Infective Endocarditis

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Despite major changes in the epidemiology, microbiology, and prognosis over the last 50 years, the diagnosis of infective endocarditis is still difficult, and serious complications including death are not uncommon. Prosthetic and right-sided valvular infections are more common and require longer periods of vigorous antimicrobial therapy than in the past. An effective short-course antibiotic regimen has been designed for sensitive microorganisms, and protocols have been established for culture-negative cases (15 percent) and empiric situations. Finally, cardiac surgery should be considered as an important modality, especially in cases of congestive heart failure.

Although Morgagni originally described infective endocarditis in the mid-1700s, and Rokitansky established its infectious cause a century later, it was William Osler, in 1885, who clearly described the clinicopathologic features of this uniformly fatal disease, which he termed malignant endocarditis.[1] Within the last half-century some remarkable changes have occurred in the epidemiology and therapeutic management of infective endocarditis. Survival rates have improved remarkably, and the leading cause of death is no longer septicemia. The average age of patients has progressively risen from 30 to 40 years in the early part of this century to 55 to 65 years in the 1970s.[2,3] Despite improved investigative technologies, however, infective endocarditis is still a difficult disease to diagnose accurately and carries a significant mortality. A wide variety of etiologic agents presenting in an equally broad clinical spectrum can challenge the best physician. Medical as well as surgical intervention must be carefully weighed to optimize outcome.

PATHOGENESIS

At least three requirements must be fulfilled for the initiation and localization of the infection[4]:

1. Predamaged valve or "jet effect"
2. Sterile platelet-fibrin thrombus
3. Bacteremia, usually transient
4. High titer of serum agglutinin antibodies, which causes infective organisms to stick together

Persons with preexisting heart disease are at a higher risk of acquiring infective endocarditis. The most common causes are rheumatic fever and a prosthetic heart valve or similar foreign body (eg, patch, graft, or suture material). The order of invasive frequency is mitral, aortic, tricuspid, and pulmonary valves. Endocarditis has most frequently been correlated with the following valve disease processes: rheumatic fever and leaflet prolapse (mitral), syphilis and arteriosclerosis (aortic), and severe pulmonary hypertension (pulmonic valve). Patent ductus ateriosus, congenital heart disease, idiopathic hypertrophic subaortic stenosis, and interventricular septal defects can also lead to endocarditis. Intravenous drug abusers more commonly develop right-sided endocarditis, particularly of the tricuspid valve.

The formation of an abnormal or reversed pressure gradient between two portions of the heart favors the deposition of particulates, such as antigen-antibody complexes from the blood. The "jet effect" (high-velocity and low lateral pressure) explains the development of infections on the ventricular aspect of the mitral valve's aortic leaflet, the undersurface of the aortic valve leaflets, and the chordae tendineae in aortic valve disease and the atrial surface of the mitral leaflets and MacCallum's patch in mitral valve disease. The turbulence and jet effect traumatize the endothelial surface directly, exposing the underlying collagen. A sterile platelet-fibrin thrombus forms that may be colonized during the transient bacteremic episodes, which occur from either focal infection or trauma to the skin or mucosa (eg, catherization and dental

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procedures). In the case of less-virulent pathogens, circulating agglutinating antibodies must also be present.

Gradually additional fibrin and platelets are deposited at the site of the lesion. With the less-virulent pathogens, the deposition may lead to the development of polypoid vegetations (present in 15 to 80 percent of cases), capable of occluding the valve itself or leading to emboli.[5] These secondary thrombi may act as a barrier, shielding the pathogens from exposure to phagocytes, complement, and other bactericidal agents present in the host's serum. The more virulent microorganisms tend to cause rapid valvular destruction. Penetration of the valvular ring may progress to ring abscess, myocardial abscess, or cardiac conduction abnormalities. Involvement of the pericardium can follow external rupture of an abscess.

The pathogens shed on a continual basis are incompletely cleared by the reticuloendothelial system of the liver and spleen. Since the introduction of antibiotic therapy, however, congestive heart failure due to valve perforations and neurologic sequela from emboli have replaced septicemia as the leading causes of death.[3,6–10] Actual occlusion of vessels with larger emboli often leads to infarcts. Infarction rarely occurs with the pathogens of subacute endocarditis because of their low virulence and rapid destruction by phagocytes. Mycotic aneurysms, more common with the less-invasive organisms, may occur through three mechanisms: embolic occlusion of the vasa vasorum, direct bacterial invasion, or injury from the deposition of immune complexes. Renal lesions are of three types: infarction due to large emboli, focal glomerulitis secondary to small emboli, and a diffuse glomerulonephritis probably due to immune complex deposition.

Osler's nodes are raised, tender papules located on the pads of the fingers and toes and the thenar and hypothenar eminences. Most commonly seen in subacute endocarditis, these nodes are probably due to aseptic necrotizing vasculitis following the deposition of circulating immune complexes. Small emboli of virulent organisms are responsible for the less common septic vasculitis of acute endocarditis. Examples of arteriolar allergic vasculitis are Janeway spots, Roth spots of the retina, petechial skin lesions, and subungual or "splinter" hemorrhages.

DIAGNOSIS

The diagnosis of infective endocarditis is based upon the clinical history, physical findings, and microbiologic confirmation.

History

Significant historical factors include the presence of a prosthetic or structurally abnormal valve, congenital heart defect, or a prior history of endocarditis.[3,6–10] Previous heart surgery is also significant, as it may result in scars or foreign bodies that may serve as a nidus for infection. A history of intravenous drug abuse is noteworthy even in the absence of preexisting heart lesions because the incidence of acute endocarditis seen in previously healthy drug addicts without cardiac lesions is high. Bacteremia-provoking procedures are also well-recognized risk factors, yet these account for only a small fraction of infections. In the majority of subacute cases, no portal of entry is recognized.[3,6–11] However, because some individuals can relate a recent dental extraction, urethral instrumentation, tonsillectomy, acute respiratory tract infection, or abortion to the development of the symptoms of endocarditis, these historical findings should raise suspicion when present in the clinical context of endocarditis. The reporting of a suppurative infection (abscess, meningitis, pneumonia, cellulitis, or septic thrombophlebitis) caused by highly pathogenic organisms (staphylococci, group A streptococci, Streptococcus pneumoniae) frequently antedates the onset of acute endocarditis. Other less-common noncardiac conditions that are predisposing include chronic obstructive pulmonary disease, peptic ulcer disease, diabetes, systemic lupus erythematosus, renal insufficiency, a variety of dermatologic conditions, and immunosuppression from any cause.

The mean duration of symptoms before presentation is 30 to 70 days for Streptococcus viridans, 40 to 100 days for enterococci, and 10 to 40 days for Staphylococcus aureus.[3,6–12] Anorexia, headache, and fever are the most common presenting symptoms of endocarditis. They are usually more pronounced in acute cases. Chills, malaise, weight loss, night sweats, dyspnea, cough, rash, and back pain are also typical symptoms of subacute cases. Chills are more common and severe in acute endocarditis, as are petechiae and embolic phenomena (chest pain, hematuria, vascular compromise, sudden blindness, or paralysis). Less commonly, mental status change, myalgias, and arthritis or arthralgias occur.

Physical Findings

The most common presenting sign is fever (76 percent) followed by a new murmur (66 percent). The murmur is more frequently a new diastolic blow (75 percent) with the remainder being a change in intensity of a preexisting murmur. Because the most common cardiac finding may be an unchanged murmur, the distinction between preexisting valvular disease and valvular infection may be difficult. Only a small percentage of patients (under 50 percent) do not have a detectable murmur, which may be due to tight mitral or aortic stenosis or right-sided endocarditis. Rales (30 percent), splenomegaly (29 percent), and mental status change (24 percent) are among the most

frequent noncardiac signs. Less commonly, microvascular lesions such as conjunctival hemorrhages, Osler's nodes, Janeway lesions, Roth spots, and petechiae are noted. Splinter or linear hemorrhages are often found under the nail plate, but they are nonspecific, being also found in cases of trauma, sepsis, severe anemia, leukemia, and trichinosis. Petechiae are not painful, do not blanch on pressure, and are located in a wide variety of mucocutaneous surfaces (upper trunk, pharynx, conjunctiva, and buccal mucosa).

Though the true prevalence of embolic phenomena has not been determined for endocarditis, such events appear to occur in about one third of cases, particularly those with vegetations and involving the aortic valve.[13] Emboli, however, may be the first sign of disease, and their presentation may be devastating. Left-sided endocarditis has been associated with the sudden development of monoplegia, hemiplegia, blindness, myocardial infarction, left upper abdominal pain with a splenic friction rub, flank pain with hematuria or renal failure, melena in association with abdominal pain, osteomyelitis, and a variety of metastatic abscess. Emboli from right-sided lesions may mimic pneumonia or pleurisy. Acute endocarditis is a frequent cause of hemoptysis and pleuritic chest pain resulting from pulmonary infarction.

Although the constellation of the aforementioned history and physical findings may provide a characteristic picture of the disease, no single finding is pathognomonic for endocarditis. Indeed, the most prevalent symptoms are nonspecific complaints, particularly in the subacute form, which may make the distinction between endocarditis and a simple viral illness a difficult one. At least 30 percent of cases are misdiagnosed at the time of admission.[3] The differential diagnosis should include rheumatic fever, occult tumors, systemic lupus erythematosus, periarteritis nodosa, poststreptococcal glomerulonephritis, atrial myxoma, and aortic dissection with regurgitation.

Laboratory Studies

The most common laboratory finding is an elevated erythrocyte sedimentation rate of 85 to 95 percent.[3,6] Normochromic, normocytic anemia may be present in 50 to 80 percent of subacute cases, but may not be initially present in acute cases.[11,12] Leukocytosis with a shift to the left is frequent, particularly in acute forms. The blood smear often reveals phagocytic reticuloendothelial cells in increased numbers.[3,6,11] Twenty-five to 50 percent of cases demonstrate microscopic hematuria, proteinuria, and a positive rheumatoid factor; these findings are more common and favor higher values in prolonged subacute cases.[3,6] The blood urea nitrogen and bilirubin levels may be slightly elevated, and the total serum hemolytic complement may be decreased. The electrocardiogram occasionally reveals conduction defects. There is often polyclonal hypergammaglobulinemia, cryoglobulinemia, and elevated levels of antiheart antibodies and circulating immune complexes. In 50 percent of patients, lumbar puncture reveals variable amounts of leukocytes. All of these findings are supportive, nonspecific, and cannot be used to confirm diagnosis.

Echocardiography

Echocardiography will detect a lesion in 55 to 80 percent of patients with the clinical syndrome of infective endocarditis.[5] Two-dimensional echocardiography is about 15 percent more sensitive than M-mode echocardiography, particularly with lesions located on the right side or on prosthetic or abnormal valves.[14] Under ideal conditions M-mode and two-dimensional echocardiography should be employed together. Echocardiography has several limitations. Only vegetations larger than 2 mm are reliably identified.[13,15] The detection of smaller lesions may be possible depending on the skill of the technician, the type of the instrument, and the presence of calcium (late lesions). Previous valve scarring or disease can complicate the interpretation, and no distinction can be made between sterile and infected vegetations.[16] The last point is especially significant because prior endocarditis is a common predisposing factor to new infection and because approximately 30 percent of vegetations persist for years despite medical cure.[17] False-positive echocardiography studies may also occur from other disorders that may mimic endocarditis (eg, clots, tumors, flail leaflet, ruptured chordae, or marasmic lesions). In experienced hands, however, these conditions can usually be distinguished from true vegetations.

In addition to being a useful tool in diagnosing endocarditis, echocardiography can aid in the determination of a likely microbial cause and in the identification of those individuals who are at risk for developing complications. Certain organisms, particularly Staphylococcus aureus, fungi, and Serratia organisms, characteristically produce large vegetations. The absence of such lesions on echocardiography is evidence against infection by one of these organisms. Patients with valvular vegetations visible on echocardiography represent a subgroup of endocarditis cases at higher risk for emboli, congestive heart failure, and other complications necessitating surgical intervention, although the probability of such an outcome cannot be predicted on the basis of size or morphology of the lesions.[16,18,19]

Cardiac catheterization with angiography may be used to demonstrate the extent of valvular lesions and to identify the degree of ventricular dysfunction and the presence of such surgical risk factors as coronary artery disease. Although there is theoretical risk of embolization from

the procedure, clinical experience suggests that such risk is small or nonexistent.[20,21] Currently, catheterization is recommended if nonemergency surgery with minimal additional risk is contemplated. Clinical judgment and echocardiography are the mainstays in the face of possible urgent surgery.

Microbiology

Bacteremia associated with endocarditis is usually continuous. Furthermore, it has been shown that if any blood cultures are positive in patients with infective endocarditis, most of the other cultures drawn will also be positive. Thus, it is rarely necessary to obtain more than three separate sets of blood cultures within a 24-hour period on two consecutive days in patients with suspected endocarditis. Ten to 20 mL of blood should be collected by sterile technique. Venous samples have been shown to yield the same culture rates and results as arterial samples. The average rate for positive blood cultures is 85 percent with a range of 60 to 95 percent.[3,6] Even when blood cultures are positive, the diagnosis of endocarditis is not guaranteed. Deep-seated abscesses of any vascular tissue can cause continual bacterial seeding of the blood. The causative organism cannot be recovered in about 15 percent of cases (range 5 to 40 percent).[3,6,12,22] The more common causes of culture-negative endocarditis usually involve prior incomplete or inappropriate antibiotic therapy. Such therapy may sterilize the blood for days or weeks while tissue infection remains unchecked. Less commonly, culture-negative endocarditis may be caused by slow-growing, fastidious, or special-growth-requirement microbes such as Brucella, Coxiella, Aspergillus, Chlamydia, Histoplasma, and Pasteurella species, and gram-negative bacilli (eg, Hemophilus species). For many of the aforementioned organisms, serologic acute and convalescent titers may aid in the diagnosis.

To improve the accuracy of blood cultures, blind subcultures should be performed routinely for four weeks after initial culturing on a variety of media (eg, chocolate agar, thiol and pyridoxine media, brain-heart infusion, and hypertonic media) and in a variety of conditions (aerobic, anaerobic, and 10 percent carbon dioxide). One bottle should be vented to help isolate fungi and Pseudomonas species, and incubated at 30 °C for at least four weeks. β-Lactamase should be added to the culture media if the patient has received a penicillin or cephalosporin derivative. Sodium polythanethiosulfonate (Liquoid) can also be added to inactivate leukocytes, immunoglobins, complement, and to some degree polymyxin and the aminoglycosides. Before a culture is discarded, it should be carefully examined, especially at the blood-broth interface, and all cultures should be Gram stained. Bone marrow and resected large emboli and valves should be cultured and examined histologically for organisms.

MEDICAL THERAPY

Medical therapy is curative in 85 percent of cases of endocarditis, and its efficacy is dependent on the correct identification of the offending microorganism and its antibiotic sensitivities.[23–27] Indeed, therapy should be delayed for several hours until the required blood cultures are collected and the microbiologic diagnosis established. In the patient with subacute endocarditis, there is no great urgency to initiate therapy as the illness has been present for months. Failure to establish the cause of the infection may result in prolonged hospitalization and multiple iatrogenic complications associated with inappropriate therapy. If, however, the patient has the acute form of the disease, therapy should not be delayed until cultures and sensitivities are known. Instead, treatment should be empiric. The treatment regimen may later be adjusted when culture results are available.

Antimicrobial management of endocarditis in the adult patient is summarized in Table 1. The reader is referred to the recent review by Cleary and Kohl [28] for the treatment of infective endocarditis in children. Therapy early in illness, the use of intravenous bactericidal antimicrobial agents, and treatment for a prolonged period are key factors in optimizing the cure rate. The choice of two antibiotics that are synergistic is often important. For instance, the use of aqueous penicillin alone for sensitive streptococci must be continued for four weeks. If streptomycin is added to the regimen, the total course of therapy need only be two weeks. The minimum inhibitory concentration, the minimum bactericidal concentration, and the serum bactericidal test should be determined for the specific drug(s) within the first 24 to 48 hours of therapy. A cardiologist and cardiovascular surgeon should also be consulted as soon as the diagnosis of endocarditis is made, because surgery may be required at any time during the course of the illness, particularly when it involves the aortic valve.[13] Blood cultures should be repeated during the first 48 to 72 hours after initiation of therapy. Cultures remaining positive after the first week, despite apparently appropriate therapy, suggest bacterial resistance, error in the dosage or administration of the antibiotic, or deep-seated focus such as aortic root or myocardial abscess.

During the course of therapy it is important to perform daily physical examinations because subtle changes in body weight, blood pressure, cardiac auscultatory findings, or jugular venous pressure may presage abrupt hemodynamic decompensation. Furthermore, if a portal of entry has been identified, it should be eliminated. Examples include poor oral hygiene, urolithiasis and urinary tract infection (enterococci), or inflammatory bowel disease and bowel cancer (Streptococcus bovis). Serial echocardiograms should be taken to detect ischemia or infarction from embolic occlusion of a coronary artery, arrhythmias

TABLE 1. ANTIBIOTIC THERAPY FOR COMMON ENDOCARDITIS PATHOGENS

Organism	Drugs	Dosage	Duration	Alternate Drugs
Unknown/empiric	IV aqueous penicillin G + IV nafcillin + IM gentamicin + IV vancomycin*	5–10 mL/U/q6h 2 g q4h 1.2 mg/kg/q8h 7.5 mg/kg/q6h	Pending culture and sensitivity results	
Penicillin-sensitive streptococcus** S viridans S pneumoniae	IV aqueous penicillin G or IM procaine penicillin G + IM streptomycin	2–5 mL/U/q6h 1–2 mL/U/q6h 7.5 mg/kg/q2h	2 wk	Cephalothin 1.5 g q4h IV or Vancomycin 7.5 mg/kg/q6h IV
Enterococci	IV aqueous penicillin G or IV ampicillin + IM gentamicin or IM streptomycin	4–6 mL/U/q6h 2–3 g/q6h 1.2 mg/kg/q8h 7.5 mg/kg/q12h	4–6 wk	Vancomycin 7.5 mg/kg/q6h IV
Methicillin-sensitive staphylococcus*** S aureus S epidermidis	IV aqueous penicillin G or IV oxacillin or IV nafcillin	4–6 mL/U/q6h 1–2 g/q6h 1–2 g/q6h	4–6 wk	Cephalothin 1.5 g q4h IV or Cefazolin 1–2 g q6h IV or 7.5 mg/kg/q6h IV or Vancomycin 7.5 mg/kg q6h IV
Methicillin-resistant staphylococcus	IV vancomycin + PO rifamycin	7.5 mg/kg/q6h 300 mg q12h	4–6 wk	Cephalothin 1.5 g q6h IV Rifamycin 300 mg q12h PO
Fungus	IV amphotericin B + IV 5-fluorocytosine + Cardiac valve replacement	0.7 mg/kg/d 150 mg/kg/d	6–8 wk	
Culture negative	IV aqueous penicillin G + IV oxacillin*** or IV nafcillin*** + IM gentamicin	5–10 mL/U/q6h 2 g q4h 2 g q6h 1.2 mg/kg/q8h	4–6 wk	Vancomycin 7.5 mg/kg/q6h IV + Streptomycin 7.5 mg/kg/q12 h IM

** For infected prosthetic valve*

*** Minimal inhibitory concentration less than 0.1 mg% and the absence of prior treatment with other antibiotics, prosthetic heart valve, penicillin allergy, shock, thrombocytopenia, unusual streptococci, or cancer. For resistant streptococci use aqueous penicillin G and streptomycin for 4 weeks at same dosage*

**** In dialysis, drug abuse, or prosthetic valve patients*

Notes: Dosages of streptomycin, gentamicin, vancomycin, and amphotericin should be adjusted for renal function; for penicillin allergies substitute vancomycin, cephalothin, or cefazolin; longer durations of treatment are used in the case of an infected prosthetic valve, ie, if 4–6 weeks is recommended, as in an enterococcal infection, 6–8 weeks would be appropriate if the underlying valve is a prosthesis

from disruption of a conduction pathway, or pericarditis secondary to an abscess.

The most reliable prognostic indicators of recovery are a reduction of fever and an improvement in the patient's general sense of well-being within two to seven days of commencing therapy. A reduction of the patient's hyperimmune state, especially a falling rheumatoid factor, is a good index of successful therapy. Defervescence may be delayed by microbe resistance, heart failure, embolic complications, and drug side effects. Cessation of therapy for two to three days is useful in identifying drug fever and is not harmful. It must be emphasized, however, that clinical improvement in a patient with endocarditis should never lead the physician to discontinue the therapy prematurely. Eradication of infection within the valve demands prolonged effective antibiotic therapy. Inadequate treatment may predispose to culture-negative endocarditis and its attendant higher risk of complications.

To detect relapses, successfully treated patients should have repeat blood cultures drawn at one- and two-month intervals after completion of antimicrobial therapy. Relapses may indicate inappropriate or incomplete therapy or the need for surgical intervention. All patients should also receive instruction in prophylactic measures.

PROPHYLAXIS

Despite the lack of proven efficacy and that few cases of endocarditis follow procedures with a proven risk of bacteremia, prophylaxis is standard therapy for the high-risk patient.[28] In addition to patients who have a history of endocarditis, patients with congenital or acquired heart disease, calcified mitral annulus, prosthetic heart valve, valvular lesions or prolapse, or ventriculoseptal patches

should receive antimicrobial prophylaxis for Streptococcus viridans immediately before dental procedures, orthodontic work, respiratory surgery or instrumentation, and tonsillectomy or adenoidectomy. Two grams of penicillin V given orally 30 to 60 minutes prior to the procedure followed by 500 mg every six hours for eight doses is recommended. One gram of streptomycin intramuscularly may also be added 30 to 60 minutes prior to the procedure. Erythromycin or vancomycin can be used in the case of penicillin allergy. Prophylaxis for at-risk patients undergoing genitourinary or gastrointestinal surgery (enterococci) includes 1 g of ampicillin intramuscularly or intravenously and 80 mg of gentamicin intramuscularly, or intravenously 30 to 60 minutes prior to the procedure. Aqueous penicillin and streptomycin can be substituted for this regimen. Vancomycin is recommended for patients with penicillin allergies.

SURGERY

Cardiac valve replacement can be lifesaving in selected patients with active endocarditis, but mortality rates are high in many centers, and it is often difficult to determine the timing and indications for surgery.[29–31] The generally accepted indications for surgery in endocarditis include congestive heart failure, recurrent embolism, uncontrolled infection, failure of antibiotic therapy, mycotic aneurysm, severe valve obstruction or dehiscence, gram-negative fungal or prosthetic valve endocarditis, or new development of conduction disturbances. Severe congestive heart failure that is due to aortic (most frequently, mortality 40 to 95 percent) or mitral (mortality 20 to 70 percent) regurgitation is the leading cause of death and the most common cause for surgical intervention.[10,26,30] A number of studies have demonstrated that valve replacement yields lower mortality (5 to 30 percent) than medical therapy (18 to 60 percent).[20,26]

The degree of opinions vary with regard to surgical intervention for uncontrolled infection, failed antibiotic therapy, or embolization. Definitional problems aside, morbidity and mortality rates following surgery are higher in patients with uncontrolled infection and valve root abscess. A single embolic episode does not usually justify valvular surgery. Multiple episodes should be individualized according to microbial cause and the size and mobility of the vegetations (serial echocardiography). Because residual infection at a surgical site after valve replacement is rare, surgery should be strongly considered in endocarditis associated with high mortality: fungal, gram-negative, and left-sided Staphylococcus aureus.[32] Persistent or relapsing infection of a prosthetic valve should prompt its removal.[33] The development of a new conduction disturbance, particularly aortic valve block, may be best managed with a pacemaker plus evaluations for possible underlying pericarditis or myocardial abscess.

PROGNOSIS

Before the advent of the antibiotic era, death from endocarditis was inevitable. Survival rates approaching 85 to 90 percent can now be expected with appropriate medical management. Survival rates are lower in the presence of congestive heart failure, drug addiction, aortic or multiple valve involvement, polymicrobial bacteremia, culture-negative agents, antimicrobial resistance, a prosthetic valve, and delay in therapy, particularly surgery. Survival rates are lowest for gram-negative and fungal infections or those involving a prosthetic valve.

Although congestive heart failure is the leading cause of death, embolization to vital organs, rupture of a mycotic aneurysm, renal insufficiency, and surgical complications are important factors leading to mortality. Sterile emboli can occur up to one year following treatment but are usually of no significance.[13]

CONCLUSIONS

Earlier diagnosis and aggressive therapy can significantly lower the morbidity and mortality of infective endocarditis. A thorough history and physical examination, coupled with improved culture techniques and noninvasive echocardiography, are the keystones in arriving at an accurate diagnosis. Carefully monitored bactericidal therapy and early surgical intervention are essential for a successful outcome. Periodic reevaluation of the patient's status can pinpoint errors in management and identify early complications. Finally, prophylaxis education and regular follow-up will improve the long-term outlook.

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