Infective Endocarditis

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Case Vignette

A 13-year-old previously healthy male presented to the emergency department with a 4-day history of fever, neck pain, headache, and vomiting with severe myalgia for 1 day. He had no history of sick contacts or upper respiratory symptoms. On physical examination he appeared tired, and his temperature was 39.5 °C, BP 110/50 mmHg, respiratory rate 20–40/min, and heart rate 90–120/min. He had diffuse muscle tenderness in his arms and legs, a soft grade 2/6 systolic murmur, and hepatosplenomegaly, which was confirmed with abdominal ultrasound. His white blood cell count was 2800/mm^3, hemoglobin 12.0 gm/dL, hematocrit 33.8%, and platelet count 70,000/mm^3, and C-reactive protein was elevated at 133 mg/L. Three separate blood cultures were drawn. He was started on IV vancomycin and ceftriaxone and admitted for further management.

A transthoracic echocardiogram revealed a bicuspid aortic valve, mild to moderate aortic valve insufficiency, and a small vegetation on the mitral valve where an aortic regurgitation jet hits the anterior leaflet. An MRI of the cervical spine obtained to investigate neck pain instead revealed a left cerebellar enhancing lesion that on further imaging was thought to be a brain microabscess. All three blood cultures subsequently grew *Staphylococcus aureus* sensitive to oxacillin. Treatment was changed to IV oxacillin plus gentamicin (for 5 subsequent days to achieve synergistic effect). Follow up two-dimensional transthoracic echocardiography confirmed the presence of an enlarging vegetation at least 10 mm in diameter. Subsequently he had acute mental changes including loss of short-term memory and disorientation. The following day, the vegetation was surgically removed, and the mitral valve was

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A. P. Sarnaik et al. (eds.), *Cardiac Emergencies in Children*,
https://doi.org/10.1007/978-3-319-73754-6_18

repaired with a bovine patch without resection of the native valve. He improved with a 6-week course of IV oxacillin. Patient returned to normal health.

Epidemiology of Infective Endocarditis

Infective endocarditis (IE) is seen less frequently in children than in adults, although over the last few decades, the incidence among children has increased in developed countries. This increase is attributed to the improved survival of patients with congenital heart diseases (CHD), the use of prosthetic devices for correction or palliation of heart defects, and more frequent and prolonged use of central venous catheters for medication infusion and blood drawing [1–5]. A recent analysis of the Healthcare Cost and Utilization Project's National Inpatient Sample (NIS) for 2000–2011 showed that the incidence of IE in the USA increased from 11 per 100,000 population to 15 per 100,000 across all age groups [6]. In another recent analysis of pediatric admissions in the same database for 2000–2010, the incidence of IE in pediatric patients was steady at 0.43 per 100,000 children throughout the study period [7].

Rheumatic heart disease was the underlying risk factor of IE in 30–50% of patients before the 1970s [9, 10]; however, recent reports show that this association has decreased to 1–5% [4, 11]. The incidence of IE is much higher in children with CHD, reaching up to 6.1 per 1000 children [12]. Children with cyanotic CHD are at higher risk [8, 11, 12]. Surgery for CHD is a major risk factor for IE. In a cohort of children with IE seen between 1980 and 2011, IE developed in 50% (24/47) of children with CHD after surgical repair. Similar rates of IE (~50%) were found in post-surgical patients with CHD in another case series [11]. In a large cohort study, aortic valve stenosis was the most common underlying CHD of IE, which developed after repair with a prosthetic valve [13]. However, between 18 and 31% of children with IE have no underlying cardiac defect [4, 8, 11]. In about 7% of children, IE is diagnosed within the first month of life, [3] and most patients in this age group (~70%) do not have an underlying CHD. Extreme prematurity, prolonged use of central venous catheters, and major surgeries are the notable risk factors in this age group [14–16].

Pathophysiology of Infective Endocarditis

Turbulent blood flow in the heart from an area of high pressure to an area of low pressure damages the endothelium on the down-pressure side, which becomes a nidus for infection and subsequent vegetation. Such turbulent blood flow can be generated by blood flowing across congenital atrial or ventricular defects, regurgitant or stenotic valves, or the endocardial cushion defect. The endothelium can also be injured by a foreign body, such as palliative shunts, conduits, and central venous catheters. The site of damaged endothelium and the exposed collagen underneath is the site of thrombogenesis where platelets, fibrin, and RBCs attach leading to the formation of sterile

vegetation called nonbacterial thrombotic endocarditis (NBTE) [2, 9]. Transient bacteremia occurring because of daily activities such as tooth brushing, flossing, or chewing food seeds the NBTE nidus. Tooth extraction, periodontal surgery, and tonsillectomy are also particularly likely to cause bacteremia. Right-sided endocarditis occurs as a result of bacteremia due to intravenous drug abuse and cardiovascular electronic leads implanted in the right side of the heart [9]. Gram-positive pathogens including *Staphylococcus aureus*, *Streptococcus* species, and *Enterococcus* species express surface molecules called adhesins that are important in attaching the pathogen to the denuded endothelium and sterile vegetations [17]. Subsequently, the formation of vegetation which is composed of bacteria, fibrinogen, and platelets traps the organisms inside which help evade the phagocytes in the circulating blood. Endocarditis in neonates often involves the right side of the heart because of the disruption of endothelium by and concomitant bacteremia caused by central venous catheter contamination. Other possible sources of transient bacteremia in neonates are parenteral nutrition, umbilical catheters, vigorous endotracheal suctioning, and trauma to skin and mucous membranes [2].

Microbiology of Infective Endocarditis

Viridans group *Streptococcus* (VGS) such as *S. sanguis*, *S. mitis*, and *S. mutans* are frequent causes of IE. *Staphylococcus* species including *S. aureus* and coagulase-negative *Staphylococcus* (CONS) are more common than streptococci in causing IE in pediatric patients. *S. aureus*, CONS, and *Candida* species are more commonly isolated from newborns with IE [9].

Historically VGS has been the most common causative agent in children with underlying heart disease after the first year of life [2, 9]. However, recent reviews indicate that *S. aureus* has become the most common pathogen in patients with underlying heart disease after the first year of life [3, 7, 18]. This change was caused by the advanced surgical care and prolonged use of central venous catheters (CVC) in patients with CHD. *S. aureus* is also the most common cause of acute onset rapidly progressing IE.

Enterococci are less commonly found in children with IE than in adults. Gram-negative oropharyngeal flora, the so-called AACEK organisms (formerly HACEK) comprising of *Aggregatibacter* (formerly *Haemophilus*) *parainfluenzae*, *Aggregatibacter* (formerly *Actinobacillus*) *actinomycetemcomitans*, *Cardiobacterium hominis*, *Eikenella corrodens*, and *Kingella kingae*, are other less common causes of endocarditis in children. Among this group *K. kingae* and *A. parainfluenzae* are the more common ones causing IE in children [19]. Enteric gram-negative bacteremia associated with central venous catheters is common, but it generally does not lead to IE, because these gram-negative bacteria cannot adhere to the denuded valves.

Rarely IE is caused by fastidious pathogens previously referred to as nutritionally variant streptococci (NVS) comprised of *Abiotrophia* and *Granulicatella* sp. These pathogens depend on nutrients (L-cysteine and pyridoxal) for their growth and are difficult to grow in regular blood culture medium.

Table 18.1 Organisms isolated in children with infective endocarditis by study and period

	Stockheim et al. [20] (1978–1996) (*n* 134)	Johnson et al. [5] (1980–2011) (*n* 47)	Alshammary et al. [18] (1985–2004) (*n* 37)	Day et al. [3] (2000–2003) (*n* 632)
Organism				
VGS	35 (26%)	17 (36%)	5 (12.5%)	124 (20%)
S. aureus	30 (22%)	12 (25%)	16 (40%)	362 (57%)
Non-VGS (not *S. pneumoniae*)	7 (5%)	2 (4%)	4 (10%)	29 (5%)
S. pneumoniae	8 (6%)	2 (4%)	3 (7.5%)	≤10 (1%)
NVS	1 (0.7%)	3 (6%)	1 (2.5%)	
CONS	13 (10%)	3 (6%)	3 (7.5%)	91 (14%)
AACEK	5 (4%)	4 (8%)		≤10 (1%)
Enterococcus sp.	4 (3%)	1 (2%)	3 (7.5%)	
Other gram-negative	12 (9%)	1 (2%)	2 (5%)	12 (2%)
Candida sp.	4 (3%)	1 (2%)		
Others	15 (11%)	1 (2%)		

VGS Viridans group *Streptococcus*, *CONS* Coagulase-negative *Staphylococcus*, *NVS* Nutritionally variant *Streptococcus*, *AACEK Aggregatibacter parainfluenzae*, *Aggregatibacter actinomycetemcomitans*, *Cardiobacterium hominis*, *Eikenella corrodens*, and *Kingella kingae*, *n* number of culture-positive cases

Culture-negative endocarditis is seen in up to 10% of the cases, which is likely the result of previous antibiotic treatment or caused by fastidious pathogens such as *Coxiella burnetii*, *NVS*, *Bartonella* sp., *Brucella* sp., *or Legionella* species [2, 9].

Organisms isolated in children with infective endocarditis from four recent reviews at large North American centers are listed in Table 18.1.

Clinical Presentation of Infective Endocarditis

Infective endocarditis can present as a subacute illness progressing over a period of a few weeks or as an acute illness with short prodrome and sepsis-like presentation. Subacute presentation is marked by a generally persistent prodrome period of nonspecific symptoms such as low-grade fever (75–100%), malaise (50–75%), anorexia/weight loss (25–50%), arthralgia (17–50%), and chest pain (0–25%) that are generally persistent over a prolonged period of time [20].

Physical signs of IE are mainly the manifestations of valvular damage, embolic phenomena, or immune complex-mediated involvement of different body systems. Cardiac manifestations of IE from valve damage such as murmurs are variable and dependent on preexisting underlying heart disease. New or changed murmurs are found in 21–50% of children with IE. Immune complex deposition in the subcutaneous tissues of extremities leads to the development of small painful Osler nodes (0–10%). Embolic phenomenon in the skin of palms and soles produces Janeway lesions (0–10%) which are painless macules. Splinter hemorrhages in the nail beds (0–10%) and Roth spots with central pallor in the retina (0–10%) are manifestations

of small hemorrhagic phenomenon. Embolization of vegetation (25–50%) from the left side of the heart to the abdominal viscera can cause sharp abdominal pain and visceral abscesses; and embolization to the brain may result in mycotic aneurysms and infarcts. Petechiae are seen in 21–50% and splenomegaly in 50–75% of patients. Glomerulonephritis due to immune complex deposition or renal infarcts due to embolization can manifest as hematuria [9, 20, 21].

Diagnosis of Infective Endocarditis

Laboratory Tests

The prompt evaluation and diagnosis of IE are critical to appropriate treatment. The hallmark for diagnosis of IE is serial positive blood cultures. Serial blood cultures (three to five specimens) should be obtained from different venipuncture sites over a period of time, at least 1 hour apart, to optimize recovery of a pathogen in the hemodynamically stable patient before beginning antimicrobial treatment [9, 22]. Modern blood culture technologies can detect nutritionally variant *Streptococcus* (*Abiotrophia* species) and AACEK group organisms. All other laboratory tests other than serial positive blood cultures are nonspecific for IE. A complete blood count may show anemia with thombocytopenia [21]. The erythrocyte sedimentation rate (ESR) is typically elevated, and the rheumatoid factor (RF) is characteristically positive especially in subacute endocarditis. Urinalysis may reveal hematuria, and serum complement levels may be low, suggestive of consumption [21].

Echocardiographic Changes

Echocardiography is paramount to evaluating IE in children and should be performed early to rapidly confirm the diagnosis. Two-dimensional imaging can detect vegetations as small as 2 mm, intracardiac abscesses, and other perivalvular abnormalities. Negative echocardiograms should be interpreted cautiously because images acquired early in the course of IE may miss small vegetations. Echocardiography should be repeated in 7–10 days if concern for IE continues. Transthoracic echocardiography (TTE) is usually adequate for initial rapid imaging and has a higher sensitivity in pediatric patients ($\geq$80%) compared to adults (40–63%) [9, 21–23]. In IE, transesophageal echocardiograph (TEE) can be useful in evaluating patients with congenital heart disease or with complex cardiac anatomy, especially patients with indwelling foreign bodies, including prosthetic valves or post-cardiac surgery patients [2, 21].

Modified Duke Criteria

In the initial emergency department or critical care evaluation of a patient with possible endocarditis, an early, definitive diagnosis of IE may not be possible because it takes time for cultures to be identified as positive for bacterial growth and for echocardiographic changes to occur. However, in patients admitted to outside

Table 18.2 Modified Duke criteria for diagnosing infective endocarditis

Definite infective endocarditis
Pathologic criteria
1. Microorganism detected by culture or histologic examination of a vegetation, an embolized vegetation, or an intracardiac abscess
2. Pathologic lesions (a vegetation or intracardiac abscess) confirmed by histologic examination showing active endocarditis
Clinical criteria[a]
1. Two major criteria
2. One major criterion and three minor criteria
3. Five minor criteria
Possible infective endocarditis
1. One major criterion and one minor criterion
2. Three minor criteria
Rejected
1. Firm alternate diagnosis explaining manifestations of infective endocarditis
2. Resolution of infective endocarditis syndrome with antibiotic therapy for ≤4 days
3. No pathologic evidence of infective endocarditis at surgery or autopsy, with antibiotic therapy for ≤4 days
4. Does not meet criteria for possible infective endocarditis, as above

[a]See Table 18.3 for definitions of major and minor criteria. These criteria have been universally accepted and are in current use [22]. Reprinted [with minor modifications] from Li et al. [24] (copyright © 2000, Oxford University Press) with permission from the publisher

facilities and then transferred to tertiary care centers for more specialized care, blood cultures may now be positive, echocardiographic findings may be distinct, or empiric treatment for IE may have begun before transfer. Therefore, it is appropriate for emergency clinicians to be familiar with the 2000 modified Duke diagnostic criteria for IE [24] (Tables 18.2 and 18.3) [23].

Recognizing Life-Threatening Presentations of IE

In addition to the common symptoms of IE reviewed above, patients with life-threatening IE can have new heart failure symptoms and may have a sepsis-like presentation. Although nearly all patients with IE have fever, only 25–50% of children with IE have heart failure, and only 0–25% have chest pain [21]. A focal neurologic deficit may be important if it is associated with an ongoing or recurrent embolic event. As vegetations grow, they may break off and embolize to the lungs in right-sided IE or to the central nervous system, spleen, or extremities in left-sided IE. These events may predominate in some patients; therefore, patients with fever and central nervous system symptoms (including severe headache, sterile meningitis, or focal neurologic signs), pneumonia, or pulmonary embolism should have immediate evaluation for IE [25, 26].

Table 18.3 Major and minor criteria in the Modified Duke Criteria for diagnosing infective endocarditis

Major criteria
1. Blood culture positive for IE
(a) Typical microorganisms consistent with IE from two separate blood cultures
(i) Viridans streptococci (including nutritionally variant strains A*biotrophia* species)
(ii) *Streptococcus bovis*
(iii) AACEK group
(iv) *Staphylococcus aureus*
(v) Community-acquired enterococci, in the absence of a primary focus
(b) Microorganisms consistent with IE from persistently positive blood cultures, defined as follows:
At least 2 positive cultures of blood drawn either >12 h apart
or
All of 3 or a majority of ≥4 separate cultures of blood
(c) Single positive blood culture for *Coxiella burnetii* or
IgG antibody titer >1:800
2. Evidence of endocardial involvement by positive echocardiogram for IE (transesophageal echocardiography recommended in patients with prosthetic valves, transthoracic echocardiography as first test in other patients) defined as follows:
(i) 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)
(ii) Abscess
(iii) New or partial dehiscence of prosthetic valve
New valvular regurgitation (worsening or changing of preexisting murmur not sufficient)
Minor criteria
1. *Predisposition*: Predisposing heart condition or injection drug use
2. *Fever*: temperature > 38° C
3. *Vascular phenomena*: Major arterial emboli, septic pulmonary infarcts, mycotic aneurysm, intracranial hemorrhage, conjunctival hemorrhages, Janeway lesions
4. *Immunologic phenomena*: Glomerulonephritis, Osler nodes, Roth spots, rheumatoid factor
5. *Microbiological evidence*: Positive blood culture but does meet a major criterion as noted above[a] or serological evidence of active infection with organism consistent with infective endocarditis

AACEK indicates *Aggregatibacter* (formerly*) parainfluenzae*, *Aggregatibacter* (formerly *Actinobacillus*) *actinomycetemcomitans*, *Cardiobacterium hominis*, *Eikenella corrodens*, and *Kingella kingae*; *IgG* immunoglobulin G, *TEE* transesophageal echocardiography, and *TTE* transthoracic echocardiograph. These criteria have been universally accepted and are in current use [22]. Reprinted [with minor modifications] from Li et al. [24] (copyright © 2000, Oxford University Press) with permission from the publisher

Managing of Infective Endocarditis in the Emergency Department

Initial Assessment and Evaluation

When IE is suspected, the most urgent evaluation in the emergency department is hemodynamic status. If heart failure is suspected, echocardiographic imaging and several closely spaced blood cultures should be obtained without delay, in addition to routine tests, such as a complete blood count with differential to assess for anemia and thrombocytopenia and a metabolic panel including renal function assessment. Hemodynamic support such as administering vasopressors and transfer to a critical care unit may be necessary including immediate empiric antimicrobial therapy (see below). Patients with confirmed heart failure may require urgent cardiac surgery [9, 21, 22].

Treating Infective Endocarditis

The American Heart Association has issued and updated comprehensive guidelines for treating IE [9, 22, 23]. Presumptive antibiotic treatment is based on the patient's age, clinical presentation, preexisting cardiac status, recent surgery, and local antimicrobial sensitivity. Antimicrobial therapy should begin only after appropriate blood cultures have been obtained. Until the cultures can be evaluated, empiric therapy is generally required [22]. Renal function should be assessed if vancomycin or gentamicin is administered. Reviewing and defining the choice of parenteral therapy with an infectious disease specialist is recommended [9, 22]. Finally, empiric therapy should be revised to a focused, narrowed therapy for any specific pathogen identified by blood culture or by other laboratory methods.

For patients with an acute clinical presentation (days) with suspected or proven native valve infection, empiric coverage for *S. aureus*, streptococci, and aerobic gram-negative bacilli may include intravenous (IV) vancomycin and cefepime. For patients with a subacute (weeks) presentation of native valve infection, empirical coverage of *S. aureus*, viridans group streptococci, AACEK, and enterococci with IV vancomycin and ampicillin-sulbactam (Unasyn®) is reasonable [22].

For patients with suspected or proven prosthetic valve infection, treating *Staphylococcus*, enterococci, and aerobic gram-negative bacilli is reasonable if the onset of symptoms is within 1 year of surgical placement of the valve. This regimen may include IV vancomycin, rifampin, gentamicin, and cefepime. However, if the onset of symptoms is >1 year after valve placement, IV vancomycin and ceftriaxone may be appropriate to cover staphylococci, viridans group streptococci, and enterococci [22].

Surgical Evaluation

In the emergency department, immediate consultation with cardiology and cardiovascular surgery may be warranted in several groups of patients:

- Patients with left-sided native valve endocarditis, prosthetic valve endocarditis (PVE), and, rarely, right-sided native valve IE, who may benefit from early valve surgery
- Patients with suspected or confirmed IE with symptoms or signs of heart failure [9, 21, 22]
- Patients with new heart block and annular or aortic abscess or destructive penetrating lesions
- Patients with PVE and heart failure secondary to valve dehiscence, intracardiac fistula, or severe prosthetic valve dysfunction and those with relapsing PVE
- Patients with recurrent emboli and persistent or enlarging vegetations despite appropriate antimicrobial therapy and those with severe valvular regurgitation and mobile vegetations at least 10 mm in diameter
- Patients with right-sided IE with tricuspid valve vegetations at least 20 mm in diameter and recurrent pulmonary embolism despite antimicrobial therapy
- Patients with IE caused by fungal pathogens or highly resistant bacterial pathogens recovered from blood cultures or previously documented at the outside referring center [9, 22, 27–29].

Complications of Infective Endocarditis

Complications of IE include valve damage, spread of infection (perivalvular), or heart failure. Heart failure may result from the incompetence of the valve after infection of the chordae tendineae with rupture or by obstructive lesions (vegetations) or other damage to key cardiac structures. Perivalvular infection extension may result in cardiac abscess, fistula, or pseudoaneurysm [21]. Additionally, in PVE, infection may cause the prosthesis to become unstable [9]. Emboli from right-sided endocarditis may cause necrotizing pneumonia and prolonged fever, whereas emboli from left-sided endocarditis can lead to systemic emboli to central nervous system, visceral organs, limbs, and coronary arteries. Septic emboli may result in hemorrhage, infarct, or abscess in intra-abdominal organs [9, 21, 22, 26]. When these septic emboli travel to the central nervous system, they may result in stroke symptoms or mycotic aneurysm [9, 21, 22, 26]. Renal failure can occur from immune complex deposition or as an adverse side effect of therapy [21].

Outcomes and Preventing Infective Endocarditis

More than 90% of children with native valve endocarditis due to viridans group streptococci can be cured. Cure rates for enterococci IE vary from 75 to 90% when treated with synergistic antibiotics; cure rates are lower for *S. aureus*, in the range of 60–75%. Gram-negative bacilli IE cure rates are even lower at less than 50%; fungal IE cure rates are under 20% [21].

The 2007 American Heart Association guidelines recommend antibacterial prophylaxis before high-risk dental procedures in the highest-risk groups. These groups include patients with a history of cardiac valve repair with prosthetic valve or material, previous IE, and certain congenital heart diseases (unrepaired cyanotic CHD, repaired CHD with prosthetic material or a device during the first 6 months postprocedure, repaired CHD with residual defects at the site adjacent to the site of the prosthetic patch or device) and recipients of heart transplants who have cardiac valvulopathy [9, 22, 30].

Infective Endocarditis Clinical Pearls

- Incidence of infective endocarditis in children has increased over the past few decades due to improved survival of children with congenital heart disease, use of prosthetic devices for correcting heart defects, and more frequent and prolonged use of central venous catheters.
- Incidence of infective endocarditis is highest in children with congenital heart disease. Surgery for congenital heart disease is a major risk factor.
- Turbulent flow in the heart from an area of high pressure to an area of low pressure damages the endothelium in the down-pressure area which becomes a nidus for infection and subsequent vegetation.
- *Staphylococcus aureus* has replaced viridans group *Streptococcus* (VGS) as the most common cause of infective endocarditis in children with underlying heart disease after the first year of life. Gram-negative oropharyngeal flora, the so-called AACEK (previously HACEK) organisms, are a less common cause of infective endocarditis in children. Rarely, fastidious pathogens, previously referred to as nutritionally variant streptococci (NVS), now comprised of *Abiotrophia* species, can cause infective endocarditis.
- Infective endocarditis can present as subacute illness progressing over a few weeks or as acute illness with sepsis-like presentation. Subacute presentation may include with nonspecific symptoms such as low-grade fever, malaise anorexia/weight loss, headache, and arthralgia. Physical signs are mainly the manifestations of valvular damage, embolic phenomenon, and immune complex-mediated involvement of different body systems.
- The hallmark diagnosis of infective endocarditis is serial positive blood cultures obtained, over a period of time, from different venipuncture sites. Blood count may show anemia and thrombocytopenia. The erythrocyte sedimentation rate is typically elevated. Urinalysis may show hematuria, and serum complement concentration may be low.

- Echocardiography is paramount to evaluating infective endocarditis in children. Two-dimensional imaging can detect vegetations as small as 2 mm. Transthoracic echocardiography is usually adequate for initial rapid imaging (sensitivity is 80% in children). Transesophageal echocardiography can be useful in evaluating patients with congenital heart disease or with complex cardiac anatomy.
- The Modified Duke Criteria are useful in making or rejecting the diagnosis of infective endocarditis. Major criteria are based on blood cultures and echocardiography results. Minor criteria are based on predisposing heart condition, fever, and signs of vascular and immunologic phenomena.
- Patients with life-threatening infective endocarditis can have heart failure symptoms and may have sepsis-like presentation. The most urgent evaluation in the emergency department is hemodynamic status. If heart failure is suspected, echocardiography and several closely spaced blood cultures should be obtained without delay. Hemodynamic support and transfer to a critical care unit may be necessary.
- Presumptive antibiotic treatment is based on the patient's age, clinical presentation, preexisting cardiac status, recent surgery, and local antimicrobial sensitivity. Reviewing and defining the choice of parenteral therapy with an infectious disease specialist is warranted. The American Heart Association has issued and updated comprehensive guidelines for treating infective endocarditis.
- In the emergency department, immediate consultation with cardiology and cardiovascular surgery may be warranted in several groups of patients including those with left-sided native valve endocarditis, prosthetic valve endocarditis, heart failure, recurrent emboli and those with tricuspid valve vegetation at least 20 mm in diameter.

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