REVIEW

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Clinical Practice Update on Infectious Endocarditis

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ABSTRACT

Infectious endocarditis is a highly morbid disease with approximately 43,000 cases per year in the United States. The modified Duke Criteria have poor sensitivity; however, advances in diagnostic imaging provide new tools for clinicians to make what can be an elusive diagnosis. There are a number of risk stratification calculators that can help guide providers in medical and surgical management. Patients who inject drugs pose unique challenges for the health care system as their addiction, which is often untreated, can lead to recurrent infections after valve replacement. There is a need to increase access to medication-assisted treatment for opioid use disorders in this population. Recent studies suggest that oral and depo antibiotics may be viable alternatives to conventional intravenous therapy. Additionally, shorter courses of antibiotic therapy are potentially equally efficacious in patients who are surgically managed. Given the complexities involved with their care, patients with endocarditis are best managed by multidisciplinary teams.

KEYWORDS: Addiction; Echocardiography; Endocarditis; Multidisciplinary care; Nuclear imaging

Infectious endocarditis (IE) is a disease process with significant in-hospital mortality ranging between 15% and 20%.[1] This is as a result of a multitude of factors including patients' preexisting comorbidities, illness acuity, delays in diagnosis, lack of or delays in surgical intervention, the need for coordination between multiple medical and surgical specialties, and lack of long-term follow-up. In addition to its significant morbidity, IE also incurs significant costs to health care delivery systems as a result of long lengths of stay and expensive diagnostic tests.[1] The increasing number of patients who inject intravenous drugs and subsequently develop endocarditis also creates new ethical dilemmas for medical providers to address.[2,3] All of this is complicated by a dearth of randomized controlled trials involving patients with endocarditis. For these reasons, navigating the care of an endocarditis patient from admission to discharge may be among the most challenging tasks today's medical providers face. Although there is an existing American Heart Association (AHA) endocarditis guideline, this article will also include recent literature not addressed in the AHA review such as updates on the diagnosis, risk-stratification, and treatment of IE as well as the role of multidisciplinary endocarditis teams.

DIAGNOSIS

The diagnosis of IE can be particularly challenging, especially in patients with negative blood cultures who comprise anywhere from 2% to 71% of all endocarditis cases.[4] The Modified Duke Criteria have been used as the primary diagnostic criteria for endocarditis since their publication in 2000 (Table 1).[5] The algorithm uses a combination of major microbiologic and echocardiographic findings as well as minor clinical and microbiological criteria to stratify

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patients as having definite, possible, or rejected endocarditis. Despite their widespread and long-standing use, the Duke Criteria have a reported sensitivity between 70% and 79%.[6] As a result, the diagnosis of endocarditis cannot be made solely by these parameters and instead is made after considering a variety of clinical factors. The relative insensitivity of the Duke Criteria can be attributed to a number of factors, including culture-negative cases, which are most commonly the result of antibiotic administration before obtaining blood cultures. The yield of blood cultures increases with the number of cultures obtained with literature demonstrating that sensitivity increases from 73%-80% with 1 culture to 85%-98% with 3.[7] Medical providers can help increase the likelihood of appropriately diagnosing endocarditis by ensuring prompt acquisition of 3 blood cultures prior to the initiation of antibiotics. Additionally, specific pathogens included in the Duke Criteria should alert physicians to their patients' increased risk of endocarditis. Gram-positive pathogens such as *Staphylococcus aureus, Enterococcus faecalis*, and alpha-hemolytic streptococcus as well HACEK (*Haemophilus* spp., *Aggregatibacter* spp., *Cardiobacterium* spp., *Eikinella corrodens*, and *Kingella kingae*) organisms are strongly associated with IE.[5] Prompt consultation with an infectious disease specialist can help guide further evaluation and, for some organisms, decrease mortality.[8] In patients undergoing surgical valve repair or replacement for culture-negative endocarditis microbiologic diagnosis can be aided by the use of 16 S ribosomal RNA (rRNA) sequencing. This relatively novel testing uses polymerase chain reaction (PCR) to identify bacterial RNA from excised native valve tissue or prosthetic material. In patients with definite endocarditis and negative blood cultures, the sensitivity of 16 S rRNA sequencing is reported to be has high as 80% with a false-positive rate of only 3%.[9]

Echocardiographic findings are the other major component of the Duke Criteria. Transthoracic echocardiography is a noninvasive tool that can screen patients for endocarditis. However, the overall sensitivity of this modality is approximately 70% in native valves and is

CLINICAL SIGNIFICANCE

- The Duke Criteria are insensitive for diagnosis of infectious endocarditis and can be enhanced by cardiac positron emission tomography (PET).
- Patients with infectious endocarditis who inject drugs pose unique challenges. Their care is ideally comanaged with addiction specialists. They may be candidates for shorter courses of intravenous antibiotics or conversion to oral or long-acting intramuscular therapy.
- Given the complexity of patients with infectious endocarditis and involvement of numerous specialists, their care is best managed by multidisciplinary teams.

Table 1 Modified Duke Criteria for Infective Endocarditis

Definite Endocarditis	Possible Endocarditis	Rejected Endocarditis
2 major criteria 1 major and ≥3 minor criteria 5 minor criteria	1 major and 1-2 minor criteria 3-4 minor criteria	0 major and 1-2 minor criteria 1 major and 0 minor criteria

Major Criteria

A. Supportive Laboratory Evidence:
Typical microorganism for infective endocarditis from two separate blood cultures: viridans streptococci, *Staphylococcus aureus*, *Streptococcus bovis*, HACEK group (*Haemophilus* spp. *Actinobacillus actinomycetemcomitans*, *Cardiobacterium hominis*, *Eikenella* spp., and *Kingella kingae*) or community-acquired enterococci, in the absence of a primary focus

Single positive blood culture for *Coxiella burnetti* or phase I antibody titer >1:800

B. Evidence of Endocardial Involvement:
Echocardiogram supportive of infective endocarditis.
Definition of positive findings: oscillating intracardiac mass, on valve or supporting structures, or in the path of regurgitant jets, or on implanted material, in the absence of an alternative anatomic explanation or myocardial abscess or new partial dehiscence of prosthetic valve.

New valvular regurgitation (increase or change in pre-existing murmur not sufficient).

Minor Criteria

A. Predisposing heart condition or intravenous drug use
B. Fever ≥38 C (100.4°F)
C. Vascular phenomena: major arterial emboli, septic pulmonary infarcts, mycotic aneurysm, intracranial hemorrhage, conjunctival hemorrhage, Janeway lesions
D. Immunologic phenomena: glomerulonephritis, Osler nodes, Roth spots, rheumatoid factor
E. Positive blood culture not meeting major criterion as noted previously (excluding single positive cultures for coagulase-negative staphylococci and organisms that do not cause endocarditis) or serologic evidence of active infection with organism consistent with infective endocarditis

closer to 50% for prosthetic valve endocarditis.[10] Additionally, transthoracic echocardiography can be limited substantially by patient habitus, positioning, and other clinical factors such as mechanical ventilation. Transesophageal echocardiography remains the preferred imaging tool for diagnosis with sensitivity between 90% and 92%.[10] However, a major study supporting this estimate was published in 1988 and used the detection of vegetations seen as its gold standard.[11] As a result, the true sensitivity of transesophageal echocardiography may be lower than what is reported in contemporary clinical guidelines. Despite its higher sensitivity than the transthoracic modality, transesophageal echocardiography is a more invasive procedure that requires at a minimum conscious sedation and, in some cases, general anesthesia that can pose significant risks to patients who are already clinically tenuous. The ability to obtain transthoracic echocardiograms in a timely fashion is also considerably variable depending on the expertise and availability of echocardiographers. Both the AHA and European Society of Cardiology (ESC) endocarditis guidelines recommend that both transthoracic and transesophageal echocardiograms be obtained for patients with moderate to high risk of endocarditis, prosthetic valves and for all patients with endocarditis diagnosed on transthoracic echocardiogram alone to look for peri-valvular complications of the disease such as abscess, pseudoaneurysm or fistula.[10,12,13]

Positron emission tomography (PET) is a newer diagnostic modality that has been shown to increase the sensitivity of the Duke Criteria to ~90% when incorporated as a major criterion for prosthetic valve endocarditis.[14,15] As a result, in 2015 the ESC recommended including cardiac PET as a component of its diagnostic algorithm.[10] The test itself has several limitations because it is only offered in a handful of tertiary care medical centers, takes 1-2 days to complete, and requires significant expertise for successful interpretations. Additionally, patients who have undergone valve replacement <3 months before the test are much more likely to have a false-positive result related to their recent procedure.[10] In cases of native valve IE, cardiac PET is limited by its relative insensitivity with a primary benefit being the high specificity of positive test results.[16] Nevertheless, in the appropriate setting and in carefully selected patients, PET is a useful adjunct in the diagnosis of endocarditis. The decision to use cardiac PET should be made in conjunction with an infectious disease specialist, cardiologist, or cardiac surgeon.

The minor Duke Criteria focus primarily on clinical features of endocarditis such as fever, associated autoimmune phenomena, presence of septic emboli, as well as risk factors for IE and microbiologic findings that do not meet a major criterion. With advances in noninvasive imaging techniques such as computed tomography (CT) along with angiography (CT-A) and magnetic resonance imaging (MRI), medical providers may be tempted to screen all patients with suspected endocarditis for emboli using these tests. There is evidence that routine neuroimaging with CT-A or MRI for patients with suspected IE can increase the sensitivity of the Duke Criteria and change management in ~20% of patients.[17,18] This has only been demonstrated in small series and is not currently explicitly recommended by either of the major consensus endocarditis guidelines. However, all patients with headache, neurologic deficits, or meningeal symptoms should undergo cerebrovascular imaging.[10,12] Glomerulonephritis is reported in as many as 22% of endocarditis cases.[19] For this reason, all physicians should include IE in the differential for patients with new glomerulonephritis. Of note, other than intravenous drug use, the Duke Criteria do not specify what factors pose an increased risk for IE. Consequently, providers should be aware of the most common risk factors including previous endocarditis, age >60, male gender, prosthetic valves, congenital heart disease, implantable cardiac devices, indwelling central venous catheters, valvular heart diseases, particularly bicuspid aortic valve and mitral valve prolapse with moderate-to-severe mitral regurgitation, and hemodialysis.[10]

RISK STRATIFICATION

Management of endocarditis involves the administration of antimicrobial therapy and, if indicated, surgical valve repair or replacement. Determining the optimal treatment plan and timing of potential surgical intervention requires a careful assessment of overall mortality, potential for septic embolism, and risk of surgical intervention. There are a number of useful tools for assessing these various risks and when used in conjunction they can allow providers to assess the risks and benefits of surgical and medical management. In 2016 the International Collaboration on Endocarditis published a 22-point calculator to predict 6-month endocarditis mortality.[20] In addition, the Society of Thoracic Surgeons (STS) has a well-validated risk calculator that can be used to assess surgical morbidity and mortality for patients undergoing aortic valve replacement and mitral valve repair or replacement specifically for endocarditis.[21] The STS risk calculator has not been studied for right-sided or multiple valve replacements. Finally, a French team has created a calculator to assess the risk of septic embolism based on patient age, presence of diabetes, atrial fibrillation, previous emboli, *Staphylococcus aureus* bacteremia, and vegetation size.[22] Vegetation size greater than 10 mm and location on the anterior leaflet of the mitral valve have both been demonstrated to be independent risk factors for future septic embolism.[12] Initiation of appropriate intravenous antibiotics decreases the risk of septic embolism significantly. The incidence of emboli in the first week of antibiotic therapy can be as high as 44.9 per 1000 patient-weeks. After 2 weeks of antibiotics, the risk of further embolism falls to 2.4 per 1000 patient-weeks.[22] This data highlights that surgical intervention to prevent recurrent septic embolism should occur within 14 days and optimally within 7 days of diagnosis. When used in conjunction with a comprehensive clinical care plan, these tools can allow providers to carefully weigh

Table 2 2015 American Heart Association Recommendations for Surgical Management of Left-Sided Native Valve Endocarditis

1. Early surgery (during initial hospitalization and before completion of a full course of antibiotics) is indicated in patients with IE who present with valve dysfunction resulting in symptoms or signs of heart failure.
2. Early surgery should be considered particularly in patients with IE caused by fungal or highly resistant organisms (eg, vancomycin-resistant Enterococcus, multidrug-resistant gram-negative bacilli).
3. Early surgery is indicated in patients with IE complicated by heart block, annular or aortic abscess, or destructive penetrating lesions.
4. Early surgery is indicated for evidence of persistent infection (manifested by persistent bacteremia or fever lasting >5-7 days and provided that other sistes of infection and fever have been excluded) after the start of appropriate antimicrobial therapy.
5. Early surgery is resonable in patients who present with recurrent emboli and persistent or enlarging vegetations despite appropriate antibiotic therapy.
6. Early surgery is reasonable in patients with severe valve regurgitation and mobile vegetations >10 mm.
7. Early surgery may be considered in patients with mobile vegetations >10 mm, particularly when involving the anterior leaflet of the mitral valve and associated with other relative indications for surgery.

IE = infective endocarditis.

the risks and benefits of surgical and medical management. At present, such calculators may be underused by physicians across specialties.

A common misconception among providers is that the presence of cerebral septic emboli is a contraindication to valve surgery because of possible hemorrhagic conversion with cardiopulmonary bypass. However, a number of studies have demonstrated that in the absence of large stroke with disabling neurologic deficits or preexisting hemorrhage, patients with septic cerebral emboli can safely undergo early surgery for their endocarditis.[23-25] Risk factors for future intracranial hemorrhage include the extent of previous infarction and the presence of cerebral microhemorrhages. However, at present there are no validated models to estimate the probability of intracranial hemorrhage in patients with septic cerebral emboli undergoing cardiopulmonary bypass. Therefore, the risk of hemorrhage with surgical intervention in patients with large-territory ischemic infarcts or cerebral microhemorrhage ideally would be weighed carefully by both an experienced stroke neurologist and cardiac surgeon. In the setting of hemorrhagic stroke both the AHA and ESC guidelines recommend waiting at least 4 weeks from the time of insult before surgical intervention because operations within this window have been associated with increased mortality.[23]

MANAGEMENT

Surgical Intervention

As previously mentioned, treatment of endocarditis requires appropriate antimicrobial therapy or cardiac surgery. A full discussion of recommended antibiotic regimens for IE is beyond the scope of this article. However, the Infectious Diseases Society of America (IDSA) and AHA have a detailed joint guideline that correlates closely with the ESC endocarditis guidelines with respect to antimicrobial therapy and is widely used by infectious diseases physicians.[10,12] Decisions surrounding the appropriateness and timing of surgical intervention are multifactorial and require the input of not only cardiac surgeons but also infectious disease specialists and cardiologists. The AHA and ESC both provide a list of Class I and Class II surgical indications for endocarditis (Table 2). Although patients may meet criteria for surgery, operative management can be complicated by several factors, including critical illness, comorbidities, and commonly the presence of cerebral emboli with or without hemorrhage. In recent years, a wealth of observational studies and 1 small randomized controlled trial have suggested improved survival with early surgical intervention when indicated.[26-28] However, there has been no consensus definition as to what constitutes "early" surgery.[10] Patient acuity is often cited as a factor for deferring surgical intervention. Although critically ill patients are at increased risk of mortality with surgery relative to stable patients with infectious endocarditis, there is evidence to suggest that the sickest patients are most likely to benefit from valve replacement.[29]

Injection Drug Use

The patient who injects drugs poses a significant ethical conundrum for medical providers and the incidence of disease in this population is increasing, comprising 11%-22% of all endocarditis cases.[2,3] These individuals have an underlying addiction, that if left untreated, makes treatment of their endocarditis particularly challenging. Although these 2 conditions are irrevocably linked, they are often treated as separate, independent entities. Almost half of patients who inject drugs who have endocarditis do not receive addiction-focused treatment during their index hospitalizations.[30] This is despite evidence suggesting that medication-assisted therapy can help prevent recurrent intravenous drug use and that targeted addiction teams can help reduce cost and length of stay for patients who inject drugs.[31,32] These individuals are often excluded as surgical candidates, particularly for repeat episodes of endocarditis after a prior surgical intervention, given the concerns surrounding subsequent infection. This is despite the fact that patients who inject drugs are often younger and have fewer comorbidities than the typical patient with endocarditis. Patients with endocarditis who inject drugs do have an increased risk of repeated infection and mortality 3-6 months after surgical valve replacement. However, by 6

months postoperatively, their mortality outcomes compare favorably with patients who do not inject drugs.[33] This finding suggests that with dedicated addiction treatment, there is the potential for increasing rates of surgical intervention and improving outcomes in this patient population.

Antibiotic Therapy

Currently, the AHA and ESC endocarditis guidelines recommend the use of intravenous antibiotics for the entirety of antimicrobial therapy, typically 4-6 weeks. This can present a number of challenges for providers as they try to coordinate the placement of peripherally inserted central catheters and outpatient antibiotic therapy. The prolonged duration of intravenous antibiotics also exposes patients to the risks associated with peripherally inserted central catheters such as bloodstream infection and vascular thromboembolic events. Previous studies, primarily in patients who inject drugs with right-sided endocarditis have evaluated 2-week courses of intravenous antibiotics or treatment with combination oral regimens with good results.[34,35] More recently, a Danish randomized controlled trial demonstrated that outcomes for IE caused by streptococci, enterococci, *Staphylococcus aureus*, and coagulase-negative staphylococcus were similar for patients with IE treated with either oral or intravenous antibiotics, after completing an initial course of 2 weeks of intravenous therapy.[36] However, their cohort of 400 patients lacked cases of methicillin-resistant *Staphylococcus aureus* (MRSA), which comprise a significant percentage of cases in North America. Importantly, patients with cardiac abscess, persistent leukocytosis, and other sites of infection were excluded from this study. Despite its limitations the paper suggests that in carefully selected patients who have completed a preliminary course of intravenous antibiotics transition to oral antibiotics may be safe and efficacious.

There is also an increasing body of evidence to support the use of shorter durations of antibiotics postoperatively. Currently the AHA guidelines recommend that course of antibiotic therapy be determined from the date of the first negative blood cultures or from a positive valve culture, whichever occurs later.[12] Rao et al demonstrated retrospectively comparable mortality and relapse rates in patients receiving <2 weeks and >2 weeks of antibiotic therapy postoperatively, even when controlling for factors such as positive valve cultures.[37] These findings were echoed by Morris et al who suggested in 2005 that no more than 2 weeks of antibiotics were required postoperatively.[38]

The novel long-acting injectable lipoglycopeptide antibiotics such as dalbavancin and oritavancin may offer an alternative modality of therapy for patients who may require longer courses of antibiotics but cannot complete intravenous or oral therapy. These agents can be dosed as infrequently as once weekly and can be administered intramuscularly. However, there is limited experience with their use in treating IE. One case series of 27 patients with endocarditis treated with dalbavancin demonstrated a cure rate of 92.4% but only after the patients were documented to have cleared their bacteremia with conventional antibiotics.[39] Although there is promise that the lipoglycopeptides could be used as part of the treatment for IE, further study is required before their use can be routinely recommended.

Endocarditis Teams

Given the complex nature of medical and surgical decision making, the high mortality of the disease, as well as the involvement of numerous medical and surgical specialties, endocarditis cases may be best managed by a multidisciplinary team, akin to a tumor board, that meets regularly to discuss affected patients. Multiple studies have demonstrated that implementation of such a group can decrease in-hospital mortality by more than half, and the ESC recommends that all tertiary care hospitals offer this service.[40-42] The ideal composition of a multidisciplinary endocarditis team (MDET) includes cardiac surgeons, cardiologists, infectious diseases and addiction specialists, neurologists, pharmacists, and radiologists.[40] In addition to assisting in diagnosis and selecting appropriate patients for surgical intervention, these teams can help adhere to antimicrobial guidelines and, in some cases, shorten antibiotic courses for patients who are surgically managed.[37] Despite their potential value, there is still a need for more multidisciplinary endocarditis teams in the United States. Adoption of this multidisciplinary approach by the AHA guideline may help to raise awareness about this valuable resource.

CONCLUSION

Although IE is still associated with significant morbidity, there are an increasing number of tools available to providers to assist with risk stratification, diagnosis, and management. Additionally, there is new literature to support the use of shorter durations of intravenous antibiotic therapy postoperatively as well as oral antibiotic treatment in certain subsets of patients. Amid the ongoing opioid crisis, patients who inject drugs pose a challenge to medical providers and hospital systems, and currently their needs with respect to addiction treatment are not being met. Expanding the role of medication-assisted therapy may serve to improve endocarditis outcomes and decrease the overall incidence of the diseases in this patient population. Given patient complexity, the large volume of literature on this topic and the involvement of several medical specialties, endocarditis cases are best managed by multidisciplinary teams that meet at regular intervals. The integration of the discussed literature into a weekly conference can help decrease mortality for this life-threatening infection.

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