

A 48-Year-Old Man With Right Lower Extremity Weakness and Pain

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CASE PRESENTATION

A 48-year-old man with no significant past medical history but a family history of collagen vascular disorders presented to the emergency department with a chief complaint of being unable to walk. The patient had been in his usual state of health until approximately three weeks prior, when he first visited the emergency department for fever, chills, and bilateral shoulder pain. The physical exam had revealed mild rhonchi bilaterally. At that time, he had a white blood cell count of 15.4 thousand cells per μL (normal 4.5 to 11.0 thousand cells per μL) (68% neutrophils, 14% bands). He was given an injection of ceftriaxone and discharged with a prescription for doxycycline for a presumed respiratory tract infection. The patient returned to the emergency department two days later with worsening shoulder pain. The physical exam did not reveal any abnormalities. A chest X-ray was reported as normal, and the patient's white blood cell count was 16.7 thousand cells per μL (normal 4.5 to 11.0 thousand cells per μL) (68% neutrophils, 2% bands). The erythrocyte sedimentation rate and C-reactive protein levels were elevated at 50 mm/hr (normal 0 to 15 mm/hr) and 22.30 mg/dL (normal <0.90 mg/dL), respectively. The patient was discharged with a prescription for pain medication and a short course of prednisone. When the patient presented to the emergency department the third time, 17 days later, his shoulder pain had worsened, he had developed urinary and bowel incontinence, and he was unable to stand secondary to severe pain and weakness in the right lower extremity.

Review of systems revealed lethargy, fever, and chills in the few days prior to this visit. He denied any further neurological complaints. He denied vision changes, dyspnea, chest pain, orthopnea, nausea, vomiting, diarrhea, constipation, melena, hematochezia, or bright red blood per rectum. The patient's medical history was significant only for a fractured right leg in 1984, with no prior surgeries. He had an 18 pack-year cigarette smoking history and occasionally smoked marijuana. The patient denied recent alcohol use or any history of intravenous drug use. He had been incarcerated for 10 years and had been released approximately one year earlier. The patient's mother and father both were deceased secondary to myocardial infarction at the ages of 65 and 57, respectively. He reported that his sister had been diagnosed with dermatomyositis, and his cousin had been diagnosed with systemic lupus erythematosus. Prior to his recent emergency department visits, the patient took no medications and had no known allergies.

On physical exam, the patient's vital signs included a blood pressure of 108/79 mm Hg, pulse of 74 beats per minute, 20 respirations per minute, and a temperature of 98.0°F. He was awake, alert, and oriented to person, place and time. He was noted to have poor dentition and a jugular venous pressure of 6 cm. Cardiac examination revealed a normal S1 and S2, and no murmurs were audible. Bilateral rhonchi were present on lung auscultation. The right lower extremity had non-pitting edema, was cyanotic and cold, with several subcutaneous hemorrhagic patches. Dorsalis pedis and tibialis posterior pulses were noted to be normal

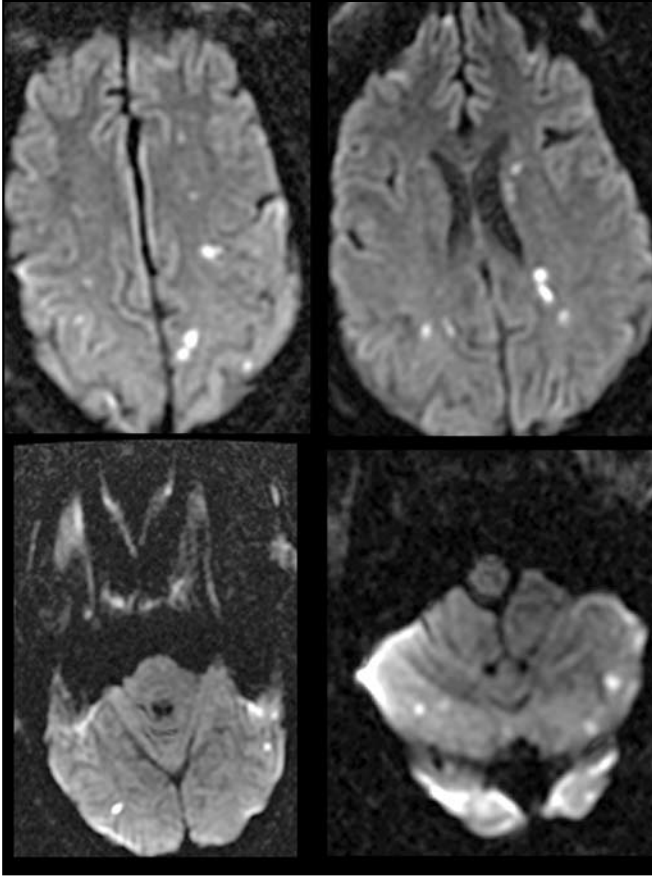


Figure 1. Multiple punctate lesions located diffusely in bilateral cerebral and cerebellar hemispheres show diffusion restriction on magnetic resonance image, most consistent with ischemic insults from an embolic event.

in the left lower extremity and absent in the right lower extremity, both manually and with Doppler ultrasound evaluation. Neurologic exam demonstrated no cranial nerve deficits. Left lower extremity strength revealed no weakness, but right lower extremity strength was 2/5 proximally and 0/5 distally. Sensation was decreased in the right lower extremity and absent below the knee. Reflexes could not be elicited in the right lower extremity. Cerebellar function was normal by finger-to-nose and rapid alternating movement tests. Gait was not able to be assessed.

Initial laboratory evaluation showed a white blood cell count of 24.7 thousand cells per μL (normal 4.5 to 11.0 thousand cells per μL) (61% neutrophils, 28% bands). Erythrocyte sedimentation rate was 54 mm/hr (normal 0 to 15 mm/hr), and C-reactive protein was 24.5 mg/dl (normal <0.90 mg/dL). Creatine kinase was 2327 U/L (normal <230 U/L), CKMB isoenzyme was 27.7 ng/mL (normal <7.7 ng/mL), and cardiac troponin was 0.68 ng/mL (normal <0.05 ng/mL). A quantitative D-dimer assay revealed a concentration of 1154 ng/mL (normal <231 ng/mL). The patient was human immunodeficiency virus negative. An electrocardiogram showed no significant abnormalities.

Surgery was consulted emergently for suspected vascular occlusion in the right lower extremity. Blood cultures were obtained, and the patient was started on broad spectrum antibiotics and intravenous fluids for empiric management of suspected sepsis. A formal arterial ultrasound examination of the right lower extremity was performed, revealing decreased blood flow throughout with occlusion of the right common femoral artery. An echocardiogram showed a 1 cm vegetation on the anterior leaflet of the mitral valve. Left ventricular function was normal with an ejection fraction of 55%.

At this time, the patient was transferred to another hospital for more specialized care. Further imaging at the second hospital was performed. A chest X-ray demonstrated cephalic redistribution of the pulmonary vasculature consistent with pulmonary venous congestion. A computed tomographic (CT) angiogram of the abdominal aorta and lower extremities revealed complete occlusion of the right common femoral artery, reflecting either a thrombus or embolus. A magnetic resonance image (MRI) of the head demonstrated multiple, focal, white matter lesions in the cerebellum, occipital, temporal, parietal, and frontal lobes (Figure 1). In addition an apparent abscess was noted in the left occipital lobe (Figure 2). These findings were determined to be consistent with thromboembolism.

The patient was taken to the operating room where a right mid-calf level amputation was performed. In addition, the embolus in the right common femoral artery was removed and sent for culture. Reassessment the following day resulted in conversion to an above-the-knee amputation of the right lower extremity. A transesophageal echocardiogram was performed to better visualize the mitral valve vegetation, revealing a 4.3 cm elongated mass attached to the base of the anterior mitral valve leaflet (Figure 3), accompanied by severe mitral regurgitation. Cardiac catheterization revealed no significant coronary artery disease. Cardiothoracic surgery was consulted to evaluate the patient for valve replacement.

Blood cultures drawn at the initial hospital grew gram-positive cocci in chains, which were identified as Group B Streptococci (*Streptococcus agalactiae*). Similarly, the embolus removed by vascular surgery was found to contain *Streptococcus agalactiae*. Based on susceptibility testing, the antibiotic regimen was narrowed to ceftriaxone. Cardiothoracic surgery replaced the patient's mitral valve with a bovine prosthesis. This procedure was successful, and there were no complications. The patient's clinical status improved following his surgical procedures, and the patient was discharged home following recovery.¹

EPIDEMIOLOGY

It is estimated that between 10,000 and 15,000 new cases of infective endocarditis (IE) occur each year.¹ Sex and age are major determining factors in the incidence of IE, with man to woman ratios from 3:2 to 9:1 reported.^{2,3} Over the past

40 years, the median age of patients with IE has increased steadily, and greater than half of all IE cases now occur in patients older than 60 years of age.² A number of different organisms are capable of causing IE, but staphylococci and streptococci account for a large majority, representing the etiological agents in 42% and 40% of cases, respectively, in a recent review.⁴ Of the staphylococci, *S. aureus* was found in 31% of cases, with coagulase-negative staphylococci accounting for 11%. In cases involving streptococci, the viridians group accounted for 17% of cases, enterococci 11%, *S. bovis* 7%, and other streptococci found in 5% of cases. Fungi, HACEK-group organisms (*Haemophilus*, *Actinobacillus*, *Cardiobacterium*, *Eikenella*, and *Kingella*) and other gram negative bacteria were each found to be responsible in approximately 2% of cases.⁴ A review of IE cases resulting from Group B streptococcal bacteremia identified that organism as the etiological agent in 30 of 1771 cases (1.7%), with a mean of 8.5 episodes of IE per 100 cases of bacteremia due to *S. agalactiae*.⁵

There are a number of different factors that predispose to the development of IE including injection drug abuse, prosthetic heart valves, and structural heart disease. In addition to the introduction of microbes from injection itself, cocaine and heroin have each been associated with a higher incidence of endocarditis.^{6,7} While the most significant risk factor for right-sided endocarditis is injection drug use, left-sided endocarditis remains more common in this population.⁸ In addition, a recent study found *S. aureus* to be the culprit organism in 82% of cases of IE associated with injecting drug users (IDU).⁹ Prosthetic valve IE occurs in 1 to 4% of valve recipients in the first year following implantation, and 1 percent per year afterwards,¹ with the total number of cases likely to expand in the future, with 100,000 prosthetic valves implanted annually in the United States.¹⁰

Structural heart disease remains the most common underlying risk factor for development of IE, with approximately three-fourths of patients with IE identified as having a cardiac abnormality at the time of disease onset,¹¹ however, the distribution of the responsible underlying abnormality continues to evolve. While rheumatic heart disease was previously found to be the most common lesion,¹² a more recent report shows rheumatic heart disease present in only 6% of patients with IE.¹¹ In contrast, degenerative valvular lesions are becoming more important as a risk factor for IE. Mitral valve prolapse, typically associated with mitral regurgitation, was recently reported to be the underlying cardiac lesion in 22 to 29 percent of cases.^{11,13} Other at-risk cardiac abnormalities are aortic valve disease, present in 12 to 30 percent of cases, and congenital heart disease, present in 10 to 20 percent of cases.¹⁴ The most common congenital heart lesions are bicuspid aortic valves, patent ductus arteriosus, ventricular septal defect, and tetralogy of Fallot, with the highest rates of IE among patients with aortic stenosis and ventricular septal defects.¹⁵ Nosocomial IE is associated with bacteremia resulting from invasive intravascular procedures or

intravenous catheter-related infections, and accounts for up to 20 percent of IE cases.^{13,16} Other predisposing factors for infective endocarditis include hemodialysis,¹⁷ pregnancy,¹⁸ peritoneovenous shunts,¹⁹ and ventriculoatrial shunts.²⁰ Patients with ulcerative lesions of the colon secondary to carcinoma or inflammatory bowel disease are at risk for developing endocarditis secondary to *Streptococcus bovis*.^{21,22}

In patients developing *S. agalactiae* IE, a review found 53% of patients to harbor an underlying systemic condition, such as alcoholism, liver cirrhosis, diabetes mellitus, neoplasia, systemic lupus erythematosus, rheumatoid arthritis, or intravenous drug abuse, in decreasing order of frequency. *S. agalactiae* IE affected a native valve in 83% of patients. In addition, 83% of patients presented with acute IE. The source of infection was identified in 37% of cases, resulting from soft tissue infection, urinary tract infection, or gynecological infection.⁵ In the patient presented here, neither an underlying systemic condition nor a source of infection was identified. Embolization to the patient's right common femoral artery occurred less than three weeks after symptoms began.

APPROACH TO DIAGNOSIS

The diagnosis of IE is typically based on a combination of clinical findings. The initial approach to diagnosis of IE requires a careful and detailed history and physical

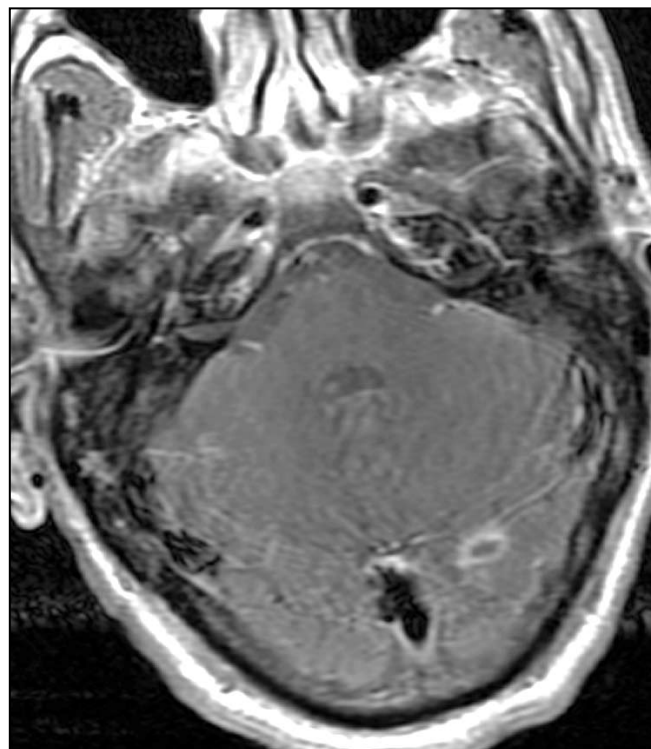


Figure 2. Post-gadolinium T1 weighted magnetic resonance image demonstrates a ring enhancing lesion in the left occipital lobe, most consistent with abscess in this patient with bacterial endocarditis and multiple septic emboli in the brain.

examination, laboratory studies, blood cultures, an electrocardiogram, chest radiograph, and echocardiogram. With regard to the patient's history, attention should be focused on known cardiac lesions, as well as potential sources of bacteremia such as indwelling catheters or intravenous drug use. During the physical examination, special attention should be paid to the cardiac exam for signs of a new regurgitant murmur or the presence of heart failure. In addition, a vigorous search for classical stigmata of IE including evidence of emboli should be pursued, with attention paid to the examination of fundi, conjunctiva, skin and digits. A thorough neurologic exam is also important, potentially revealing evidence of focal neurologic impairment as well as providing a baseline for comparison should abnormalities arise at a later time.

Cutaneous and mucocutaneous findings associated with IE include petechiae, splinter hemorrhages, Janeway lesions, Osler's nodes, and Roth spots. Petechiae, while not specific for IE, are the most common skin finding, usually found on the extremities or on mucous membranes such as the palate or conjunctiva. Splinter hemorrhages are found on the nail bed. Janeway lesions are macular, blanching, nonpainful, erythematous lesions found in a palmoplantar distribution. Osler's nodes are painful, violaceous nodules found in the pulp of fingers and toes, more often seen in subacute than acute IE. Roth spots are edematous, hemorrhagic lesions of the retina.

Blood cultures can significantly contribute to the diagnosis of IE in the absence of classical findings and should always be obtained in suspected cases of IE prior to antibiotic therapy. A minimum of three sets of blood cultures from distinct sites should be obtained in a time frame that corresponds to the severity of the patient's illness. Confounding the interpretation of positive blood culture results is the possibility that organisms usually found as skin contaminants may also cause IE. For organisms likely to cause IE (see epidemiology section above), persistent bacteremia is defined as two positive blood culture samples collected more than 12 hours apart. For organisms considered to be common skin contaminants such as *Propionibacterium* species, *Bacillus* species, *Corynebacterium* species, or coagulase-negative staphylococci, three or a majority of four or more separate blood cultures must be positive.

Apart from blood cultures, other nonspecific laboratory findings may be present in patients with IE. These include an elevated erythrocyte sedimentation rate (ESR) and/or C-reactive protein (CRP), a normochromic normocytic anemia, an elevated white blood cell count and/or thrombocytopenia. Other potential laboratory findings are hyperglobulinemia, cryoglobulinemia, immune complex deposition, decreased complement levels, elevated rheumatoid factor levels, and false positive serologic tests for syphilis. In contrast, an antiphase I IgG titer of greater than 1:800 for *Coxiella burnetii* is a major criteria for diagnosis of IE.²³ A baseline electrocardiogram is also recommended as part of the initial evaluation. Potential findings include ischemia, infarction, heart block, or a conduction delay, providing clues to emboli in the coronary circulation or extension of an infection to the valve annulus and adjacent septum. Chest radiographs may rarely show calcification of a cardiac valve, which may raise the suspicion of IE in a febrile patient. In right-sided IE, patients often present with radiographic evidence of septic pulmonary emboli. An echocardiogram should be performed in all patients with a moderate or high suspicion of IE. Transthoracic echocardiography (TTE) can provide confirmation of a diagnosis of IE via detection of a vegetation; however, TTE has a relatively low sensitivity in detection of a vegetation (29 to 63 percent).²⁴ Transesophageal echocardiography (TEE) has a higher spatial resolution than TTE and is significantly more



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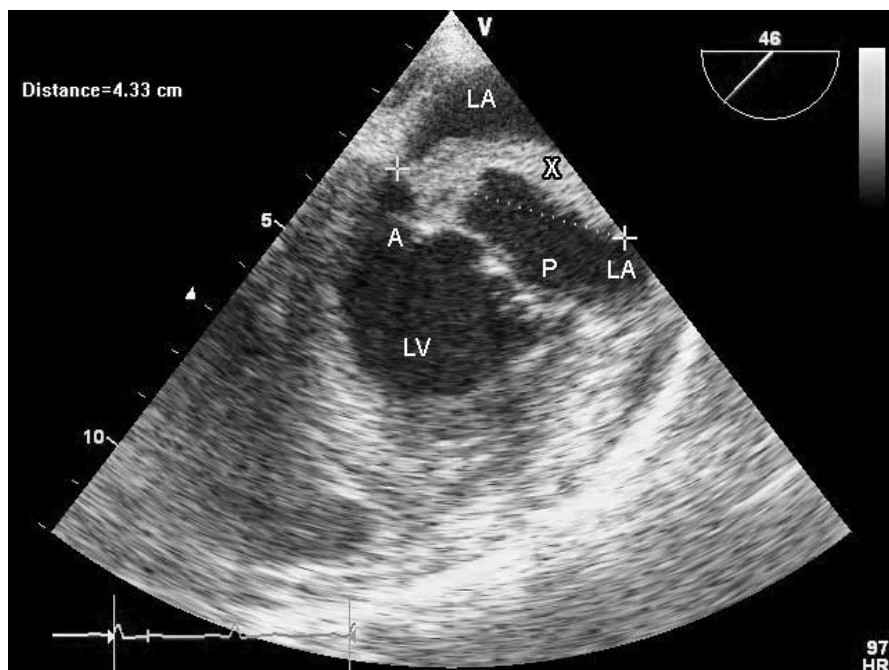


Figure 3. Transesophageal echocardiogram. Two chamber view showing the left ventricle (LV) and left atrium (LA). There is a 4.3 cm vegetation (X) located on the anterior leaflet (A) of the mitral valve. The posterior leaflet (P) of the mitral valve is also visible.

sensitive in detection of IE.²⁴ TEE is especially important for patients with aortic or mitral prosthetic valves, due to both acoustic shadowing caused by the prosthetic valve and the increased risk of IE this patient population. With TEE, the negative predictive value is near 100% in patients with native valves; however, in patients with prosthetic valves, it is important to realize that IE can still be missed.

MODIFIED DUKE DIAGNOSTIC CRITERIA

Infective endocarditis has been recognized as a distinct clinical entity for over a century; however, in the absence of classical symptoms, a diagnosis can be difficult. Initial case definitions for IE relied on pathological analysis of tissue removed at surgery or autopsy.²⁵ This method, while specific, lacked sensitivity and was not clinically practical. Subsequently, the case definition of IE has been progressively modified to the current Duke criteria, first reported in 1994.^{23, 26, 27} Cases are categorized into definite IE, possible IE, or rejected IE. Definite IE is defined by the presence of one or more of the following criteria: direct evidence of IE based on histological findings, positive gram stain results or cultures of specimens obtained at surgery or autopsy, two major clinical criteria, one major criteria and three minor criteria, or five minor criteria. Possible IE is defined as one major and two minor criteria, or three minor criteria. The diagnosis of IE is considered to be rejected if any of the following are met: a firm alternate diagnosis is made, resolution of clinical manifestations occurs after four days of antibiotic therapy or less, or clinical criteria for possible or definite IE are not

met. The major clinical criteria are: 1) persistently positive blood cultures for organisms that are typical causes of IE, 2) vegetations or other typical findings of IE present on echocardiography including new or partial dehiscence of a prosthetic valve or an abscess in the tissues surrounding a heart valve, 3) evidence of endocardial damage such as a new regurgitant murmur, 4) serological or culture evidence of infection with *Coxiella burnetii*.²³ The minor clinical criteria are: 1) fever, 2) the presence of a predisposing valvular condition, defined as a prosthetic heart valve or a valve lesion that leads to significant regurgitation or turbulence of blood flow, or intravenous drug abuse, 3) "vascular phenomenon" such as emboli to organs or the brain, hemorrhages in the mucous membranes around the eyes, 4) "immunologic phenomenon" such as glomerulonephritis, or lesions such as Roth's spots, Janeway lesions, Osler's nodes, or a positive rheumatoid factor test, 5) positive blood cultures that do not meet the strict definitions of a major

criterion. The original Duke criteria and modified Duke criteria for diagnosis of IE have been validated in multiple studies.^{26, 28, 29}

ANTIMICROBIAL PROPHYLAXIS

The pathogenesis of IE is thought to require a particular sequence of events. Initially, there is formation of a small noninfected thrombus on an abnormal endothelial surface. Next, infection of this nidus occurs with bacteria that are transiently circulating in the bloodstream. Finally, there is proliferation of bacteria resulting in the formation of vegetations on the endothelial surface. As the occurrence of a bacteremic state is critical to initiation of the series of events leading to IE, it is thought to be reasonable that preventing transient bacteremia will reduce the occurrence of IE in the presence of a predisposing cardiac lesion. Current American Heart Association (AHA) recommendations for antimicrobial prophylaxis for dental and other procedures is focused on available evidence, limiting prophylaxis to patients with the highest risk of developing IE,^{30, 31} while previous guidelines advocated prophylaxis for patients at both high and moderate risk.³² High risk patients include those with prosthetic heart valves, a history of IE, unrepaired cyanotic congenital heart disease, repaired congenital heart disease involving prosthetic material in the first six months after the procedure, repaired congenital heart disease with residual defects at or adjacent to the site of the prosthetic material, and cardiac valvulopathy in a transplanted heart.³¹ Notable differences from previous guidelines are

the removal of the recommendation for prophylaxis in patients with bicuspid aortic valves, acquired aortic or mitral valve disease, and hypertrophic cardiomyopathy with latent or resting obstruction. Procedures for which prophylaxis is indicated in patients with the above cardiac defects are those likely to result in transient bacteremia with organisms capable of causing IE. These include: 1) dental procedures that involve manipulation of either the gingival tissue or periapical region of teeth, or perforation of the oral mucosa; 2) procedures involving incision or biopsy of the respiratory tract mucosa, such as tonsillectomy, adenoidectomy, or bronchoscopy involving biopsy. The most recent AHA guidelines do not consider any genitourinary or gastrointestinal procedures high risk, and, as such, prophylaxis is not indicated even in high risk patients.³¹ However, in high risk patients that harbor an underlying infection, prophylaxis is recommended prior to virtually all invasive procedures. For patients undergoing a dental procedure, the preferred regimen is oral amoxicillin, two grams given 30 to 60 minutes prior to the procedure. Otherwise, the antibiotic to be used is specific to both the patient and the procedure.³¹ Importantly, the present guidelines are not intended to be the standard of care in all situations. Physicians are encouraged to use their own judgement in the use and duration of prophylaxis in individual cases.³¹

TREATMENT

Prior to the advent of effective antimicrobial therapy, IE was invariably fatal. Standard antimicrobial therapy for IE is generally administered to patients characterized as definite or probable by the Duke criteria, as defined above. Ideally, therapy should be tailored to the specific organism isolated from blood cultures.³³ However, in acutely ill patients, whereby a delay in therapy would lead to an unacceptable risk of further complications, empirical therapy may be necessary. Empirical therapy should only be started after at least two, and preferably three, blood cultures have been obtained from distinct sites. In general, the choice of antimicrobial therapy should reflect the pathogens most likely to be involved, providing coverage for staphylococci (both methicillin-susceptible and resistant), streptococci, and enterococci. Vancomycin and gentamicin is an appropriate empiric regimen in most patients. The counting of days of recommended duration of therapy starts on the first day in which blood cultures were negative.³³ At least two sets of blood cultures should be obtained every 24 to 48 hours until bloodstream infection is cleared. In general, native valve IE is treated with four weeks of intravenous antibiotics, while prosthetic valve IE and complicated native valve IE are treated for six weeks; however, dependent on the specific organism, resistance, and risk factors involved, the treatment duration will vary.³³ In IE caused by *S. agalactiae*, recommended antibiotic therapy is penicillin G or ceftriaxone for 4 to 6 weeks plus gentamicin for the first two weeks.^{34, 35}

SURGICAL INTERVENTION

Early consultation with cardiothoracic surgery should be obtained in all cases in which complications are observed or expected. Recommendations for surgical replacement of native valves in IE include heart failure, especially if moderate to severe, caused by infected valve dysfunction, severe mitral or aortic regurgitation with evidence of abnormal hemodynamics, IE resulting from fungal or other highly resistant organisms, and perivalvular abscess or fistula formation.³¹ In addition, there are a number of possible indications for surgical intervention. These include: embolic events occurring while the patient is on an appropriate antibiotic regimen or associated with a large vegetation (greater than 10mm in diameter); and large vegetations, in the absence of embolic events, if mobile and associated with other signs of severe disease. Positive blood cultures after 5 to 7 days of appropriate therapy, or a lack of clinical improvement after seven days of treatment is also considered to be an indication for surgical intervention, but only after a complete search for a metastatic abscess (focus of infection) is performed.³¹ Large vegetations and valve destruction are common sequelae of IE caused by *S. agalactiae*, necessitating cardiac surgery in a large percentage of cases.³⁶⁻³⁸

EMBOLIZATION

The risk of embolization from IE varies from 13 to 44 percent in various studies, rapidly declining after the initiation of appropriate antimicrobial therapy, and becoming uncommon several weeks after therapy is initiated.³⁹ In IE resulting from *S. agalactiae* infection, embolic phenomena have been found in approximately 50% of patients³⁶⁻³⁸ and frequently represent the manifestation leading to the diagnosis of IE.⁵ There is no defined number of embolic events required as a prerequisite for surgical intervention, although a second embolic event after initiation of antimicrobial therapy is commonly used as an indication. Emboli can obstruct or damage almost any size vessel, in either the systemic or pulmonary circulation, resulting in stroke, blindness, ischemic or gangrenous extremities, unusual pain syndromes secondary to renal or splenic infarction, hypoxia due to pulmonary emboli, or paralysis resulting from brain or spinal cord emboli. As in the brain emboli of our case patient, emboli are often clinically silent, so it is important to perform appropriate imaging studies to document embolization in a high risk patient. An important consideration is surgical risk in the context of a recent embolic stroke; however, a recent review of patients with IE undergoing cardiac surgery showed no significant difference in perioperative mortality among patients with embolic infarcts versus those without.⁴⁰

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