43, 84%) and on prosthetic valves (7/43, 16%) and predominantly involved left-sided cardiac structures. More than 70% of cases occurred in the setting of disseminated histoplasmosis. Although the respiratory route is the portal of entry for *H. capsulatum*, the authors' series demonstrated that active pulmonary histoplasmosis was generally not present at the time of endocarditis diagnosis.

The treatment of *Histoplasma* endocarditis remains poorly defined. Although traditional dogma for the management of FE dictates a combined medical–surgical approach, studies addressing this issue for *Histoplasma* endocarditis are inconclusive. In the meta-analysis by Ellis et al. [339], the survival rate was 63% (5/8) for patients treated with antifungal agents alone, compared to 35% (8/23) for patients treated with antifungal agents and surgery. Similarly, Bhatti et al. [350] demonstrated that of 10 patients who underwent combined modality treatment, 8 survived, which was comparable to the 8/11 patients who survived with medical therapy alone. However, Kanawaty and colleagues recommended combined modality treatment, based on 71% survival rate (5/7 patients) for those receiving medical–surgical therapy compared to 44% survival rate (4/9 patients) among those who received medical therapy alone [449]. None of the results demonstrated statistical significance.

Of the antimycotic agents used in the management of *Histoplasma* endocarditis, amphotericin B is the most commonly reported. The mean cumulative dose reported was 3.4 g (range: 1.3–7 g) [350]. The use of azoles is limited to case reports as adjunctive therapy to amphotericin B and is restricted to ketoconazole and itraconazole [350]. The role of newer generation imidazoles (e.g., voriconazole) or echinocandins (e.g., caspofungin) in the treatment of *H. capsulatum* FE, or in the prophylaxis of individuals at high risk for reinfection, is unknown.

Coccidiomycosis is a fungal infection caused by *Coccidioides* species endemic to deserts of the southwestern United States, as well as to Central and South America. The *Cocccidioides* genus currently consists of two species: *C. immitis* and *C. posadasii*; the two species are morphologically identical but genetically and epidemiologically distinct [450]. *C. immitis* is geographically limited to California's San Joaquin valley region, whereas *C. posadasii* is found in the desert southwest of the United States, Mexico, and South America. The two species appear to coexist in the desert southwest and Mexico [450]. Clinical microbiology laboratories do not currently routinely distinguish these two species.

Endocarditis due to *C. immitis/posadasii* has been reported in six patients [451]. In all cases, no valvular destruction was identified, but all cases manifested with impaired valvular function and evidence of disseminated disease. Serologic tests using the complement fixation method revealed a wide range of titers (1:2 to 1:2,048). Histopathologic examination of the involved cardiac valves demonstrated spherules, the predominant form of Coccidioides spp. in human tissue. In addition to valve involvement, *C. immitis/posadasii* has been reported to cause myocardial abscesses [451].

The optimal treatment of coccidioidal endocarditis is unknown. Of the six patients identified in the English literature, only two survived. Their treatment consisted of surgical excision and amphotericin B (one with deoxycholate, one with liposomal complex) for an unspecified period of time, followed by suppressive azole therapy (one with itraconazole, one with fluconazole, censored follow-up).

Non-Valvular Cardiovascular Infections

Although non-valvular cardiovascular infections are much less common than valvular endocarditis, they nonetheless have the potential to be fatal. Certain cardiovascular infections, such as infected pacemakers and implantable defibrillators, as well as prosthetic graft infections, are discussed in other chapters. This chapter will focus on myocardial abscesses, mural endocarditis, and mycotic aneurysms.

Myocardial abscesses are rare but can develop by several mechanisms. A classification system by Chakrabarti [452] divides myocardial abscesses into the following categories: (A) endocarditis-related, (B) septicemia-related, or (C) miscellaneous (see Table 9.6). The most commonly identified cause of myocardial abscess (MA) is endocarditis-related, resulting from contiguous extension of valvular or mural endocarditis [452]. Hematogenous seeding during bacteremia or fungemia is also relatively common [452]. In this latter case, several areas of myocardium are often involved [453], and abscesses in multiple organs, typically the brain, lungs, and kidneys, also occur [452]. Miscellaneous causes of myocardial abscesses include trauma and penetrating injuries, iatrogenic (e.g., catheterization, angioplasty), and anatomic abnormalities (e.g., aneurysm infection, infection of infarcted myocardium, infection of myxoma) [452]. *S. aureus* is the most frequently reported bacterial isolate in patients with MAs; other causes include streptococci, *C. perfringens*, *Bacteroides* spp., *E. coli*, *Candida* spp., and *Aspergillus* spp. [452,453]. Fungal MAs are more common in immunocompromised patients. Paravalvular MAs are usually recognized in the context of endocarditis that is failing to improve or clinically deteriorating. Non-paravalvular MAs are usually subtle, with most previous cases diagnosed at autopsy. The major complication of MAs is rupture. In MAs that develop in an area of recent myocardial infarction, the risk of rupture is increased sevenfold [454]. Rupture can result in tamponade, hemopericardium, and/or purulent pericarditis. Other complications include fistulae, cardiac arrhythmias, or septic shock. Although conduction disturbances detected by serial electrocardiograms in a patient with suspected or proven endocarditis is highly suggestive of a paravalvular MA, the diagnostic modality of choice for all MAs is TEE [452]. The management of non-paravalvular MAs is poorly defined. No comparative studies have been reported in the English literature that compare differences in outcome between patients treated with medical therapy alone versus those treated with combined (medical/surgical) therapy. The management of peri-annular MA is more clearly defined. Identification of an abscess as an extension of valvular endocarditis is an indication for surgery [1,455], in conjunction with adequate antimicrobial coverage. Furthermore, early surgery is advocated, with the goal of achieving more rapid control of the infective process, to improve the chances of survival and to prevent the development of further perivalvular destruction [456]. Surgical intervention usually requires drainage of abscess, debridement of necrotic tissue, closure of any fistulous tracts that have developed, as well as valve replacement (for paravalvular MAs) [1,52]. There is some limited evidence that in select patients, paravalvular MAs may be treated successfully with medical therapy alone [52]. Recommended criteria for this form of management include those who have small (< 1 cm) abscess as well as those who do not have evidence of abscess-related complications (e.g., heart block, progression of abscess during therapy, valvular dehiscence, or valvular

Table 9.6. Antibiotic Treatment for NVE Due to *Staphylococcus* spp.

Category	First-line	Duration	Second-line	Duration	Comments
Penicillin S (MIC ≤0.1 μg/mL, and β-lactamase negative)	High-dose penicillin G (e.g., 24 million units/day) IV	4 weeks if uncomplicated IE; 6 weeks if complicated IE (e.g., metastatic septic complications)			Penicillin-sensitive *Staphylococcus* spp. are very uncommon
			Vancomycin 30 mg/kg/day IV q12h	6 weeks	Vancomycin indicated only for patients unable to tolerate β-lactams
Penicillin R, Methicillin S (MSSA)	Nafcillin or oxacillin 2 g IV q4h ± gentamicin 3 mg/kg/day IV Cloxacillin 100–150 mg/kg/day (e.g. 2 g IV q4h) ± gentamicin 3 mg/kg/day IV	β-lactam: 4 weeks if uncomplicated IE; 6 weeks if complicated IE (e.g., metastatic septic complications) Gentamicin: 3–5 days			Gentamicin therapy optional, and when used, should be in divided daily doses (see text) Recommended duration is for left-sided IE or complicated right-sided IE Uncomplicated right-sided IE may be treated for 2 weeks (see text)
	Flucloxacillin 2 g IV q4 to 6 h				Recommended by BSAC (not available in N. America)
			For "penicillin-allergy" history (i.e., NOT type 1/ immediate-type hypersensitivity): cefazolin 2 g IV q8h ± gentamicin 3 mg/kg/day IV	6 weeks	Use cefazolin with caution, as clinical failures associated with isolates producing β-lactamase type A have been reported (see text)
			For patients with type 1 (immediate-type) hypersensitivity reactions: Vancomycin 30 mg/kg/day IV q12h ± gentamicin 3 mg/kg/day IV		Vancomycin has inferior efficacy compared to β-lactams. AHA also recommends considering β-lactam desensitization
Methicillin R (i.e., MRSA, MRSE)	Vancomycin 30 mg/kg/day IV q12h	6 weeks			AHA recommendation; strongly consider consultation with an infectious disease specialist.
	Vancomycin 1 g IV q12h + 1 of the following: rifampin (300–600 mg po q12h) OR Gentamicin 1 mg/kg IV q8h OR Sodium fusidate (500 mg po q8h)	4–6 weeks			BSAC recommendation Vancomycin and gentamicin doses are modified for renal function Selection influenced by antimicrobial susceptibility testing Strongly consider consultation with an infectious disease specialist
Vancomycin-resistant staphylococci (i.e., VISA, h-VISA, VRSA, VRSE)	Strongly consider consultation with an infectious disease specialist				

S = susceptible; R = resistant

insufficiency) [52]. In these patients, the potential for complications does however continue to exist, and so it is recommended that such patients be monitored closely with serial TEEs (i.e., at 2, 4, and 8 weeks after completion of antimicrobial therapy) [52]. The duration of antimicrobial therapy after surgical intervention remains poorly defined. One review suggests the following approach [457]: Patients undergoing surgical intervention for NVE should be treated for a minimum of four to six weeks with appropriate intravenous antibiotics; the full duration

of antibiotic therapy after valve replacement or repair is based on the intraoperative culture results. If the intraoperative cultures were negative and the patient preoperatively had already received a complete course of medical therapy, treatment with intravenous antibiotics for seven more days is sufficient. If the intraoperative cultures are negative but the patient had not received a full course of preoperative therapy, antibiotics are continued for a total of four to six weeks (including both the preoperative and postoperative period). If the intraoperative cultures were positive, the antibiotics should be continued for an additional four to six postoperative weeks. This latter recommendation is a conservative estimate, athough a retrospective single-center review of 358 patients concluded that it was unnecessary to continue treatment for patients with negative valve culture results for an arbitrary four- to six-week period after surgery [458]. The authors concluded that two weeks of treatment appears to be sufficient to prevent relapse, and, for those operated on near the end of the standard period of treatment, simply completing the planned course should suffice [458].

Mural endocarditis typically results from seeding of an abnormal area of endocardium during bacteremia or fungia; alternatively, it may develop as an extension of infection from underlying myocardial abscesses [453]. The organisms associated with mural endocarditis include *Staphylococcus* spp., viridans streptococci, *Enterococcus* spp., *Salmonella* spp., *Klebsiella* spp., *Bacteroides fragilis* group, *Candida* spp., and *Aspergillus* spp. [453]. Mural endocarditis most commonly presents with nonspecific constitutional symptoms, i.e., fever and chills. The diagnosis of mural endocarditis may be difficult. Blood cultures may be positive, although the data reflecting the sensitivity of this procedure on diagnosis is unknown. Echocardiography is likely the most useful diagnostic modality, with TEE probably superior to TTE [441,459–462]. Nonetheless, echocardiography may be negative in some cases. The complication most frequently associated with mural endocarditis is peripheral embolization, although cardiac rupture and the development of fistulae have been reported [453]. Although no studies exist to guide optimal therapy of this condition, it is likely that a combined approach is necessary, with early surgical intervention warranted to prevent the development of complications [453,459].

A mycotic vascular aneurysm is a localized dilation of the blood vessel wall that is infected. Infection of a vascular wall can occur as a complication of bacteremia by one of two mechanisms: Firstly, bacteria circulating in the intraluminal space can seed an atherosclerotic lesions, with subsequent local invasion, and formation of a true aneurysm. Alternatively, circulating bacteria can invade the vasa vasorum (the blood vessels ramifying on the outside of a major artery), leading to necrosis of the tunica intima, with subsequent pseudoaneurysm formation. Arterial bifurcation points are the most common sites of mycotic aneurysm formation [52], due to turbulence of blood flow that creates a temporary ebb, which permits circulating bacteria to adhere to the vascular wall. Mycotic aneurysms can be anatomically divided into two categories: Intracranial mycotic aneurysms (IMAs), which is the most frequent mycotic aneurismal complication of endocarditis [52], and extracranial mycotic aneurysms (EMAs), which include mycotic aneurysms of the aorta, of the visceral arteries, and the arteries of the extremities.

IMAs are an infrequent but potentially fatal complication of endocarditis. The overall mortality rate is approximately 60%, although this rate is dependent on the status of the aneurysm: for unruptured IMAs, the mortality rate is 30%, whereas the rate increases to ~80% once rupture has occurred [52,463]. IMAs occur more frequently in the anterior circulation, especially the distal middle cerebral artery and its branches, and may be multiple [463,464]. The clinical presentation of patients with IMAs is nonspecific, with the majority being asymptomatic until rupture occurs. The most common manifestations include fever and chills, headache, lethargy/altered level of consciousness; focal neurologic deficits (e.g., aphasia, hemiparesis) can also occur [52,463]. The variable presentation is likely a reflection of the location and progression of the aneurysm, and whether there is any mass effect.

The diagnosis of an IMA should be suspected in a patient with known endocarditis who develops neurological signs and symptoms, at which point rupture with either subarachnoid hemorrhage, intraventricular hemorrhage, or direct intracerebral destruction of the brain has probably occurred. Of note, the development of IMAs can be quite rapid. In an animal model, it has been demonstrated that the time interval from septic embolism to aneurismal dilatation can be as short as 24 hours [463]. The propensity of IMAs to bleed is the principal reason why anticoagulation should be avoided, if possible, in the

management of patients with NVE. The differential diagnosis of new neurological deficit in such a patient should also include embolic infarction and, less commonly, bacterial meningitis. Cerebrovascular imaging is thus required. Computed tomodensitometry (CT) of the cerebrovascular system, without contrast, is useful as an initial diagnostic modality, with sensitivity of 90–95% for detecting an intracerebral hemorrhage (ICH) [52]; it may also be able to identifiy the location of the IMA. In the absence of an ICH, angiography should be performed (either magnetic resonance angiography (MRA) or CT angiography (CTA)) to detect IMAs. Both of these modalities have excellent sensitivities and specifities (90–95% each) [52]. Both techniques may be false-negative, however, for aneurysms < 5 mm in diameter, in which case, conventional cerebral angiography may be used [52]. Examination of the cerebrospinal fluid (CSF) does not aid in diagnosing the presence of an IMA or in consistently identifying the etiologic pathogen [463].

The diagnosis of IMAs in a patient without known endocarditis may be more difficult. Clues suggestive of an infectious etiology when an incranial aneurysm is identified include a fusiform appearance or an atypical location [465]. In these situations, an IMA should be suspected and investigations for endocarditis should be pursued.

The management of IMAs primarily involves a prolonged course of appropriate antibiotics that achieve therapeutic levels in the central nervous sytem. The surgical management of IMAs remains controversial: its presence is not an unequivocal indication for surgical intervention. Resolution of IMAs with antimicrobial therapy alone is well documented. On the other hand, rupture of an IMA is associated with significant morbidity and unacceptable mortality. Unfortunately, no clinical data exist that have reliably identified patients at risk for rupture, in whom prophylactic surgery would be of greatest benefit. As such, the role of surgery in the management of IMAs must be individualized, based on the patient and aneurysm characteristics. One algorithm suggested, based on the authors' experiences at the Mayo Clinic, is as follows [463]: Patients with unruptured IMAs should be observed during antibiotic therapy, with a serial angiograms (MRA or CTA) at four to six weeks. If the IMA enlarges, surgical resection should be considered. If the IMA regresses, surgery can be deferred. If the IMA persists after an adequate course of antimicrobial therapy, surgical intervention could be considered if the residual aneurysm is large, if the patient wishes it, and if the patient's general condition permits. Of note, new IMAs can form after the initial ones have regressed, underscoring the need for regular follow-up of these patients until all of the aneurysms have regressed, or until ≥ two serial angiograms have demonstrated stability in size.

For IMAs that are peripherally located that have ruptured, surgical resection should be performed, provided that the patient's condition can allow for surgical anesthesia. For IMAs that are proximately located, a more conservative approach may be considered, because clipping of these aneurysms in the acute stage may be difficult. In these situations, a trial of antibiotic therapy can be pursued. This will allow fibrosis of the vascular wall, which may make subsequent clipping feasible. If the patient has multiple aneurysms, then the ruptured one should be resected, along with other accessible peripheral aneurysms. The remaining ones are treated with antimicrobial therapy, with serial angiographic imaging; if there is evidence of enlargement, resection should be considered.

The role of endovascular occlusion of IMAs has been described in case series, although the limited power and follow-up of the patients prevents any robust conclusion about the efficacy of this modality [463].

Extracranial mycotic aneurysms (EMAs) can involve the aorta, the visceral arteries, or the arteries of the extremities. Infected aneurysm or pseudo-aneurysm of the aorta is a rate but lifethreatetning condition. The overall hospital mortality ranges from 5–40%, although the anatomic location of the EMA, the infecting pathogen, and accompanying comordities are important factors affecting prognosis. In a single-center retrospective study of 17 patients over 20 years, the operative mortality for supra-renal EMAs was 43%, while that for infra-renal EMAs was 10% [466].

The most common organisms involved in EMAs are *S. aureus* and *Salmonella* spp. [321,467,468]. The latter is discussed in the section on Salmonella NVE. Other common pathogens include *Streptococcus* spp. (*S. pneumoniae* [469], viridans streptococci [470], β-hemolytic streptococci [471]), Gram-negative rods (e.g., *E. coli* [472]), and anaerobes (e.g., *B. fragilis* group, *Peptostreptococcus* spp., and *P. acnes*) [468].

The standard management of EMAs involves a combined approach. Medical therapy (i.e., adequate antimicrobial coverage of long-term duration) is required, but in itself is not sufficient because of the difficulty of antibiotics to penetrate into aneurysms [473]. Therefore, debridement/resectionof the infected aorta and the surrounding infected tissue, followed by revascularization (either in situ or extra-anatomic grafting) is also required [474]. Traditionally, aortic ligation with extra-anatomic bypass was the standard treatment for mycotic aortic aneurysms [474]. However, extra-anatomic bypass may not be practical or feasible if visceral arterial involvement is present; for example, in mycotic aneurysms of the suprarenal aorta, no remote or extraanatomic routes may be available to maintain perfusion to the viscera. As well, in the presence of bacteremia, even a remote graft may be at risk for hematogenous seeding. Furthermore, long-term patency may be compromised. An alternative procedure is in situ reconstruction of the infected aorta with a prosthetic graft. Placement of a foreign body into an infected surgical field seems counter-intuitive, as it has potential for developing early- and late-graft infection. Indeed, such a complication has been previously reported, necessitating a high rate of reoperation [475–477]. However, reports of the safety, durability, and efficacy of in situ reconstruction in the presence of a mycotic aortic aneurysm have also been described [478,479]. To further decrease the risk of in situ graft infection, various modifications (e.g., omental wrapping [477], antimicrobial-coated graft [480,481], cryopreserved allograft [482,483]) have been used. Although there are no guidelines regarding the proper indication for in situ reconstruction, the presence of gross purulent infection at the aortic site is likely a contraindication to this procedure.

The optimal duration of antibiotic treatment for aortic EMAs is not well defined. Recommendations have varied from ≥4–6 weeks to lifelong therapy [474], the latter being especially recommended in the presence of an in situ prosthetic graft.

Endovascular repair is an emerging field in vascular surgery. Although most experience is in the repair of sterile aneurysms, cases of successful treatment of infected aneurysms have been reported [479,484]. In the absence of more robust evidence, it has been suggested that this modality may be currently best suited as a temporalizing measure to rapidly stop the bleeding of a ruptured aortic EMA, followed by definitive surgery [474].

The Role of Surgery

Despite medical progress in the diagnosis and antimicrobial therapy of IE, more than half of patients with IE suffer a serious complication, and the mortality rate is unacceptably high: ~20% during the initial hospitalization and ~40% at one year [485]. The major causes of death are structural complications and hemodynamic instability. As such, cardiac surgery, principally valve replacement, has become an important adjunct to medical therapy. Cardiac surgery is currently used in 25–50% of cases, and several studies suggest that combined medical and surgical therapy can reduce both early and late mortality in patients with a complicated course.

Several indications for surgery in patients with IE have been proposed by Olaisson and Peterson [1], as well as the AHA, with varying strengths of evidence. The former are provided in Table 9.8 Consensus indications for surgery during IE include the following: acute anatomical cardiac destruction; congestive heart failure (CHF); hemodynamically significant valvular dysfunction; perivalvular extension of infection (abscess or fistula); persistent (uncontrolled) infection; and lack of effective antimicrobial therapy available (or alternatively, difficult-to-treat pathogens). Surgery is also indicated for the majority of cases of prosthetic valve endocarditis (discussed in chapter 11) and for the management of mycotic aneurysms (see above). There is a lack of consensus on the indications of surgery in the management of embolic complications.

CHF, regardless of the pathogenesis, is the strongest predictor of mortality in patients with IE. As such, it is the strongest indication for surgery [1]. Among patients with NVE who develop moderate-to-severe (New York Heart Association III or IV) CHF and are treated with medical therapy alone, the mortality rate is 56–86%; among patients treated with combination medical and surgical therapy, the mortality rate is 11–35% [1]. Therefore, CHF is a bad prognostic factor. Furthermore, patients with IE who undergo cardiac surgery have higher perioperative mortality rates if they do so in CHF

Table 9.7. Classification of Myocardial Abscesses (Adapted from Chakrabarti [452])

1. Endocarditis-related	1. Contiguous from a. Valvular IE (perivalvular abscess) b. Mural IE 2. Hematogenous seeding of myocardium
2. Septicemia-related	Hematogenous seeding of myocardium, usually in association with abscesses elsewhere
3. Miscellaneous	1. Trauma and penetrating injuries 2. Iatrogenic (e.g., catheterization, angioplasty) 3. Anatomic abnormalities (e.g., aneurysm infection, infection of infarcted myocardium, infection of myxoma)

(15–35%), when compared to patients without CHF (5–10%) [455]. As such, early cardiac surgery, ideally at the onset of CHF and before the onset of physiologic compromise, should be performed. Of note, the beneficial effect of surgery persists even in the presence of co-morbidities; as such, the development of other complications (e.g., acute renal failure) is not a contraindication to proceed to surgery [486].

Anatomical destruction, such as acute valvular destruction with insufficiency, rupture of the chordae tendinae or papillary muscles, will usually manifest as CHF, necessitating cardiac surgical intervention. Other sequelae of acute destruction include rupture into the pericardium and septal perforation; these may manifest with acute hemodynamic compromise. In these situations, emergent surgery is indicated.

Physiologically significant valve dysfunction can manifest as insufficiency, producing a syndrome of CHF, or with valvular obstruction. The latter may occur, for example, as a result of large vegetations or thrombi superimposed on a stenosed native or on a prosthetic valve. Such obstruction can compromise cardiac output; hence the need for urgent surgery.

Perivalvular extension of infection can develop as paravalvular myocardial abscess or

Table 9.8. Indications for Surgical Intervention in the Management of IE (Olaison and Petersson [1]) Reprinted from Infectious Disease Clinics of North America V. 16, Olaison L, Pettersson G, Current best practices and guidelines: Indications for surgical intervention in infective endocarditis, 453–475, Copyright (2002), with permission from Elsevier.

Indications for surgery in patients with infective endocarditis Indication	Evidence Based
Emergency indication for cardiac surgery (same day)	
1. Acute AR with early closure of mitral value	A
2. Repture of a sinus Valsalva aneurysm into the right heart chamber	A
3. Rupture into the pericardium	A
Urgent indication for cardiac surgery (within 1–2 d)	
4. Valvular obstruction	A
5. Unstable prosthesis	A
6. Acute AR or MR with heart failure, NYHA III–IV	A
7. Septal perforation	A
8. Evidence of annular or aortic abscess, sinus or aortic true or false aneurysm, fistula formation, or new onset conduction disturbances	A
9. Major embolism + mobile vegetation > 10mm + appropriate antibiotic therapy < 7–10	B
10. Mobile vegetation > 15 mm + appropriate antibiotic therapy < 7–10 d	C
11. No effective antimicrobial therapy available	A
Elective indication for cardiac surgery (earlier is usually better)	
12. Staphylococcal prosthetic valve endocarditis	B
13. Early prosthetic v alve endocarditis (≤2 mo after surgery	B
14. Evidence of progressive paravalvular prosthetic leak	A
15. Evidence of valve dysfunction and persistent infection after 7–10 d of appropriate antibiotic therapy, as indicated by presence of fever or bacteremia, provided there are no noncardiac causes for infection	A
16. Fungal endocarditis caused by a mold	A
17. Fungal endocarditis caused by a yeast	B
18. Infection with difficult-to-treat organisms	B
19. Vegetation growing larger during antibiotic therapy > 7 d	C

Abbreviations: A, Strong evidence or general agreement that cardiac surgery is useful and effective; AR, aortic regurgitation; B, Inconclusive or concflicting evidence or a divergence of opinion about the usefulness/efficacy of cardiac surgery, but weight of evidence/opinion of the majority is in favor; C, Inconclusive or conflicting evidence or a divergence of opinion; lack of clear consensus on the basis of evidence/opinion of the majority. MR, mitral regurgitation; NYHA, New York Heart Association classification.

as an intracardiac fistula. The former has been previously discussed. Intra-cardiac fistulous tracts usually develop from either aortic root abscesses or pseudoaneurysms that rupture into adjacent chambers. These fistulae may be single or multiple and generally extend from the aorta to the right atrium, right ventricle, or the left atrium [456]. As well, aortic insufficiency from IE may produce a septic regurgitant jet that strikes subaortic structures, creating secondary sites of infection. Abscesses form at such sites in the left ventricular outflow tract, especially in the mitral-aortic intervalvular fibrosa or junctional tissue between the anterior mitral leaflet and the aortic valve. This leads to pseudoaneurysm formation and rupture into the left atrium, creating a left ventricular-left atrial shunt [487]. The diagnostic modality for detection of these fistulous tracts is TEE [487].

Persistent bacteremia has been defined as bacteremia with an organism identical to the initial isolate, despite ≥7 days of antimicrobial therapy to which the isolate was susceptible [1,488,489]. However, positive blood cultures after 1–4 days of antibiotic therapy have been predictive of complicated bacteremias [490–492]. In the absence of an extracardiac source (e.g., metastatic septic foci), persistent bacteremia indicates a failure of antimicrobial therapy and the most likely source would be intracardiac. As such, diagnostic imaging (e.g., TEE) should be pursued. Persistent fever is not synonymous with persistent bacteremia. In acute uncomplicated infective endocarditis, defervescence occurs within 1 week of effective antimicrobial therapy in 75% of patients and by two weeks in 90% of patients [493]. The presence of fever during therapy should be categorized as "persistent" if there has been no defervescence after one to seven days, or as "recurrent" if there was an initial period of decreased temperature [492,494]. Persistent fever after the first week of hospitalization suggests a septic embolic focus (e.g., visceral abscess) or an intracardiac complication, either of which may or may not be the result of inadequate antibiotic therapy [492]. Recurrence of fever suggests a focal septic complication, non-infectious embolic phenomenon (e.g., visceral infarct), a drug-hypersensitivity reaction (drug fever), or, least commonly, the emergence of a resistant strain [492]. In a single-center, prospective study of 193 patients with IE, 57% of patients had "persistent" or "recurrent" fever. Of the patients with "persistent" fever, 56% were due to cardiac complications. "Recurrent" fever was most often caused by hypersensitivity reactions to β-lactams [494].

The presence of difficult-to-treat pathogens is an indication for surgical intervention (1). Frequently cited examples include *Pseudomonas aeruginosa*, fungi (e.g., *Candida* spp., *Aspergillus* spp.), *Coxiella burnetti*, and *Brucella* spp., organisms for which antimicrobial therapy exists, but when used alone, unlikely to lead to eradication. It is becoming clear, however, that even for pathogens with "adequate" antimicrobial agents available, surgical intervention combined with medical therapy may be the superior treatment of choice. Examples of such situations include NVE with *S. aureus*, certain coagulase-negative staphylococci, and β-hemolytic streptococci (see previous sections). This decision is particularly true in the prsence of any of the above complications.

The role of surgery in preventing CNS complications remains ill-defined. Neurological complications occur in 20–40% of patients with IE [52,495], and can manifest as brain infarction, mycotic aneurysms with/without intracerebral hemorrhage, bacterial meningitis, or toxic encephalopathy. The purpose of surgery would be to prevent septic embolic phenomena. Emboli, however, can occur before diagnosis, during therapy, or after treatment is completed. Identification of predictive factors to estimate an individual patient's risk of embolization has been difficult. Previous attempts to use echocardiography to identify high-risk vegetation characteristics, and thus to identify a subgroup of patients who may benefit from prophylactic surgery, have produced conflicting results. More recent studies have demonstrated that the large majority of embolic complications occur before the diagnosis and institution of antimicrobial therapy [213,214]. Even with antibiotic treatment, the risk of embolization remains elevated for the first two weeks [496]: in one study [162], 65% of embolisms occurred during this period. The risk decreases to 15% after one week of treatment, and then to 1% after four weeks of treatment [455]. Thus, the preventative effect of surgery would be maximal in the first few days of treatment. However, this potential benefit is tempered by the fact that early cardiac surgery would expose a number of patients, who would not have otherwise developed this complication, to the risks inherent with surgery. As

well, these patients would be exposed to the risks associated with prosthetic valves (i.e., lifelong anticoagulation for metallic prosthetic valves, re-do surgery for bioprosthetic devices, risk of prosthetic valve endocarditis). As such, the traditional indication for valvular surgery for IE to avoid embolization has been the development of ≥ 2 major embolic events, although this recommendation is arbitrary [52]. Objective risk factors that may aid in decision-making include the size of the vegetation at baseline, the progression of the vegetation size on therapy, and the infecting microorganism.

Vegetation size intuitively should correlate with risk of embolization. Larger, pedunculated vegetations are potentially more friable at the surface or the neck; when such pieces are disrupted, it results in emboli. Although early data correlating vegetation size to risk of embolization were inconsistent, several subsequent large studies [162,497–499] and a meta-analysis [500] have shown that vegetation size (specifically >10 mm) is a strong predictor of thrombo-embolic events. There is some concern, though, that this "threshold" size not be dogmatic in determining the need for surgery. Vegetation size alone does not precisely identifiy all high-risk patients: not all patients with large vegetations invariably develop embolic complications, and conversely, some patients with relatively small vegetations do. Therefore, other factors clearly must be contributing to the likelihood of embolization. In addition to vegetation size, valvular location has been reported to be important in some studies [162]. As well, the infecting microorganism may play a role, but the data is not adequately powered [162,496]. In addition to vegetation size, vegetation echogenicity theoretically may contribute to predicting a patient's risk for embolizaton. Low-density vegetations are fresh, and thus friable, and would have a greater capacity to embolize than a high-density vegetation, which is more typical of a chronic and healed vegetative mass [162]. Several studies [162,501], however, demonstrated that there was no relationship between vegetation echogenicity and the risk of embolization.

Change in vegetation size is a useful sign. One study suggests that a decrease in vegetation size on antimicrobial therapy is indictive of a rapid healing process [502]. In practical terms, however, most vegetations remain constant in size, despite appropriate antimicrobial therapy; this occurred in ~84% of vegetations in one study [162]. Failure of the vegetation to regress, however, was not associated with a worse prognosis. Growth of vegetation on antimicrobial therapy is ominous. Several studies [162,502] have demonstrated that this feature is associated with poor control of the infection and a higher incidence of embolization.

In conclusion, future studies are required to better delineate the risk factors that most accurately predict embolization and whether prophylactic cardiac surgery in such patients is beneficial.

For the patient with IE who has already developed neurological deficit(s), cardiac surgery may still be indicated if the risk of recurrent embolism is high or if there are concomitant complications. Management thus is determined by the nature of the neurologic lesion, as well as the nature of these other complications. Although the most common CNS complication is embolic disease without hemorrhage [503], a CT scan of the head should be the first step to determine the presence of intracranial hemorrhage [52,495,503].

In the absence of any hemorrhage, only small studies exist to guide management. Maruyama and colleagues report the development of severe neurologic deterioration in 29% (4/14 patients) who underwent valve replacement within five days of an acute, non-hemorrhagic, cardiogenic embolism [504]. Matsushita et al. also reported fatal neurologic deterioration in two patients who underwent emergency cardiac surgery within five days of their stroke [505]. They also noted better outcomes among patients with ischemic events if they were medically treated for 11 days prior to surgery and for 23 days prior to surgery if they had hemorrhagic strokes. Other groups have demonstrated similar results [495,503]. Thus, it has been recommended that, when possible, cardiac operation be delayed two to four weeks for patients who have non-hemorrhagic, cardiogenic emboli [52,495,503,506].

If hemorrhage is identified on CT, the most likely cause is ruptured mycotic aneurysm. As such, angiogram (e.g., MRA, CTA, or conventional) should be performed. Neurosurgical consultation should be obtained to assist in management. Cardiogenic embolism with hemorrhage is associated with an increased risk for perioperative stroke in cardiac surgery [507]. Therefore, surgical management of the

aneurysm (e.g., clipping) may be necessary. In patients who undergo aneurysm clipping, subsequent valve replacement should be delayed for two to three weeks, if the patient is stable [503]. Cardiac operations should be performed only when there is stabilization of the neurologic status clinically, and CT imaging demonstrates resolution of cerebral edema with no ongoing bleeding. If surgical intervention for the aneurysm is not deemed necessary, and the patient is stable, an interval of four weeks between the neurologic event and cardiac surgery is recommended [495,503].

For patients with intracerebral hemorrhage and progressive cardiac failure, the prognosis is extremely poor. In this situation, the benefit from cardiac surgery may outweigh the risk of cerebral deterioration associated with the surgery.

Splenic involvement in IE can be divided into two complications: splenic infarct and splenic abscess. These two conditions are not mutually exclusive, but represent a pathophysiological spectrum. Splenic infarct in IE occurs as a result of arterial compromise, due to embolization of portions of sterile fibrinous vegetations embolizing into the terminal arteries of the spleen. Splenic abscess is a suppurative collection which can develop in patients with IE either as a result of septic emboli or infection of prior infarct. The incidence of splenic complications of IE is unclear, largely because septic infarcts typically have no symptoms or localized findings, and thus may go unrecognized, whereas the incidence rates for splenic abscesses have been based on retrospective studies, and is thus influenced by recall bias. With these limitations, the incidence rate of splenic complications in IE has been estimated at 35–40% [52,508]. Clinically recognized splenic abscess occurred in 2–5% of IE cases [508,509]. Among cases of splenic abscess from all causes, 10–20% are due to endocarditis [510]. One study has demonstrated that the risk of splenic embolization in IE is equivalent for aortic and for mitral vegetations [511].

Splenic infarcts are most often asymptomatic [511], although in patients at high risk for venous thromboembolism, such as IE, the most common presenting symptom is left upper quadrant abdominal pain [512]. The diagnosis can be easily obtained by abdominal ultrasonography (U/S) or CT. CT demonstrates superior sensitivity when compared to U/S (~96% vs. 75–90%, respectively) [510]. On CT, splenic infarcts typically appear as multiple, peripheral-based, wedge-shaped hypodense lesions without significant contrast enhancement [511,513]. They may vary in size, but they rarely involve the entire organ. CT also has the capacity to identify lesions as small as several millimeters [510]. The clinical significance of splenic infarcts is that these lesions are at risk for intra-abdominal hemorrhage during valvular surgery for the IE, as a result of anticoagulation during cardiopulmonary bypass [511]. Furthermore, splenic infarcts may predispose to splenic rupture. Other complications include pseudocyst formation, as well as superinfection with subsequent development of splenic abscess [514]. In the absence of any complications, an isolated splenic infarction can be managed safely with medical treatment [511,514].

Splenic abscesses, on the other hand, are usually symptomatic, with evidence of sepsis being most prominent [511]. The classic triad consists of fever, leukocytosis, and left-upper-quadrant abdominal pain [510,515]. Fever is by far the most common symptom, occurring in >90% of cases [510,515]. Thus, patients with endocarditis, abdominal complaints, signs of sepsis (e.g., recurrent or persistent fever), or recurrent or persistent bacteremia should be evaluated for any potential foci for relapse, particularly the spleen. CT is very useful for identification of a splenic abscess, which typically appears as a solitary, round-to-irregular shape, centrally located, hypodense lesion that is contrast enhancing [511]. Air within the cavity is pathognomonic of abscess [511]. There is, however, considerable overlap between the CT patterns of splenic infarcts and abscesses. In addition to the morbidity to the patient, the major clinical signficance for a splenic abscess is that it may serve as a source of subsequent bacteremia and seeding of a prosthetic valve inserted for management of IE. The other major complications of splenic abscesses include rupture into the peritoneal cavity, which is the most common, as well as rupture into contiguous spaces, producing visceral abscesses, peritonitis, or empyema [515].

The management of a splenic abscess requires a combined medical and surgical approach. Splenic abscesses respond poorly to antibiotic therapy alone. Although antibiotics are effective in clearing the bacteremia of IE, they do not penetrate well into splenic abscesses; consequently, organisms in the abscess are not

eradicated and can still be cultured. Previous studies have demonstrated 100% mortality rates for patients undergoing medical therapy alone. Robinson and colleagues [509] identified 27 patients who developed splenic abscesses among 564 patients with IE between 1970 to 1990. Of these, there were 13 deaths: 10/13 (77%) of the patients who did not undergo splenectomy died, compared to 3/17 (18%) of the patients who underwent splenectomy. A literature review by Johnson et al. [516] demonstrated that the survival rate for 17 patients with splenic abscess who did not undergo splenectomy was 0%, compared to 95% who did. In situations in which antimicrobial therapy alone appears successful initially, recurrence of abscess formation is common. Based on this evidence, the recommended definitive management of splenic abscesses in patients with IE has been splenectomy [52,509,515,517–519], of which the goal is to eradicate the extra-cardiac focus of infection as a prerequisite to successful management of IE. If possible, the AHA 2005 guidelines [52] recommend that splenectomy be perfomed prior to valve replacement surgery, to minimize the risk of contaminating the valve prosthesis as a result of bacteremia from manipulation of the abscess. This recommendation, although conceptually logical, is not based on evidence in the literature. However, in one series of ten patients with IE in whom splenectomy was performed for splenic abscesses, the splenectomies were staged and performed at a mean time interval of 11.2 days *after* valve replacement (range: 3–24 days) [511]. Although follow-up data is not completely provided, three of ten (30%) of the patients who underwent splenectomy died: one in the postoperative period from bleeding, and two at unspecified times from "cardiac causes." Another study suggests that splenectomy can be performed before or after valvular surgery, depending on the patient's clinical status [509]. Laparoscopic splenectomy for splenic abscess, although potentially more difficult technically, appears to be a safe and effective alternative to open surgery [517,518].

More recently, radiographically guided percutaneous aspiration or catheter drainage has become popular. The advantage is that it spares the spleen, and thus avoids the risks of the hyposplenic state (e.g., overwhelming post-splenectomy sepsis). Success rates with this procedure have ranged from 75% to 100%, although several catheterizations may be needed to achieve cure [510]. Furthermore, this procedure has been associated with high rates of failed attempts, which subsequently have required rescue splenectomies [515]. However, the need for a rescue splenectomy does not appear to be significantly associated with increased mortality rates [510,515]. It has been recommended that percutaneous aspiration or catheter drainage be contraindicated in a select subgroup of patients, namely those with multiloculated abscesses, septations, tenaciously thick abscess contents, or abscess rupture/bleeding [510,515].

In conclusion, the role for surgery in the management of IE or its complications is expanding. Although the risks for surgical intervention in patients with complicating features such as those discussed in this chapter are real, there is ample evidence that combined modality treatment is beneficial in specific instances.

Key Points

1. The diagnosis of infective endocarditis (IE) requires early clinical suspicion, based on history and physical examination, and can be supported by appropriate microbiological laboratory investigations (e.g., blood culture, serology) and/or imaging (e.g., echocardiogram).
2. Empiric antimicrobial therapy, based on the most likely pathogens identified from clinical evaluation, may need to be instituted, particularly in patients who are clinically unwell. Once a pathogen has been identified, antimicrobial susceptibility testing must be performed, including determination of the minimal inhibitory concentration (MIC) and the presence of in vitro synergy, where applicable.
3. Effective antimicrobial therapy requires the administration of bactericidal agents for an extended period of time.
4. Health care providers should be aware of the possible intracardiac and extracardiac complications of IE.
5. The role of surgical intervention in the management of IE has likely strongly contributed to reduced mortality rates. Indications for surgical intervention exist, with congestive heart failure (from any cause) being the principal need for surgery. When appropriate, early surgical intervention should be performed.

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10

Blood-Culture-Negative Endocarditis

Stephanie Smith and Thomas J. Marrie

Case Study

This 76-year-old female was admitted to hospital on June 3, 1991, with an eight-day history of fever, chills, anorexia, nausea, vomiting, and weakness, along with hip and knee pain. Four days prior to admission she saw her family doctor and was treated with ciprofloxacin.

Because of progression of her illness to the point where she was unable to look after herself (she lived alone), she came to the hospital. At this time she gave a history of hospitalization for pancreatitis six months earlier. She underwent upper gastrointestinal endoscopy while hospitalized and in retrospect feels that she has been febrile ever since.

She was in mild distress and her temperature was 37.8°C orally. There was a III/VI pansystolic murmur at the apex with radiation to the axilla. Bilateral knee effusions were present. The white blood cell count was 9.6 × 10 9 /L; serum creatinine, 85 mM/L. Blood cultures were drawn and treatment was begun with cloxacillin for what was assumed to be cellulitis.

One day later she complained of shortness of breath and crackles were noted at both bases. A chest radiograph was compatible with mild congestive heart failure. The blood cultures were reported as negative the next day and a consultation was sought with Infectious Diseases. The consultant ordered a transesophageal echocardiogram, which showed three plus mitral regurgitation and a large vegetation on the posterior leaflet of this valve. Therapy was begun with vancomycin. On day 7 a respiratory arrest occurred and after resuscitation she was transferred to the intensive care unit. On day 12 her mitral valve was replaced. A paravalvular abscess was present. The valve had myxoid features and a vegetation was evident (Figure 10.1). A Gram stain showed scant intracellular gram positive cocci (Figure 10.2). Despite prolonged incubation the cultures of the valve remained negative. She had a complicated postoperative course but eventually she made a full recovery.

This is a classical case of culture negative endocarditis due to prior treatment with antibiotics. The endocarditis was due to a Gram-positive coccus. Molecular methods (as discussed in this chapter) could have been used to identify the microorganism. Given the combination of fever and a reguritant murmur, endocarditis should have been suspected at the time of admission. At least three blood cultures should have been done but whether these would have let to an etiological diagnosis is speculative. The clinicians could have waited a couple of days before starting antibiotics and performed additional sets of blood cultures.

Introduction

One of the greatest challenges facing a physician is that of infective endocarditis with negative blood cultures. Having arrived at the diagnosis, the physician still faces many challenges: further diagnostic work-up to determine the etiology, choice of antibiotics, and duration of treatment. Given these difficult diagnostic and management issues, it is not surprising that blood culture endocarditis (BCNE) is associated with higher

Figure 10.1. Photograph of mitral valve from patient with culture negative endocarditis. The red areas represent residual vegetation.

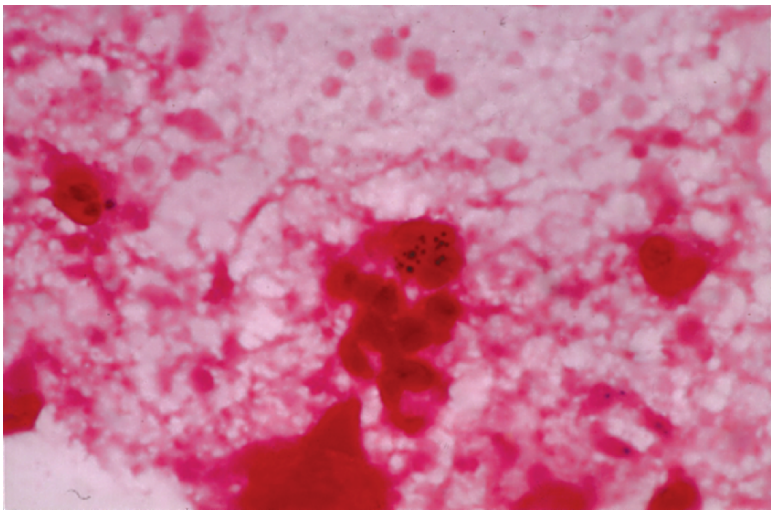

Figure 10.2. Gram stain of material from the paravalvular abscess. Note the Gram-positive material within white blood cells. Magnification ×1,000.

morbidity and mortality compared with blood culture positive endocarditis. In a study by Murashita et al. [1]. BCNE was found to be an independent predictor of decreased survival and increased events after surgery. Another study by Zaorano et al. [2]. showed that patients with true BCNE had a significantly higher mortality and need for surgical repair than those with negative blood cultures due to previous antibiotic use.

The goals of this chapter are to provide up-to-date knowledge on blood-culture-negative endocarditis and to suggest strategies for diagnosis and treatment of this problem.

Definition and Incidence

Blood-culture-negative endocarditis is defined as definite or probable endocarditis in which three or more aerobic and anaerobic blood cultures collected over 48 hours remain negative despite prolonged (greater than one week) incubation [3]. Definite or probable endocarditis is defined according to Duke criteria [4].

The incidence of BCNE ranges from 2.5 to 31% [5]. A more recent study by Werner et al. [6] found that of 116 episodes of endocarditis,

20% were culture negative. Forty-five percent of these episodes were preceded by antibiotic use. Studies using comprehensive diagnostic methods including serology, microscopy, and PCR report an incidence of 5% [7]. This decrease in the incidence of BCNE can be explained by improved knowledge of clinical symptoms and risk factors as well as improvement in bacterial culture techniques including longer incubation times, use of enriched culture media, and timed subcultures. Serologic and molecular tests have also allowed for identification of a variety of organisms not previously detected by blood culture [8].

Etiology of BCNE

A list of causes of BCNE can be seen in Table 10.1. There are a large number of bacteria that occasionally cause endocarditis anywhere in the world. These uncommon cause of endocarditis include *Mycobacterium* spp. (31 cases), *Mycoplasma* spp. (2 cases), *Campylobacter fetus* (21 cases), *Pasturella* spp. (20 cases), *Bordatella* spp., *Francisella tularensis, Aeromonas hyrophilia* (1 case each), *Yersinia entoercolitica* (12 cases), *Streptobacillus moniliformis, Neisseria gonorrhea* (40 cases), *Listeria moncytogenes* (58 cases), *Lactobacillus* spp. (30 cases), *Nocardia* spp. (3 cases), *Erysipelothrix rhusiopathiae* (44 cases), *Clostridium* spp. (21 cases), and non-toxigenic *Corynebacterium diptheria* (67 cases) [9]. Although these are uncommon causes, not all of these would be classified as BCNE according to strict criteria as many of them can be cultured using routine blood culturing methods.

The HACEK organisms, which are uncommon causes of endocarditis, have traditionally been classified as BCNE, although with newer culturing techniques, these may be detected using routine blood culture methods with subculturing on enriched media.

A number of recent studies have looked at the etiology of BCNE when strict definitions are applied. Houpikian and Raoult [10] studied 348 cases of culture-negative endocarditis in Marseille, France, from 1983 to 2001. Forty-eight percent of the cases were due to *Coxiella burnetii*. A further 20% were due to *Bartonella* species and 5% were due to *T. whippeli, Abiotrophia* spp., *Mycoplasma hominis,* and *Legionella pneumophila*. Of the 73 cases with no etiology, 58 occurred in patients who had been receiving antibiotics prior to blood cultures, 6 had right-sided endocarditis and 4 had a permenant pacemaker. In five patients, there was no explanation for the culture negative endocarditis.

Table 10.1. Etiologic Agents of BCNE

A. Previous antibiotic therapy
B. Organisms not easily isolated using standard culture techniques
   a. *Mycobacteria*
   b. *Mycoplasma* spp.
   c. *Tropheryma whippelii*
   d. Gram-negative bacilli:
      Coxiella burnetii
      Chlamydia spp
      HACEK
      Campylobacter fetus
      Pasturella spp.
      Brucella spp.
      Francisell tularensis
      Bordatella spp.
      Aeromonoas
      Yersinia
      Streptobacillus moliliformis
   e. Gram-negative cocci:
      Neisseria spp.
   f. Gram-positive bacilli:
      Listeria spp.
      Lactobacillus
      Nocardia
      Erysipelothrix
      Clostridium spp.
      Non-toxigenic *Corynebacterium*
   g. Gram-positive cocci:
      Abiotrophia
      Gemella
   h. Molds and yeasts
C. Miscellaneous
   a. Right-sided endocarditis
   b. Infected mural thrombi
   c. Infected pacemaker wires
D. Non-infectious thrombotic endocarditis

Clinical Approach to the Patient with BCNE

All patient encounters start with a medical history; and in the case of BCNE, the patient's history can provide valuable clues to the possible etiology and can therefore direct further investigations. A history of previous antibiotic therapy should be elicited as this is the most common cause of BCNE. It has been shown that even a short course of antibiotic treatment can

Table 10.2. Characteristics of the Most Common Agents of BCNE

Organism	Frequency/# Cases	Risk factors/ Predisposing Conditions	Clinical Presentation	Diagnosis	Therapy
Coxiella burnetii (Q fever)	3–5% of IE, > 400 cases worldwide	Rural life, exposure to farm animals, raw milk	Subacute fever, heart failure, immune-complex disease	Serology (phase I IgG ≥ 1:800, shell vial culture, PCR, valve histology	Doxycycline + hydroxy chloroquin for 1–3 yearrs; follow serology
Bartonella henselae	2% of cases worldwide (including *B. quintana*)	Bites/cat scratches, exposure to cat fleas, valvular heart disease	Subacute, fever, large vegetations, aortic valve, clubbing, hepatosplenomegaly	Serology (IgG ≥ 1:800), PCR, histology	Ceftraixone or doxycy cline × 6 weeks + gentamicin × 2 weeks VR necessary 80%
Bartonella quintana		Homelessness, chronic EtOH use, body lice	Same as *B. henselae*	Same as *B. henselae*	Same as *B. henselae*
HACEK	2–3% of all cases > 300 cases reported	Young age, recent dental work, valvular heart disease	Subacute fever, congestive heart failure, mitral valve vegetations	Prolonged incubation of blood cultures, subculture-enriched media	Ceftriaxone × 6 weeks
Fungi (mostly Candida)	1–5% of cases	CVC, long-term antibiotic therapy, immunocompromised, prosthetic heart valves, valvular heart disease	Large vegetations with embolic phenomenon, heart failure	Culture, histology (PAS) of valves	Amphotericin B + an -azole VR usually required
Abiotrophia	1–2%	Valvular heart disease	Subacute fever, heart failure	Subculture with pyridoxine or L-cysteine	Penicillin or Ampicillin + gentamicin × 6 weeks
Mycobacteria	32 cases	Prosthetic valves, contaminated water or prosthesis, milliary TB	Fever, acute cardiac failure	Prolonged blood culture or histology of excised valves	Based on individual mycobacterium, treat for > 6 mo + VR often necessary
Legionella	11 cases	Nosocomial infection, prosthetic valves	Chronic fever, nightsweats, weight loss,	Subculture on BCYE agar, PCR, histology	Erythromycin + rifampin or ciprofloxacin × 3–6 mo ± VR
Mycoplasma	2 cases, underdiagnosed	Prosthetic valves, immunosuppression	Fever, prosthetic valve dysfunction, no vegetations on valves	Culture from infected valve, serology	Tetracyclines, VR
Whipple's disease bacillus	Unknown	Elderly men, many have sx of Whipple's disease	Fever, diarrhea, arthralgias, aortic valve involvement	PCR, histology (PAS) from valves or duodenal biopsy	Ceftraixone or penicillin + gentamicin × 6 weeks then co-trimoxazole × 1–2 years

cause long lasting suppression of bacterial activity [11].

A variety of animal exposures may predispose to certain microbiologic etiologies. Contact with sheep and cows should suggest infection with *C. burnetii*. The human body louse has been implicated in transmitting *Bartonella quintana* and *Bartonella henselae* should be suspected in cat owners. Travel to the middle east and ingesting unpasturized milk should suggest infection with *Brucella* spp. Legionella should be considered in a patient with a history of recent hospitalization. Immunosuppression or prolonged antibiotic therapy should suggest endocarditis due to fungi. Physical examination may be helpful in establishing a diagnosis of endocarditis but is unlikely to aid in defining the etiology. In a study carried out at St. Thomas' Hospital from 1975 to 2000, a total of 63 patients with BCNE were identified [12]. In this study 17% of patients were afebrile; 20% had cerebral emboli; 19% had splinter hemorrhages; 17%, hematuria; 15%, splenomegaly; 13%, rash; 10%, clubbing; 8%, pulmonary emboli; 4%, peripheral emboli; 4%, subconjuctival hemorrhage; and 4%, Osler's nodes.

Approach to Treatment

When a diagnosis of possible infective endocarditis is made, diagnostic studies to determine the etiologic agent, especially in the case of

BCNE, may take days to weeks. A prospective epidemiologic study by Werner et al. [6] looked at total symptom duration until hospitalization and until treatment in 111 cases of BCNE. They found a symptom duration until hospitalization time of 23 days and a symptom to treatment time of 27 days. Delays in initiation of treatment can significantly increase morbidity and mortality. When choosing empiric treatment, a history of previous antibiotic use, recent exposures (animals, IVDU, travel, dental procedures), underlying medical conditions (prosthetic versus native heart valves), as well as knowledge of prevalence rates of causative organisms can help to guide therapeutic choices. When the patient is acutely ill and while awaiting results of various diagnostic studies, empiric treatment should be initiated. Rational empiric treatment should include an antibiotic that is active against the bacterial cell wall (cloxacillin 12 g/day or vancomycin 1 g every 12 hours) and an aminoglycoside (e.g., gentamicin 1 mg/kg every eight hours) [13]. If a patient has had significant exposure to farm animals, treatment with ciprofloxacin 750 mg every 12 hours in combination with rifampin 600 mg once daily or doxycycline can be initiated to cover for *Bartonella* or *Coxiella* infection. If the patient continues to deteriorate despite initiation of empiric therapy, treatment for HACEK, *Abiotrophia,* and *Bartonella* can be initiated with ceftriaxone and gentamicin [13].

Diagnostic Methods

Culture

Culture of three sets of blood drawn within a 24–48-hour period is usually sufficient to make a diagnosis of culture positive endocarditis and alternatively indicate a possibility of BCNE [14]. Because of the almost linear relationship between the yield of bacteria from the blood and the volume of blood drawn, 10–20 mL of blood is optimal for each culture [15]. If the patient has received antibiotics, blood should be processed in the presence of an antimicrobial agent removal device such as cationic or polymeric adsorbent resins with sodium polyanetholsulfonate. These are now included in many commercially available blood-culturing systems.

In the modern microbiology laboratory isolation of fastidious organisms from the blood should not be problematic. The key to successful isolation is to ensure the laboratory is aware the patient is suspected of having endocarditis. Most organisms of the HACEK group can be isolated on enriched or chocolate agar, with the exception of *Actinobacillus* which may take up to 30 days to grow [14]. *Abiotrophia* spp. are now readily isolated due to the addition of B6 in commercial blood-culture media [16,17].

Specific media are required for some pathogens. *Legionella* spp. require buffered charcoal yeast extract for optimal growth. Most *Mycobacteria* spp. can be isolated in standard blood culture systems but the use of Middlebrook 7H13 broth should be considered especially for *Mycobacterium tuberculosis* [9]. Intracellular bacteria such as *Coxiella burnetii* and *Bartonella* spp. require cultivation in cell cultures [18,19].

The shell vial technique has been successfully used for isolation of *Tropheryma whippelii* and *Chlamydia psittaci* [20,21].

Histology

Histologic analysis of excised valves can aid in making a diagnosis of infective endocarditis. Histologic parameters are now included in the Duke criteria [4,22]. The absence of inflammation makes the diagnosis of IE very unlikely.

A number of different stains can be used to help identify various organisms implicated in IE as well as confirm the presence of inflammation. Hematoxylin and eosin staining can identify a pattern of inflammation consistent with IE. Tissue Gram stains allow differentiation between Gram-positive and -negative organisms as well as giving skilled technicians information about morphology. This may allow for a preliminary identification [23]. The Gram stain is limited in that it can only detect organisms with a cell wall. Therefore species such as *Mycoplasma* may not be detected.

The periodic acid-Schiff (PAS) stain is especially valuable for detection of *Tropheryma whippelii* [24]. Tissue infected with *Tropheryma whippelii* stained with PAS will demonstrate foamy histiocytes with infiltrates of neutrophils, lymphocytes, and mononuclear cells [25]. The PAS stain can also be used to detect the presence of fungi.

The Giemsa stain, traditionally used for detection of parasites, can detect a variety of bacteria including *Bartonella* species. The presence of

inflammation is also highlighted since Giemsa stains white blood cells [26].

The acradine orange stain is a nonspecific fluorscent stain, which can detect any living organism including bacteria, *Mycobacteria* spp., and a variety of fungi. The Warthin–Starry silver impregnation technique is a very sensitive method for detection of a variety of bacteria, even those that stain weakly with Gram stain methodology [14].

A variety of specific stains can also be used based on clinical indications. If the patient has risk factors for a mycobacterial infection, valves should be stained with Ziehl–Nielsen staining for acid-fast bacteria. The Gimenez stain allows detection of *C. burnetii* and *Legionella* species [23]. The Kinyoun stain can also detect mycobacterial species. It also stains large macrophages containing dark red granules seen in *Chlamydia* endocarditis.

For detection of fungi, the Gomori–Grocott's silver stain provides the best contrast [23,27].

Immunohistologic Methods

Specific antibodies have been developed to detect a variety of pathogens in tissue. Immunoperoxidase stains, enzyme-linked immunosorbent (ELISA) assays, and direct immunofluorescence have all been used to detect causative agents of BCNE. *Coxiella burnetii* has been detected using these techniques [28,29]. Direct immunofluorescence has the advantage of being effective for paraffin-embedded tissue [30].

Electron Microscopy

Although EM is able to resolve morphological details that cannot be seen with light microscopy, its usefulness is limited [31]. It is both expensive and time consuming and therefore is reserved for only very difficult cases of BCNE where other methods have failed.

Serology

Serologic testing for *C. burnetii, Bartonella* spp., *Mycoplasma pneumoniae, Legionella* spp., *Chlamydia* spp., and *Brucella* spp. are included as diagnostic criteria for IE according to both the Duke and modified Duke criteria [4,32].

C. burnetii and *Bartonella* spp. are the most common agents of BCNE detected serologically. Serologic tools are available to identify these two species and they therefore should be used systemicatically for every patient with BCNE. On the other hand, positive serologic tests for *Mycoplasma, Legionella, Chlamydia,* and *Brucella* should be interpreted with caution due to low positive predictive value and frequent cross-reactions [14,33].

Molecular Techniques

Sequence analysis of bacterial 16S rRNA genes using polymerase chain reaction (PCR) has been used directly on clinical specimens to establish and etiological diagnosis in BCNE. This molecular technique has been shown to be more sensitive than conventional blood culturing techniques for the detection of bacteria [8,34]. The infecting pathogen was identified in 2.4% of clinical specimens where standard bacterial culture had failed. Its main advantages are that it is culture independent and that most bacteria can be detected in a single reaction. Cases of BCNE due to previous antibiotic therapy represent an excellent indication for application of PCR [35].

In one study of 51 patients (52 valves) with suspected endocarditis and 16 patients with no endocarditis, this approach had a sensitivity of 41.2%, a specificity of 100%, a positive predictive value of 100%, and a negative predictive value of 34.8%. This was compared with 7.8%, 93.7%, 80%, and 24% for culture and 11.8%, 100%, 100%, and 26.2% for Gram stain [36].

This technique is limited by the number and quality of DNA sequences available in GenBank and the EMBL databases. As some of the reference sequences are too short or contain too many undetermined nucleotides, confident assignment of clinically derived sequences cannot be made. Microbial DNA contamination can also occur. Therefore caution must be exercised in the interpretation of PCR-based sequence analyses when the organism has not been observed in stained valve tissue [37].

As our databases improve, molecular techniques will be used increasingly in the assessment of patients with CNE [38,39].

Selected Infectious Agents of BCNE (Table 10.2)

Coxiella burnetii

Coxiella burnetii is an obligate intracellular bacterium and the causative agent of Q fever. Q fever is a zoonosis that can cause acute and chronic disease. It demonstrates phase variation (phase 1 to phase 2), which can be helpful in diagnosis as only *C. burnetii* cells expressing phase 1 lipopolysaccharide are infectious.

Epidemiology

Q fever is prevalent in all countries where it has been studied [40]. It accounts for 3–5% of infective endocarditis worldwide (except New Zealand) [13]. A recent study performed in France looked at the etiologic diagnosis of 348 cases of definite culture negative endocarditis according to Duke criteria [10]. In this study, *Coxiella burnetii* accounted for 48% (167) of all cases. Over 400 cases have been reported in the literature to date [9,41]. Over half of all cases have been reported from one laboratory in France [42].

Endocarditis is the most common manifestation of the chronic form of Q fever accounting for 78–80% of all cases and 8–11% of all cases of Q fever, acute or chronic [19]. More cases have been reported from Great Britain, France, and Israel than from North America.

Farm animals such as sheep, goats, and cattle are the primary reservoir of disease, although cats and dogs have also been affected. When infected, all of these animals shed dessication resistant *C. burnetii* in urine, feces, milk, and birth products [9]. Because *C. burnetii* is very resistant to physical agents, it is able to survive in the environment for long periods and can spread over long distances by wind. It is thought that humans become infected by inhalation of dust contaminated by fluids from infected livestock. Persons may also become infected by ingesting unpasturized milk or milk products [42]. In a recent study by Houpikian and Raoult, [10] risk factors for Q fever endocarditis included male sex, age older than 60 years, valvular disease, rural life, exposure to animals, and drinking raw milk.

Signs and Symptoms

The diagnosis of Q fever endocarditis is often delayed due to lack of echocardiographic findings and negative blood cultures. The most common symptoms include low-grade or intermittent fever, fatigue, and weight loss. Fever and congestive heart failure are the most common signs of Q fever endocarditis and are seen in 68% of patients [9]. Splenomegaly and hepatomegaly may be prominent and may lead the clinician to investigate for causes of liver disease or hematolgic malignancy causing further diagnostic delays. Clubbing was found in one-third of patients, which is higher than for other causes of endocarditis [43]. Other possible signs include immune complex deposition related renal impairment and purpuric skin rash [44]. As with other causes of endocarditis, Q fever endocarditis can present with embolic manifestations such as stroke.

Laboratory findings of Q fever endocarditis include circulating immune complexes, positive rheumatoid factor, anemia, thrombocytopenia, and microscopic hematuria [43]. Serum transaminases especially aspartate aminotransferase and alkaline phosphatase may also be elevated.

Diagnosis

Transthoracic echocardiography only picks up 12% of vegetations in patients with Q fever endocarditis, [43] although transesophogeal echo has improved sensitivity. On pathologic examination of the valves of patients with Q fever endocarditis, vegetations have a nodular appearance with a smooth surface or the valves may actually appear normal. Histologic examination reveals changes of both acute and chronic inflammation.

Immunohistochemical staining reveals *C. burnetii* only in macrophages at sites of inflammation and valvular injury and only in the vegetations [45].

Coxiella burnetii should be considered as a possible etiologic diagnosis in anyone with BCNE. Diagnosis can easily be made using serologic testing, detecting antibodies to phase 1 and phase 2 antigens. Q fever endocarditis is characterized by high titers to both phase 1 and phase 2 antigens of *C. burnetii*. An IgG titer of $\geq$ 1:800 is very sensitive and has high positive predictive

value [46]. C burnetti can also be isolated from blood or from valves. It can be cultured using a shell vial technique but needs to be done in a level III laboratory. Detection of *C. burnetii* DNA by PCR can also be done on blood or heart valves [47].

Prognosis and Treatment

Untreated Q fever endocarditis has a high mortality rate, and the poor outcomes reported in older literature were most likely due to diagnostic delays. With newer detection methods and a variety of treatment options, the morality is now 5–13% [48,49]. The standard treatment for Q fever endocarditis has been a tetracycline in combination with a quinolone for three to four years. Despite this prolonged course, relapses and positive valve cultures still occurred [50]. This is related to the fact that in vitro, these antibiotics are only bacteriostatic. The addition of hydroxychloriquine to doxycycline was studied by Raoult et al. [50]. The combination of doxycycline and hydroxychloriquine compared with doxycycline and ofloxacin shortened the duration of therapy but had no effect on mortality, valve surgery, or tolerance. Therefore a combination of doxycycline and hydroxychloriquine should be used for a minimum of 18 months. Surveillance of antibody titers to phase 1 antigens should be measured every two months and treatment can be stopped when IgG phase 1 antibodies decrease below a titer of 800 [9]. Surgery should be reserved for those with hemodynamic instability as no studies have shown a beneficial effect.

***Bartonella* spp.**

Bartonella spp. are small, facultative, intracellular Gram-negative bacteria. They cause a variety of clinical syndromes. *B. henselae* is the causative agent of cat scratch disease, meningoencephalitis, and bacillary angiomatosis and hepatic peliosis in HIV-infected patients [51]. *B. qunitana* causes trench fever, lymphadenopthy and bacillary angiomatosis. Endocarditis has been reported with *B. henselae, B. qunitana, B. elizabethae,* and *B. vinsonii*, *B. henselae,* and *B. quintana* together account for approximately 3% of all cases of infective endocarditis [13], whereas *B. elizabethae* and *B. vinsonii* are exceedingly rare as causes of endocarditis.

Epidemiology

Bartonella spp. have a worldwide distribution but the majority of cases have been reported in North America and Western Europe. *B. henselae* is transmitted to humans by a cat scratch or bite or the bite of an infected flea, the cat being the resevoir. *B. quintana* is carried by the human body louse and humans are the most likely reservoir. Risk factors associated with *B. henselae* include underlying valve injury and contact with cats. The risk factors associated with *B. quintana* are homelessness and alcoholism (conditions associated with body lice) [52]. Prothetic valve infection with *Bartonella* spp. has been rarely reported. The mean age of *Bartonella* endocarditis is 48 years, which is much lower than for other causative agents of infective endocarditis. *Bartonella* endocarditis affects predominantly men.

Signs and Symptoms

Bartonella spp. generally cause a subacute insidious form of endocarditis, often leading to delay in diagnosis. At presentation, most patients have fever and they often present with signs and symptoms of heart failure [52]. Aortic valves are preferentially affected. Patients often present with manifestations of embolic phenomenon most likely as a result of delayed diagnosis and the large size of vegetations.

Due to the large size, echocardiography can identify vegetations in 100% of patients with *B. henselae* and 95% of patients with *B. qunitana* endocarditis [52].

Examination of excised valves shows destruction and inflammation of valvular tissue with no well-formed granulomas. Giemsa and Wharthin–Starry stains are best at showing granular organisms in the vegetation or valvular tissue. Gram staining and PAS are not helpful [53].

The etiologic diagnosis can also be documented using serology. Serologic testing can be done using enzyme immunoassays or IFA assays. An IgG titer over 1:800 is considered positive. These tests can often not differentiate between *Bartonella* spp. There is also low-level cross-reactivity with *C. burnetii* and significant cross-reactivity with *C. pneumonia* [54]. Inoculation of blood or valvular tissue in tissue culture or on blood agar can be used. More recently PCR

detection has been used. It is rapid and can distinguish between *Bartonella* species [18].

Treatment and Prognosis

Bartonella spp. have in vitro susceptibility to ß-lactam agents, aminoglycosides, macrolides, tetracyclines, and rifampin. A standard antibiotic regimen has not been definitely established, but retrospective data support a combination of gentamycin for two weeks and doxycycline or ceftraixone for four to six weeks [55]. A large proportion of patients require valvular surgery due to the destructive nature of both *B. henselae* and *B. quintana*. In one series, valve replacement was performed in 80% of cases of *Bartonella* endocarditis [55]. In this series the mortality rate in 101 patients with *Bartonella* endocarditis was 12%. Improved survival was associated with aminiglycoside therapy.

HACEK Group Bacteria

Hacek group bacteria are small Gram-negative bacteria which have been recognized as agents of endocarditis for many years. With newer culturing techniques, they are less likely to be agents of culture negative endocarditis as they are readily cultured on enriched media with the exception of *Actinobacillus actinomycetemcomitans*. The HACEK group include *Haemophilus pararinfluenzae, H. influenzae, H. aphrophilus, H. paraphrophilus, Actinobacillus actinomycetemcomitans, Cardiobacterium hominis, Eikenella corrodens,* and *Kingella* spp. The HACEK organisms frequently colonize the mouth and and pharynx, are slow growing with growth being enhanced in the presence of carbon dioxide. They account for approximately 3% of all cases of infective endocarditis with over 400 cases being reported in the literature [13].

Epidemiology

Risk factors common to all the HACEK group bacteria include young age, recent dental work, and underlying valvular disease [13]. Endocarditis caused by *Haemophilus* species is often associated with dental work and has a predisposition to the mitral valve. Between 10% and 30% of patients in the literature had prosthetic valves [56]. *Actinobacillus actinomycetemcomitans* is the most frequent agent of endocarditis among the HACEK organismsm, with over 100 cases reported in the literature [57]. The organism is frequently associated with valvular disease and one-quarter of patients had prothetic valves. Endocarditis due to *C. hominis* tends to affect the aortic valve more frequently than other valves [9]. *Eikenella corrodens* has been found with a high frequency in intravenous drug users due to contamination of needles with saliva before injection. Infection is often polymicrobial and often infects the tricuspid valve [58,59]. The majority of *Kingella* endocarditis is due to *Kingella kingae*. This infection is more frequent in very young children. In one review, 40% of patients were less than 20 years of age and approximately half had underlying heart disease [60].

Diagnosis

The HACEK group of bacteria are generally detected by blood culture within three to five days although up to 30 days may be required. HACEK organisms can be grown on chocolate agar and incubated at 35˚C in aerobic conditions with 10% CO_2. *Haemophilus* can be speciated using nutrient-rich, non-selective media lacking X and V factors and applying paper discs infiltrated with X, V, or X and V factors to the surface medium or using commercially available kits such as the API 10E or API 20E (Biomerieux Vitek, St. Lousi, MO) *A. actinomycetemcomitans* can be identified by its positve oxidase and alkaline phosphatase reactions. Molecular techniques using 16S rRNA can also be used to differentiate members of the HACEK group.

Echocardiography can also help to make a diagnosis of HACEK endocarditis as vegetations are detected in 60–80% of patients [61].

Treatment and Outcome

HACEK-associated endocarditis has a favorable outcome in 85–90% of patients who are treated either medically or medically and surgically. Standard recommended treatment should include a ß-lactamse-stable cephalosporin such as ceftriaxone. It is important to note that standard dental prophylaxis is amoxicillin or clindamycin in those who are penicillin allergic.

Forty percent of *A. actinomycetemcomitans* strains are now resistant to both clindamycin and amoxicillin [57].

Brucella

Brucella spp. are small, facultative Gram-negative intracellular bacteria. The reservoir is domesticated animals such as cattle, goats, and sheep. *B. melitensis* occurs in goats and sheep and it is this strain which causes most cases of human brucellosis.

Epidemiology

Brucella spp. are found worldwide. Infection in humans is caused by ingestion of unpasturized milk or milk products contaminated with the bacteria or by close contact with livestock or their bodily fluids. Brucellosis can present as an acute, subacute, or chronic disease. Endocarditis is a rare complication of brucellosis occurring in 0.6% of those with *Brucella* infection and accounting for 1–4% of all cases of infective endocarditis [62,63]. Risk factors include vavular heart disease and appropriate exposure [64].

Signs and Symptoms

Brucella endocarditis generally presents as a subacute illness with progression over one to three months. Symptoms and signs are generally nonspecific but include fever, myalgias, fatigue, and hepatosplenomegaly. In patients with prosthetic valves, relapse of bacteremia after appropriate treatment for acute brucellosis should be a clue.

Brucella endocarditis predominantly affects the aortic valves and is generally destructive to the valve, resulting in ulcerative lesions and ring abscesses. Myocardial abscesses have been found in 43% of patients in a postmortem study [65].

Diagnosis depends on isolation of *Brucella* spp. from blood or cardiac tissue. Although cultures of *Brucella* require longer incubation periods, 80% of cases have positive blood cultures. Automated blood culture instruments generally yield positive cultures in 4–10 days, but it is still suggested that cultures be held for 21 days [66]. Serology is a safer and effective method of diagnosing *Brucella* infection. At least two serological tests have to be combined to avoid false-negative results. Serum agglutination is used first for screening and complement fixation will confirm its results [66]. A titer of 1:160 is considered positive for active infection. One must be aware that serologic cross-reactivity occurs between *Brucella, Yersenia,* and *Francisella* spp. [67].

Treatment and Prognosis

Surgical treatment in combination with medical therapy is necessary in the majority of patients with *Brucella* endocarditis. In a series by Reguera et al. [64], 72% of 11 patients required valve replacement. Survival in this series was 91%. Standard therapy should include a combination of doxycycline and rifampin or streptomycin for a minimum of three months. If valve replacement is undertaken, antimicrobial therapy should continue for six to eight weeks postoperatively [62]. Antibody titers can be used to monitor response to treatment.

Fungi

Fungal endocarditis has become an important cause BCNE due to increasing numbers of patients who are immunocompromised or who have prosthetic valves. Fungal pathogens account for 1–6% of all cases of infective endocarditis [68]. The most common fungi to cause endocarditis are *Candida* spp., which account for 48–50% of all cases [69]. Of these, half are non-Candida spp. *Aspergillus* spp. accounts for a further 24% and *Histoplasma* spp. cause 6% of infections. The remainder of reported infections are caused by a variety of yeasts and moulds including *Trichosporon, Cryptococcus, Pseudallescheria boydii, Trychophyton,* and *Scopulariopsis brevicaulis* [68].

Epidemiology

Yeasts and moulds are ubiquitous in the environment but generally do not cause clinical disease unless under exceptional circumstances. The risk factors for the development of fungal

endocarditis are similar to those for any invasive fungal infection. These are well outlined in a review by Pierrotti et al. [68] that looked at 143 cases of fungal endocarditis over a five-year period. These include underlying cardiac abnormalities, prosthetic valves, presence of central venous catheter, and use of broad-spectrum antibiotics. Immunosuppression and total parenteral nutrition have also been identified as strong risk factors for the development of fungal endocarditis.

Signs and Symptoms

The most common features of fungal endocarditis do not allow distinction from other forms of endocarditis. They include fever, new heart murmur, periperal embolization, focal or general neurological symptoms, and heart failure. In a review of 270 cases, Ellis et al. [69] found that 45% of patients had major embolization causing ischemia at the time of diagnosis. This is much higher than for other causes of endocarditis.

Echocardiography is able to identify vegetations in approximately 80% of cases of fungal endocarditis giving a sensitivity of 77% [69]. Echocardiography identified vegetations more often in those with native valves compared with those with prosthetic valves [68].

Routine blood culturing systems detect fungal pathogens in 46–54% of cases of fungal endocarditis. Positive blood cultures were seen more frequently in yeast-related IE than in mold-related IE [68].

Histologic examination of excised valves provided the most sensitive means of pathogenic identification in cases of fungal endocarditis. Ellis et al. [69] reported a sensitivity of 95%.

Treatment and Prognosis

Treatment for fungal endocarditis should generally include both medical and surgical therapy. Amphotericin B should be the drug of choice until susceptibility testing can be completed. Other options include the addition of flucytosine to amphotericin B, or fluconazole. Newer agents such as voriconazole have not been well studied for fungal endocarditis. Generally, patients require greater than six months of therapy and may need lifelong suppressive therapy. Even with optimal surgical and medical management, the prognosis for those with fungal endocarditis has been poor compared with endocarditis caused by other pathogens. In the two largest series of patients reported in the literature, the mortality rates were 77% and 56%, respectively [68,69]. Patients with mould endocarditis had a higher mortality rate than those with yeast endocarditis.

Abiotrophia spp.

Abiotrophia spp., formerly known as nutritionally variant streptococci, was reclassified as a new genus based on analysis of 16S rRNA sequences [70].

Epidemiology

A. adjacens and *A. defectiva* account for approximately 2% of all cases of infective endocarditis with more than 100 cases being reported in the literature [71]. Risk factors include underlying heart disease, which is found in approximately 90% of patients with *Abiotrophia* endocarditis. They are part of the normal oral, genitourinary, and intestinal floras.

Signs and Symptoms

IE caused by *Abiotrophia* often presents as a slow indolent course. Embolization occurs in approximately one-third of patients [9]. Classic peripheral manifestations of endocarditis including clubbling, petechiae, and Osler nodes are not usually present. Mitral and aortic valves are affected with equal frequency.

Diagnosis

Abiotrophia spp. require cysteine for growth. Now that cysteine is routinely added to culture media, both *A. adjacens* and *A. defectiva* can be detected in routine blood cultures within two to three days. Subcultures require addition of pyridoxal hydrochloride or L-cysteine for growth. Alternatively, *Staphylococcus aureus* can be used to induce satellite growth. Gram staining and morphology are variable. Commercially available identification systems such as Rapid ID 32

Strept can differentiate *Abiotrohia* from viridans streptococci.

Vegetations are seen in 64% of all cases of *Abiotrophia* endocarditis and can therefore be helpful in making a diagnosis. Histological identification of *Abiotrophia* species in excised valves is difficult as bacteria are morphologically altered within the vegetation [71].

Prognosis and Treatment

Despite improvements in culture techniques, infective endocarditis due to *Abiotrophia* spp. continues to have a higher mortality when compared to other forms of viridans streptococci. Approximately one-quarter of patients require valve replacement and one-third fail initial antimicrobial therapy. This is most likely due to the fact that more than 30% of *Abiotrophia* strains are resistant to penicillin. Treatment outcomes have improved with the addition of gentamicin to penicillin [72].

Mycobacterium spp.

Mycobacteria are acid fast bacteria that rarely cause endocarditis. Eighteen cases of *Mycobacterium tuberculosis* endocarditis have been reported in the literature. Generally these cases are in the context of disseminated or military TB and diagnosis of endocarditis was made incidentally at autopsy [73]. Most cases involved patients with valvular heart disease. Non-tuberculous mycobacterial endocardtis has been reported with *Mycobacterim chelonae, Mycobacterium fortuitum,* and *Mycobacterium avium-intracellulare* [9]. The majority of cases occurred in prosthetic valves, with only two cases of native valve non-tuberculous mycobacteria endocarditis being reported in the literature. It is felt that these infections are due to nosocomial infection at the time of surgery.

Diagnosis may be made by isolation of mycobacteria from blood culture although the diagnosis may be made more quickly by histologic examination of excised valves. Acid fast bacilli can be detected using Ziehl–Neelsen staining [74].

Combination therapy is necessary as for any mycobacterial infection, but duration of therapy has not been well studied due to the paucity of cases. Combined surgical and medical therapy may have improved outcomes compared with medical therapy alone, although there are not studies to confirm this.

Mycoplasma spp.

Only two cases of *Mycoplasma* endocarditis have been reported in the literature [75,76]. One case occurred in a prosthetic valve and the other in a patient with valvular heart disease. The role of *Mycoplasma* in endocarditis is most likely underrecognized and reported as *Mycoplasma* cannot be detected by Gram stain or routine blood culture systems. Both serological testing and PCR techniques may help to *Mycoplasma* as a possible etiologic agent of BCNE in future.

Legionella spp.

Legionella spp. are small Gram-negative intracellular bacteria that are associated with nosocomial pneumonia. Eleven cases of *Legionella* endocarditis have been reported in the literature. The first case was reported in 1984 in a patient with a bioprosthetic valve [77]. The second report was a series of seven patients all with prosthetic valves at Stanford University Hospital Cente [78]. There are two further case reports of prosthetic valve endocarditis [79,80]. One case of endocarditis in a patient with aortic root replacement is reported [81].

Epidemiology

Legionella spp. are normally found in water. There have been a number of nosocomial outbreaks of legionellosis related to contaminated water systems, including hot water tanks and air-conditioning systems. All documented cases of legionella endocarditis have been nosocomial in origin.

Signs and Symptoms

Patients often have nonspecific symptoms such as low-grade fever, malaise, and weight loss. Anemia and thrombocytopenia were frequently observed. There have been no reports of embolic phenomenon.

Vegetations are rarely reported on echocardiography and direct visualization of excised valves revealed only small vegetations in six of eight surgically treated patients.

Diagnosis

Legionella spp. can be cultured using routine blood culture systems but the amount of growth is often inadequate. It is therefore advisable to subculture blood to buffered charcoal yeast extract (BCYE) agar periodically if one is suspecting *Legionella* as the cause of endocarditis. The roles of serologic testing and PCR assays are promising but are not yet commercially available.

Prognosis and Treatment

Valve replacement in combination with antimicrobial therapy has been used in the majority of cases. Erythromycin in combination with rifampin, ciprofloxacin, and doxycycline have all been used to treat *Legionella* endocarditis. Duration of therapy was at least five months and no relapses or deaths have been reported.

Whipple's Disease Bacterium

Whipple's disease is a rare bacterial infection that causes a chronic systemic illness characterized by arthralgias, weight loss, diarrhea, abdominal pain, and generalized lymphadenopathy. It occurs primarily in men over the age of 40 years. The Whipple's disease bacterium, also known as *Tropheryma whippelii,* was first isolated in 2000 [20]. Over 35 cases of endocarditis attributed to Whipple's disease bacteria have reported in the literature [82]. There are no consistent signs and symptoms that may lead one to consider *T. whippelii* as a cause of endocarditis. Although many patients have signs and symptoms of Whipple's disease, Richardson et al. [83] reported two cases of *T. whippelii* endocarditis without fever or gastrointestinal or arthritic manifestations.

Diagnosis is made by histologic examination of tissue. PAS staining reveals PAS positive macrophages and the presence of *T. whippelii.* PCR identification can also be used from either a valve or a duodenal biopsy specimen.

Treatment of *T. whippelii* endocarditis has not been standardized. Most patients with Whipple's disease are treated with cotrimoxazole, ceftraixone, or doxycycline for a minimum of six weeks and more frequently for six months to a year [82]. The prognosis of *T. whippelii* endocardtis is as yet unknown.

Culture-Negative Endocarditis Due to Right-Sided Endocarditis

It has traditionally been believed that right-sided endocarditis is more likely to be culture-negative due to bacteria being filtered by the lungs. There is very little evidence in the literature to support this claim. In our clinical practice, the majority of right-sided endocarditis is identified through routine blood culture and or transesophogeal echoardiography. Risk factors for right-sided endocarditis include intravenous drug use and valvular heart disease.

Non-Infectious Causes of Endocarditis

Non-infectious causes of endocarditis are classified as nonbacterial thrombotic endocarditis (NBTE). A review of 171 cases of NBTE found that 59% of cases were in patients with underlying malignancy; carcinoma of the ovaries, billiary system, pancreas, lung, and stomach were most commonly reported [84]. The vegetations were located predominantly on the mitral and aortic valves. The majority of patients in this series had no underlying valvular heart disease. There was a high rate of systemic emboli (41% of patients). This study suggests that the main risk factor for the development of NBTE is an underlying hypercoagulable state whether congenital or acquired.

Conclusions

Blood-culture-negative endocarditis still remains a formidable clinical challenge. Molecular diagnostic methods combine with serological studies have greatly improved the diagnostic yield.

Key Points

1. About 5–20% of all cases of endocarditis are culture negative.
2. A systematic approach to diagnosis and treatment is necessary for a successful outcome.
3. Previous antibiotic treatment is a common cause of BCNE, and in this instance the blood culture should be processed in the presence of antimicrobial agent removal device.
4. Specific media and prolonged culture are required to isolate fastidious organisms.
5. Molecular diagnostic techniques such as PCR on valvular vegetations and good serological tests for agents such as *Coxiella burnetii* are very helpful in making etiological diagnoses in these cases.

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11

Prosthetic Valve and Other Cardiovascular Device-Related Endocarditis

Wendy Sligl and Karen Doucette

Case Study

A 45-year-old male presented with a one-week history of fever, fatigue, shortness of breath on exertion, orthopnea, and chest pain. His past medical history included a congenital bicuspid aortic valve with subsequent aortic insufficiency requiring mechanical aortic valve replacement five weeks prior. Anticoagulation had been therapeutic since discharge from hospital four days postoperatively. Physical examination revealed an unwell, febrile, tachycardic patient. Conjunctival hemorrhages and peripheral embolic lesions on the palms and soles were observed. There was evidence of congestive heart failure, with bibasilar crackles on pulmonary auscultation, an elevated jugular venous pressure, and a third heart sound. A II/VI decrescendo diastolic murmur was heard at the left lower sternal boarder. A chest X-ray confirmed pulmonary edema, and an ECG showed sinus tachycardia with first-degree AV block. Laboratory investigations demonstrated anemia (hemoglobin 104 g/L) and an elevated white blood cell count (22.1×10^6/L) with neutrophil predominance (81%). Blood cultures were positive for Gram-positive cocci in clumps in 3/3 bottles, prompting the initiation of empiric therapy with vancomycin, gentamicin, and rifampin for prosthetic valve endocarditis. A transesophageal echocardiogram confirmed a large vegetation (2×3 cm) on the aortic valve with a flail leaflet and perivalvular abscess. The patient was taken to the operating room for aortic valve replacement after 48 hours of antibiotic therapy. Final cultures grew methicillin-sensitive *Staphylococcus aureus*. Antimicrobial therapy was completed with a total of six weeks of cloxacillin and rifampin, in addition to gentamicin for the first two weeks.

Epidemiology and Pathogenesis of Prosthetic Valve Endocarditis and Other Cardiovascular Device-Related Infections

Prosthetic valve and other cardiovascular device-related infections are relatively uncommon, with specific rates depending on the particular device (Table 11.1) [1-5]. With an increasing population at risk due to the continual expansion of indications for placement of devices; these infections will undoubtedly become more common in the future. Complicated management strategies, and the frequent need for removal of devices, make this a challenging and constantly evolving area of medicine.

Prosthetic valve endocarditis and other cardiovascular device-related infections share areas of commonality, particularly with respect to the epidemiology and pathogenesis of infection. All of these prosthetic devices may be contaminated

Table 11.1. Prosthetic Valve and Other Cardiovascular Device-Related Infection Rates

Infection site	Incidence of infection (%)
Prosthetic valves	0.1–2.3/year
Pacemakers*	0.13–19.9 (0.5)
Defibrillators*	0–3.2 (0.5–0.6)
LVADs*	25–75 (6.6)
Total artificial hearts	Rare, limited data
Cardiac suture lines	Rare
Patent ductus arteriosus occlusion devices	Rare
Atrial septal defect closure devices	Rare
Intra-aortic balloon pumps**	≤ 5–26
Coronary artery stents	Rare

*Overall rates of infection (including generator pocket infections), rates of infective endocarditis in parentheses.
** Rate of infection related to duration of device use, see text.

with microbes, predominantly skin flora, at the time of surgical insertion. Less commonly, infection may be the result of hematogenous seeding from a distant site or spread of contiguous infection. In the presence of foreign material the number of microorganisms needed to establish infection is greatly reduced and microbial adherence to prostheses provides effective protection against host immunity.

Staphylococci account for the majority of prosthetic valve and device-related infections and are the most well studied microorganisms with respect to their ability to adhere to foreign material and to form biofilms. Host proteins are exposed in areas of endothelial disruption at sites of contact with prosthetic devices. Multiple adhesins, collectively known as microbial surface components responsible for attachment to molecular molecules (MSCRAMM's), allow *Staphylococcus aureus* to bind to host proteins that coat the surface of prosthetic devices [6]. Through this mechanism, *S. aureus* is able to bind to fibrinogen, fibronectin, and collagen, as well as to gene regulators that control the expression of these adhesins.

Biofilm formation is the second important virulence mechanism that accounts for the predominance of staphylococci as the causative microorganisms in prosthetic infections. Biofilms consist of infecting microorganisms and an extracellular matrix on the surface of prosthetic devices. Both coagulase-negative staphylococci (CoNS) and *S. aureus* are able to produce biofilms on the surface of prosthetic cardiovascular devices. Formation of a biofilm protects these microorganisms from the host immune response and from antimicrobial therapy, thereby reducing susceptibility to antibiotics and making cure of infection difficult without device removal.

Bacteria and fungi may both cause prosthetic valve and other cardiovascular device-related infections with CoNS and *S. aureus* accounting for the majority of infections. Other skin flora, such as *Corynebacterium* species and *Propionibacterium acnes* can cause infections of prosthetic material. Streptococci are the predominant pathogens responsible for native valve endocarditis (NVE) but may also cause prosthetic valve and device-related infections. Viridans group streptococci account for the majority of streptococcal infections; however, *Abiotrophia defectiva* and *Granulicatella* (previously known as nutritionally variant streptococci), may also cause prosthetic valve and device-related infections. Enterococci, HACEK organisms (a group of fastidious Gram-negative microorganisms including *Hemophilus parainfluenzae, Hemophilus aphrophilus, Actinobacillus actinomycetemcomitans, Cardiobacterium hominis, Eikenella corrodens, and Kingella kingae*), and aerobic gram-negative bacilli account for the majority of remaining infections.

Fungal infection, although less common than bacterial infection, has been increasingly recognized as a cause of prosthetic valve and cardiovascular device infections. Fungal infection is generally acquired nosocomially, with *Candida* species being the most frequent pathogens. *C. albicans* is the most common species isolated, followed by *C. parapsilosis*. *Aspergillus* species and other filamentous fungi are far less common, and generally seen in immunosuppressed patients—predominantly transplant recipients and those with hematologic malignancy.

Prosthetic Valve Endocarditis

Prosthetic valve endocarditis (PVE) is defined as endovascular infection of valve prostheses or reconstructed native valves. Early infections are generally nosocomial, while late infections tend to be community-acquired.

The incidence of PVE ranges from 0.1% to 2.3% per year [7]. Rates range from 1% to 3% within the first year; however, the highest rate of infection occurs in the first three postoperative months. By six months, rates stabilize to 0.4%

annually [8]. PVE accounts for 16–32% [2–5] of all cases of infective endocarditis. Infection occurs with equal frequency at aortic and mitral valve sites. Mechanical and bioprosthetic valves are equally affected during the first postoperative year; however, bioprosthetic valves carry a greater risk for infection than mechanical valves after 18 months, presumably due to degenerative changes in the leaflets over time. Patients undergoing valve replacement for native valve endocarditis have an increased risk of PVE, of approximately 5%, when compared to those with valve replacement performed for other indications.

Infections of prosthetic heart valves usually originate when fibrin and thrombi occur at the site of the suture line and/or annulus, allowing microorganisms to subsequently adhere. Endothelialization of the valve, which is generally completed within three weeks postoperatively [9], decreases the risk of infection.

The microbiology of PVE is unique from NVE (Table 11.2); staphylococci, HACEK organisms, and fungi occur more frequently in PVE, whereas streptococci and enterococci more commonly cause NVE. The majority of early-onset PVE (≤2 months) is caused by staphylococci—both coagulase-negative species and *S. aureus*, as these organisms have a high affinity for prosthetic material as previously discussed. Gram-negative bacilli, diphtheroids (*Corynebacterium* species), and candida generally account for the remainder of early cases. Late PVE, occurring more than 1 year postoperatively, is commonly caused by the usual microorganisms that cause NVE, in addition to coagulase-negative staphylococci. Intermediate infections (from 2 to 12 months) may be due to any of the pathogens implicated in either early or late PVE.

Table 11.2. Common Microorganisms causing PVE and Other Cardiovascular Device-Related Endocarditis

Coagulase-negative Staphylococci (CoNS; predominantly *S. epidermidis*)
Staphylococcus aureus
Common skin flora other than CoNS:
Corynebacterium species, *Propionibacterium acnes*
Streptococci (predominantly viridans group streptococci)
Enterococci
HACEK organisms:
Hemophilus parainfluenzae, Hemophilus aphrophilus, Actinobacillus actinomycetemcomitans, Cardiobacterium hominis, Eikenella corrodens, Kingella kingae
Aerobic Gram-negative bacilli
Fungi (predominantly *Candida* species)

Typical clinical signs and symptoms of infective endocarditis, particularly positive blood cultures, and echocardiographic evidence of valvular vegetation(s), establish the diagnosis. The Duke criteria, although initially proposed for diagnosis of NVE, can also be used for the diagnosis of PVE [10]. The majority (>95%) of patients with PVE have fever. Peripheral stigmata of endocarditis (immune-mediated and/or embolic) may or may not be present, and depends on the specific microorganism implicated, valve(s) affected and postoperative timing. Extension of infection to adjacent tissues is common, with resultant valve ring, aortic root, or myocardial abscesses seen in 27–82% of patients [11,12]. Septal involvement may result in abnormal conduction; commonly complete atrioventricular block. Additional complications may include sepsis, shock, and heart failure.

Blood cultures are positive in >90% of patients not pretreated with antibiotics. Multiple positive blood cultures help to distinguish true infection from contaminated specimens, which can be difficult to distinguish when infection is caused by skin flora, such as coagulase-negative staphylococci. Transesophageal echocardiography (TEE) is the diagnostic imaging test of choice. It is more sensitive without loss of specificity compared to transthoracic imaging (82–96% vs. 17–36%, respectively) regardless of prosthesis type or anatomic position [13]. TEE is also required to assess for perianular complications and to accurately define vegetation size. Recently, El-Ahdab et al. found that approximately half of all patients with prosthetic valves who developed *S. aureus* bacteremia were proven to have definite endocarditis, independent of type, location, or age of the prosthetic valve [13a]. Given these findings, in addition to the high mortality associated with *S. aureus* PVE (25–40%), all patients with a prosthetic valve who develop *S. aureus* bacteremia should be aggressively screened and followed for endocarditis.

Treatment of PVE is based on microbiologic etiology (Table 11.3) and functional hemodynamic status. Patients should have multiple blood cultures collected followed by empiric therapy with antimicrobials. The major difference between empiric treatment of PVE compared to NVE is the need for therapy directed against coagulase-negative staphylococci. Based on this consideration, vancomycin plus gentamicin and rifampin is recommended for empiric

Table 11.3. Common Microorganisms and Treatment Regimens in PVE

Microorganism	Antimicrobial Regimen	Duration (weeks)
Staphylococci (coagulase-negative and *S. aureus*)		
Methicillin-susceptible (assume penicillin resistance)	Cloxacillin 2g IV q4h PLUS	6–8
	Gentamicin 1 mg/kg IV q8h PLUS	2
	Rifampin 300 mg po q8h	6–8
Methicillin-resistant	Vancomycin 15 mg/kg IV q12h PLUS	6–8
	Gentamicin 1 mg/kg IV q8h PLUS	2
	Rifampin 300 mg po q8h	6–8
Streptococci		
Penicillin-susceptible (MIC ≤ 0.1 μg/mL)	Penicillin G 18–24 million units IV daily divided q4h PLUS	6
	Gentamicin 1 mg/kg IV q8h	2
	OR in non-IgE-mediated penicillin allergy:	
	Ceftriaxone 2 g IV daily PLUS	6
	Gentamicin 1 mg/kg IV q8h	2
	OR in IgE-mediated or other severe β-lactam allergy:	
	Vancomycin 15 mg/kg IV q12h	6
Relatively penicillin-resistant streptococci (MIC > 0.1 μg/mL)	Penicillin G 24–30 million units IV daily divided q4h PLUS	6
	Gentamicin 1 mg/kg IV q8h	4
Enterococci		
In vitro susceptibilities with MICs to penicillin and vancomycin, β-lactamase production, and high-level resistance to gentamicin and streptomycin required for optimal regimen to be determined	Penicillin G 24–30 million units IV daily divided q4h PLUS	6
	Gentamicin 1 mg/kg IV q8h	6
	OR	
	Ampicillin 2 g IV q4h PLUS	6
	Gentamicin 1 mg/kg IV q8h	6
	OR	
	Vancomycin 15 mg/kg IV q12h PLUS	6
	Gentamicin 1 mg/kg IV q8h	6
HACEK organisms	Ceftriaxone 2 g IV daily	6
	OR	
	Ampicillin 2 g IV daily divided q4h PLUS	6
	Gentamicin 1 mg/kg IV q8h	4
Gram-negative bacilli	Determined by in vitro susceptibility testing, combination therapy recommended	6
Fungi		
Usually *Candida* spp., rarely *Aspergillus* spp.	Determined by in vitro susceptibility testing; anti-fungal choices include amphotericin B, fluconazole, caspofungin, and voriconazole	
Diphtheroids	Penicillin G 18–24 million units IV daily divided q4h PLUS	6
	Gentamicin 1 mg/kg IM or IV q8h	6
	OR	
	Vancomycin 15 mg/kg IV q12h	6

therapy of PVE pending blood culture results. Once identification of the microorganism and in vitro susceptibilities are known, a minimum of six weeks of directed parenteral antibiotic therapy should be completed [14]. High doses should be used in order to achieve optimal penetration into the vegetation and, in general, bactericidal therapy should be used.

PVE due to coagulase-negative staphylococci and *S. aureus* are treated similarly with the choice of a cell-wall active antimicrobial based on methicillin susceptibility. Vancomycin is the drug of choice for methicillin-resistant isolates. For methicillin-susceptible staphylococci a semisynthetic penicillinase-resistant penicillin (cloxacillin, nafcillin or oxacillin) should be used. A first-generation cephalosporin (cefazolin) may be substituted in patients with non-anaphylactic penicillin allergy. Rifampin has a unique ability to penetrate biofilms and sterilize foreign bodies [15]; it is therefore added in staphylococcal infections. An aminoglycoside should be administered for synergy during the first two weeks of therapy if the isolate is susceptible. In the setting of aminoglycoside resistance, preliminary animal and human data suggest a fluoroquinolone may be used instead of an aminoglycoside [15,16], although further studies are needed to confirm efficacy.

Other than a longer duration of therapy, PVE due to viridans group streptococci or *Streptococcus bovis* is treated in a similar manner to NVE caused by these pathogens. Penicillin with or without an aminoglycoside is

recommended for penicillin-susceptible streptococci (minimum inhibitory concentration, MIC ≤ 0.1 μg/mL). An aminoglycoside may be administered during the first two weeks of therapy; however, this combination has not been shown to be superior to β-lactam monotherapy. PVE due to penicillin-resistant streptococci (MIC > 0.1 μg/mL) should be treated with combination therapy (β-lactam plus an aminoglycoside) for six-weeks. In patients with non-anaphylactic penicillin allergy, a third-generation cephalosporin may be substituted. Vancomycin should be reserved for those with IgE-mediated or other severe penicillin allergy.

Enterococcal infections require a prolonged course of combination therapy with a cell-wall active agent in combination with an aminoglycoside. Standard therapy includes penicillin, ampicillin, or vancomycin plus an aminoglycoside for synergy. Therapy should be guided by in vitro susceptibilities, particularly with recent observations of increasing antibiotic resistance. When aminoglycoside resistance prevents treatment with combination therapy, a prolonged course (≥ 8 weeks) of a cell wall active agent should be used; however, even prolonged therapy often fails, and surgical therapy should be considered. Limited data exist regarding the treatment of vancomycin-resistant enterococcal (VRE) endocarditis. In vitro and animal data, as well as case series studies in humans, suggest quinupristin-dalfopristin, linezolid, daptomycin, and some new glycopeptides may be effective [17–19].

HACEK microorganisms often produce β-lactamases; however they are uniformly susceptible to third-generation cephalosporins. Treatment with cefotaxime or ceftraixone for six weeks has therefore become standard therapy. Treatment of PVE caused by enteric gram-negative bacilli should be based on in vitro susceptibilities. Combination therapy is usually administered, as multi-drug resistant strains are common in hospital-acquired infections.

Endocarditis due to *Corynebacterium* species should be treated with a combined regimen of penicillin plus gentamicin synergy if gentamicin susceptible [20]. Vancomycin monotherapy should be used in patients with penicillin allergy or when gentamicin resistance is demonstrated.

Fungal endocarditis is predominantly due to *Candida* species. Amphotericin B is the drug of choice for treatment, with the addition of flucytosine for synergy. Surgical intervention is generally required for cure, although cases of cure with medical therapy alone have been reported [21]. Even with surgery, however, relapse is not uncommon and long-term suppressive therapy may be required.

Indications for surgical intervention in PVE are outlined in Table 11.4 [13,22]. They include CHF refractory to medical treatment, perivalvular extension (including fistulization, abscess, or new atrioventricular block), periprosthetic dehiscence, obstruction or leaflet perforation, large (> 1 cm) mobile vegetations (particularly with anterior mitral leaflet involvement), thromboembolic events with residual thrombus still evident, uncontrolled infection (defined as positive blood cultures after ≥ 5 days of appropriate antimicrobial therapy), increasing vegetation size despite appropriate antimicrobial therapy, or relapse after optimal medical therapy. In addition, PVE due to specific microorgansims often requires surgery for cure. These include *S. aureus*, *P. aeruginosa*, *Candida* species, and other fungi. For multi-drug-resistant microorganisms (including enterococcal endocarditis) in which there is no synergistic bactericidal regimen and in cases of culture-negative PVE unresponsive to empiric antimicrobial therapy, surgical therapy should also be considered.

Deciding when to perform surgery in patients with PVE is complex and often affected by multiple variables. The timing of surgical intervention must be individualized as much as possible;

Table 11.4. Surgical Management of PVE

Indications for Surgery
CHF refractory to medical treatment
Perivalvular extension (including fistulization, abscess, or new atrioventricular block), periprosthetic dehiscence, obstruction, or leaflet perforation
Large (> 1 cm) mobile vegetations, particularly with anterior mitral leaflet involvement
Thromboembolic events with residual thrombus still evident
Uncontrolled infection—positive blood cultures after ≥ 5 days of appropriate antimicrobial therapy
Increasing vegetation size despite appropriate antimicrobial therapy
Relapse after optimal medical therapy
Specific microorganisms including—
Staphylococcus aureus
Pseudomonas aeruginosa
Candida species and other fungi
Multi-drug-resistant Gram-negative bacilli or Gram-positive microorganisms (includes aminoglycoside-resistant enterococci)
Culture-negative PVE unresponsive to empiric antimicrobial therapy

indications are not absolute, and the benefits and risks of surgery must be carefully considered in each case. Patients with severe heart failure, hemodynamic instability, and acute severe valvular dysfunction should undergo urgent surgery (within 24 hours). Postoperative mortality has been shown to be proportional to the severity of hemodynamic impairment at the time of surgery [23]. Those with atrioventricular block, subacute valvular dysfunction, mild to moderate heart failure unresponsive to medical therapy, recurrent systemic emboli, and specific microorganisms requiring surgery should generally undergo surgery within one week; however, this may be delayed longer if hemodynamics remain stable and a response to medical therapy is observed. Limited delays in surgery may allow time for stabilization of other acute medical problems that may affect operative mortality.

The risk of re-infection following valve replacement for active infective endocarditis, however, is extremely low, with re-infection rates ranging from 0% to 1.4%. Therefore surgery, when indicated, should not be delayed solely for the provision of pre-operative antimicrobial therapy [24,25]. In one small study (65 patients) in fact, early surgical therapy, within three days of admission, resulted in fewer pre-operative complications and was associated with a significantly lower postoperative complication rate than in those who underwent operations more than three days after starting antimicrobial therapy [24].

Multiple surgical techniques have been described and the choice of surgical approach depends on the experience and preferences of the surgical team. Surgical debridement of infected material and drainage of abscesses are necessary prior to reconstruction and/or valvular reimplantation. Studies have shown improved survival rates with cryopreserved aortic allografts [26]. Allografts may be more resistant to infection compared to mechanical prostheses or fabric grafting; however, they have the disadvantage of decreased durability [27].

Nonvalvular Cardiovascular Device-Related Infections

Infection of cardiovascular devices developed over recent years and used to replace or assist damaged or dysfunctional tissues has resulted in an expansion of the definition of infective endocarditis [1]. Despite a wide variety of devices, the clinical manifestations, microbiology, pathogenesis, diagnosis, treatment, and prevention of these infections share significant commonality with each other and with PVE.

The pathogenesis of device-related infections is complex and includes virulence factors of microorganisms, host response to the presence of a prosthetic device, and characteristics of the device. Pathogenic virulence factors include tissue and foreign body adherence molecules and foreign body surface biofilm formation as described previously in PVE pathogenesis. Abnormal blood flow due to cardiac devices may increase the potential for infection and concurrently decrease the response to therapy. In addition, all devices provide an artificial surface to the blood, which may affect neutrophil and monocyte function and decrease antibiotic penetration. Lastly, T-cell function seems to be adversely affected by prosthetic cardiac device implantation. Endothelialization is a major protective factor. The specific physical characteristics of prosthetic materials may also affect infection risk. Lower critical surface tension prostheses, with decreased platelet and fibrinogen attraction, are less likely to become infected.

Pacemakers and Implantable Cardioverter-Defibrillators

Device-related endocarditis continues to cause significant morbidity and mortality despite lower peri-operative morbidity with transvenous lead placement compared to open procedures (thoracotomy or sternotomy). The clinical use of cardiac devices has grown over the past two decades; with more patients undergoing pacemaker and implantable cardioverter-defibrillator (ICD) surgery, an increasing population will be at risk for infection.

In 2000 there were an estimated 3.25 million patients with pacemakers worldwide [28]. The true incidence of pacemaker infections is difficult to determine; however, in a large series of over 8,000 pacemaker insertions pacemaker-associated infection occurred in 5.6%, with endocarditis in 0.5% of patients [29]. Another recent study reported the rate of pacemaker-related infective endocarditis to be 550

cases/million pacemaker recipients per year [30]. Fewer data are available regarding ICDs; however, a recent review reported infection requiring surgical intervention in 0.7% of recipients [31]. Most infections occur in ICD generator pockets; only a minority (approximately 10%) constitute pacemaker endocarditis. Distinguishing pocket infections from device-related endocarditis may be difficult however, and complicates the accurate reporting of cases.

Risk factors for infection are both host and implantation related. Host factors include immunosuppression (including corticosteroids), cancer, malnutrition, underlying chronic medical illness, and diabetes mellitus. Anticoagulation may predispose to infection by contributing to hematoma formation at the pocket site. Recurrent surgical manipulation of the generator pocket site, prolonged operative time, two-staged procedures and pectoral compared to abdominal placement also increase the risk of infection [32,33].

The most common pathogens causing pacemaker/ICD-related endocarditis include skin flora inoculated at the time of insertion, predominantly coagulase-negative staphylococci, *S. aureus*, and *Corynebacterium* species. Hematogenous seeding from distant sites may account for other less common pathogens such as viridans group streptococci, enterococci, enteric gram-negative bacilli, and fungi (predominantly *Candida* species).

Pocket infections are the most common clinical presentation of device-related infection. Systemic manifestations are occasionally present, but not common. Occult bacteremia or fungemia, however, may occur in the absence of local symptoms. In a recent series, pacemaker endocarditis presented with fever in all but one of 45 patients [30]. Device-related endocarditis should be suspected in any patient with an intracardiac device and unexplained fever. Patients may present with embolic complications, the majority of which are right-sided (pleuritic chest pain and multiple pulmonary infiltrates on chest x-ray); however, left-sided emboli may occur (predominantly due to patent foramen ovale or atrial septal defect, left-sided devices, or hematogenous seeding of left-sided structures).

The diagnosis of device-related endocarditis can be difficult, particularly when attempting to distinguish endovascular infection from isolated soft tissue infection. Pocket infections are usually apparent, with inflammatory changes to overlying skin, pain at the site, and occasionally spontaneous drainage from the incision site. Purulent drainage from pocket infections should be gram stained and cultured to identify the specific pathogen. Ultrasound can be helpful in documenting fluid in the pocket site and guiding percutaneous aspiration. Nuclear medicine scans may be helpful in differentiating non-infected postoperative fluid from abscess. Infected vegetations on leads may be visualized using echocardiography. In those with infection of endovascular components of a device, blood cultures are usually positive. Culture-negative cases are frequently due to the administration of antibiotics prior to collection of cultures; however, more fastidious organisms, such as the HACEK group, have been reported to cause device-related infections. These microorganisms often take longer to grow and may require specific laboratory culture techniques.

There are multiple imaging modalities that may be useful in diagnosing device-related infections. Plain radiographs have a limited role; however, they may be useful in identifying displaced devices. Ultrasound, as mentioned above, may be used to identify fluid collections around a device and provide guidance in percutaneous aspiration for diagnostic and therapeutic purposes. CT scanning carries some risk of contrast nephropathy; however, it may occasionally be helpful in identifying deep collections around a device. MRI is generally contraindicated in patients with electrophysiologic devices; however, may be useful with other types of cardiovascular devices. Nuclear medicine scans can be used to identify focal infection, particularly in difficult cases where a focus of infection may not be evident. Echocardiography is the gold standard for diagnosis of intracardiac device-related infections. Transesophageal echocardiography has been demonstrated in a number of studies to be superior for visualization of valvular vegetations, pericardial effusions, or device-related thrombus. The sensitivity of transthoracic echocardiography in demonstrating valvular or lead vegetations was 30%, compared to 91% with transesophageal echocardiography in a recent review [34].

Treatment of intracardiac device infection generally includes antimicrobial therapy and device removal when possible. The choice of antimicrobial therapy is similar to that for PVE (Table 11.3) and should be based on culture

results and in vitro susceptibilities. Therapy should be bactericidal, administered parenterally, and the duration of therapy should be based on the extent and site of infection [1]. For pocket infections, 10–14 days is generally adequate. For bacteremic patients, a minimum of 14 days should be administered after removal of the device and the first negative blood culture. If vegetations are present parenteral therapy should continue for 4–6 weeks. A minimum of 4 weeks should be administered in patients with complete removal of hardware [1]. For patients with complicating features, such as left-sided endocarditis or metastatic seeding of distant sites, a minimum of six weeks of therapy is recommended. Lifelong antimicrobial suppression therapy may be required if removal of infected hardware is not possible.

A recent study by Del Rio et al. found that conservative treatment without explantation of all pacemaker/ICD hardware failed in all patients [35]. Surgical treatment during antibiotic therapy was effective in eradicating infection but was associated with a mortality rate of 12.5%. The only patient characteristic associated with treatment failure or death was the absence of surgical removal of hardware. Complete extraction of the pacemaker or ICD should be considered as standard therapy for patients with device-related endocarditis.

Klug et al. reported intravascular lead segment cultures to be positive in 72% of a subgroup of 50 patients with manifestations of infection strictly limited to the pacemaker implantation site [36]. Infection, unfortunately not defined as pocket or endovascular infection, recurred in 4/8 (50%) patients without complete lead extraction versus only 1/97 (1.0%) whose leads were totally extracted. Although successful management of pocket infections has been reported [37], combined therapy with antimicrobials and complete device removal is generally recommended as recurrenct infection is more common in those treated with antibiotics alone or with antibiotics and removal of the generator alone [33].

Lead removal may be technically difficult due to neo-endothelization. Complications include tearing or perforation of the myocardial wall with resultant tamponade, superior vena cava lacerations, and arrhythmias. The risk of incomplete or failed extraction increases with implant duration [38]. Previously all patients underwent thoracotomy or sternotomy for removal of devices; however, several newer and safer techniques have recently become available. Locking stylet, laser extraction, and video-assisted thoracoscopic techniques are currently being used; however, open procedures are still occasionally required for removal. Success rates of 81–93% have been reported with laser extraction, with major complications including tamponade (0–3.3%) and death (0–0.8%) [39]. Failure to extract the entire lead can lead to persistent infection. Removal of larger (≥10 mm diameter) vegetations attached to infected leads has been associated with risk of pulmonary embolization; however, there have been no deaths reported due to this complication and only rarely do symptoms result [34].

Following device removal, re-implantation should be at a new site, and should be performed when the patient is no longer bacteremic. Temporary devices are commonly required for several days prior to re-implantation. A significant proportion of patients, however, may not require re-implantation; in a study from the Cleveland Clinic, 18% of patients did not require further device therapy after re-evaluation of their cardiac status[28].

Left Ventricular Assist Devices

Left ventricular assist devices (LVADs) are an effective treatment option as a bridge to transplantation in selected patients with end-stage heart failure and have been increasingly used in recent years. Normalization of hemodynamics leads to improved end-organ function, with 70% of patients surviving to transplant. LVADs may also be used for short-term support, while awaiting recovery of cardiac function following an acute insult, or as long-term myocardial replacement ("destination") therapy in a subset of patients with end-stage cardiac disease who are not candidates for transplantation.

Although LVADs often lead to hemodynamic stabilization, LVAD-related infection is common. This complication may delay or prevent transplantation and is a significant cause of death in non-transplant patients who undergo LVAD implantation as long-term myocardial replacement therapy [40]. Longer duration of implantation has been associated with an increased risk of infection, with 85% of

LVAD infections occurring after two weeks of placement [41]. Rose et al. found that infection complicated 28% of cases within three months of LVAD placement [40]. Most of the infections described affected the driveline tract and pocket, and were thereby treated with local measures and antibiotics. Fatal sepsis, however, was also common in this series. LVAD endocarditis has been associated with significant pre-transplantation mortality. The most recent study of 76 patients with LVAD-related infection [42] identified infections in 50% of patients who underwent LVAD implantation as a bridge to transplantation. There were 29 episodes of LVAD-related bloodstream infection, including 6.6% that were classified as endocarditis.

There are currently several LVADs approved in the USA. Five are approved by Health Canada (Novacor® Left Ventricular Assist System [LVAS], HeartMate® Implantable Pneumatic LVAS, HeartMate® Vented Electric LVAS, Thoratec® VAD and Abiomed BVS 5000® Bi-Ventricular Support System) for bridge-to-transplant [43,44]. All include either cannulas or drivelines that run percutaneously, contributing significantly to the high risk of infection. The development of totally implanted systems, with the elimination of percutaneous drivelines, is ongoing and should significantly reduce infection risk.

As briefly mentioned above, LVAD infections can affect the driveline, pocket, or valves and/or endovascular lining of the device. Driveline infections generally present with local inflammatory changes and drainage at the exit site. Pocket infections present similarly, with local inflammatory changes. LVAD endocarditis usually presents with fever, bacteremia, embolic events, valvular incompetence and/or LVAD mechanical dysfunction.

The induction of immunodeficiency has been postulated to predispose to LVAD infection. LVADs have been shown to increase the susceptibility of circulating $CD4^+$ T-cells to activation-induced apoptosis, leading to a progressive decline in cellular immunity. This cellular immunodeficiency may predispose to opportunistic infections, including increasing the risk of candida infections [45].

LVAD removal may be required to control infection; however, device removal is often not possible. Local drainage or debridement of infected tissue should be performed if device removal is not feasible. Suppressive antimicrobial therapy, directed by culture results, may be effective until the LVAD can be removed and cardiac transplant performed. Antimicrobial therapy before, during, and after transplantation is usually. LVAD infection is not a contraindication to cardiac transplantation; however, it has been associated with a delay in transplant. While some studies have found an increase in early post-transplant mortality, particularly in the setting of LVAD endocarditis, others have failed to confirm this and LVAD infection does not appear to impact long term survival [42,46,47].

Total Artificial Hearts

The development of the Jarvik-7 in the 1980s was a significant landmark in the history of medicine. The device, however, was associated with numerous infectious and thrombotic complications. Multiple newer generations of total artificial hearts (TAH) are currently under study. The use of the first fully implantable device, the AbioCor™, has been reported in 11 recipients to date with no infectious complications [48]. The main complications have been thromboembolic. Preclinical animal studies with the second-generation model, AbioCor™ II, are ongoing, and clinical trials are planned to begin in 2006. The SynCardia temporary CardioWest™ total artificial heart, also fully implantable, was recently approved in 2004 by the Food and Drug Administration, and will become an alternative to heart transplantation for selected patients with end-stage cardiac disease.

Cardiac Suture Line Infections

Left ventriculotomy may be performed as part of aneurysm repair, in anti-arrhythmic surgery, and during placement of LVADs. Infection of the left ventricular suture line is an uncommon complication. A review published in 1988 reported only 25 cases in the literature [49]. Infection presented on average 16 months after surgery. Staphylococci and gram-negative bacilli were the most frequent pathogens. Left ventricular false aneurysms were identified in 15 of 25 patients. Treatment with antibiotics alone was insufficient. Excision of all infected sutures

and Teflon pledgets along with adequate debridement of the infected suture line was required to achieve cures.

Cardiac suture line infections may present with chest wall or epigastric involvement, bronchopulmonary infection, or endocarditis with bacteremia or fungemia. Chest wall or epigastric involvement is most common, presenting as a chronic draining sinus, subcutaneous mass or local pain. Endocarditis and bronchopulmonary presentations (including hemoptysis, bronchiectasis, pneumonia, and empyema) are less common.

Treatment should include early surgical debridement, with removal of any prosthetic material, and parenteral antimicrobial therapy directed by culture results.

Closure Device Treatment of Patent Ductus, Atrial Septal Defect, and Ventricular Septal Defect

Therapeutic cardiac catheterization with closure of various congenital defects has become increasingly common. Placement of devices for the closure of patent ductus arteriosus, arteriovenous fistulae, and secundum atrial septal defects has been successful and avoids open-heart surgery. Infectious complications are rare; only three cases have been reported since 1999 with a variety of devices and microorganisms [50–52]. All infections occurred early (<3 months) post-procedure. Two were cured with a combination of surgical and medical management. One case was cured with medical management alone [51]. In all cases, device-related vegetations were identified by echocardiography.

Intra-Aortic Balloon Counterpulsation

The intra-aortic balloon pump is used to increase coronary perfusion by diastolic augmentation and enhances systolic function by decreasing afterload. Indications for its use include refractory cardiogenic shock, severely low cardiac output states, difficulty weaning from cardiopulmonary bypass, refractory myocardial ischemia, and prophylactic perioperative insertion in left main coronary disease or severe triple vessel disease.

The risk of infection is predominantly related to the duration of placement. Other factors associated with infection include contamination of the femoral area during insertion, insertions performed in coronary care or intensive care units, and emergent insertions. A study of in-hospital and late complications related to percutaneous placement of 240 intraaortic balloon pump catheters reported an average pump duration of 44 hours [53]. Infectious complications were rare with one episode each of bacteremia and superficial wound infection.

Coronary Artery Stents

Infection of intracoronary stents is extremely rare, despite the large number of procedures performed per year—approximately 457,000 procedures in the United States in 1999. Percutaneous coronary intervention (PCI) has a greater potential for infection compared to cardiac catheterization alone due to the prolonged procedure time and introduction of prosthetic devices into the vascular system. Femoral access and femoral sheaths left in place for long duration add additional risk for the development of infection. Only five cases of known coronary stent infection have been reported [54]. Fever and bacteremia within 4 weeks of stent placement were present in all cases. *Staphylococcus aureus* and *Pseudomonas aeruginosa* were the implicated pathogens.

Of the five cases, four patients underwent surgical debridement and stent extraction, two of which subsequently died despite prolonged intravenous antibiotic therapy. Of the two patients who survived, one underwent stent removal and partial excision of the coronary artery without bypass, while the other had surgical debridement, coronary artery bypass, and partial stent extraction. Both received parenteral antibiotics. The patient who did not undergo surgical exploration died of progressive heart failure. Complications of infection included false aneurysm of the stented artery, abscess with pericardial empyema, and severe inflammation with complete destruction of the arterial wall.

Although intracoronary stent infection rarely occurs, the mortality rate is high, so a clinical history and course of illness suggestive of the diagnosis should raise clinical suspicion. Based

on this limited experience, therapy should include parenteral antibiotics, surgical drainage, and repair of the involved artery. Coronary bypass may be necessary, and stent removal should be performed if possible.

Prevention of Prosthetic Valve and Cardiac Device-Related Infection

Patients with prosthetic cardiac valves are at high risk for the development of PVE and should receive prophylactic antibiotics for specific procedures, as per American Heart Association guidelines [55]. High-risk procedures include specific dental/oral, respiratory, gastrointestinal, and genitourinary procedures. Prophylaxis is routinely administered one hour pre-operatively and repeated at a reduced dosage six hours following the procedure (see Chapter 4: Prophylaxis of Endocarditis for a full discussion of endocarditis prevention). Patients should be educated to maintain good oral hygiene to prevent late-onset PVE caused by oral microflora.

The risk of developing infection of other cardiovascular devices is less well quantified. Most experts would not recommend prophylaxis for patients with non-valvular implanted cardiovascular devices [56].

Key Points

1. Prosthetic valve endocarditis (PVE) and other cardiovascular device-related infections are life-threatening conditions with high mortality rates, prompting the need for rapid diagnosis and treatment.
2. In the presence of foreign material the number of microorganisms needed to establish infection is greatly reduced. Microbial adherence to prostheses also provides effective protection against host immunity. Therefore, definitive treatment of infections involving prosthetic devices generally requires removal of the device.
3. The microbiology of prosthetic valve endocarditis and other cardiovascular device-related infections is similar, with a distinction between early and late postoperative infections. Early infection is commonly caused by staphylococci (*Staphylococcus aureus* and coagulase-negative staphylococci) and occasionally by Gram-negative bacilli, diphtheroids, and *Candida* species. Late disease is usually due to the same spectrum of microorganisms causing community-acquired native valve endocarditis, with the exception that coagulase-negative staphylococci also make up a significant proportion of cases.
4. Antimicrobial therapy is based on microbial etiology and is generally prolonged (6–8 weeks). Depending on the clinical condition, microbiology, and presence of complications, surgery may be an integral part of the management of PVE.
5. Infection of cardiac devices, such as pacemakers, implantable cardiac defibrillators, left ventricular assist devices, and total artificial hearts, requires similar treatment to PVE, with prolonged antibiotic treatment accompanied by device removal if possible.

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12

Pediatric Infective Endocarditis and Congenital Heart Disease

Sarah Forgie

Case Study

A child was diagnosed with a heart murmur at three years of age, but further investigations were not undertaken at that time. At four years of age he presented with a ten-week history of daily fever and myalgia. He had been evaluated by his family physician and diagnosed with otitis media six weeks previously, and was treated with azithromycin, which did not affect his fever.

The past history was remarkable for a deep dental cavity that was filled and capped 27 weeks prior to presentation, and a hypospadias repair 12 weeks prior to presentation. Prophylactic antibiotics were not given for either procedure. This child lived on a farm with four outdoor cats, but no other animals. His immunizations were up to date.

Physical exam revealed a non-toxic child in no distress. His heart rate was regular, 90 beats per minute, blood pressure in his right arm was 90/50 mm Hg. His respiratory rate was 30 breaths per minute. There were no peripheral stigmata of endocarditis. His chest was clear on auscultation, and he had a 2/6 short systolic murmur and 2/6 early diastolic murmur. His liver was 3 cm below the costal margin, and his spleen tip was palpable in the left upper quadrant of his abdomen. A chest radiograph was interpreted as normal and a transthoracic echocardiogram revealed a bicuspid aortic valve with vegetations and moderate aortic insufficiency.

Laboratory investigations performed at the time of presentation revealed a white blood cell count of 5×109/L (with 7% bands), hemoglobin of 105 g/l with microcytic indices, and platelets of 237×109/L. His erythrocyte sedimentation rate was elevated at 48 mm/h. His urinalysis showed moderate hematuria, and two sets of blood cultures were drawn at the time of presentation.

He was started empirically on ampicillin, cloxacillin, and gentamicin. However, within 15 hours, gram-positive cocci in chains were recovered from all blood culture bottles, and within 24 hours *Enterococcus faecalis* was confirmed as the pathogen in the blood cultures. His therapy was changed to ampicillin and gentamicin, and repeat blood cultures were sterile. Unfortunately, his aortic valvular function deteriorated and he developed severe heart failure, which necessitated an aortic valve replacement four weeks later.

Introduction

Pediatric infective endocarditis (PIE) is an infection of the endocardial surface of a child's heart with bacteria, rickettsia, chlamydia, mycoplasmas, or fungi [1]. Any part of the endocardium where turbulent blood flow occurs can become a nidus for infective endocarditis [2]. (Table 12.1).

Children with abnormal hearts from congenital heart disease (CHD) are at higher risk for PIE. It is difficult to determine the incidence of CHD among live-born infants because many cardiac lesions are not diagnosed in the neonatal period. A conservative estimate of the number of

Table 12.1. Areas of a Child's Heart that May Serve as a Nidus for PIE

Heart valves	Normal native valves
	Abnormal native valves
	Prosthetic valves
Septal defects	Septal defect preoperatively
	Repaired septum postoperatively
Artriovenous shunts	Native shunt
	Artificial conduits
Arterioarterial shunts	Patent ductus arteriosus
Endocardium	Especially at sites of "jets" or turbulent flow

American children with CHD detected in the first year of life is nine cases per 1,000 live births [3]. Risk factors for the development of CHD are diverse, and can include maternal diabetes; exposure to rubella or teratogenic drugs such as indomethacin, cocaine, or alcohol during pregnancy; and certain genetic syndromes. There are more than 35 recognized cardiovascular defects, and these defects can be divided into two broad categories—cyanotic and acyanotic CHD. In the latter group, the largest proportion are ventricular septal defects, while atrial septal defects, atrioventricular canals, pulmonary valve stenosis, patent ductus arteriosus (PDA), aortic valve stenosis, and coarctation of the aorta are some of the other types of acyanotic CHD. Among the cyanotic heart lesions, tetralogy of Fallot and transposition of the great arteries are the most common [3].

The American Heart Association has further defined the risk of PIE in children with CHD (whether repaired or unrepaired). Those at highest risk include children with prosthetic valves, a past history of PIE, cyanotic congenital heart disease, and aortopulmonary shunts. Children at moderate risk for PIE include those with most congenital heart malformations and valvular heart disease (whether congenital or acquired). Children at low risk for PIE include those with non-repaired isolated secundum atrial septal defects, atrial septal defects or ventricular septal defects six months after repair, and repaired patent ductus arteriosus lesions [4].

Epidemiology

The epidemiology of PIE continues to change. Well into the twentieth century, one-third to one-half of PIE was a direct result of underlying rheumatic heart disease with seeding of damaged heart valves by alpha-hemolytic streptococci. As effective antibiotic therapies for streptococcal pharyngitis emerged, the incidence of rheumatic heart disease decreased. Despite this decrease in rheumatic heart disease, the incidence of PIE has been continuing to increase [5]. There are several reasons for these epidemiological changes, but the most plausible involves the huge advances in many areas of medicine, including increased successful cardiac surgeries for extremely complicated cardiac defects, premature neonates surviving at earlier gestational ages, and the increased use of intravascular devices [6–7].

Over half of PIE cases are related to surgery for congenital heart disease. The *type of surgery* is an important determinant in the risk for PIE. Overall, the highest annualized risk for PIE is in children that have had repair or palliation of cyanotic congenital heart disease (especially repair of pulmonary valve stenosis or pulmonary valve atresia or aortic valve replacement). In contrast, those that had repair of atrial septal defect secundum or mild pulmonic stenosis are at low risk for PIE. In addition to the type of surgery, the *time from surgery* also alters the risk for PIE. Generally, the incidence of PIE immediately after most surgical procedures is low, but increases over time. However, there are exceptions. First of all, when prosthetic valves or conduits are used, the risk for PIE is high even in the first two weeks after surgery [6,8]. Secondly, for certain surgeries, such as a patent ductus arteriosus (PDA) repair, ventricular septal defect (VSD) repair, or atrial septal defect (ASD) repair, the risk of PIE is negligible six months after surgery [9,10].

Premature neonates are another group at risk for PIE. These premature infants often have PDA lesions, which puts them at risk for PIE. Additionally, as the gestational age decreases, more invasive procedures are required for survival. Transient bacteremias from skin trauma and mucous membrane trauma, coupled with the use of high lipid total parenteral nutrition, an immature immune system and frequent use of central venous catheters put these children at high risk for bacteremia. The central venous catheters not only breech the skin, they also induce trauma to the right side of the heart (both endocardium and valves) and often induce clot formation and intracardiac thrombi [11,12]. Use of these catheters in the neonatal population and congenital heart disease (including PDA) are the top risk factors for PIE [2].

In 10% of children, there is no identifiable underlying risk factor [13]. These children develop bacteremia and seed normal heart valves. Intravenous drug abuse and degenerative heart disease—common risk factors for endocarditis in adults, rarely play a role in PIE.

Etiology

The etiology of PIE is slightly different than IE in adults. Overall, causative agents isolated from blood cultures include the Gram-positive cocci—viridans streptococci (32–43% of isolates), *Staphylococcus aureus* (27–33% of isolates), coagulase-negative staphylococci (2–12% of isolates), and *Streptococcus pneumoniae* (3–7% of isolates). Unlike adults, enterococci and bacteria from the HACEK group (*Haemophilus* species, *Actinobacillus actinomycetemcomitans, Cardiobacterium hominis, Eikenella* species, and *Kingella kingae*) are isolated less frequently [14]. However, organisms from the HACEK group (especially *H. parainfluenzae*) are the most common cause of gram negative PIE [15]. (Although gram *negative* enteric organisms such as *Escherichia coli* and *Pseudomonas aeruginosa* frequently cause bacteremia in infants and older compromised children, these organisms rarely cause PIE). Fungi such as *Candida albicans* and other *Candida* species are seen more commonly in premature neonates, who require central venous catheters. Five to fifteen percent of neonates with candidemia will develop PIE [16].

In children with prosthetic material (including indwelling lines, patches, conduits or artificial heart valves) PIE is usually caused by *S. aureus* or coagulase-negative staphylococci. Both of these organisms can be implanted at the time of surgery, and if infection occurs, it can be seen within weeks to months after surgery. The timing of infection varies between these organisms. *S. aureus* is often seen within two months of surgery, while coagulase-negative staphylococci can be seen up to one year after surgery. Although rare, *Staphylococcus lugdenensis* deserves special mention. This coagulase-negative organism may be misidentified as *S. aureus* with slide coagulase testing, because it produces a clumping factor. In contrast with other coagulase-negative staphylococci, it is associated with more aggressive infections, similar to *S. aureus*. In adults, the case fatality of *S. lugdenensis* endocarditis is 50% versus 40% for *S. aureus* [17,18]. This organism is resistant to oxacillins but often sensitive to penicillins, and despite use of appropriate antibiotics, 80% of cases require surgery [19].

In children with native valve endocarditis, the most common isolates are viridans streptococci and *S. aureus*. *Abiotrophia defectiva*, *Granulicatella* species, *Gemella* species and enterococci are seen less commonly. PIE in children more than two months after cardiac surgery can also be caused by viridans streptococci, *Abiotrophia* species and/or enterococci [37].

In premature neonates, coagulase-negative staphylococci, *S. aureus*, and *Candida* species are the most common etiologic agents. Rarely, *S. pneumoniae* and *Streptococcus agalactiae* (Group B streptococci) are isolated as causes of PIE in this population [9,20].

In 5–7% of children with PIE, the blood cultures are negative [14]. The most common reasons for negative blood cultures include previous antibiotic therapy; inadequate blood-culture technique or PIE caused by an organism with special in vitro growth requirements. Fastidious organisms associated with culture-negative endocarditis may include *Legionella pneumophilia*, *Bartonella henselae* and *quintana*, *Brucella melitensis* and *abortus*, *Coxiella burnetii*, *Pasteurella* sp., *Chlamydia* sp., and filamentous fungi [21–22].

Diagnosis

Sometimes, the diagnosis of PIE can be easy to make—an older adolescent with bacteremia, a new heart murmur, and peripheral stigmata fits classic descriptions of infective endocarditis. However, in most cases of PIE, the presentation and subsequent diagnosis is not as straightforward. A multifaceted diagnostic approach that uses clinical findings, laboratory evidence, and echocardiographic findings is required that is sensitive enough to detect PIE, but specific enough to reject cases that are not PIE. In adult medicine, the Duke criteria offer a combination of subjective and objective findings to diagnose endocarditis [23]. The Duke criteria are superior to several other criteria for the diagnosis of PIE. [14,24]. There have been some changes made to the original Duke criteria, and the modified Duke criteria are even more sensitive than the previous criteria in diagnosing PIE (Tables 12.2, 12.3) [25].

Table 12.2. Use of the Modified Duke Criteria to Classify a Child with Suspected Endocarditis as a Definite Case, a Possible Case or a Rejected Case of PIE

Definite Infective Endocarditis According to the Modified Duke CriteriA

Pathological criteria
Microorganisms demonstrated by culture or histological examination of a vegetation, a vegetation that has embolized, or an intracardiac abscess specimen OR—
Pathological lesions, vegetation, or intracardiac abscess confirmed by histological examination showing active endocarditis

Clinical criteria
2 major criteria OR—
1 major criterion and 3 minor criteria OR—
5 minor criteria

Possible Infective Endocarditis According to the Modified Duke Criteria
1 major criterion and 1 minor criterion OR—
3 minor criteria

Rejected Infective Endocarditis According to the Modified Duke Criteria
Firm alternative diagnosis explaining evidence of infective endocarditis OR—
Resolution of infective endocarditis syndrome with antibiotic therapy for < 4 days, OR—
No pathological evidence of infective endocarditis at surgery or autopsy, with antibiotic therapy for < 4 days OR—
Does not meet criteria for possible infective endocarditis as above

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Table 12.3. Terms Used in the Modified Duke Criteria To Make a Diagnosis of PIE

The Major Criteria
1. Positive blood cultures
   a. With certain organisms known to be associated with endocarditis; or
   b. Sustained bacteremia as shown by persistently positive blood cultures; or
   c. Single positive blood culture or positive serology for *Coxiella burnetii*
2. Evidence of Endocardial Involvement
   a. With a positive echocardiogram

The Minor Criteria
1. Predisposition to PIE OR—
2. Fever OR—
3. Vascular phenomena OR—
4. Immunologic phenomena OR—
5. Microbiological evidence

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Defining the Terms Used in the Modified Duke Criteria for Diagnosis of PIE

In order to make a diagnosis of PIE with the Duke criteria, certain findings must be satisfied. Major criteria provide evidence of a sustained bacteremia with certain organisms and concomitant endocardial involvement.

The Major Criteria

Evidence of Bacteremia with Certain Organisms

Two separate blood cultures with viridans Streptococci, Streptococcus bovis, HACEK group, Staphylococcus aureus, or community acquired enterococci in the absence of a primary focus [86].

The typical organisms that cause endocarditis in children include viridans Streptococci, *S. aureus*, coagulase-negative staphylococci, and *S. pneumoniae*. Rarely, enterococci and organisms from the HACEK group can be isolated. To maintain high specificity, certain organisms are given more weight than others. Bacteremia with viridans Streptococci, organisms from the HACEK group, and now *S. aureus* are given primary diagnostic weight, because these organisms are almost always associated with PIE [26,27,86]. However, other organisms, such as enterococci, may be associated with bacteremia in the absence of PIE. The Duke Criteria only gave diagnostic weight to this organism if it was community acquired and there was no primary focus [28]. For organisms such as *S. pneumoniae* and coagulase-negative staphylococci, in order to satisfy a major criterion, evidence of sustained bacteremia must be seen.

Evidence of Sustained Bacteremia

Number of Positive Blood Cultures

At least two positive cultures must be drawn more than 12 hours apart, or all of three, or a majority of ≥ 4 separate positive blood cultures (with the first and last sample drawn at least one hour apart) [86].

In order to show sustained bacteremia, according to the modified Duke criteria, a certain number of blood cultures must be positive over a period of time. Two or three cultures are more than adequate to detect episodes of bacteremia and fungemia caused by common pathogens. The dogma of using more than three cultures dates back to conventional non-automated blood culture methods [29]. However, with continuous blood culture monitoring systems that are used in most microbiology labs, virtually all clinically important bloodstream infections can be detected with two blood cultures [30]. *It is rarely necessary to collect more than two cultures in a 24-hour period unless the patient has been on antibiotics or the initial cultures are negative* [31]. So why do the Duke criteria recommend more than two cultures? Because the patterns of positivity vary depending on the type of bacteremia. In other words, two blood cultures are sufficient to detect bacteremia, but more are required to substantiate the diagnosis of continuous bacteremia and endocarditis. A single positive blood culture is difficult to interpret. However, several positive blood cultures are more easily interpreted. For example, with infective endocarditis (continuous bacteremia), if the first blood culture is positive, the probability that subsequent cultures will be positive is between 95% and 100%. With a true bacteremia, but no endocarditis, if the first blood culture is positive, the probability of subsequent cultures being positive is lower (between 75% and 80%). If only one blood culture is positive and the subsequent ones negative, it is more likely that the first isolate was a contaminant [35].

Timing of Blood Cultures

There does not seem to be a significant difference in detection of bacteremia if the cultures are obtained simultaneously or over intervals in a 24-hour period, but to determine if the bacteremia is continuous, drawing the cultures over a period of time is useful [32]. If the child is not acutely ill, withholding antibiotics and repeating cultures is justified; otherwise it is prudent to draw two sets of blood cultures from different sites simultaneously and then give antibiotics.

Volume of Blood Drawn for the Blood Culture

The volume of blood inoculated into the blood culture vials is very important in children. Unlike adults, where a standard volume of blood is inoculated into several sets of tubes, no such standard exists for children. At times, very minute amounts of blood are used to inoculate the pediatric blood culture bottle. Reasons for this include difficult venous access, fear of withdrawing too much blood or the belief that children have much higher levels of bacteremia (so less blood is needed to reveal a positive blood culture) [33–34]. However, using small volumes of blood may miss bacteremias, because over 60% of infants and children with sepsis have low level of bacteremias (< 10 colony-forming units (CFU) per milliliter of blood) [35]. These low-level bacteremias can only be detected when larger amounts of blood are cultured (up to 4.5% of a child's total blood volume). Therefore, the volume of blood drawn for culture should be based on the child's total blood volume, which can be determined by the child's age and weight [36–37]. For example, a child who weighs more than 30 kg who has 60 mL (or two sets of adult blood cultures drawn) and an infant who weighs less than one kilogram who has 2 mL of blood drawn will both lose 3% of their total blood volume. Some centers have created simple policies where children over a certain weight (such as 30 kg) will have adult blood cultures drawn (10 mL each in an aerobic and anaerobic vial), while smaller children have a minimum of 1 mL (but preferentially 3 mL) of blood inoculated into a pediatric blood culture bottle [38].

Evidence of a Coxiella burnetii Infection

There must be a single positive blood culture for Coxiella burnetii or anti-phase 1 IgG antibody titer > 1:800 [86].

Unlike adults, most children have few symptoms when infected with *C. burnetii* [39]. Self-limited febrile illnesses and pneumonia have been reported, and rarely, chronic infections manifest as osteomyelitis or endocarditis. Five published cases of Q-fever endocarditis revealed that the median age of the children was 7 (range 3.5–11 years); and only one child had underlying CHD [40–41]. A high index of suspicion in

children that have been in contact with farm animals and/or pets is required to make the diagnosis of Q fever.

Evidence of Endocardial Involvement

Echocardiogram positive for PIE with an oscillating intracardiac mass on valve or supporting structures, in the path of regurgitant jets, or on implanted material in the absence of an alternative anatomic explanation; or abscess; or new partial dehiscence of a prosthetic valve; new valvular regurgitation (worsening or changing of preexisting murmur not sufficient) [86].

Since the late 1970s, echocardiography has been a useful adjunctive test for the diagnosis of infective endocarditis [42]. It can show the site of infection, and determine the extent of valvular damage. Cardiac function can also be determined and used as a comparison later in the course of the infection [43]. In adults, transthoracic echocardiography (TTE) has a sensitivity of 70% in detecting vegetations. When used in patients with high-risk for infective endocarditis, transesophageal echocardiography (TEE) is a far more sensitive and specific test [44,45].

Unfortunately, there is little data for children and the optimal use of these technologies. Two published studies showed a sensitivity of 46% and 67% for TTE using the Duke criteria [46,47]. One study has examined the additional benefit of TEE in children who satisfied the Duke criteria for PIE. Using TEE as the gold standard, TTE had a sensitivity of 86% for all events and 93% sensitivity for detecting vegetations. The authors concluded that TTE has a high degree of sensitivity for supplying supportive evidence of endocarditis and that TEE had little additional benefit. However, there are times when a TTE may be falsely negative: if the vegetations are very small (that is, below the detectable limit for TTE at 2 mm) or if the vegetations have already embolized [27]. Additionally, TTE may not be effective in children with a poor thoracic window, like the obese or very muscular adolescent, in children with repaired complex heart defects (whose artificial grafts conduits and valves may interfere with TTE), or in children with pulmonary hyperinflation [48]. In those cases, TEE should be used as an adjunct to TTE [6,49]. TEE should also be considered in children with a suspicion of aortic root abscess (*S. aureus* bacteremia, and/or changing aortic root dimensions on TTE) since abscesses in this area are difficult to assess with TTE [50–51]. Please see Table 12.4.

The Minor Criteria

Predisposition to PIE

Children who have had cardiac surgery—especially those with underlying cyanotic congenital heart lesions are at high risk for PIE [6,52]. Within that group, the risk of PIE is highest in children who have had repair of pulmonary atresia or stenosis, and children who have had replacement of their aortic valve. Children with other implanted foreign material (such as vascular conduits) are also at high risk for PIE if hemodynamic problems and turbulent flow persist postoperatively [9]. Neonates with CHD (including PDA) and/or indwelling intravascular devices are also at high risk for PIE [14].

Fever

A temperature over 38˚C is another minor criterion. Since many children present to their physicians with a fever, distinguishing between a viral infection and PIE can be difficult. It is important to maintain a high index of suspicion for PIE in children with CHD and draw blood cultures under the following circumstances: if a child presents with more than 48 hours of low-grade fevers and flu-like symptoms (such as, decreased

Table 12.4. Determining When To Use TTE or TEE in Children with Suspected PIE

TTE—Use as a first line test for supportive evidence of PIE in children who satisfy the Modified Duke Criteria for PIE
TEE—As an adjunct to TTE, consider TEE use in—
1. Children with a poor thoracic window from—
obesity OR—
excess muscularity OR—
implanted prostheses in a surgically repaired heart OR
pulmonary hyperinflation
2. Children who are at risk for aortic root abscess—
with S.aureus bacteremia AND/OR
changing aortic root dimensions on TTE

intake, fatigue, weakness, arthralgias, myalgias, rigors, and/or diaphoresis) or if a child presents acutely with high fevers but a source cannot be found on history or physical examination [53].

Vascular Phenomena

Signs and symptoms of vascular phenomena are more common in adults. *Arterial emboli* in large vessels, *septic pulmonary infarcts, mycotic aneurysms, intracranial hemorrhages, conjunctival hemorrhages* and *Janeway lesions* (flat, non-tender lesions on the palms and soles) are listed as minor clinical criteria in this category. [54,86]. If conjunctival hemorrhages are seen, they are often accompanied by other petechiae on the hands, feet, and trunk and in the mouth.

Immunologic Phenomena

In children with PIE, *glomerulonephritis* is more common than *Osler's nodes* (painful erythematous nodules in the pulp space of the fingers) or *Roth's spots* (retinal hemorrhages). All three of these findings along with a *positive rheumatoid factor* are considered minor criteria in this category.

Microbiological Evidence

If an organism is isolated, but does not meet the major criteria (too few positive cultures or inadequate time delay between cultures), it can still be included as a minor criterion. (An exception is a single positive culture for coagulase-negative staphylococci or organisms that usually do not cause PIE). If blood cultures are negative, but there is serological evidence of active infection with an organism consistent with PIE, this can also fit into this category.

Signs and Symptoms of PIE

The signs symptoms of PIE vary with the underlying pathology. Generally, there are four underlying phenomena associated with PIE that can cause various signs and symptoms. These may include *bacteremia, valvulitis, immune response* and/or *septic emboli*.

Children with bacteremia may present subacutely with flu-like symptoms such as decreased food or fluid intake, fatigue, weakness, arthralgias, myalgias, rigors, and/or diaphoresis. If these symptoms persist, it is important to rule out PIE. Children with bacteremia and CHD can also present acutely with high fevers, and if a source cannot be found on history or physical examination, other serious illnesses such as PIE must be ruled out [65].

Neonates and premature infants with bacteremia and PIE may present with symptoms which are indistinguishable from sepsis or heart failure. Symptoms may include apneas, temperature instability, increased work of breathing, feeding difficulties, and/or blood pressure instability.

Babies with valvulitis and heart failure may present with failure to thrive and tiring during feeds, a new or changing murmur, tachycardia, tachypnea, an enlarged heart and/or an enlarged liver.

The most common symptoms from the *immune phenomena associated with PIE* are hematuria from glomerulonephritis. Certain findings, such as Roth's spots, Janeway lesions, and Osler's nodes, which are common in adults, are rarely seen in children with PIE.

Septic emboli in children with PIE have various presentations. Fever and increased work of breathing may be one presentation of pneumonic emboli. Neonates often present with extra-cardiac foci of infection such as osteomyelitis or pneumonia. Children with surgical repair of cyanotic heart disease may present with declining oxygen saturations as an indication of graft infection and shunt obstruction. Infants or children with catheter-related right-sided PIE may present with pulmonary signs related to septic emboli in the lungs.

Ancillary Tests

A complete blood count is useful in a child with fever, and can be helpful in diagnosing serious illnesses such as PIE [65]. Hemoglobin is often low, and the anemia may be caused by hemolysis or anemia of chronic disease. Leukocytosis may or may not be present, accompanied by a left shift. Elevated acute phase reactants (ESR, CRP) are present in a large proportion of patients. A urinalysis may show hematuria from immune complex glomerulonephritis, and this

may be accompanied by red cell casts, proteinuria, and renal failure.

Newer diagnostic tests such as the polymerase chain reaction are proving to be useful in certain instances. This test offers high specificity and positive predictive value in patients with definite IE versus rejected IE. It can be used for surgically resected material in cases of possible IE, on blood for cases of suspected IE if cultures are sterile, or in cases where the organism grows in blood culture but only minor criteria are met [55].

Treatment

Overall, the approach to treatment of PIE is very similar to that of adults [31]. In patients who are not acutely ill and whose blood cultures are negative, antibiotics may be withheld for greater than 48 hours while additional blood cultures are obtained [52]. When therapy is started, certain principles apply. Cidal, intravenous antimicrobials must be used for prolonged periods.

Cidal antimicrobials should be used to treat endocarditis to reduce the risk of relapse or failure to control the infection [56]. Bactericidal drugs may be used alone, but certain drug combinations such as a ß-lactam plus an aminoglycoside act synergistically to sterilize vegetations caused by bacteria such as enterococci faster than either drug alone. When combination therapy is used, the drugs should be administered at the same time, or following each other in order to maximize the synergistic killing effect on the pathogen.

Parenteral drugs are recommended over oral drugs because of higher bioavailability and sustained concentrations in the bloodstream. Smaller children and neonates have smaller muscle mass, and the intramuscular route for prolonged therapy of endocarditis is not recommended.

Prolonged therapy is required for several reasons. First of all, the infection is in an area of impaired host defense–the bacteria are encased in a mesh of fibrin, and can multiply in this area protected from the immune system. Secondly, when bacteria reach high population densities within the vegetation, they start to reproduce more slowly. This slowed metabolic rate is a distinct disadvantage for certain antibiotics which require active cell-wall synthesis for maximal activity [57]. Finally, short-term therapy is often associated with relapse.

Treatment of PIE Caused by Viridans Streptococci in the Absence of Prosthetic Material [52]

If the organisms are penicillin-susceptible (penicillin minimum inhibitory concentration or MIC < 0.12 μg/ml), there are several options for therapy which offer high cure rates: a four-week course with monotherapy or shorter therapeutic courses with combination therapy. Shorter courses *should not* be used in children with prolonged symptoms (more than three months), abnormal renal function and/or extracardiac foci of infection or abscesses.

There are several choices for antimicrobial monotherapy. Four weeks of *penicillin G* (200,000 units/kg/day in four to six divided doses) or *ampicillin* (300,000 mg/kg/day in four to six divided doses) are especially advantageous in children with renal or otic problems because aminoglycosides are avoided [58]. An alternative monotherapeutic agent is parenteral *ceftriaxone* (100 mg/kg/day), which offers the advantage of once daily dosing. Although its efficacy has not been proven in children, extrapolation from adult data and other pediatric infections indicate that it is likely effective [59].

In uncomplicated PIE, combination antimicrobial therapy can be used for shorter treatment durations. Antimicrobial combinations that have been successful over two week treatment intervals include ß-lactams (*penicillin G, ampicillin, or ceftriaxone*) plus *gentamicin*. Adult guidelines offer the option of once daily dosing of gentamicin (3 mg/kg) when treating endocarditis caused by viridans streptococci [31]. There is some data about the use of once daily dosing of gentamicin in pediatric patients with gram negative infections associated with urinary tract infections, febrile neutropenia, and cystic fibrosis. Doses in these studies ranged from 4 to 7.5 mg/kg/day [60]. There is little data about once daily dosing of gentamicin with PIE, but decreased toxicity, lower cost, and ease of administration make it an attractive option. The gentamicin dose for treatment of PIE caused by viridans streptococci is 3 mg/kg/day in one or three divided doses.

If the viridans streptococci are relatively penicillin resistant (penicillin MIC > 0.12 μg/mL and ≤ 0.5 μg/mL), combination therapy is more effective. *Penicillin G* (at a higher dose of 300,000 u/kg/day in four to six divided doses) or parenteral *ceftriaxone* (100 mg/kg/day) should

be used for a minimum of four weeks, and during the first two weeks of therapy, *gentamicin* (3 mg/kg/day in one or three divided doses) should be added.

Certain Gram-positive organisms are very difficult to treat when they cause PIE. They are either streptococci that are highly resistant to penicillin (MIC > 0.5 μg/mL) or certain organisms such as *Abiotrophia defectiva*, *Granulicatella* species, or *Gemella* species. For these organisms, combination therapy with *penicillin G* (300,000 mg/kg/day in 4–6 divided doses) or *ampicillin* (300,000 mg/kg/day in four to six divided doses) plus *gentamicin* (3 mg/kg/day in three divided doses) for the entire course of four to six weeks is needed.

For children who are unable to tolerate beta lactams, *vancomycin* (40 mg/kg/day in two to four divided doses) can be used in their place for the treatment of PIE. Vancomycin levels must be monitored, and a peak of 30–45 μg/mL (one hour after the drug infusion has finished), and a trough of 10–15 μg/mL (drawn just prior to next dose) is required.

Treatment of PIE Caused by Viridans Streptococci with Prosthetic Material in Place [52]

If the strains are susceptible to penicillin (MIC ≤ 0.12 μg/mL) treat with *penicillin G* (200,000 units/kg/day in four to six divided doses) or parenteral *ceftriaxone* (100 mg/kg/day) for six weeks and consider adding *gentamicin* (3 mg/kg/day in one or three divided doses) for the first two weeks. If the organism is relatively penicillin resistant (MIC > 0.12 μg/mL and ≤ 0.5 μg/mL) use combination therapy with a ß-lactam and aminoglycoside for six weeks minimum. If the child has intolerance to ß-lactams, vancomycin can be used as a substitute.

Treatment of PIE Caused by Staphylococci (*S. aureus*, coagulase-negative Staphylococci) [52]

Methicillin-sensitive *S. aureus* PIE in the absence of prosthetic material can be treated with *cloxacillin* (200 mg/kg/day in four to six divided doses) or *cefazolin* (100 mg/kg/day in three to four divided doses) for a minimum of six weeks. *Gentamicin* (3 mg/kg/day in three divided doses) can be added for the first three to five days because it may accelerate the killing of the organisms.

Most coagulase-negative staphylococci are resistant to methicillin and penicillin (with the exception of *Staphylococcus lugdenensis,* which is often sensitive to penicillin) and the rates of methicillin resistant *S. aureus* (MRSA) are increasing. If the staphylococcus is resistant to methicillin, then *vancomycin* (40 mg/kg/day in two to four divided doses) should be used for six weeks, with or without *gentamicin* for the first three to five days.

PIE caused by staphylococci in the presence of prosthetic material is often caused by coagulase-negative staphylococci. Treatment consists of a minimum of six weeks of *vancomycin* (40 mg/kg/day in two to four divided doses) and oral or intravenous *rifampin* (20 mg/kg/day in three divided doses) plus *gentamicin* (3 mg/kg/day in three divided doses) for the first two weeks. Methicillin-susceptible *S. aureus* PIE in the presence of prosthetic material should be treated with six weeks of *cloxacillin* (or cefazolin) and *rifampin* plus *gentamicin* for the first two weeks.

Treatment of PIE Caused by S. pneumoniae

Optimal therapy for PIE caused by this organism has not been established. When treating PIE caused by this organism, it is important to determine if other sites (such as the meninges) have been seeded and to determine the antimicrobial susceptibilities of the organism. Once these have been determined, a treatment regimen can be developed. If the organism is sensitive to penicillin (MIC ≤ 0.06 μg/mL), and there is no meningitis, four weeks of therapy with *penicillin G* (200,000 units/kg/day in four to six divided doses) or *ceftriaxone* (100 mg/kg/day) alone or in combination with *gentamicin* (3 mg/kg/day in three divided doses) have been used successfully. If the organism is of intermediate (> 0.12 and ≤ 1 μg/mL) or high-level resistance (≥ 2 μg/mL) to penicillin and there is no meningitis, higher doses of *penicillin G* (300,000 u/kg/day in four to six divided doses) over a six-week course have been used successfully. If meningitis is present with PIE, and the organism is highly resistant to penicillin, a third-generation cephalosporin such as *cefotaxime* (200 mg/kg/day in four divided doses) or parenteral *ceftriaxone* (100 mg/kg/day) can be used for six

weeks. If the organism is resistant to cefotaxime (MIC ≥ 2 μg/mL) and meningitis is present, consider the addition of *vancomycin* and *rifampin* to a third-generation cephalosporin [61,62].

Treatment of PIE Caused by Enterococci [52]

The treatment of PIE caused by enterococci can be challenging. These organisms are resistant to the cephalosporins (so this class of drugs cannot be used in enterococcal PIE), relatively resistant to penicillin and vancomycin, and impermeable to the aminoglycosides. All *E. faecium* are resistant to amikacin and tobramycin, while *E. faecalis* are often resistant to amikacin. Monotherapy only inhibits growth—combination therapy is required for bactericidal effects. Combinations may include penicillin G or vancomycin plus gentamicin. Penicillin or vancomycin damages the cell wall, giving gentamicin access to the cytoplasm where it then targets the ribosomes and kills the bacterial cell.

Treatment of PIE caused by penicillin and gentamicin susceptible enterococci when no prosthetic material is present consists of a minimum of four to six weeks of *penicillin G* at high doses (300,000 u/kg/day in four to six divided doses) plus *gentamicin* for the entire course (3 mg/kg/day in three divided doses—once-daily dosing is not recommended) [31]. If the child cannot tolerate penicillin, vancomycin can be used (dose 40 mg/kg/day in two or three divided doses), in combination with gentamicin. However, because of vancomycin's decreased activity against enterococci, six weeks' minimum therapy is required.

If prosthetic material is present with enterococcal PIE, the same antimicrobials should be used but the duration of treatment should be a minimum of six weeks.

Treatment becomes more challenging when enterococci are resistant to different antimicrobials. The duration of therapy is usually extended to a minimum of six weeks, and antimicrobial susceptibility testing is very important in guiding therapy. If the organism is penicillin-susceptible but gentamicin-resistant, then *streptomycin* can be used in combination with penicillin. The dose of streptomycin is 30–40 mg/kg/day in two equally divided doses. Enterococci that are resistant to penicillin, but sensitive to other antimicrobials can be treated with *vancomycin* and *gentamicin*. Few therapeutic options exist for multiply resistant enterococci and vancomycin-resistant enterococci (VRE). *Linezolid* and *quinupristin-dalfopristin* are used in adults, and have been effective in the treatment of VRE bactremias in children, but little data exists about the use of these drugs in PIE [63].

Treatment of PIE Caused by Gram-Negative Organisms [52]

Therapy for HACEK organisms consists of a four-week course of a third-generation cephalosporin such as parenteral *ceftriaxone* (100 mg/kg/day) alone, or *ampicillin* (300 mg/kg/day in four to six divided doses) plus *gentamicin*.

Therapy for other Gram-negative organisms must be guided by their sensitivity profile, and combination therapy for a minimum of six weeks is usually needed.

Treatment of PIE Caused by Fungi

For amphotericin-susceptible Candida, therapy consists of amphotericin B (1 mg/kg/day) and valve replacement. The amphotericin should be continued for a minimum of six weeks, and if the child cannot tolerate amphotericin B, a lipid formulation can be considered [31]. Because these fungal infections can relapse years later, lifelong suppressive therapy with an oral azole is prudent [64].

Treatment of Culture-Negative Endocarditis

In some cases of PIE, blood cultures are negative. Common reasons for this include previous antibiotic use, inadequate blood culture samples, or unusual organisms that require specific lab techniques for diagnosis. When an etiologic agent is not identified, therapy should be aimed at the most common organisms causing PIE (streptococci, staphylococci, and HACEK organisms). A third-generation cephalosporin combined with gentamicin offer good coverage, and if Staphylococci are suspected, addition of cloxacillin or vancomycin should be considered. If the child has animal exposures or contact with contaminated milk, he may be at risk for organisms such as *Bartonella* sp., *Coxiella burnetii*, *Pasteurella* sp., or *Brucella* sp. Therapy may need to be modified if these organisms are suspected [31].

The Role of Anticoagulants and Thrombolytics in PIE Therapy

Dissolution of the fibrin mesh in the vegetation may offer some theoretical advantages in the treatment of PIE. Indeed, when further vegetation formation is inhibited with anticoagulants, organisms are eradicated more rapidly. In vitro data examining the use of tissue plasminogen activator shows that it does not enhance the effect of antimicrobials. However, there have been case reports in extremely low birth weight infants with PIE who have been successfully treated with recombinant tissue plasminogen activator (rTPA) and prolonged antibiotics [13].

Surgery in PIE Therapy

Surgery is necessary for some children with PIE, because medical therapy alone will not be adequate. High-risk clinical situations include children with PIE caused by certain organisms (fungi or *S. aureus*), PIE on prosthetic material (valves and conduits), PIE and CHD (cyanotic CHD or systemic-to-pulmonary shunts), prolonged signs and symptoms of PIE (longer than three months), large vegetations involving the aortic or mitral valve (especially if valvular function is compromised), recurrent PIE, and a poor response to medical therapy alone [52].

Prevention

Vaccines

The pneumococcal conjugate vaccine has been shown to decrease the rates of invasive *S. pneumoniae* disease, including bacteremia. Since 80% of the isolates from children with *S. pneumoniae* PIE would have been covered by the vaccine, widespread use of the vaccine may lead to decreased pneumococcal PIE [65]. Presently, there are no vaccines to cover the other common etiologic agents of PIE.

Antibiotic Prophylaxis

Antibiotic prophylaxis is recommended by several national guidelines for the prevention of IE [4,66,67]. Unfortunately, compliance with prophylaxis is an issue, both for health care providers and parents. Only 50% of parents of children with CHD are aware of PIE, and only one-third are aware of procedures and situations where antibiotic prophylaxis is warranted [68]. Health care providers must approach the issue of antibiotic prophylaxis on an individual basis. They must take into account the degree to which the child's underlying heart defect creates a risk of PIE, the risk of bacteremia with the procedure and the potential adverse effects, and cost of the prophylactic agent to be used [69]. A child's heart defect can be classified as high, moderate, or low risk for PIE [70]. Children at high risk include those with prosthetic cardiac valves (including bioprosthetic and homograft valves), complex cyanotic congenital heart disease (single ventricle states, transposition of the great arteries, tetralogy of Fallot) and/or surgically constructed systemic pulmonary shunts. Children at moderate risk include those with CHD (including patent ductus arteriosus, ventricular septal defect, primum atrial septal defect, coarctation of the aorta, and bicuspid aortic valve), and mitral valve prolapse with regurgitation or thickened valves.

The risk of bacteremia varies with different procedures. Dental work and oral procedures put the child at risk for bactremias with viridans streptococci. Prophylaxis is recommended for procedures associated with significant bleeding from hard or soft tissues, periodontal surgery, scaling, and tooth cleaning. Other procedures involving the respiratory, gastrointestinal, and genitourinary tract also warrant antimicrobial prophylaxis. Although guidelines do not exist for body piercing, many physicians recommend prophylaxis for their patients with CHD prior to piercing [71,72]. It certainly can be considered a high-risk procedure, because it is invasive, many of the sites pierced cannot be adequately cleaned prior to the procedure, and it is often difficult to keep the areas clean after the procedure. Healing time is very prolonged (6 weeks for the tongue and 12 months for the navel) and the procedure may not be carried out by medically qualified personnel under appropriately clean conditions. Over the last decade, the number of adolescents with piercings has increased dramatically in North America. In 2002, a survey amongst college students in New York showed that 42% of men and 60% of women had body piercings [73]. The most frequent complication of these piercings are localized infections. Infective

endocarditis is a relatively rare complication of this procedure, but the incidence has been increasing. Generally, case reports of PIE related to piercings involve patients between ages 13 and 20 years, and most cases involved tongue piercing (followed by ear, nose, and nipple/navel).

Conclusion

This chapter described the epidemiology, etiology, diagnosis, treatment, and prevention of pediatric infective endocarditis—focusing on children with congenital heart defects. Surgical and medical advances have allowed children to overcome severe heart defects, extreme prematurity, and illnesses requiring indwelling lines. Unfortunately, many of the interventions that allow these children to survive put them at risk for PIE. In the future, the incidence of PIE will likely continue to increase and the etiologic agents will likely become more difficult to treat as antimicrobial resistance increases. Research is needed in the areas of primary prevention of PIE, improved diagnostic methods for PIE, and effective therapies for PIE caused by multi-drug-resistant pathogens. In the interim, health care providers need to be cognizant of PIE in children with CHD because early diagnosis and therapy can decrease morbidity and mortality.

Key Points

1. Many children who develop infective endocarditis often have a preexisting cardiac abnormality.
2. The diagnosis of pediatric infective endocarditis is supported by clinical findings, specifically fever, changing heart murmur, and/or splenomegaly. Embolic phenomena are observed less commonly, but do occur.
3. When the diagnosis of pediatric infective endocarditis is suspected, blood cultures should be drawn using adequate blood volumes. The volume of blood drawn for culture should be based on the child's total blood volume, which can be determined by the child's age and weight.
4. Other laboratory findings may support the diagnosis of pediatric infective endocarditis, including leukopenia or leukocytosis, anemia, elevated erythrocyte sedimentation rate, and/or hematuria.
5. In children, a transthoracic echocardiogram is usually adequate to reveal cardiac vegetations when infective endocarditis is suspected.

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13

Systemic Embolism in Endocarditis: Incidence, Risk Factors, Clinical Significance, and Treatment Strategies

Omid Salehian and Kwan-Leung Chan

Case Studies

Case 1

A 19-year-old man presented at the emergency department with sudden onset of right hemiplegia and dysphasia, after having had fever and malaise for several weeks. A computed tomogram showed left cerebral hemorrhagic infarct. He underwent emergency surgery to evacuate the intracranial hematoma. A transthoracic echocardiogram showed vegetations on a congenitally bicuspid aortic valve and moderate aortic regurgitation. A transesophageal echocardiogram showed a large vegetation on the aortic valve (Figure 13.1). Blood cultures subsequently grew S*taphylococcus aureus*.

Case 2

A 56-year old man with no history of valvular disease had fever, chills, and fatigue for one week and was diagnosed to have infective endocarditis (IE) after blood cultures grew S*taphylococcus aureus*. He responded well to treatment and did not develop significant valvular dysfunction. He was well for one year before the sudden occurrence of left-upper-quadrant abdominal pain due to splenic infarct confirmed by gallium scanning tomography. He did not have fever and blood cultures were negative. A transesophageal echocardiogram showed a 6-mm diverticulum on the posterior mitral leaflet which communicated with the left ventricle via a narrow neck and contained small echo densities within its cavity likely the source of the non-infective splenic infarct (Figure 13.2).

Embolic event in IE usually occurs early and can be the presenting symptom as illustrated by case 1. The differential diagnosis in patients suffering an embolic event should always include IE. Case 2 shows that embolic event can be a late complication as a result of unusual sequelae of IE, and transesophageal echocardiography plays an important role in the assessment of these patients.

Introduction

Embolism is a dreaded complication in patients with IE, as it is a major contributor to mortality and morbidity in these patients. Cerebral embolism accounts for the majority of systemic embolic events and most commonly affects the territory of the middle cerebral artery resulting in severe disability. Cerebral microemboli are also common but more difficult to recognize since the manifestations may be subtle or absent. Embolism to other organs is often clinically silent and confers less aggregate morbidity or mortality compared to cerebral embolism. The incidence of systemic embolism in IE is

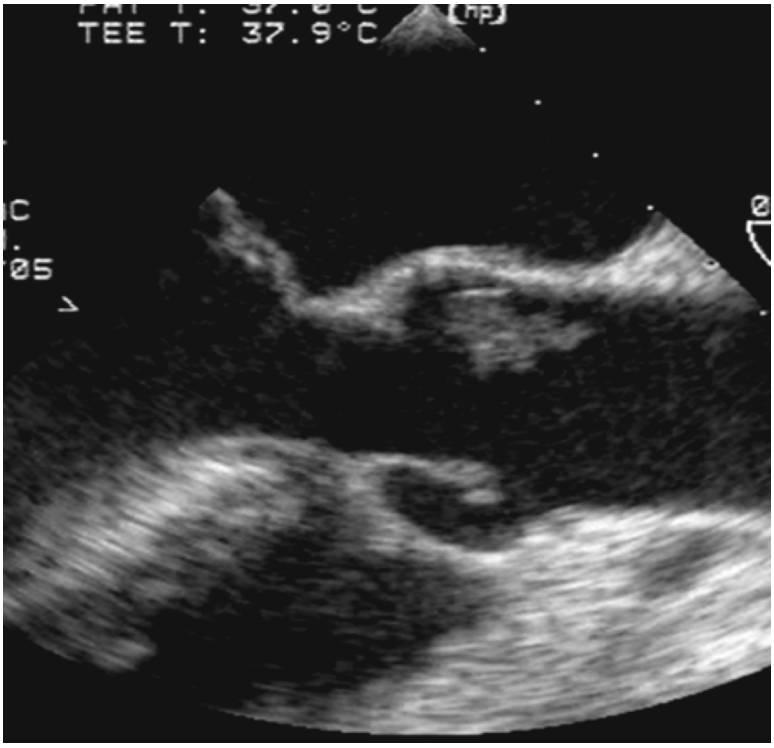

Figure 13.1. Transesophageal echocardiogram shows a large multilobulated vegetation on the aortic valve.

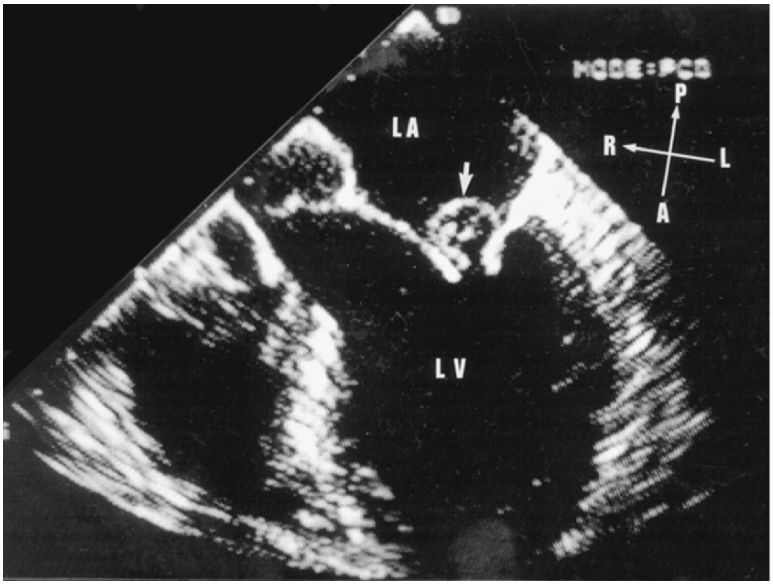

Figure 13.2. Transesophageal echocardiogram shows a large diverticulum on the posterior mitral leaflet. There were small echo dense masses within the diverticulum which communicated with the left ventricle (**LV**) Left atrium (**LA**). Reproduced with permission from Teskey et al.: Diverticulum of the mitral valve complicating bacterial endocarditis: Diagnosis by transesophageal echocardiography. *Am Heart J* 118:1064. Reprinted from *Am Heart J*, V. 118, Teskey et al., Diverticulum of the mitral valve complicating bacterial endocarditis: Diagnosis by transesophageal echocardiography, 1064, Copyright (1989), with permission from Elsevier.

about 30%, although various studies have reported a wide range from 10% to 50%. The high incidence has not decreased significantly over the years despite improvements in medical and surgical treatments.

Embolic events tend to occur early in the course of the disease, frequently present in patients before the diagnosis of endocarditis has been made. Indeed embolic events such as stroke may be the presenting symptom such

that endocarditis should always be in the differential diagnosis when dealing with a patient who has suffered an embolic event. After proper treatment has been initiated, the risk of embolism is lower with most events occurring within the first two weeks of treatment. This chapter reviews the risk factors and potential therapeutic treatments for systemic embolism in endocarditis.

Risk Factors Associated with Embolic Events

Infecting Organism

Many case series have showed that the risk of systemic embolization is related to the infecting organism. For example, a higher incidence of embolic events is well documented in patients with Staphylococcal endocarditis [1,2]. In one of the early studies Pruitt et al. reviewed the records of 218 cases of IE and reported a total of 86 (39%) neurologic complications [3]. There were 49 cases of *Staphylococcus aureus* IE, 53% of which had neurologic complication, of which 13 cases (26.5%) were due to cerebral emboli, representing the highest embolic risk among all the infecting organisms. In a more recent study by Heiro et al. among 218 cases of IE over a 17 year period (1980–96) in a teaching hospital in Finland, there were 55 patients (25%) with neurologic complications, 23 (42%) of which had cerebral embolic events documented on an imaging study or at autopsy [2]. They also reported a higher incidence of neurologic complications in patients with *S. aureus* IE, accounting for 29% of the 55 cases of neurologic complications. Neurologic complications in this study included embolic events (n = 13), transient ischemic attacks (n = 10), cerebral hemorrhage (n = 4), meningitis (n = 9), brain abscess (n = 1), toxic encephalopathy (n = 11), and headache (n = 7). It is not clear from this study if *S. aureus* was associated with a higher risk of embolic events alone.

In the study by Di Salvo et al., there were a total of 43 patients with Staphylococcal endocarditis, 23 of whom (53%) suffered an embolic event compared to 32% in patients with IE due to other organisms ($P = 0.023$) [1]. However on multivariate analysis, infection due to Staphylococci was no longer a significant predictor of embolic events, whereas vegetation size and mobility remained as independent predictors of embolic events. The recent study by Thuny et al. suggests that embolic events are more common in IE patients with *Streptococcus bovis* or *Staphylococcus aureus* infection [4].

Fungal endocarditis, although relatively rare, carries a high mortality and morbidity. The association between fungal IE and embolic events has been well established with often devastating complications due to the occlusion of major arteries by large emboli [5]. In an excellent review of the world literature covering a 30-year span (1965–95) of 270 cases of fungal endocarditis, Ellis and et al. reported that 45% of the patients had major arterial embolization, and cerebral emboli occurred in 47 patients, which was 17% of the total population [6]. A further 24 patients had non-focal neurologic findings. In cases of fungal endocarditis, most clinicians advocate early surgical intervention to avoid systemic embolic events and the current American College of Cardiology guidelines recommend that patients with fungal endocarditis be considered for surgical management (Class I indication) [7].

Valve location

A number of studies suggested a higher risk of systemic embolization in patients with mitral valve endocarditis. Pruitt et al. reported a higher rate of cerebral as well as other systemic embolization in patients with IE affecting the mitral valve in their study of 218 patients with IE [3]. There were 74 cases of aortic valve endocarditis 10 of which developed major cerebral emboli (13%), while 23 of 81 cases of mitral valve endocarditis (27%) had major cerebral emboli. These authors hypothesized that the higher rates of embolic events associated with mitral valve endocarditis might be due to the associated enlarged left atrium with lower flow leading to a more congenial environment for production of larger and more friable vegetations. Cabell et al. reported that in 145 patients with IE, mitral valve endocarditis was associated with a greater risk of stroke (32.5% vs 11.3%, $P = 0.003$) [8]. However, vegetations on the mitral valve were also significantly larger than those on the aortic valve. Hence, the higher incidence of embolic events with mitral valve endocarditis might be due to the larger and more

mobile vegetations, rather than inherent differences of specific valve location. It is also unclear whether this difference in vegetation size between mitral and aortic endocarditis may be related to a difference in the duration of infection. The recently published multicenter European study reported no difference in the rate of embolization between mitral and aortic valve endocarditis. Embolic events occurred in 70 of 191 patients (37%) with mitral valve endocarditis and 67 of 214 patients (31%) with aortic valve endocarditis [4].

The incidence of embolic events in patients with right-sided endocarditis is likely considerable but remains not well defined. Embolism has been estimated to be 70% in patients with isolated pulmonary valve endocarditis. Large vegetation size (>15 mm) appears to be associated with recurrent embolization and persistent infection despite antibiotic treatment [9].

Vegetation Morphology

Vegetation is not only the hallmark of endocarditis but also the substrate for embolic events which are usually the result of fragmentation and embolization of the vegetation. The embolic risk is low but not nonexistent in patients with no vegetations on echocardiography. There have been ongoing efforts to relate the embolic risk to various morphologic parameters of the vegetation such as size, extent, and mobility (Figure 13.2). This is best exemplified by the study of Sanfilippo et al., who studied 204 patients with endocarditis, 85 of whom had left-sided native valve endocarditis. Clinical cerebral embolic events were detected in 22% of patients with left-sided native valve endocarditis. They used a semi-quantitative grading system that incorporates multiple echocardiographic parameters (Table 13.1). They found that vegetation size, vegetation mobility, and valve location (mitral compared to aortic) were independent predictors of complications including death and heart failure. In addition, the vegetation score was also a predictor of adverse outcome.

Among the parameters, vegetation size is the parameter that has been most extensively studied. There is now a considerable body of evidence showing a positive association between vegetation size and risk of systemic embolism. One frequently cited study is by Mugge et al. who prospectively studied 105 patient with active IE [10]. There were a total of 33 (31%) major embolic events, 28 (27%) of which involved the central nervous system. When patients were stratified based on the size of the vegetation, the 47 patients with vegetations >10 mm had a higher incidence of embolic events (46.8%) than that of the 58 patients with small or no detectable vegetations (18.9%, $P < 0.05$). On multivariate analysis, only vegetation size larger than 10 mm predicted systemic embolization, particularly in patients with mitral valve endocarditis. There was, however, considerable overlap in vegetation size between patients with and without embolic events (Figure 13.3), so that in an individual patient the clinical usefulness of vegetation size is limited.

Di Salvo et al. also showed a significant relationship between vegetation size and embolic events in a retrospective study of 178 patients with IE assessed by transesophageal echocardiography (TEE) [1]. Embolic events were more frequent in patients with very large vegetations, with 70% of the embolic events occurring in 43 patients with vegetation length >15 mm compared to 27% of embolic events in 135 patients with vegetation size ≤15 mm. There was also a significant relationship between vegetation mobility and embolic events in this population. Of the 73 patients with moderate and severely mobile vegetations 45 (62%) had embolic events compared to 21 events (20%) seen in the 105 patients with low mobility scores ($P < 0.001$).

Table 13.1. Vegetation Scoring System from Sanfilippo et al. [2]

Score	1	2	3	4
Size (mm)	<6	7–10	11–15	>15
Mobility	Fixed	Fixed base with a mobile free edge	Pedunculated	Prolapsing
Extent	Single vegetation	Multiple vegetations limited to a single valve leaflet	Involvement of multiple valve leaflets	Vegetations that extend into extravalvular structures

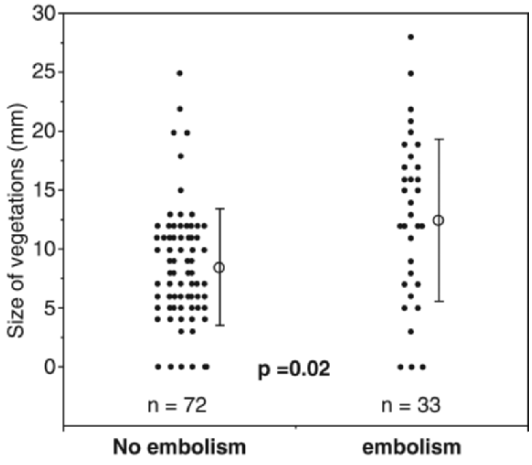

Figure 13.3. This plot shows that there was a large overlap of vegetation size between patients with and without embolic events, even though there was a statistical difference in vegetation size between the two groups. Reprinted from *J Am Coll Cardiol*, V. 14, Mugge A. et al., Echocardiography in infective endocarditis: Reassessment of prognostic implications of vegetation size determined by the transthoracic and the transesophageal approach, 631, Copyright (1989), with permission from American College of Cardiology Foundation.

Of the 30 patients with both severely mobile and large vegetation (>15 mm), 83% had embolic events. On multivariate analysis, vegetation size, and mobility were the only predictors of embolic events.

In a retrospective study of 145 patients with aortic or mitral valve endocarditis, Cabell et al. showed vegetation length >7 mm to be an independent predictor of stroke (OR 1.21; 95% CI 1.02–1.44, $P = 0.03$) [8]. Vegetation size was also an independent predictor of mortality at both 30 days and 1year. In the study by Deprele et al. data from 80 patients with endocarditis diagnosed using TEE were analyzed [11]. On univariate analysis, vegetation mobility and vegetation size >10 mm were risk factors for systemic embolization but on multivariate analysis, only vegetation mobility remained an independent risk factor for embolization. In the study by Steckelberg et al., transthoracic echocardiograms were performed prior to initiation of antibiotics in 207 patients with left-sided IE [12]. In their study only 27 patients (13%) had an embolic event from the time of initiation of effective antibiotic therapy to completion of therapy, death, cardiac surgery, or hospital discharge. They did not find a relationship between the size of the vegetation and risk of embolic events. There was no significant difference in the risk of embolic events among patients with vegetations >10 mm compared to those with smaller or absent vegetations. A recent prospective study on 384 patients with endocarditis reported that vegetation size (>10 mm) and severe mobility were predictors of new embolic events, even after adjustment for etiologic agent such as *Staphylococcus aureus*. Vegetation size (>15 mm) was also a predictor of one-year mortality.

Tischler and Vaitkus published a meta-analysis of ten studies published in English of embolic events in left-sided IE patients to assess if vegetations ≥10 mm increased the risk of complications [10,12,14,15-22]. The pooled odds ratios for systemic embolization (in ten studies with total of 738 patients) and death (in six studies with total of 476 patients) in the presence of vegetations ≥10 mm were 2.80 (95%CI 1.95–4.02, $P < 0.01$) and 1.55 (95% CI 0.92-2.60, $P = 0.1$), respectively. Seven of the studies in this meta-analysis used transthoracic echocardiography alone for detection of vegetations, but the pooled odds ratio for systemic embolization from these seven studies, 2.85 (95% CI 1.86–4.38), was similar to the pooled odds ratio from the three studies, 2.66 (95% CI 1.36–5.24) that used both transthoracic and transesophageal echocardiography [10,13,15–19,20, 21,22]. Since the publication of this meta-analysis in 1997, there have been additional studies involving patients with endocarditis in which vegetation size and embolic events were recorded [1,8,11,23–26]. We performed a meta-analysis including a total of 15 studies: 10 from the original meta-analysis by Tischler and Vaitkus, one study by Wann and colleagues not included by Tischler and Vaitkus, and four recent studies [14,27]. Our analysis of 1,168 patients in 15 studies with 371 systemic embolic events reveals a pooled odds ratio for systemic embolization with vegetations ≥10 mm of 3.09 (95%CI 2.35–4.05, $P < 0.001$) (Figure 13.4).

Echocardiographic parameters of vegetations convey useful prognostic information in patients with IE, but clinical decision as to whether to proceed with surgery should not be based on echocardiographic findings alone because considerable differences are present among the studies, no standardized method of measuring vegetation size is generally accepted and there is a large overlap in vegetation size between patients with and without embolic events.

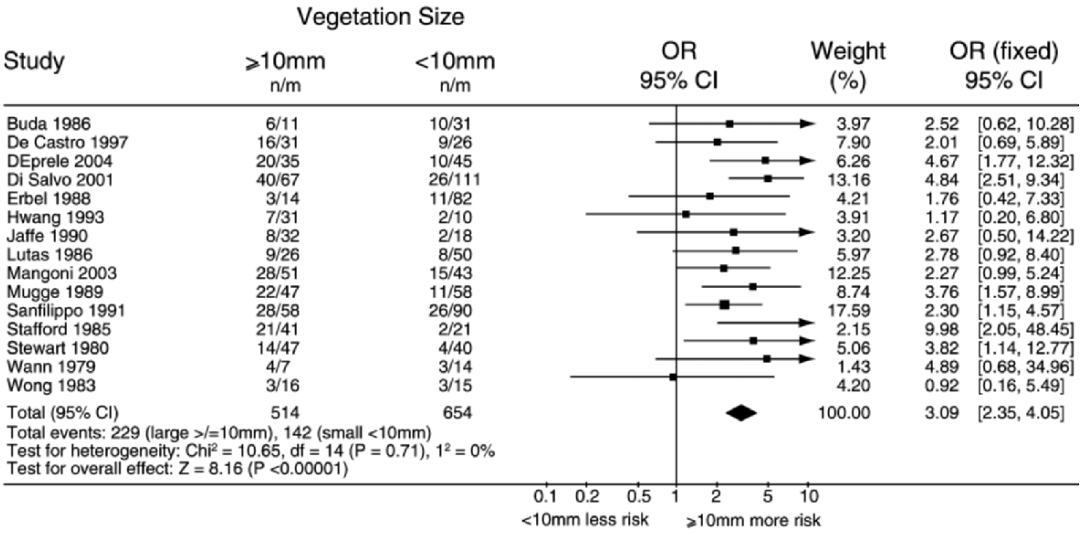

Figure 13.4. Pooled analysis of 15 studies examining the effect of vegetation size on the risk of systemic embolism. Odds ratios (**OR**) and 95% of confidence intervals (**CI**) are shown.

Age

Older patients with IE have a higher mortality and morbidity than younger patients. Overall most studies showed that the rates of embolic events are similar between the older and the younger patients, although cerebral embolization is a much stronger predictor of mortality in older patients [28].

Abnormalities of Coagulation and Fibrinolysis

Patients with IE have abnormalities in the coagulation cascade. Systemic bacterial infections in the absence of any cardiac involvement is an independent risk factor for embolic events, which may be related to inflammation-induced procoagulant changes in the endothelial lining, and increased levels of antiphospholipid antibodies [29–32].

Kupferwasser et al. showed that IE patients with embolic events had significantly higher levels of antiphospholipid antibodies [33]. They reported that patients with elevated antiphospholipid antibodies (14.3% of the population) had a higher risk of embolic events compared to those with undetectable levels (61.5% vs 23.1%, $P = 0.008$). Patients with elevated antiphospholipid antibody levels and embolic events also had higher levels of thrombin and plasminogen activator inhibitor, as well as reduced levels of activated protein C. It is biologically plausible that this intravascular milieu of increased thrombin generation combined with impaired fibrinolysis would lead to an increased risk of thromboembolism.

Recently research has focused on the potential role for soluble adhesion molecules in the pathophysiology of IE [34,35]. Soluble forms of P and E-selectins have been shown to be secreted from activated platelets and endothelial cells and appear to be early mediators of endothelial dysfunction in the setting of inflammatory response. Korkmaz et al. reported elevated levels of both P and E-selectins in IE patients with embolic events [36]. This study included 76 patients with IE, 13 of whom had an embolic event (17.1%). Patients with embolic events had higher P-selectin levels than patients without events and normal controls. E-selectin levels were similarly elevated in patients with IE and embolic events. This increase in E-selectin may reflect the endothelial dysfunction secondary to injury, with induction of a pro-adhesive and pro-thrombotic surface leading to thrombus formation, and the higher P-selectin levels are associated with enhanced platelet activation, which has a direct impact on thrombin generation.

These data support the notion that IE patients with embolic events have a sustained hypercoaguable state which likely contributes to the development of embolic events as a result of increased systemic coagulation activation, enhanced platelet activity, and impaired fibrinolysis. Despite the above-mentioned abnormalities of coagulation and fibrinolysis which promote thrombus development, patients with IE are also at significant risk for bleeding secondary to consumptive coagulopathy as well as a decrease in production of coagulation factors by the liver [37]. The co-existence of a hypercoagulable state and increased propensity of bleeding is a formidable clinical challenge in the management of patients with IE.

Strategies To Decrease Embolic Risk

Antibiotic Therapy

Effective antibiotic therapy reduces but does not abolish the risk of events. A reduction in vegetation size is associated with a lower rate of embolic complications. Rohmann et al. prospectively studied 183 patients with IE and valvular vegetations detected by TEE, who were treated with appropriate antibiotic regimens [38]. A total of 16.4% of these patients suffered an embolic event during the follow-up period of 76 weeks. A significant reduction in vegetation size during antibiotic treatment was associated with a reduction in embolic events and mortality. A reduction in vegetation size $> 49\%$ was associated with no risk of embolic events ($P < 0.05$). In patients with a decrease in vegetation size $> 37\%$, there was no mortality. Thus antibiotic therapy remains the most effective treatment to prevent embolic events in patients with IE.

Fibrinolytic Therapy

Since vegetations contain a significant amount of thrombin and fibrin, the use of fibrinolytic therapy might be helpful in breaking down vegetations leading to a decrease in embolic events. Another potential benefit of fibrinolytic therapy is a synergistic effect with antibiotics. Exposing the bacterial surfaces normally buried in the fibrin-platelet rich matrix of the vegetation to antibiotics may enhance the effectiveness of antibiotics [39,40]. Animal studies have shown a substantial reduction in vegetation size with a high proportion of cure and less damage to the valves in animals treated with fibrinolytic therapy but this reduction in the vegetation size occurs at a cost of more and larger cerebral infarcts likely as a result of embolization of the vegetation fragments [41].

There are reports of successful treatment using fibrinolytic agents in children with IE and large vegetations [42,43]. Levitas et al. prospectively examined the effect of treatment with tissue plasminogen activator in seven infants with enlarging vegetations despite intensive medical treatment, including antibiotics [44]. In all patients, fever resolved within two to three days, blood cultures became sterile thereafter, and vegetations diminished in size and were no longer seen after four days. No embolic or hemorrhagic complications in this population were reported.

There are few case reports of fibrinolytic therapy in adults patients with IE with mixed results [45,46]. The use is mostly in patients with coronary artery embolization. There may be a limited role for fibrinolysis in very selected cases of IE such as those with prohibitive surgical risks and enlarging vegetations despite appropriate antibiotic therapy, because intracranial hemorrhage and death are real concerns. This therapy should be undertaken only after careful consideration has excluded the possibility of surgical therapy.

Anticoagulant Therapy

Given the previously described abnormalities in soluble adhesion molecules and other humoral factors leading to a hypercoaguable state, it would be logical to suspect that anticoagulant therapy in patients with IE may decrease the risk of embolic events. Warfarin treatment is postulated to decrease fibrin generation and its adhesion to the valve surfaces, which may then decrease the bacterial colonies adherent to the valve surface. Using a rabbit model of IE with *Staphylococcus epidermidis,* Thörig and coworkers showed that warfarin treated rabbits needed a larger bacterial inoculum to induce infection [47]. Despite this reduction in infectivity there was a significant reduction in survival in the warfarin-treated rabbits mainly as a result of pulmonary hemorrhage. Other studies have

also shown this increase in mortality associated with warfarin treatment in animal models of IE [48,49].

There have been no controlled randomized studies on the use of anticoagulants to prevent embolism in IE. An early study showed that the use of heparin or dicumarol did not reduce embolism but was associated with a high rate of cerebral hemorrhage [50]. Similar findings have been reported in the review by Pruitt et al., which showed that five of seven patients treated with anticoagulants developed embolic events, of whom three had hemorrhagic cerebral infarction, while only 10 of 211 patients not receiving anticoagulants had hemorrhagic cerebral infarction.

Patients with prosthetic valve endocarditis are at a high embolic risk despite continuation of anticoagulation treatment, and the risk is higher in the absence of adequate anticoagulation. Wilson et al. retrospectively studied 52 patients with prosthetic valve (Starr–Edwards) endocarditis [51]. Central nervous system complications occurred in 10 of 14 (71%) patients without adequate anticoagulation therapy and 3 of 38 (8%) patients with adequate anticoagulation. Mortality was 57% among the patients without adequate anticoagulation and 47% among those with adequate anticoagulation. Autopsy findings showed that central nervous system complications were the primary cause of death in 63% of the cases without adequate anticoagulation. In the study of Paschalis et al. patients already anticoagulated for prosthetic valves had the same embolic risk as those on no anticoagulation [52]. Davenport and Hart examined 62 episodes of prosthetic valve IE in 61 patients and found that the risk of embolic events was lower in patients with bioprosthetic valves than those with mechanical valves who were on anticoagulation [53]. The deleterious effects of anticoagulation should be considered in patients with prosthetic valve endocarditis, as these patients are at high risk for intracranial hemorrhage, which can result in death.

Despite the hypercoaguable state in patients with IE, anticoagulation does not provide significant protection against systemic embolization, and is potentially harmful. However, in patients who have other indications for anticoagulation, such as mechanical valves, benefits of anticoagulation likely outweigh the risks of excessive bleeding, but these patients continue to have a high embolic risk despite adequate anticoagulation. Current guidelines by the American College of Chest Physicians on antithrombotic and thrombolytic therapy recommend continuation of vitamin K antagonists (Warfarin) in patients with mechanical valve endocarditis in the absence of other contraindications [54].

Aspirin and Other Antiplatelet Agents

Damage to the valvular endothelial surfaces has been shown to promote adhesion of platelets to the collagen rich subendothelial surface [55]. Platelet activation and continued fibrin deposition lead to larger and more friable vegetations, which have a higher risk for embolization. Hence there is a biological basis that platelet inhibitors such as aspirin could enhance vegetation resolution and reduce embolic events. Among the antiplatelet agents, aspirin has received the most attention and has been shown to be beneficial in animal models [56,57]. The incidence of stroke and change in echocardiographic vegetation area were prospectively studied in a small study involving nine IE patients randomized to receive either low-dose aspirin (75 mg per day) in four patients or no aspirin in five patients [58]. During a follow-up of 343 days, two cerebral embolic events and one case of presumed embolic myocardial infarction occurred in the control group, compared with no events in the aspirin treated patients. There was a decrease in the mean vegetation area of 0.24 cm^2 in the aspirin treated group, compared to an increase area of 0.35 cm^2 in controls. In this study aspirin treatment was not associated with an increase in bleeding complications. This study, although small, provided the first human evidence of potential benefit of aspirin therapy in patients with IE.

This hypothesis was further tested in a larger randomized double-blind, placebo-controlled trial [23]. In this study 115 patients were randomized to receive four weeks of either 325 mg per day of aspirin (60 patients) or placebo (55 patients). Both native valve and prosthetic valve endocarditis were included. The overall embolic event rate was 29% when the randomized and non-randomized patients were pooled. There were 17 patients (28.3%) with embolic events in the aspirin group and 11 patients (20%) in the placebo group. There was no significant reduction in embolic events with aspirin treatment but there was a trend towards a higher incidence

of major and minor bleeding in the aspirin-treated group. One of the limitations of this study was that only 31% of the target sample size was recruited and hence the trial may be underpowered to detect a small beneficial effect of aspirin therapy on the risk of embolic events. Another potential limitation is the low dose of aspirin used in the study. However, at the present time this trial is the largest randomized controlled study evaluating a therapeutic strategy to reduce systemic embolization in IE. Some investigators believe that there may still be a role for aspirin therapy in patients with IE due to *S. aureus*, as there are platelet binding sites for staphylococcal proteins providing a mechanism for interruption of bacterial cell adhesion to sites of vascular injury leading to thrombosis [34,59].

There is evidence from experimental IE in animals models to support other antiplatelet agents such as thienopyridines alone or in combination with aspirin but there are no reported studies of thienopyridine therapy in patients with IE [60–62]. The potential benefits of antiplatelet agents must be balanced with the real risk of increased bleeding in patients already at an elevated risk for bleeding.

Surgical Therapy

There are a number of studies that suggest combined medical and surgical therapy for IE is superior to medical therapy alone and can decrease morbidity and mortality. Currently, the strongest indications for surgical therapy are congestive heart failure and uncontrolled infection despite optimal antimicrobial therapy. It has been suggested that surgical intervention is also indicated if there have been two or more embolic events, or one episode of systemic embolization with a large residual vegetation.

There are significant sequelae of central nervous system embolization not the least of which is the risks to these patients during cardiovascular surgery. In a retrospective study of 181 IE patients with neurologic complications who underwent surgery, higher rates of postoperative morbidity and mortality were present in those patients operated within a short time span from their neurologic event. When the surgical intervention was performed within one week after the neurological event, the risks of mortality and worsening neurologic deficit were 31.3% and 43.8%, respectively, compared to risks of 7.0% and 2.3% respectively when the operation was more than four weeks after the neurologic event.

Based on the available data one approach to left-sided native valve IE in patients who have suffered a cerebral embolic or hemorrhagic event is to delay the cardiac surgery, a minimum of two weeks after an embolic event and a minimum of four weeks after a cerebral hemorrhagic event [63–65].

When to perform surgery to prevent systemic embolism remains a difficult clinical decision. Although echocardiographic parameters of vegetations provide useful prognostic information, clinical decision-making should not be based on these findings alone but should include careful analysis of all the clinical variables. Early diagnosis with prompt initiation of appropriate antibiotics remains the most effective strategy in the prevention of embolic events. The current American College of Cardiology (ACC) guidelines recommend surgical therapy in native valve endocarditis in patients with recurrent emboli after appropriate antibiotic therapy (class IIa), and in those patients with mobile vegetations >10 mm in length (class IIb) [7]. In patients with prosthetic valve IE ACC guidelines recommend surgical intervention in patients with recurrent peripheral emboli despite therapy (class IIa), and in those patients with vegetations of any size on or near the prosthesis (class IIb).

Conclusion

Despite advances in medical and surgical therapy, infective endocarditis continues to have a high morbidity and mortality. The rate of systemic embolization has remained relatively constant over the past two or three decades. Risk factors such as vegetation size and mobility allow us to identify patients at a higher risk for embolic complications. However, no single therapy with the exception of prompt and appropriate antibiotic treatment has shown effectiveness in reducing systemic embolization. Treatments to enhance vegetation resolution including fibrinolytics, anticoagulants and antiplatelet agents have shown no benefits but are associated with an increased risk of bleeding. Current recommendations reflect this lack of effective and safe

therapy in these high-risk patients. Decision to proceed with cardiac surgery to reduce the embolic risk needs to consider all the clinical variables and should not be based solely on the echocardiographic findings.

Key Points

1. Systemic embolism is a common complication occurring in about 30% of patients with IE.
2. Embolic events occur early in the course of the disease.
3. Morphologic parameters of vegetation particularly size appear to be a predictor of the embolic risk, but they have limited clinical usefulness in individual patients.
4. Fibrinolytics, anticoagulants, and antiplatelet agents have not been shown to reduce the embolic risk, but they likely enhance the risk of bleeding.
5. Early diagnosis with prompt initiation of antibiotic therapy remains the most effective means to reduce the embolic risk.

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14

Neurological Complications of Endocarditis: Pathophysiologic Mechanisms and Management Issues

Christopher R. Skinner

Case Study

A 45-year-old man presented to the emergency department with acute right-sided weakness and aphasia. Computed tomography (CT) showed an evolving left middle cerebral artery infarct with some hemorrhagic transformation. Thrombolytic treatment was considered but withheld due to the presence of partial hemorrhage on CT.

According to his family he had been in excellent health until the last three to six months, when he developed periods of confusion, intermittent fever, and weight loss. His family physician had performed some basic investigations and found no specific cause for his symptoms.

Once in hospital, he developed swinging fever and tachypnea. He showed decreased air entry in his lungs and tachycardia without a heart murmur. His electrocardiogram was normal. Chest x-ray showed no pneumonia. Blood cultures were drawn and he was started on broad-spectrum antibiotics.

Three days after admission he suddenly became comatose and showed bilateral upper and lower limb weakness. Magnetic resonance imaging (MRI) showed infarction of the mid and left pons and midbrain with patchy areas of increased signal in the distribution of the basilar and posterior cerebral arteries. Echocardiography revealed friable vegetations on the aortic valve consistent with infectious endocarditis (IE). *Staphyloccocus aureus* was cultured and the antibiotics were appropriately adjusted. After 48 hours in the intensive care unit, he did not regain consciousness and had lost all of his brainstem reflexes including a positive apnea test. After consultation with the family, ventilatory support was withdrawn and he died.

This case illustrates the insidious nature of the development of IE in a previously healthy individual. The occurrence of an acute neurological event in the context of a three-month history of nonspecific constitutional symptoms should alert the clinician to the possibility of IE. A delay in the diagnosis and treatment must be avoided to improve the outcome of these patients.

Introduction

The occurrence of a neurological event due to IE can be sudden and catastrophic. It is frequently perceived as an unfortunate but generally unavoidable event. However when one looks at the sequence of the pathophysiologic process of the disease, often there are telltale systemic and neurological signs and symptoms prior to the main event, which could be essential in making an early diagnosis. Early diagnosis may lead to measures, which could be useful to mitigate the catastrophic event.

This chapter is an attempt to document the sequence of the pathophysiological processes in which the nervous system gets progressively involved in the disease process of IE. Infective

endocarditis will be the primary focus, but a brief discussion of marantic endocarditis will be included.

Full appreciation of the different neurological events in IE must take into consideration the pathophysiological processes, the etiological agent and the neurological localization over the dimension of time from preclinical defining event, to the defining event and to the evolutional changes following the defining clinical event. This chapter provides a neurological diagnostic framework for the practicing clinician based on the current literature.

Historical Perspective

The clinical triad of fever, heart murmur and stroke were recognized by Osler and others before him to indicate the presence of IE [1,2]. However, present-day clinicians strive to recognize the endocarditis complex before permanent damage to heart, brain, and other target organs has occurred. Despite the use of modern imaging, there remains a significant delay in diagnosis and treatment in many IE patients.

The major historical milestones in the diagnosis and treatment of IE have been the development of antibiotics; cardiac imaging, including angiography and echocardiography; and the various options of surgical treatment from valve replacement or repair to extensive reconstruction of aortic or mitral annulus.

From a neurological standpoint, advancements in imaging, including CT, MRI, and digital cerebral angiography, have helped enormously in terms of localization of lesions and treatment planning. These are usually employed after the defining event has occurred. More attention has to be paid to the use of these tools earlier in the course of the disease before the defining event to provide information which may mitigate the event. Treatment from a neurological standpoint may include in selected cases the use of thrombolytics to hasten resolution of a septic embolus and the use of valve surgery to prevent an impending embolic stroke.

The use of neurological interventional techniques to deal with septic aneurysms has lead to the development of aneurysm hardware for coiling and clipping mycotic aneurysms. There are many case reports on treatment of these aneurysms using neuroradiological interventional techniques. However, there are no clinical trials to assist the clinical determination of the best treatment of these aneurysm from a risk benefit standpoint.

Epidemiology

The occurrence of neurological complications in IE is 20–40% [3]. Neurological deficits have been reported in up to 40% of patients with endocarditis of the left side of the heart [4]. Once neurological damage has occurred a mortality rate of 50% has been reported versus 21% in patients with IE without neurological complications [5]. Therefore prevention of neurological complications must become a priority.

Neurological complications are either the chief complaint or one of the major presenting symptoms in about a quarter of patients with IE [5]. The presence of congestive heart failure and non-cardiac shock with neurological damage increases the mortality and morbidity significantly [6,7].

Pathophysiological Mechanisms

The first matter to consider is the sequence of the pathophysiological processes by which IE affects the nervous system either directly or indirectly (Table 14.1). The life history of IE starts with the development of damage to the endocardium in particular the heart valve with the initiation of an inflammatory process on the surface of a valve, which then leads to progressive destruction of the endocardial, then myocardial and conducting system tissue.

In the early stages, the inflammatory process does not usually lead to the formation and liberation of thromboembolic material but rather initiates more nonspecific inflammatory responses, which affect the nervous system indirectly. In the preclinical-event stage, there is release of inflammatory cytokines such as Il-8 and tumor necrosis factor as well as other humoral responses. These humoral factors can affect the brain often causing nonspecific encephalopathic responses such as fatigue, anorexia and malaise. The detection of the presence of these cytokines could be used as markers

Table 14.1. Symptoms, Signs, and Pathological Changes in Different Stages of Neurological Involvement in Infective Endocarditis

Stage	Symptom	Signs	Echo	Neuroradiology	Electrophysiology	CNS Pathology
Pre-event early	Fever, malaise, weight loss, encephalopathy	Inattention, personality change	Normal, pre-existing valvular disease or prosthetic valve, VSD, ASD, PFO	Normal	Normal, possible intermittent slowing corticothalamic synchronization disturbances	Vasculitis, cytokine effects, increased inflammatory cells
Pre-event late	Increased systemic symptoms	Increased deterioration of mental status, seizures	Valve thickening and micro thrombus formation	Areas of increased signal on T2 and FLAIR at cortex/white matter junction	EEG slowing, sleep fragmentation	Vascular thinning, Immunglobulin and complement deposition on blood vessels
Initial event	Focal numbness weakness or visual loss, sudden headache	Loss of visual field, weakness, sensory loss	Progressive valve destruction, friable thrombus on valve	Areas of increased signal in brain parenchyma or subarachnoid space	Focal slowing or periodic lateralized epileptiform discharges	Ischemic and or hemorrhagic infarction, pyogenic destruction of medium sized distal vessels, mycotic aneurysms
Secondary event	Severe headache, numbness, weakness, loss of consciousness	Coma, loss of brain stem reflexes, brain death	Progressive valve destruction, friable thrombus on valve	Signs of midline shift and uncal/tonsillar hermiation	Loss of background rhythm, burst suppression, electrocerebral silence	Multiple areas of ischemic necrosis with and without hemorrhage with uncal/tonsillar hermiation
Late effects	Loss of functional status, inability to ADLs or work	Permanent deficits of mental status vision, sensation, motor	Sequellae of infected valve or replacement prosthesis	Encephalomalacia in areas damaged by hemorrhage or infarct, hydrocephalus due SAH	Focal slowing, focal seizure focus in areas of cortical damage, sleep fragmentation decreased SWS, PLMs	Areas of gliosis and hemosiderin deposition; encephalomalacia, axonal disruption, permanent vascular damage

ADL = activity of daily living; ASD = atrial septal defect; FLAIR = fluid attenuated inversion recovery; PFO = patent foramen ovale; PLM = periodic limb movement; SAH = subarachnoid hemorrhage; SWS = slow wave sleep; VSD = ventricular septal defect.

of disease activity. The symptoms are difficult to explain in terms of precise localization, but these humoral factors are present in 30–50% of patients subsequently developing clinical neurological events. The cytokines probably affect those areas of brain, which are sensors of systemic disturbance such as the area postrema, pituitary, and pineal glands.

The second preclinical pathophysiological process, which results from the initial inflammatory process, is the development of diffuse vascular inflammatory reaction or vasculitis. This is usually a diffuse, small-vessel process, which affect the brain diffusely, leading to nonfocal signs and symptoms of cognitive decline, such as inattention, character changes, somnolence, or irritability. At this stage endocarditis can masquerade as vasculitis and vice versa.[8]. Rarely do clinicians when confronted with this nonspecific clinical picture look to the heart for the underlying cause.

The diagnostic investigations, which may be of help at this stage, include a detailed history and physical examination with particular attention to the presence of a new heart murmur, splenomegaly and the presence of peripheral embolic events such as Roth spots and Janeway lesions. Laboratory investigations should include serum for immune complexes, protein electrophoresis, and complement studies. MRI of the brain with gadolinium may demonstrate increased contrast in the small vessels of the cortex-white matter junction, which is quite distinctive from other inflammatory patterns. EEG may show nonspecific changes of bilateral slowing. Sleep disruption in this stage has not been well studied but fragmentation of sleep architecture and lack of slow wave sleep might be expected.

The so-called immune complex vasculitis, which can predate or accompany endocarditis, involves small blood vessels in the brain and

elsewhere often leading to other complications such as glomerulonephritis and renal dysfunction. Recognition and prompt antibiotic treatment at this stage can prevent serious neurologic deficits.

The next stage of evolution at the endocardial level consists of progressive destruction of endocardium to the point of producing thromboembolic material which then affects the nervous system directly. The size and infectivity of this material depends on the duration of infection, the degree of destruction and the organism.

From a neurological standpoint the context and clinical history of the embolic ictus is vitally important. Carotid or simple cardiac emboli usually arise abruptly without any encephalopathic prodrome. If altered mental status precedes a cerebral thromboembolic event for more than minutes, there must be a strong suspicion of systemic disease such as IE with propensity for embolic events. The presence of various risk factors for IE listed in Table 14.2 should heighten the clinical suspicion for IE.

With respect to the brain, the site of embolization from a central source embolus such as a heart valve can involve any of the four arteries, which supply the circle of Willis. As a rule, the site of embolization for larger emboli tends to reflect sites of higher flow such as the middle cerebral artery territory, which is the language-dominant hemisphere.

The spinal cord and peripheral nerves remain relatively immune to peripheral embolization from the heart. Occasionally emboli to muscle can occur and can present a sudden onset of an unusually severe localized pain in an isolated muscle of any limb or the back with unexplained high levels of creatinine kinase of skeletal muscle origin.

The issue of the timing of the emboli causing neurological deficits is an important one in that it may determine the decision with respect to surgical management of the valvular disease.

Table 14.2. Clinical Risk Factors for the Development of Infective Endocarditis

Presence of a prosthetic valve
Intravenous drug use
Body piercing, especially tongue
Congenital heart disease especially right to left shunts
Previous intra-cardiac surgery
Presence of intracardiac catheters, shunts, tubing, or other prostheses

Clinical observation suggests that in some patients with IE there is a bimodal distribution to the development of neurological deficit. The inital embolic event may be small and causes either a reversible event or minor deficit. Then when things seem to have improved a larger more devastating embolus occurs three to four days later. This phenomenon may be a reflection of the relationship between the size of the valvular vegetation and the risk of embolization. Large vegetations of >10 mm have been shown to have a higher risk of embolization than smaller vegetations, implying that the longer the vegetation is allowed to grow on the valve, the more likely it is to embolize when it gets to a larger size and to cause more damage [9].

Recent MRI studies have shown that most transient focal neurological deficits lasting more than 30 minutes are in fact small emboli, which cause changes on diffusion-weighted MRI studies. Therefore, the occurrence of any focal neurological deficit longer than 30 minutes in a patient with endocarditis should trigger vigorous search for the source and consideration of the merit of preemptive valve surgery with the usual precautions to rule out a hemorrhage. This is discussed in greater detail in Chapter 13.

For large and small emboli, the pathophysiological mechanisms include ischemia due to blockage of vessels, hemorrhage into an area of ischemia, and infection of the area nested by the embolus. Ischemia from large emboli tends to be cortical and lobar conforming the flow pattern of the supplying artery. For instance, a large speech-dominant hemisphere middle cerebral artery infarct will lead to the constellation of aphasia and contralateral hemiplegia of the face, arm, and to a lesser extent the leg. For small vessels, the pattern is much more random, with cortical, subcortical, and brainstem infarcts occurring concurrently. The neurological signs and symptoms in this case may be very discordant suggesting multiple localizations.

Cardiac emboli, which travel through the vertebrobasilar system, tend to fragment on their journey up the basilar artery seeding the brain stem in several places and then terminate in the posterior cerebral arteries, the so-called "top of the basilar syndrome" (Figure 14.1).

Often the prodrome is an acute unexplained cranial neuropathy sometimes as simple as a Bell's palsy. On closer examination often the anatomical neighbors of the facial nerve, cranial nerves 5, 6, or 8 are involved on the same side

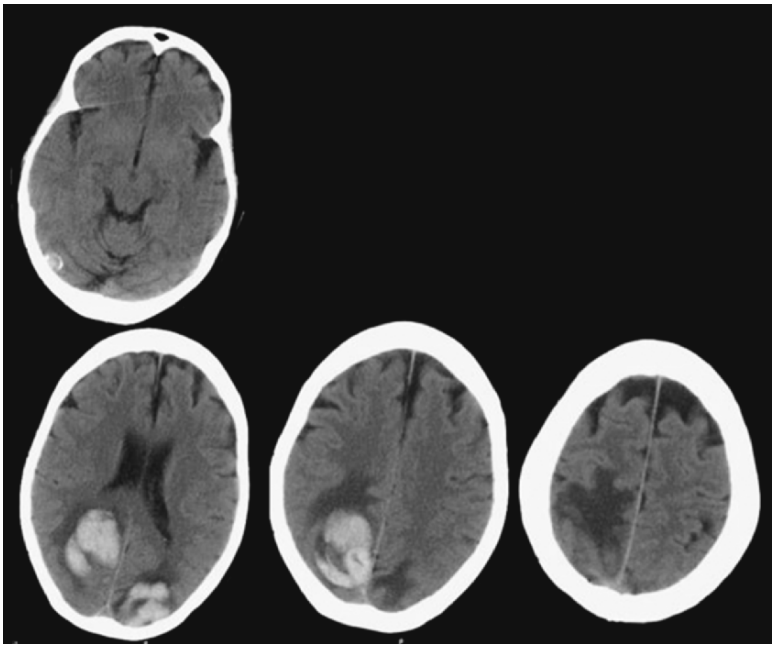

Figure 14.1. This figure shows bilateral hemorrhagic infarction from an embolus traveling up the vertebrobasilar system and fragmenting into a left- and right-sided occipital thromboemboli.

indicating more widespread pontine damage. This is an important clue to trigger the search for a central source of emboli before a larger embolus is released.

Following the seeding of the nervous system with septic emboli the next phase of damage may involve vascular damage due to the infected emboli invading the blood vessels directly. The development of septic or mycotic aneurysms in the brain should be considered a late complication in which there has been adequate time for the blood vessels, which are relatively resistant to infectious invasion to be affected and to develop weakening of the collagen support structure (Figures 14.2 and 14.3). The frequency of intracranial mycotic aneurysms is 2–10% in patients with IE [10]. Mycotic aneurysm frequently occurs in patients with IE and no clinical evidence of embolic stroke, such that stroke due to a ruptured mycotic aneurysm can be the defining neurological event.

There is no literature to suggest that individuals with qualitative abnormalities of collagen such as Ehlers Danlos syndrome type 4 or polycystic kidney disease or fibromuscular dysplasia have a higher risk of mycotic aneurysms than the normal population. Common sense would dictate that these individuals might have a higher risk of more severe destruction of cerebral vessels when affected by septic emboli.

The use of MRI and magnetic resonance angiography (MRA) has improved our ability to diagnose mycotic aneurysms, which are often silent clinically until they reach a size, which causes mass effect or rupture. The usual rules involving size of aneurysm and risk of rupture used in berry aneurysms do not apply to mycotic aneurysms. Once identified serial angiography has been recommended to follow aneurysm growth [11]. The advances in CT angiography provide the ability to image both the interior and exterior anatomy of the vessels in three dimensions to allow examination of these serial changes. The neuroradiologist needs to be alerted to the clinical problem to be studied as the various types of rendering such as volume rendering may be inappropriate when maximum projection rendering may be more appropriate to visualize the interior of the vessel.

Mycotic aneurysms of the vertebrobasilar system are rare but have been reported on the posterior cerebral artery [12]. Extracranial arteries can be affected to cause neurological deficits such as in the iliofemoral system. Mycotic aneurysms of the extracranial carotid arteries

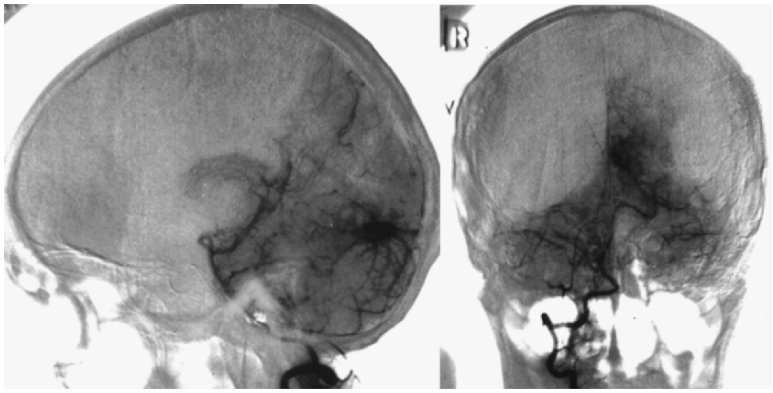

Figure 14.2. This cerebral angiogram shows a nidus a distal branch of the left posterior cerebral artery, which caused a subarachnoid hemorrhage, and was subsequently resected. Courtesy Dr. H. Lesiuk.

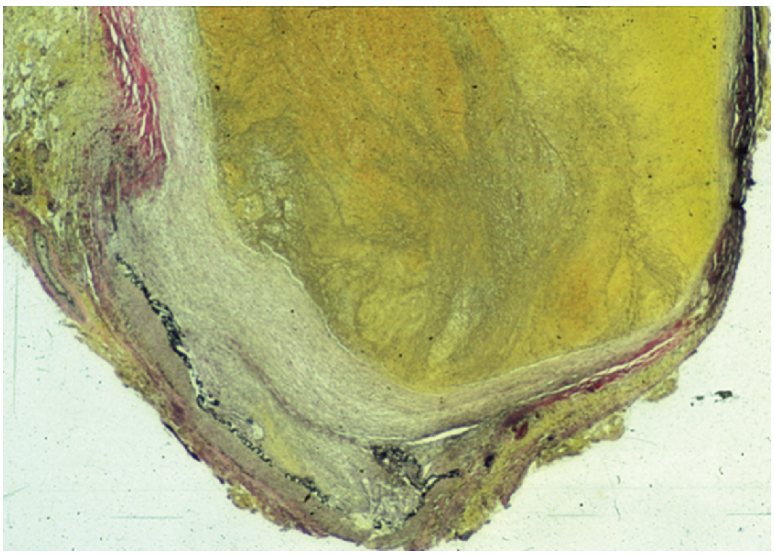

Figure 14.3 This is the photomicrograph of the mycotic aneurysm shown above that was resected surgically. There is a collection of purulent necrotic material in the aneurysm, which spread through the intima and media to the point of failure of the arterial wall. Courtesy Dr. H. Lesiuk.

are rare but have been reported in the extracranial portion of the internal carotid arteries [13,14].

Subarachnoid hemorrhage from mycotic aneurysms occurs in approximately 1–1.7% of cases of infective endocarditis with a mortality rate of 80% [10,15]. The source of bleeding, such as a ruptured mycotic aneurysm, often is not identified. Some authors have suggested that subarachnoid hemorrhage in the context of IE may have different mechanisms, such as leakage from damage due to pyogenic necrosis instead of rupture of mycotic aneurysms [16]. Mycotic aneurysms should be considered in the differential diagnosis of non-traumatic subdural hematoma [17,18]. Mycotic aneurysms when successfully treated either medically or with interventional techniques have been shown to resolve over time and presumably present minimal long-term risk of rupture after stabilization.

The relative neurological damage from any of these processes depends on the localization and the severity with interaction with age and presence of other medical problems. The presence of hyperglycemia, hypertension, or hypotension all adds to ischemic damage caused by thromboemboli, especially if these are septic. Hemorrhage complicating septic emboli can lead to sudden rapid herniation syndromes and brain death (Figure 14.4). Long-term neurological complications of thromboembolic events and sepsis in the brain beside the focal deficits caused by local destruction of brain tissue

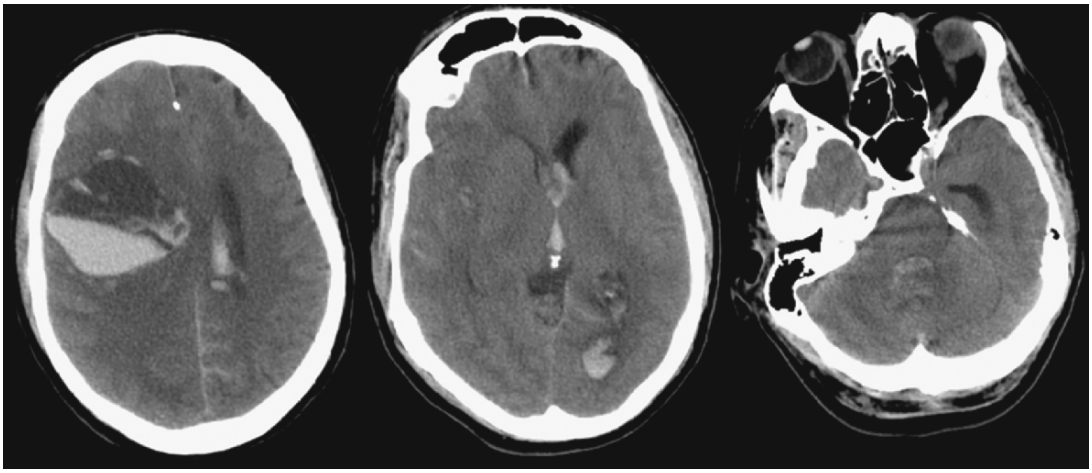

Figure 14.4. CT scan of 45-year-old man with mechanical aortic valve with *S. aureus* endocarditis develops sudden left-sided weakness and brain death in 36 hours. CT scan shows large right hemisphere infarct with hemorrhage extending into the lateral third and fourth ventricles.

include seizure disorders, movement disorders, personality changes, cognitive dysfunction, and dementia. Other complications to the nervous system following seeding, infarction, and infection include the development of brain abscesses, meningitis, and ventriculitis.

Infective endocarditis is associated with multiple types of neuropathological lesions, which may contribute to its poor clinical outcome and activation of cells of monocyte-microglial lineage throughout the brain [19]. The various types of lesions include infarction, hemorrhage, abscess, meningitis, and vasculitis. One study of the histopathology of intracranial hemorrhage due to IE found that hemorrhagic transformation of the ischemic infarct due to septic emboli is the most frequent mechanism, leading to intracerebral hemorrhage encountered in patients dying of IE and that rupture of pyogenic arteritis or rupture of mycotic aneurysms as an alternative mechanism in the other cases [20].

Etiological Agents

The major factor determining the outcome of neurological events due to infectious endocarditis is the metastatic infectivity of the etiological agent. *Staphylococcus aureus,* a common organism causing IE, often results in multifocal cerebral septic emboli.

There is little literature which links the pattern of thromboemboli with specific organisms. It has been stated that more virulent organisms cause thromboemboli earlier in the course of the disease as opposed to more subacute clinical courses involving less virulent organisms, such as *Streptococcus viridans*. Some organisms, such as non-typhi *Salmonella,* cause mycotic aneurysms of large vessels such as the aortic arch with the potential for shock and significant downstream damage, leading to very poor outcomes [21].

Different organisms seem to produce different profiles of cytokine and humoral pro-inflammatory responses. It remains to be determined whether these could be used for the purpose of early diagnosis of IE in the context of new onset unexplained mental status change.

Neurological Localization

The approach to localization in patients with IE and neurological involvement should mirror the time course of the pathophysiological processes listed above. The pathophysiological mechanism of the early involvement of cortical and subcortical structures to produce "confusion" or "personality change and altered levels of consciousness" is not well understood. The liberation of systemic cytokines is known to affect the sleep and attention centers in the hypothalamus.

Close attention has to be paid to the history of an abrupt change in mental status with no other medical explanation in terms of systemic illness or change in medication. Often this prodrome can precede the thromboembolic events by many days or weeks and therefore there is a long potential window for intervention.

The various brain localizations mentioned above include territories served by middle cerebral, vertebrobasilar, and anterior cerebral vessels. When the neurological localization conforms to one of these patterns, the presence of large vessel emboli is most likely. The appearance of concurrent multifocal localizations would suggest the liberation of small emboli to multiple territories in the nervous system, which can include the spinal cord, peripheral nerves, and muscle.

The appearance of dysfunction of the neuromuscular junction in a patient with culture-negative endocarditis should raise the possibility of marantic endocarditis and a paraneoplastic etiology for the neurologic manifestation. A search should be considered for a neoplasm, most likely a small cell tumor in the lung.

Clinical History

The clinical history is essential to assist in determining the presence of risk factors for the development of endocarditis (Table 14.2). The suspicion of endocarditis should raise the following crucial questions: what is the source of the infection, what is the most likely organism, and where has the vegetation embolized to?

The symptoms can be nonspecific, such as low back pain and hematuria [22,23]. The occurrence of TIA or stroke prior to the acute illness is essential in terms of determining a baseline neurological status. In the patient with new onset of fever and encephalopathy, the family or friends can be the richest source of information to guide the search for the source of the infection and to provide information on baseline mental state.

When reviewing a patient with IE and recent cardiac surgery, other factors must be considered in determining the cause of the neurological deficits. In particular there are factors relating to other cardiac conditions and the surgical procedure itself, which may have a role in causing the deficits (Table 14.3).

Table 14.3. Potential Causes of Stroke in Patients Who Have Undergone Cardiac Surgery

Intracardiac thrombus or intracardiac shunts
Embolism of fragments of valve tissue or calcium
Air emboli
Aortic atherosclerosis, which is a source of emboli during surgery
Embolism of thrombus formed at aortic cannulation sites
Watershed stroke due to hypotension during the procedure

Treatment Methods To Prevent Embolic Stroke

From a neurological standpoint the treatment options depend on many factors, such as which phase of the illness is the patient in, from pre-defining event status, to event status, to post-event status. In the pre-event phase, it is possible to diagnose the presence of IE and to commence treatment to prevent the growth and propagation of valvular vegetation. Conventional treatment with antibiotics is appropriate. From the neurological standpoint, the risk analysis for treatment with anticoagulants has to take into consideration all the variables. These would include the presence of arrhythmias, presence of prosthetic heart valves, and the presence of previous cerebral damage from stroke or hemorrhage. Anticoagulants should be continued in patients in whom it is indicated prior to IE, but there is no evidence for its use to prevent embolism in IE patients. The presence of diffuse microvascular disease is a known risk factor for cerebral hemorrhage with anticoagulants and therefore MRI scan may be appropriate. Also there should be a low threshold to perform MRI or CT scan to look for cerebral mycotic aneurysms, especially in patients infected with virulent organisms.

In the pre-event stage, if encephalopathy is present, the treatment should be focused on maintaining optimal metabolic and nutritional balance with correction of any potential or pre-existing nutritional deficiency such as B12, folate, thiamine, or thyroid hormone in addition to appropriate antibiotic therapy. There is no evidence to support the use of anticonvulsants prophylactically at this stage.

The use of platelet paretics during this stage to prevent the formation and propagation of thromboemboli material from a damaged valve has to balance the risk of embolization with the risk of causing hemorrhage from compromised

cerebral vessels. A study comparing the use of aspirin at a dose of 325 mg versus placebo did not show a positive effect for prevention of infarct but conferred a slightly higher risk of hemorrhage. Aspirin had no effect on vegetation resolution and valvular dysfunction [24].

Patients with IE and coexisting coronary disease may have been taking both clopidogrel and aspirin. This combination has been found to confer a higher risk of spontaneous cerebral hemorrhage. Although studies in a population with endocarditis treated with both agents have not been performed, great caution and close monitoring for bleeding are warranted in IE patients taking both agents.

Treatment After Occurrence of Stroke

After a neurological defining event such as an embolus has occurred, the treatment focus shifts to that of acute stroke care. There are a few series in which the use of thrombolytics has been safely carried out in children, but there is little evidence to support the safety of thrombolytics in adults in the acute state [25,26]. The use of these agents in the face of endocarditis can have potential disastrous results, since the risk of bleeding is real particularly if there are unsuspected mycotic aneurysms already formed. This emphasizes the need for urgent high resolution imaging of the neurovascular tree prior to the initiating of thrombolytic therapy in any patient with an acute deficit and suspected IE.

The decision with respect to anticoagulation after an acute event in a patient with endocarditis requires weighing the risk of bleeding into an area of non-hemorrhagic infarction against the daily risk of embolization. Overall, anticoagulation is not indicated in this situation, because patients with IE have an increased risk of bleeding and there is no data to support a beneficial effect of anticoagulation.

Whether to perform valve surgery in a patient with embolic stroke and persistent valvular vegetation is a clinical dilemma. The decision has to be individualized. Valve surgery may be reasonable in a patient who has had a small cerebral infarct but still has large mobile valvular vegetations.

The surgical treatment of mycotic aneurysms presents technical challenges not present with berry aneurysms of the circle of Willis. The localization of mycotic aneurysms is more difficult because they tend to be more distal, are more friable and may be obscured by hematoma. The basic surgical principle is to render the infectious nidus safe from further necrosis, breakdown, and bleeding. This often requires taking the whole vascular apparatus including the feeding artery, the aneurysm and the draining vein. This type of surgery has a high risk of causing collateral ischemic damage in the area served by the vessel, which have to be sacrificed to make the aneurysm safe from further bleeding.

New techniques such as wand guided MRI/MRA-guided frameless stereotaxy have been developed to overcome these challenges [27]. The use of stereotactic angiography to localize mycotic aneurysms has been described [28]. Advanced techniques such as stereoscopic synthesized brain-surface imaging can be used to precisely localize the aneurysm and minimize the size of the craniotomy required [29].

Neuroradiological interventional techniques for treating mycotic aneurysms include coiling, glue embolization, or stenting. The options for treatment are multiple and there are few evidence-based guidelines to assist the decision making in this regard. In many cases, it is a matter of reviewing the anatomy of the mycotic aneurysm or aneurysms in a multidisciplinary neurovascular forum to decide on the best course of action considering factors, such as the size of the aneurysm, the location, the size of the neck, and the surgical accessibility.

The debate concerning neurosurgical versus neuroradiological intervention follows the same pattern as with berry aneurysm treatment. The location of the aneurysm, the size, the clinical stability of the patient, and the availability of a facility with experience performing the procedures all figure into the decision as to which might be a better choice. There are case reports of both surgery and coiling used for different cerebral mycotic aneurysms in the same patient [33]. In patients with IE and mycotic aneurysms, the mycotic aneurysm should be properly treated before valvular surgery is performed.

With respect to the timing of cardiac surgery after a cerebral embolism, the risk depends on the size and location of the infarct and the risk of reperfusion injury after the patient comes off the bypass pump. Some series have suggested that in patients with IE who have suffered neurological

deficits that delayed surgery up to three weeks may have better outcomes [4]. The most common practice is to delay cardiac surgery a minimum of two weeks after an embolic infarct with little or no hemorrhage and four weeks after a cerebral hemorrhagic event.

Marantic Endocarditis

Marantic endocarditis or nonbacterial thrombotic endocarditis is a rare clinical entity, which features the occurrence of sterile fibrin-platelet deposits on the surface of mitral, tricuspid, or aortic valves [31]. In patients with chronic diseases or malignancy, the occurrence of recurrent strokes should alert the clinician to the possibility of marantic endocarditis [32]. The presence of embolic material on a heart valve without evidence of infection should trigger a search for the primary malignancy. Gynecological neoplasms seem to have the highest potential for developing ischemic stroke related to microemboli due to marantic endocarditis [33]. The embolic events can precede any symptoms from the underlying malignancy for months to years. Occasionally treatment of the underlying malignancy leads to improvement of the endocarditis and the prothrombotic state [34]. Common neurological findings are altered mental status, seizures, and hemiplegia. Pneumonia, hypoxia, disorders of coagulation, and renal failure are frequently present in these seriously ill patients.

Differences in the MRI appearance of infarcts in marantic endocarditis versus IE using diffusion-weighted imaging have been reported [35]. Infarcts due to the former have been found to show multiple, widely distributed, small and large strokes.

Summary

Unexplained neurological events in the presence of a subacute systemic illness or a prosthetic valve should make clinicians alert to the possibility of IE. The most cost-effective investigation remains a comprehensive history of the illness, which should be gleaned from any and all sources, including the patient, the family, and the primary care provider. A high index of suspicion coupled with the proper investigations to image the heart and the nervous system are essential to prevent further damage.

In the face of IE, when one neurologic event occurs, be on the alert for the second, more devastating event. The optimal care for these patients requires a team approach incorporating cardiac, cardiac surgical, neurological, neurosurgical, and neuroradiological expertise. The occurrence of IE should have the same urgency and alerting protocol similar to that for stroke and myocardial infarction.

Preventing recurrence in patients who have IE and stroke remains a clinical challenge. In the event of mycotic aneurysms, early involvement of the neurosurgical and neuroradiological teams is essential to prevent further neurological damage. Once stabilized, mycotic aneurysms present minimal long-term risk of rupture and rebleeding, given that the source of infection has been identified and rectified. Compared to adults, children have better outcomes from the treatment of mycotic aneurysms and the use of thrombolytic therapy.

Mortality and morbidity from IE remain high despite technological advances. Optimal treatment of these patients requires a structured institutional approach, timely utilization of clinical and laboratory resources, and on-going research.

Key Points

1. Endocarditis is a major threat to the nervous system.
2. Early recognition and treatment during the pre-embolic phase is essential to prevent serious morbidity and mortality.
3. In the case of an acute neurological deficit in a patient known to have valvular disease, congenital heart disease or previous valvular surgery, embolization due to endocarditis must be considered in the differential diagnosis.
4. Serial imaging of the brain and brain vasculature is required to monitor the formation and progression of mycotic aneurysms. Both MRI/MRA and high resolution CT/CTA are appropriate tools to use for this purpose.
5. Multidisciplinary neurovascular consultation is required once mycotic aneurysms have bled or been imaged
6. Once stabilized mycotic aneurysms have a good prognosis.

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