AHA Scientific Statement

Infective Endocarditis in Adults: Diagnosis, Antimicrobial Therapy, and Management of Complications

A Scientific Statement for Healthcare Professionals From the American Heart Association

Endorsed by the Infectious Diseases Society of America

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Background—Infective endocarditis is a potentially lethal disease that has undergone major changes in both host and pathogen. The epidemiology of infective endocarditis has become more complex with today's myriad healthcare-associated factors that predispose to infection. Moreover, changes in pathogen prevalence, in particular a more common staphylococcal origin, have affected outcomes, which have not improved despite medical and surgical advances.

Methods and Results—This statement updates the 2005 iteration, both of which were developed by the American Heart Association under the auspices of the Committee on Rheumatic Fever, Endocarditis, and Kawasaki Disease, Council on Cardiovascular Disease of the Young. It includes an evidenced-based system for diagnostic and treatment recommendations used by the American College of Cardiology and the American Heart Association for treatment recommendations.

Conclusions—Infective endocarditis is a complex disease, and patients with this disease generally require management by a team of physicians and allied health providers with a variety of areas of expertise. The recommendations provided in this document are intended to assist in the management of this uncommon but potentially deadly infection. The clinical variability and complexity in infective endocarditis, however, dictate that these recommendations be used to support and not supplant decisions in individual patient management. **(*Circulation*. 2015;132:00-00. DOI: 10.1161/CIR.0000000000000296.)**

Key Words: AHA Scientific Statements ■ anti-infective agents ■ echocardiography ■ endocarditis ■ infection

Infective endocarditis (IE) is an uncommon infectious disease with an annual incidence ranging from 3 to 7 per 100 000 person-years in the most contemporary population surveys.[1–3] Although relatively rare, IE continues to be characterized by increased morbidity and mortality and is now the third or fourth most common life-threatening infection

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syndrome, after sepsis, pneumonia, and intra-abdominal abscess. Globally, in 2010, IE was associated with 1.58 million disability-adjusted life-years or years of healthy life lost as a result of death and nonfatal illness or impairment.[4]

Epidemiological surveys from France and the International Collaboration on Endocarditis have confirmed that the epidemiological profile of IE has changed substantially. Although the overall IE incidence has remained stable,[1,2,5–9] the incidence of IE caused by *Staphylococcus aureus* has increased, and *S aureus* is now the most common causative organism in most of the industrialized world. The emergence of *S aureus* IE is due in part to the increasing importance of healthcare contact as a leading risk associated with infection. Characteristics of IE patients have also shifted toward an increased mean patient age, a higher proportion of prosthetic valves and other cardiac devices, and a decreasing proportion of rheumatic heart disease. Moreover, the proportion of IE patients undergoing surgery has increased over time to reach ≈50%.[1,10,11]

In addition to these temporal epidemiological changes, major new findings from multiple diagnostic, prognostic, and therapeutic studies have been published since the last iteration of the American Heart Association (AHA) statement on diagnosis and management of IE complications was published in 2005.[12] For example, the rapid detection of pathogens from valve tissue from patients undergoing surgery for IE by polymerase chain reaction (PCR) has been validated. Moreover, diagnostic innovations have emerged through new imaging techniques such as 3-dimensional (3D) echocardiography, "head-to-toe" multislice computed tomography (CT), and cardiac magnetic resonance imaging (MRI). Furthermore, the role of cerebral MRI and magnetic resonance angiography in the diagnosis and management of IE has been better defined in several studies. In addition, several risk stratification models for quantifying morbidity and mortality in IE patients overall and particularly in those undergoing valve surgeries have been developed and validated. Finally, daptomycin has been evaluated in the treatment of *S aureus* bacteremia and IE in a randomized, controlled trial.[13] Several rigorously conducted observational studies[11,14–16] and a randomized, controlled trial[17] have examined the impact and timing of valve surgery in IE management. In addition, updated international management guidelines have been published.[18,19]

The present AHA IE Writing Committee conducted comprehensive and focused reviews of the literature published between January 2005 and October 2013 to update the previous version of the guidelines. Literature searches of the PubMed/MEDLINE databases were undertaken to identify pertinent articles. Searches were limited to the English language. The major search terms included endocarditis, infective endocarditis, infectious endocarditis, intracardiac, valvular, mural, infection, diagnosis, bacteremia, case definition, epidemiology, risks, demographics, injection drug use, echocardiography, microbiology, culture-negative, therapy, antibiotic, antifungal, antimicrobial, antimicrobial resistance, adverse drug effects, drug monitoring, outcome, meta-analysis, complications, abscess, heart failure, embolic events, stroke, conduction abnormalities, survival, pathogens, organisms, treatment, surgery, indications, valve replacement, valve repair, ambulatory care trials, and prevention. In addition, the present statement includes a new section, Surgical Therapy. This work addresses primarily IE in adults; a more detailed review of the unique features of IE in children is available in another statement from the AHA Committee on Rheumatic Fever, Endocarditis, and Kawasaki Disease.[20] The committee also published statements on endocarditis that complicates electrophysiological (pacemakers, intracardiac defibrillators),[21] ventricular assist, and other nonvalvular cardiac devices.[22]

Evidenced-Based System for Diagnostic and Treatment Recommendations

The writing group was charged with the task of performing an evidence-based assessment of the data and providing a class of recommendation and a level of evidence for each recommendation according to the American College of Cardiology/AHA classification system (http://circ.ahajournals.org/manual/manual_IIstep6.shtml). The class of recommendation is an estimate of the size of the treatment effect, considering risks versus benefits, in addition to evidence or agreement that a given treatment or procedure is or is not useful or effective or in some situations may cause harm. The level of evidence is an estimate of the certainty or precision of the treatment effect. The Writing Group reviewed and assessed the strength of evidence supporting each recommendation with the level of evidence ranked as A, B, or C according to the specific definitions included in Table 1. For certain conditions for which data were either unavailable or inadequate, recommendations were based on expert consensus and clinical experience, and these were ranked as Level of Evidence C. The scheme for the class of recommendations and levels of evidence is summarized in Table 1, which also provides suggested phrases for writing recommendations within each class of recommendation.

Diagnosis

The diagnosis of IE is straightforward in the minority of patients who present with a consistent history and classic oslerian manifestations: sustained bacteremia or fungemia, evidence of active valvulitis, peripheral emboli, and immunological vascular phenomena. In most patients, however, the "textbook" history and physical examination findings may be few or absent. Cases with limited manifestations of IE may occur early during IE, particularly among patients who are injection drug users (IDUs), in whom IE is often the result of acute *S aureus* infection of right-sided heart valves. Acute IE may evolve too quickly for the development of immunological vascular phenomena, which are more characteristic of the later stages of the more insidious subacute form of untreated IE. In addition, valve lesions in right-sided IE usually do not create the peripheral emboli and immunological vascular phenomena that can result from left-sided valvular involvement. Right-sided IE, however, can cause septic pulmonary emboli.

The variability in clinical presentation of IE and the importance of early accurate diagnosis require a diagnostic strategy that is both sensitive for disease detection and specific for its exclusion across all forms of the disease. In 1994, Durack and colleagues[23] from the Duke University Medical Center proposed a diagnostic schema that stratified patients with suspected IE into 3 categories: definite, possible, and rejected cases (Tables 2 and 3).

Table 1. Applying Classification of Recommendations and Level of Evidence

ESTIMATE OF CERTAINTY (PRECISION) OF TREATMENT EFFECT	SIZE OF TREATMENT EFFECT			
	CLASS I *Benefit >>> Risk* Procedure/Treatment **SHOULD** be performed/ administered	**CLASS IIa** *Benefit >> Risk* *Additional studies with focused objectives needed* **IT IS REASONABLE** to perform procedure/administer treatment	**CLASS IIb** *Benefit ≥ Risk* *Additional studies with broad objectives needed; additional registry data would be helpful* Procedure/Treatment **MAY BE CONSIDERED**	**CLASS III** *No Benefit* or **CLASS III** *Harm* Procedure/Test / Treatment **COR III: No benefit** — Not Helpful / No Proven Benefit **COR III: Harm** — Excess Cost w/o Benefit or Harmful / Harmful to Patients
LEVEL A Multiple populations evaluated* Data derived from multiple randomized clinical trials or meta-analyses	■ Recommendation that procedure or treatment is useful/effective ■ Sufficient evidence from multiple randomized trials or meta-analyses	■ Recommendation in favor of treatment or procedure being useful/effective ■ Some conflicting evidence from multiple randomized trials or meta-analyses	■ Recommendation's usefulness/efficacy less well established ■ Greater conflicting evidence from multiple randomized trials or meta-analyses	■ Recommendation that procedure or treatment is not useful/effective and may be harmful ■ Sufficient evidence from multiple randomized trials or meta-analyses
LEVEL B Limited populations evaluated* Data derived from a single randomized trial or nonrandomized studies	■ Recommendation that procedure or treatment is useful/effective ■ Evidence from single randomized trial or nonrandomized studies	■ Recommendation in favor of treatment or procedure being useful/effective ■ Some conflicting evidence from single randomized trial or nonrandomized studies	■ Recommendation's usefulness/efficacy less well established ■ Greater conflicting evidence from single randomized trial or nonrandomized studies	■ Recommendation that procedure or treatment is not useful/effective and may be harmful ■ Evidence from single randomized trial or nonrandomized studies
LEVEL C Very limited populations evaluated* Only consensus opinion of experts, case studies, or standard of care	■ Recommendation that procedure or treatment is useful/effective ■ Only expert opinion, case studies, or standard of care	■ Recommendation in favor of treatment or procedure being useful/effective ■ Only diverging expert opinion, case studies, or standard of care	■ Recommendation's usefulness/efficacy less well established ■ Only diverging expert opinion, case studies, or standard of care	■ Recommendation that procedure or treatment is not useful/effective and may be harmful ■ Only expert opinion, case studies, or standard of care
Suggested phrases for writing recommendations	should is recommended is indicated is useful/effective/beneficial	is reasonable can be useful/effective/beneficial is probably recommended or indicated	may/might be considered may/might be reasonable usefulness/effectiveness is unknown/unclear/uncertain or not well established	COR III: No Benefit: is not recommended; is not indicated; should not be performed/ administered/ other; is not useful/ beneficial/ effective COR III: Harm: potentially harmful; causes harm; associated with excess morbidity/mortality; should not be performed/ administered/ other
Comparative effectiveness phrases†	treatment/strategy A is recommended/indicated in preference to treatment B treatment A should be chosen over treatment B	treatment/strategy A is probably recommended/indicated in preference to treatment B it is reasonable to choose treatment A over treatment B		

A recommendation with Level of Evidence B or C does not imply that the recommendation is weak. Many important clinical questions addressed in the guidelines do not lend themselves to clinical trials. Although randomized trials are unavailable, there may be a very clear clinical consensus that a particular test or therapy is useful or effective.

*Data available from clinical trials or registries about the usefulness/efficacy in different subpopulations, such as sex, age, history of diabetes, history of prior myocardial infarction, history of heart failure, and prior aspirin use.

†For comparative effectiveness recommendations (Class I and IIa; Level of Evidence A and B only), studies that support the use of comparator verbs should involve direct comparisons of the treatments or strategies being evaluated.

A diagnosis of IE with the original Duke criteria was based on the presence of either major or minor clinical criteria (Tables 2 and 3). The Duke criteria gave diagnostic weight to bacteremia with staphylococci or enterococci only, on the basis of the location of acquisition and without an apparent primary focus; these types of bacteremia have the highest risk of being associated with IE.[23,25,26] The Duke criteria incorporated echocardiographic findings into the diagnostic strategy (Tables 2 and 3; see the Echocardiography section). Six common but less specific findings of IE were included as minor criteria in the original Duke schema (Tables 2 and 3).

In the mid to late 1990s, direct analyses of the Duke criteria were made in 12 major studies[27–38] including nearly 1700 patients composed of geographically and clinically diverse groups (adult, pediatric, and older adult [≥60 years of age] patients; patients from the community; IDU and non-IDU patients; and those with both native and prosthetic valves). The studies[27–38] confirmed the high sensitivity and specificity of the Duke criteria and the diagnostic utility of echocardiography in identifying clinically definite cases. Moreover, a retrospective study of 410 patients showed good agreement (72%–90%) between the Duke criteria and clinical assessment by infectious disease experts blinded to underlying IE risk factors.[39]

Table 2. Definition of IE According to the Modified Duke Criteria*

Definite IE
Pathological criteria
Microorganisms demonstrated by culture or histological examination of a vegetation, a vegetation that has embolized, or an intracardiac abscess specimen; or pathological lesions; vegetation or intracardiac abscess confirmed by histological examination showing active endocarditis
Clinical criteria
2 Major criteria, 1 major criterion and 3 minor criteria, or 5 minor criteria
Possible IE
1 Major criterion and 1 minor criterion, or 3 minor criteria
Rejected
Firm alternative diagnosis explaining evidence of IE; or resolution of IE syndrome with antibiotic therapy for ≤4 d; or no pathological evidence of IE at surgery or autopsy with antibiotic therapy for ≤4 d; or does not meet criteria for possible IE as above

IE indicates infective endocarditis.
Modifications appear in boldface.
*These criteria have been universally accepted and are in current use.
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Several refinements have been made to both the major and minor Duke criteria. In the original Duke criteria, bacteremia resulting from *S aureus* or enterococci was considered to fulfill a major criterion only if it was community acquired because ample literature suggested that this parameter was an important surrogate marker for underlying IE.[27] However, an increasing number of more contemporary studies documented IE in patients experiencing nosocomial staphylococcal bacteremia. For example, of 59 consecutive patients with *S aureus* IE, 45.8% had nosocomial infections, and 50.8% had a removable focus of infection.[39] In an analysis of 262 patients at the Duke University Medical Center who had hospital-acquired *S aureus* bacteremia, 34 (13%) were subsequently diagnosed with definite IE. Therefore, the modified Duke criteria (Tables 2 and 3) recommend the inclusion of *S aureus* bacteremia as a major criterion, regardless of whether the infection is hospital acquired (with or without a removable source of infection) or community acquired.[24]

Specific serological data have been included in the Duke IE diagnostic schema to establish the pathogenic agents of culture-negative IE more precisely (ie, as a surrogate for positive blood cultures). These serological criteria would be applied in circumstances in which the pathogenic organism is slow growing in routine blood cultures (eg, *Brucella* species) or requires special blood culture media (eg, *Bartonella* species, *Legionella* species, *Tropheryma whipplei*, fungi, and *Mycobacterium* species) or in which the organism is not culturable (eg, *Coxiella burnetii,* the agent of Q fever). For example, in the original Duke criteria, a positive serology for Q fever was considered a minor microbiological criterion. Subsequently, Fournier et al[40] studied 20 pathologically confirmed cases of Q fever IE. When the original Duke criteria were used, 4 of the 20 patients were classified as having possible IE. When Q fever serological results and a single blood culture positive for *C burnetii* were considered to be a major criterion, however, each of these 4 cases was reclassified from possible IE to definite IE. On the basis of these data, specific serological data as a surrogate marker for positive blood cultures have now been included in the Duke criteria. Thus, an anti–phase I immunoglobulin G antibody titer ≥1:800 or a single blood culture positive for *C burnetii* should be a major criterion in the modified Duke schema.[24]

Serological tests and PCR-based testing for other difficult-to-cultivate organisms such as *Bartonella quintana* or *Tropheryma whippelii* also have been discussed as future major criteria. At present, there are significant methodological problems associated with proposing antibody titers that are positive for *Bartonella* and *Chlamydia* species or PCR-based testing for *T whippelii* as a major criterion in the Duke schema. For example, IE caused by *Bartonella* and *Chlamydia* species often are indistinguishable in serological test results because of cross-reactions.[41] Low sensitivity is a major limitation of PCR unless cardiac valvular tissue is available for testing.[42–45] Few centers provide timely PCR-based testing for these rare causes of IE. Therefore, the inclusion of these assays as major criteria should be deferred until the serodiagnostic and PCR approaches can be standardized and validated in a sufficient number of cases of these rare types of IE, the aforementioned technical problems are resolved, and the availability of such assays becomes more widespread.

The expansion of minor criteria to include elevated erythrocyte sedimentation rate or C-reactive protein, the presence of newly diagnosed clubbing, splenomegaly, and microscopic hematuria also has been proposed. In a study of 100 consecutive cases of pathologically proven native valve IE (NVE), inclusion of these additional parameters with the existing Duke minor criteria resulted in a 10% increase in the frequency of cases being deemed clinically definite, with no loss of specificity. The major limitations of the erythrocyte sedimentation rate and C-reactive protein are that they are nonspecific and particularly challenging to interpret in patients with comorbid conditions. These additional parameters have not been formally integrated into the modified Duke criteria,[24] however, which are universally accepted.

One minor criterion from the original Duke schema, "echocardiogram consistent with IE but not meeting major criterion," was re-evaluated. This criterion originally was used in cases in which nonspecific valvular thickening was detected by transthoracic echocardiography (TTE). In a reanalysis of patients in the Duke University database (containing records collected prospectively on >800 cases of definite and possible IE since 1984), this echocardiographic criterion was used in only 5% of cases and was never used in the final analysis of any patient who underwent transesophageal echocardiography (TEE). Therefore, this minor criterion was eliminated in the modified Duke criteria.[24]

Finally, adjustment of the Duke criteria to require a minimum of 1 major plus 1 minor criterion or 3 minor criteria as a "floor" to designate a case as possible IE (as opposed to "findings consistent with IE that fall short of 'definite' but not 'rejected'") has been incorporated into the modified criteria to reduce the proportion of patients assigned to the IE possible category. This approach was used in a series of patients initially categorized as possible IE by the original Duke criteria.

Table 3. Definition of Terms Used in the Modified Duke Criteria for the Diagnosis of IE*

Major criteria
Blood culture positive for IE
Typical microorganisms consistent with IE from 2 separate blood cultures: Viridans streptococci, *Streptococcus bovis*, HACEK group, ***Staphylococcus aureus***; or community-acquired enterococci in the absence of a primary focus, or microorganisms consistent with IE from persistently positive blood cultures defined as follows: at least 2 positive cultures of blood samples drawn >12 h apart or all 3 or a majority of ≥4 separate cultures of blood (with first and last sample drawn at least 1 h apart)
Single positive blood culture for *Coxiella burnetii* or anti–phase 1 IgG antibody titer ≥1:800
Evidence of endocardial involvement
Echocardiogram positive for IE **(TEE recommended for patients with prosthetic valves, rated at least possible IE by clinical criteria, or complicated IE [paravalvular abscess]; TTE as first test in other patients)** defined as follows: 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; abscess; or new partial dehiscence of prosthetic valve or new valvular regurgitation (worsening or changing or pre-existing murmur not sufficient)
Minor criteria
Predisposition, predisposing heart condition, or IDU
Fever, temperature >38°C
Vascular phenomena, major arterial emboli, septic pulmonary infarcts, mycotic aneurysm, intracranial hemorrhage, conjunctival hemorrhages, and Janeway lesions
Immunological phenomena: glomerulonephritis, Osler nodes, Roth spots, and rheumatoid factor
Microbiological evidence: positive blood culture but does not meet a major criterion as noted above (excludes single positive cultures for coagulase-negative staphylococci and organisms that do not cause endocarditis) or serological evidence of active infection with organism consistent with IE
Echocardiographic minor criteria eliminated

HACEK indicates *Haemophilus* species, *Aggregatibacter* species, *Cardiobacterium hominis*, *Eikenella corrodens*, and *Kingella* species; IDU, injection drug use; IE, infective endocarditis; IgG, immunoglobulin G; TEE transesophageal echocardiography; and TTE, transthoracic echocardiography.

Modifications appear in boldface.

*These criteria have been universally accepted and are in current use.

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With the guidance of the "diagnostic floor," a number of these cases were reclassified as rejected for IE.[24]

Follow-up in these reclassified patients documented the specificity of this diagnostic schema because no patients developed IE during the subsequent 12 weeks of observation.

Thus, on the basis of the weight of clinical evidence involving nearly 2000 patients in the current literature, it appears that patients suspected of having IE should be clinically evaluated, with the modified Duke criteria as the primary diagnostic schema. It should be pointed out that the Duke criteria were originally developed to facilitate epidemiological and clinical research efforts so that investigators could compare and contrast the clinical features and outcomes of various case series of patients. Extending these criteria to the clinical practice setting has been somewhat more difficult. It should also be emphasized that full application of the Duke criteria requires detailed clinical, microbiological, radiological, and echocardiographic queries. Because IE is a heterogeneous disease with highly variable clinical presentations, the use of these criteria alone will never suffice. Criteria changes that add sensitivity often do so at the expense of specificity and vice versa. The Duke criteria are meant to be a guide for diagnosing IE and must not replace clinical judgment. Clinicians may appropriately and wisely decide whether or not to treat an individual patient, regardless of whether the patient meets or fails to meet the criteria for definite or possible IE by the Duke criteria. We believe, however, that the modifications of the Duke criteria (Tables 2 and 3) will help investigators who wish to examine the clinical and epidemiological features of IE and will serve as a guide for clinicians struggling with difficult diagnostic problems. These modifications require further validation among patients who are hospitalized in both community-based and tertiary care hospitals, with particular attention to longer-term follow-up of patients rejected as having IE because they did not meet the minimal floor criteria for possible IE.

The diagnosis of IE must be made as soon as possible to initiate appropriate empirical antibiotic therapy and to identify patients at high risk for complications who may be best managed by early surgery. In cases with a high suspicion of IE based on either the clinical picture or the patient's risk factor profile such as injection drug use, another focus of cardiovascular infection, including catheter-related bloodstream infections caused by *S aureus*, or a history of previous IE, the presumption of IE often is made before blood culture results are available. Identification of vegetations and incremental valvular insufficiency with echocardiography often completes the diagnostic criteria for IE and affects the duration of therapy. Although the use of case definitions to establish a diagnosis of IE should not replace clinical judgment,[46] the recently modified Duke criteria[24] have been useful in both epidemiological and clinical trials and in individual patient management. Clinical, echocardiographic, and microbiological criteria (Tables 2 and 3) are used routinely to support a diagnosis of IE, and they do not rely on histopathological confirmation of resected valvular material or arterial embolus. If suggestive features are absent, then a negative echocardiogram should prompt a more thorough search for alternative sources of fever and sepsis. In light of these important functions, at least 3 sets of blood cultures obtained from separate venipuncture sites should be obtained, with the first and last samples drawn at least 1 hour apart. In addition, echocardiography should be performed expeditiously in patients suspected of having IE.

Recommendations

1. **At least 3 sets of blood cultures obtained from different venipuncture sites should be obtained, with the first and last samples drawn at least 1 hour apart (*Class I; Level of Evidence A*).**
2. **Echocardiography should be performed expeditiously in patients suspected of having IE (*Class I; Level of Evidence A*).**

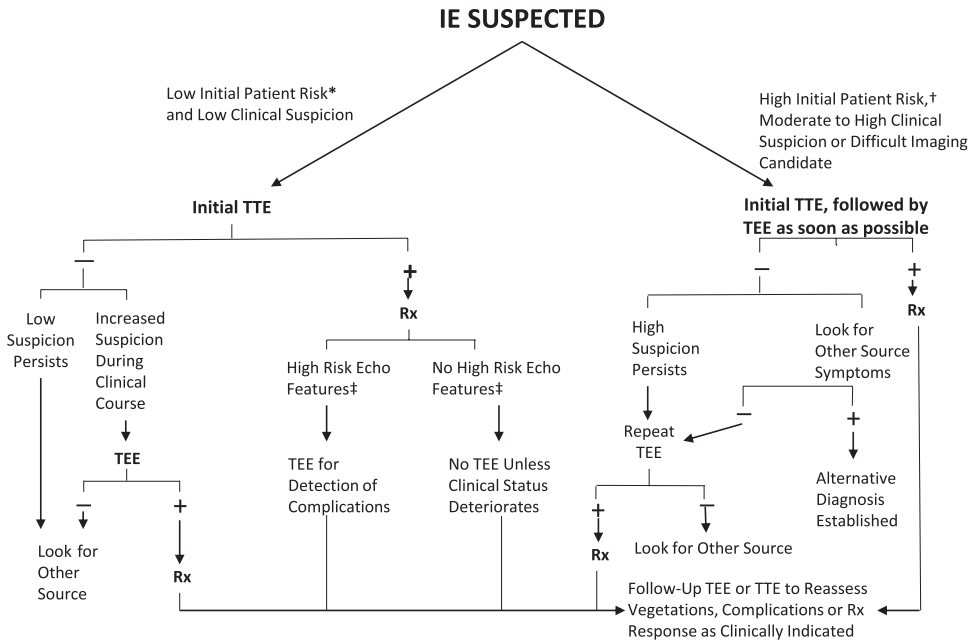

Figure. An approach to the diagnostic use of echocardiography (echo). Rx indicates prescription; TEE, transesophageal echocardiography; and TTE, transthoracic echocardiography. *For example, a patient with fever and a previously known heart murmur and no other stigmata of infective endocarditis (IE). †High initial patient risks include prosthetic heart valves, many congenital heart diseases, previous endocarditis, new murmur, heart failure, or other stigmata of endocarditis. ‡High-risk echocardiographic features include large or mobile vegetations, valvular insufficiency, suggestion of perivalvular extension, or secondary ventricular dysfunction (see text). Modified from Baddour et al.[12] Copyright © 2005, American Heart Association, Inc.

Echocardiography

Echocardiography is central to the diagnosis and management of patients with IE. As previously stated (Table 3), echocardiographic evidence of an oscillating intracardiac mass or vegetation, an annular abscess, prosthetic valve partial dehiscence, and new valvular regurgitation are major criteria in the diagnosis of IE.

Both TTE and TEE are done in many patients with IE during initial evaluation and subsequent follow-up and provide complementary information. Therefore, TTE should be done initially in all cases of suspected IE (Figure). If any circumstances preclude the securing of optimal echocardiographic windows, including chronic obstructive lung disease, previous thoracic or cardiovascular surgery, morbid obesity, or other conditions, then TEE should be performed as soon as possible after TTE. When TTE is negative and clinical suspicion remains low, then other clinical entities should be considered. If TTE shows vegetations but the likelihood of complications is low, then subsequent TEE is unlikely to alter initial medical management. On the other hand, if clinical suspicion of IE or its complications is high (eg, prosthetic valve or new atrioventricular block), then a negative TTE will not definitely rule out IE or its potential complications, and TEE should be performed first. Investigation in adults has shown TEE to be significantly more sensitive than TTE for the detection of vegetations and abscesses.[47] In the setting of a prosthetic valve, transthoracic images are greatly hampered by the structural components of the prosthesis and are inadequate for assessment of the perivalvular area where those infections often start.[48] Although cost-effectiveness calculations suggest that TEE should be the first examination in adults with suspected IE (Table 4), particularly in the setting of staphylococcal bacteremia,[49,50] many patients are not candidates for immediate TEE because of having eaten within the preceding 6 hours or because the patients are in institutions that cannot provide 24-hour TEE services. When TEE is not clinically possible or must be delayed, early TTE should be performed without delay. Although TTE will not definitively exclude vegetations or abscesses, it will allow identification of very-high-risk patients, establish the diagnosis in many, and guide early treatment decisions. Although interesting results suggest that there may be a high negative predictive value of TTE in some patients,[51] further work is needed to better define the subgroup of patients with bloodstream infection caused by *S aureus* who need only TTE to evaluate for IE.

Many findings identified by TEE also can be detected on TTE. Concurrent TTE images can serve as a baseline for rapid and noninvasive comparison of vegetation size, valvular insufficiency, or change in abscess cavities during the course of the patient's treatment should clinical deterioration occur. For tricuspid vegetations or abnormalities of the right ventricular outflow tract, visualization may be enhanced by choosing TTE rather than TEE.[52] Finally, many cardiologists believe TTE is superior to TEE for quantifying hemodynamic dysfunction manifested by valvular regurgitation, ventricular dysfunction, and elevated left and right ventricular filling pressures and pulmonary artery pressure. These echocardiographic findings can occur in patients who have no heart failure symptoms.

Both TEE and TTE may produce false-negative results if vegetations are small or have embolized.[53] Even TEE may miss initial perivalvular abscesses, particularly when the study is performed early in the patient's illness.[54] In such cases, the

Table 4. Use of Echocardiography During Diagnosis and Treatment of Endocarditis

Early
Echocardiography as soon as possible (<12 h after initial evaluation)
TEE preferred; obtain TTE views of any abnormal findings for later comparison
TTE if TEE is not immediately available
TTE may be sufficient in small children
Repeat echocardiography
TEE after positive TTE as soon as possible in patients at high risk for complications
TEE 3–5 d after initial TEE if suspicion exists without diagnosis of IE or with worrisome clinical course during early treatment of IE
Intraoperative
Prepump
Identification of vegetations, mechanism of regurgitation, abscesses, fistulas, and pseudoaneurysms
Postpump
Confirmation of successful repair of abnormal findings
Assessment of residual valve dysfunction
Elevated afterload if necessary to avoid underestimating valve insufficiency or presence of residual abnormal flow
Completion of therapy
Establish new baseline for valve function and morphology and ventricular size and function
TTE usually adequate; TEE or review of intraoperative TEE may be needed for complex anatomy to establish new baseline

TEE indicates transesophageal echocardiography; and TTE, transthoracic echocardiography.

incipient abscess may be seen only as nonspecific perivalvular thickening, which on repeat imaging across several days may become more recognizable as it expands and develops a cavity. Similarly, perivalvular fistulas and pseudoaneurysms develop over time, and negative early TEE images do not exclude the potential for their development.

False-positive results from TEE or TTE studies may occur when valvular abnormalities are seen that may not be related to a current infection. Previous scarring, severe myxomatous change, and even normal structures such as Lambl excrescences may be indistinguishable from active changes in the valves. As echocardiographic technology improves with higher frequencies and refined beam-forming technology, subtle findings continue to be recognized and may add to the category of indeterminate findings. One approach to minimizing confusion from these latter structures is to exploit the high frame rates that are often available with current equipment to improve temporal resolution and to clearly visualize rapidly moving structures such as microcavities from prosthetic valves or fibrillar components.

Several echocardiographic features identify patients at high risk for a complicated course or with a need for surgery (Table 5). These features include large (>10 mm in diameter) vegetations, severe valvular insufficiency, abscess cavities or pseudoaneurysms, valvular perforation or dehiscence, and evidence of decompensated heart failure.[21] The ability of echocardiographic features to predict embolic events is limited.[55–57] The greatest risk of embolic complications appears to occur with large (≥10 mm) vegetations on the anterior mitral leaflet.[58] Vegetation size and mobility may be taken into account, along with bacteriological factors and other indications for surgery, when considering early surgery to avoid embolization, although mobility characteristics alone should not be the principal driver as a surgical indication.[59]

Recommendation

1. **TTE should be performed in all cases of suspected IE (*Class I; Level of Evidence B*).**

Repeat Echocardiography

If the initial TTE images are negative and the diagnosis of IE is still being considered, then TEE should be performed as soon as possible (Table 4). Among patients with an initially positive TTE and a high risk for intracardiac complications, including perivalvular extension of infection, TEE should be obtained as soon as possible. Repeating the TEE in 3 to 5 days (or sooner if clinical findings change) after an initial negative result is recommended when clinical suspicion of IE persists.[60] In some cases, vegetations may reach a detectable size in the interval, or abscess cavities or fistulous tracts may become evident. An interval increase in vegetation size on serial echocardiography despite the administration of appropriate antibiotic therapy has serious implications and has been associated with an increased risk of complications and the need for surgery.[60] Repeat TEE should be done when a patient with an initially positive TEE develops worrisome clinical features during antibiotic therapy. These features, including unexplained progression of heart failure symptoms, change in cardiac murmurs, and new atrioventricular block or arrhythmia, should prompt emergent evaluation by TEE if possible.

Recommendations

1. **TEE should be done if initial TTE images are negative or inadequate in patients for whom there is an ongoing suspicion for IE or when there is concern for intracardiac complications in patients with an initial positive TTE (*Class I; Level of Evidence B*).**
2. **If there is a high suspicion of IE despite an initial negative TEE, then a repeat TEE is recommended in 3 to 5 days or sooner if clinical findings change (*Class I; Level of Evidence B*).**
3. **Repeat TEE should be done after an initially positive TEE if clinical features suggest a new development of intracardiac complications (*Class I; Level of Evidence B*).**

Intraoperative Echocardiography

Preoperative surgical planning for patients with IE will benefit from echocardiographic delineation of the mechanisms of valvular dysfunction or regions of myocardial abscess formation (Table 5). The use of aortic homografts is facilitated by preoperative estimates of annular size, which allow the selection of appropriately sized donor tissues.[61,62] Intraoperatively, echocardiographic goals include assessment of not only

Table 5. Clinical and Echocardiographic Features That Suggest Potential Need for Surgical Intervention

Vegetation
Persistent vegetation after systemic embolization
Anterior mitral leaflet vegetation, particularly with size >10 mm*
≥1 Embolic events during first 2 wk of antimicrobial therapy*
Increase in vegetation size despite appropriate antimicrobial therapy*†
Valvular dysfunction
Acute aortic or mitral insufficiency with signs of ventricular failure†
Heart failure unresponsive to medical therapy†
Valve perforation or rupture†
Perivalvular extension
Valvular dehiscence, rupture, or fistula†
New heart block†‡
Large abscess or extension of abscess despite appropriate antimicrobial therapy†

See text for a more complete discussion of indications for surgery based on vegetation characterizations.

*Surgery may be required because of risk of embolization.

†Surgery may be required because of heart failure or failure of medical therapy.

‡Echocardiography should not be the primary modality used to detect or monitor heart block.

the obviously dysfunctional valve but also the other valves and contiguous structures. Post– cardiopulmonary bypass images should confirm the adequacy of the repair or replacement and document the successful closure of fistulous tracts. Perivalvular leaks related to technical factors should be documented to avoid later confusion about whether such leaks are the result of recurrent infection. During postpump imaging, it is often necessary to augment afterload to reach representative ambulatory levels to avoid underestimation of regurgitant jet size and significance and to ensure that abnormal communications were closed.[63] Afterload augmentation, however, may not mimic actual "awake physiology" and may still lead occasionally to an inaccurate evaluation of the awake postoperative hemodynamic state.

Echocardiography at the Completion of Therapy

All patients who have experienced an episode of IE remain at increased risk for recurrent infection indefinitely. Many believe that it is extremely important for the future care of these patients to establish a new baseline for valvular morphology, including the presence of vegetations and valvular insufficiency, once treatment has been completed. Documentation of heart rate, heart rhythm, and blood pressure at the time of echocardiographic study is important because changes in these conditions may explain future differences in valvular insufficiency independent of pathology (Table 4). TTE is reasonable for this evaluation because spectral Doppler interrogation for functionality metrics is more thorough than TEE. TEE, however, may be merited to define the new baseline in some patients with poor acoustic windows or complicated anatomy such as after extensive debridement and reconstruction. Although intraoperative postpump TEE views may be adequate for this new baseline, they should be reviewed for adequacy and repeated if necessary. Some patients will have significant valvular dysfunction at the end of otherwise successful antimicrobial treatment that will require eventual valvular surgery. Posttreatment echocardiography can guide both medical management and the discussion of the appropriate timing of such interventions.

Recommendation

1. **TTE at the time of antimicrobial therapy completion to establish baseline features is reasonable (*Class IIa; Level of Evidence C*).**

3D Echocardiography and Other Imaging Modalities

Although newer imaging modalities are undergoing preliminary evaluation, echocardiography will continue to be pivotal in patients with IE for the foreseeable future. In this regard, early investigations[64,65] of 3D TEE have demonstrated advantages over 2-dimensional TEE (which is routinely used) to better detect and delineate vegetations and to identify IE complications and their relationships with surrounding structures. Unfortunately, the lower temporal and lateral resolution with 3D echocardiography compared with 2-dimensional echocardiography leads to an overestimation of vegetation size and technically challenging visualization of fast-moving structures.

Although cardiac CT is used principally to evaluate great vessels and coronary artery disease, there may be a role for this tool[66–68] in cases of IE in which definitive evidence of IE and its complications is not secured with TEE. Moreover, coronary CT angiography can provide coronary artery evaluation in patients who are to undergo cardiac surgery for IE complications. In addition, this methodology may be useful in head-to-toe preoperative screening, including evaluation for central nervous system (CNS) lesions, and in intra-abdominal lesions (eg, silent splenic abscesses). Limitations include the associated exposure to radiation, nephrotoxicity associated with contrast dye, and relative lack of sensitivity in 1 study to demonstrate valve perforations.[67]

MRI has had a major impact on IE diagnosis and management, especially as a tool to detect cerebral embolic events, many of which are clinically silent.[69] Indications for the routine use of MRI and magnetic resonance angiography in IE management, however, are not well established. Comments related to mycotic or infectious aneurysms are provided in a later section of this document.

More study is needed to define the utility of ^{18}F-fluorodeoxyglucose positron emission tomography/CT in the diagnosis and management of IE. In a prospective study of 25 IE cases, ^{18}F-fluorodeoxyglucose positron emission tomography/CT was useful in identifying peripheral embolization in 11 patients and in detecting IE extracardiac manifestations in 7 patients who did not demonstrate any clinical manifestations of IE.[70]

The use of multimodality imaging in IE may increase in the future as the risks and benefits of each diagnostic tool are defined.[71]

Antimicrobial Therapy

Therapeutic Principles

The primary goal of antibiotic treatment is to eradicate infection, including sterilizing vegetations, although the unique characteristics of infected vegetations can pose a variety of challenges. These characteristics include focal infection with high bacterial density, slow rate of bacterial growth within biofilms, and low microorganism metabolic activity.[72] Host characteristics such as impaired immunity also contribute to challenges in therapeutics. In addition, antibiotics may fail to eradicate infection as a result of increased binding of the drug to serum proteins, perturbations of antibiotic penetration into the vegetation, and unique antibiotic pharmacokinetic/pharmacodynamic (PK/PD) features. Therefore, prolonged, parenteral, bactericidal therapy is required for attempted infection cure.

Inoculum Effect

The effect of high bacterial densities on antimicrobial activity is called the inoculum effect in which certain groups of antimicrobials commonly used to treat IE such as β-lactams and glycopeptides (and, to a lesser extent, lipopeptides such as daptomycin) are less active against highly dense bacterial populations.[73–75] Therefore, the effective minimum inhibitory concentration (MIC) at the site of infection with bacterial densities of 10^8 to 10^{11} colony-forming units per 1 g tissue can be much higher than anticipated by in vitro susceptibility tests that use a standard inoculum ($10^{5.5}$ colony-forming units per milliliter). In addition, bacteria that are otherwise killed at low densities by bactericidal antibiotics such as penicillins can be relatively resistant to or tolerant of their bactericidal effect in dense populations. An inoculum effect has been demonstrated with penicillin versus streptococci in both in vitro and animal models. For example, the curative dose of penicillin for streptococcal infections in animal models has been shown to increase markedly with the number of organisms inoculated and the duration of the infection, presumably because of the interim increase in the number of organisms in the infected host.[76] In addition, the stationary growth-phase conditions make it less likely that bacterial cell wall–active antibiotics (β-lactams and glycopeptides) are optimally effective.[77–79] Stationary-phase organisms have been associated with a loss of penicillin-binding proteins that are the active target sites required for β-lactam antibacterial activity. This loss of penicillin-binding proteins during stationary-phase growth may be responsible in part for the inoculum effect observed in vivo and may account for the failure of penicillin in both experimental and human cases of severe streptococcal infections.[80] Importantly, fluoroquinolones and aminoglycoside antibiotics are less affected by the size of the inoculum because of their different mechanisms of bactericidal activity.[81,82]

An inoculum effect also occurs with β-lactamase–susceptible β-lactam antibiotics versus β-lactamase–producing bacteria, presumably because more β-lactamase is present in denser β-lactamase–producing bacterial populations, as observed in vitro with some enterococci,[83] *S aureus,*[84] and Gram-negative bacilli[85]; in animal models of experimental IE[86,87]; and clinically.[88]

High inocula are also more likely to have antibiotic-resistant subpopulations that can emerge in the setting of antibiotic therapy. For example, in an in vitro PD model, the activity of vancomycin against heterogeneous vancomycin-intermediate *S aureus* (hVISA) and non-hVISA isolates was reduced in the presence of a high inoculum amount (10^8 colony-forming units per milliliter).[75]

Bactericidal Drugs

Data from animal models of IE and clinical investigations support the need for bactericidal antibiotics to sterilize vegetations in IE with high bacterial densities.[89] For enterococci, bactericidal activity can be achieved by the combination of certain β-lactam antibiotics (eg, penicillin, ampicillin, and piperacillin) with an aminoglycoside. The bactericidal effect achieved by a combination of antibacterial drugs that alone only inhibit bacterial growth is called synergy. The rate of bactericidal activity against some other organisms can also be enhanced by a combination of a β-lactam antibiotic plus an aminoglycoside.

Duration of Antimicrobial Therapy

The duration of therapy in IE must be sufficient to ensure complete eradication of microorganisms within vegetations. Prolonged therapy is necessary because of the high bacterial densities within vegetations and the relatively slow bactericidal activity of some antibiotics such as β-lactams and vancomycin. When the bactericidal activity is known to be more rapid or the likely vegetation bacterial burden is lower, then the clinician may prescribe a shorter duration of antimicrobial therapy in unique instances. Combination therapy with penicillin or ceftriaxone and an aminoglycoside for 2 weeks is highly effective in viridans group streptococci (VGS) IE[90] in very select patients with uncomplicated infection. Both β-lactam therapy alone and combination therapy with nafcillin and an aminoglycoside for only 2 weeks have been effective in patients with uncomplicated right-sided IE caused by *S aureus*[91]; monotherapy with a β-lactam would be selected for use in cases of uncomplicated IE.[92]

Of interest, right-sided vegetations tend to have lower bacterial densities, which may result from host defense mechanisms, including polymorphonuclear activity or platelet-derived antibacterial cationic peptides.[90,91,93]

Drug Penetration

The penetration of antibiotics is a significant issue in the treatment of IE because cardiac vegetations, which are composed of layers of fibrin and platelets, pose a considerable mechanical barrier between the antibiotic and the embedded targeted microorganisms.[94,95] The efficacy of antimicrobial drugs varies, depending on the degree of penetration into the vegetation, pattern of distribution within the vegetation, and vegetation size.[96,97] Patterns of diffusion differ by class of antibiotic, which may have implications for therapeutic outcomes in patients being treated for IE.[98–100]

PK/PD and Dosing Implications in IE

In the design of dose regimens for the treatment of IE, it is important to fully optimize the PK/PD parameter for the selected antibiotic to increase the likelihood of success

and to decrease the potential for developing resistance.[101] Antibiotic PK/PD is related to both PK and microorganism susceptibility to the drug.[102] With the use of in vitro and in vivo evaluations, antibiotics are categorized on the basis of whether they possess concentration-dependent or time-dependent effects on microorganisms and on the basis of 4 common PK/PD parameters that predict antibiotic efficacy: the ratio of the maximum serum concentration to the MIC, the ratio of the area under the 24-hour plasma concentration-time curve to the MIC (AUC_{24}/MIC), the duration of time that the serum concentration exceeds the MIC, and the duration of the postantibiotic effect.[101,103] More detailed discussion of the calculation of these parameters has been given previously.[100]

Whereas both the ratio of maximum serum concentration to MIC and the AUC_{24}/MIC ratio have been shown to predict efficacy as the optimized PD parameters for aminoglycoside, fluoroquinolone, and daptomycin therapy, the AUC_{24}/MIC is the optimized PD activity for glycopeptides such as vancomycin, teicoplanin, telavancin, oritavancin, and lipopeptides such as daptomycin. β-Lactam efficacy, in contrast, is best predicted by the percent duration of time that the serum concentration exceeds the MIC.[102] For penicillins and cephalosporins to achieve a bacteriostatic effect in a murine model, the time the free drug must exceed the MIC is 35% to 40% of the dosing interval, whereas a bactericidal response requires 60% to 70% of the dosing interval.[104] Two retrospective studies examined the continuous infusion of 2 β-lactams (cefazolin and oxacillin) for methicillin-sensitive *S aureus* (MSSA) infections, including IE, with results supporting continuous infusion of these drugs. More study is needed, however, before a strong recommendation can be made.[105,106]

For concentration-dependent antibiotics such as aminoglycosides and fluoroquinolones, a ratio of maximum serum concentration to MIC of >10 was associated with improved efficacy in patients with Gram-negative pneumonia, whereas an AUC_{24}/MIC >125 was associated with an improved clinical efficacy for ciprofloxacin against infections caused by *Pseudomonas aeruginosa.*[107,108] Liu et al[109] demonstrated that the minimal AUC_{24}/MIC requirement for daptomycin with an 80% kill efficacy in a *S aureus* infection mouse model was ≈250, which would be easily achieved by the recommended dose of 6 $mg \cdot kg^{-1} \cdot d^{-1}$ for complicated bacteremia, including right-sided IE.

Some experts have recommended daptomycin doses of 8 to 10 $mg \cdot kg^{-1} \cdot d^{-1}$ for the treatment of complicated methicillin-resistant *S aureus* (MRSA) bacteremia, particularly IE. This recommendation is based on the concentration-dependent properties of daptomycin, improved efficacy for infections caused by organisms with reduced susceptibility to daptomycin, and an attempt to reduce the emergence of resistance to daptomycin after vancomycin therapy.[110] The evidence for these recommendations has come largely from in vitro PK/PD models using high-inoculum–simulated endocardial vegetations with *S aureus*[111] and enterococci and from animal models of IE.[112]

With regard to vancomycin, an AUC_{24}/MIC ≥400 is recommended as the targeted PK/PD parameter for patients with serious *S aureus* infections.[112] In an evaluation of 320 MRSA patients with complicated bacteremia, including IE, Kullar et al[113] demonstrated that an AUC_{24}/MIC >421 was significantly associated with improved patient outcomes. This AUC_{24}/MIC ratio was associated with trough serum concentrations >15 mg/L, attainable if the vancomycin MIC was <1 mg/L.

Antimicrobial Treatment Perspectives

In many cases, the initial therapy of IE is empirical; typically, results of blood cultures are monitored for hours to days until a pathogen is identified. During this time, empirical antimicrobial therapy is administered with the expectation that the regimen will be revised once a pathogen is defined and susceptibility results are obtained. The selection of an optimal empiric regimen is usually broad and is based on factors that relate to patient characteristics, prior antimicrobial exposures and microbiological findings, and epidemiological features. Therefore, infectious diseases consultation should occur at the time of empirical therapy initiation to help define a regimen[114,115] because the selection of a regimen is highly variable. In this regard, please refer the Culture-Negative Endocarditis section of this statement and the related Table 6 for additional details.

Results of clinical efficacy studies support the use of most treatment regimens described in these guidelines. Other recommendations listed in this section are based largely on in vitro data and consensus opinion and include the following management considerations. It is reasonable for the counting of days for the duration of therapy to begin on the first day on which blood cultures are negative in cases in which blood cultures were initially positive. It is reasonable to obtain 2 sets of blood cultures every 24 to 48 hours until bloodstream infection is cleared. However, if a patient undergoes valve surgery and the resected valve tissue is culture positive or a perivalvular abscess is found, then an entire course of antimicrobial therapy is reasonable after valve surgery. If the resected tissue is culture negative, then it may be reasonable for the duration of postoperative treatment given less the number of days of treatment administered for native valve infection before valve replacement. This, however, has been challenged by retrospectively collected data from 2 different medical centers[116,117] that suggest that 2 weeks of antibiotic therapy may be sufficient in patients who undergo valve surgery and have negative valve tissue cultures, particularly in IE cases caused by VGS or *Streptococcus gallolyticus (bovis)*. Whether a 2-week treatment course would be sufficient after valve surgery in patients with positive valve cultures either was not addressed in 1 survey[116] or included only 5 patients in the other.[117] Histopathological evidence of bacteria with valve tissue Gram staining in patients with negative tissue cultures can represent killed organisms and is not a factor in defining the length of therapy after valve surgery.[110]

For patients with NVE who undergo valve resection with prosthetic valve replacement or repair with an annuloplasty ring, there is a lack of consensus as to whether the postoperative treatment regimen should be one that is recommended for prosthetic valve treatment rather than one that is recommended

Table 6. Epidemiological Clues That May be Helpful in Defining the Etiological Diagnosis of Culture-Negative Endocarditis

Epidemiological Feature	Common Microorganism
IDU	*S aureus*, including community-acquired oxacillin-resistant strains
	Coagulase-negative staphylococci
	β-Hemolytic streptococci
	Fungi
	Aerobic Gram-negative bacilli, including *Pseudomonas aeruginosa*
	Polymicrobial
Indwelling cardiovascular medical devices	*S aureus*
	Coagulase-negative staphylococci
	Fungi
	Aerobic Gram-negative bacilli
	Corynebacterium sp
Genitourinary disorders, infection, and manipulation, including pregnancy, delivery, and abortion	*Enterococcus* sp
	Group B streptococci (*S agalactiae*)
	Listeria monocytogenes
	Aerobic Gram-negative bacilli
	Neisseria gonorrhoeae
Chronic skin disorders, including recurrent infections	*S aureus*
	β-Hemolytic streptococci
Poor dental health, dental procedures	VGS
	Nutritionally variant streptococci
	Abiotrophia defectiva
	Granulicatella sp
	Gemella sp
	HACEK organisms
Alcoholism, cirrhosis	*Bartonella* sp
	Aeromonas sp
	Listeria sp
	S pneumoniae
	β-Hemolytic streptococci
Burn	*S aureus*
	Aerobic Gram-negative bacilli, including *P aeruginosa*
	Fungi
Diabetes mellitus	*S aureus*
	β-Hemolytic streptococci
	S pneumoniae
Early (≤1 y) prosthetic valve placement	Coagulase-negative staphylococci
	S aureus
	Aerobic Gram-negative bacilli
	Fungi
	Corynebacterium sp
	Legionella sp
Late (>1 y) prosthetic valve placement	Coagulase-negative staphylococci
	S aureus
	Viridans group streptococci
	Enterococcus species
	Fungi
	Corynebacterium sp
Dog or cat exposure	*Bartonella* sp
	Pasteurella sp
	Capnocytophaga sp
Contact with contaminated milk or infected farm animals	*Brucella* sp
	Coxiella burnetii
	Erysipelothrix sp
Homeless, body lice	*Bartonella* sp
AIDS	*Salmonella* sp
	S pneumoniae
	S aureus
Pneumonia, meningitis	*S pneumoniae*
Solid organ transplantation	*S aureus*
	Aspergillus fumigatus
	Enterococcus sp
	Candida sp
Gastrointestinal lesions	*S gallolyticus (bovis)*
	Enterococcus sp
	Clostridium septicum

HACEK indicates *Haemophilus* species, *Aggregatibacter* species, *Cardiobacterium hominis*, *Eikenella corrodens*, and *Kingella* species; IDU, injection drug use; and VGS, viridans group streptococci.

for native valve treatment. In regimens that contain combination antimicrobial therapy, it is reasonable to administer agents at the same time or temporally close together to maximize the synergistic killing effect on an infecting pathogen.

Recommendations

1. **Infectious diseases consultation should be obtained to define an optimal empirical treatment regimen at the time of initiation of antimicrobial therapy (*Class I; Level of Evidence B*).**
2. **It is reasonable that the counting of days for the duration of antimicrobial therapy begin on the first day on which blood cultures are negative in cases in which blood cultures were initially positive (*Class IIa; Level of Evidence C*).**
3. **It is reasonable to obtain at least 2 sets of blood cultures every 24 to 48 hours until bloodstream infection has cleared (*Class IIa; Level of Evidence C*).**
4. **If operative tissue cultures are positive, then an entire antimicrobial course is reasonable after valve surgery (*Class IIa; Level of Evidence B*).**
5. **If operative tissue cultures are negative, it may be reasonable to count the number of days of antimicrobial therapy administered before surgery in the overall duration of therapy (*Class IIb; Level of Evidence C*).**
6. **It is reasonable to time the administration of antimicrobial therapy at the same time or temporally close together for regimens that include >1 antimicrobial agent (*Class IIa; Level of Evidence C*).**

Overview of VGS, *Streptococcus gallolyticus* (Formerly Known as *Streptococcus bovis*), *Abiotrophia defectiva*, and Granulicatella Species

VGS are common pathogenic agents in community-acquired NVE in patients who are not IDUs. The taxonomy of VGS is evolving. The species that most commonly cause IE are *S sanguis*, *S oralis (mitis)*, *S salivarius*, *S mutans*, and *Gemella morbillorum* (formerly called *S morbillorum*). Members of the *S anginosus* group (*S intermedius*, *anginosus*, and *constellatus*) also have been referred to as the *S milleri* group, and this has caused some confusion. In contrast to other α-hemolytic streptococcal species, the *S anginosus* group tends to form abscesses and to cause hematogenously disseminated infection (eg, myocardial and visceral abscesses, septic arthritis, and vertebral osteomyelitis). In addition, although the *S anginosus* group usually is sensitive to penicillin, some strains may exhibit variable penicillin resistance. The recommendations that follow are intended to assist clinicians in selecting appropriate antimicrobial therapy for patients with IE caused by VGS and *S gallolyticus (bovis*, a nonenterococcal penicillin-susceptible group D *Streptococcus*). *S gallolyticus (bovis)* expresses the group D antigen, but it can be distinguished from group D *Enterococcus* by appropriate biochemical tests. Patients with either *S gallolyticus (bovis)* bacteremia or IE should undergo a colonoscopy to determine whether malignancy or other mucosal lesions are present.

Certain VGS have biological characteristics that may complicate diagnosis and therapy. *A defectiva* and *Granulicatella* species (*G elegans*, *G adiacens*, *G paraadiacens*, and *G balaenopterae)*, formerly known as nutritionally variant streptococci, are detected by automated blood culture systems but may yield pleomorphic forms by Gram stain and will not grow on subculture unless chocolate agar or other media supplemented with pyridoxal or cysteine is used.

Treatment regimens outlined for VGS, *A. defectiva*, and *Granulicatella* species are subdivided into categories based on penicillin MIC data.

Native Valve

Highly Penicillin-Susceptible VGS and *S gallolyticus (bovis)* (MIC ≤0.12 μg/mL)

Bacteriological cure rates ≥ 98% may be anticipated in patients who complete 4 weeks of therapy with parenteral penicillin or ceftriaxone for IE caused by highly penicillin-susceptible VGS or *S gallolyticus (bovis)*[118,119] (Table 7). Ampicillin is a reasonable alternative to penicillin and has been used when penicillin is not available because of supply deficiencies.

The addition of gentamicin sulfate to penicillin exerts a synergistic killing effect in vitro on VGS and *S gallolyticus (bovis)*. The combination of penicillin or ceftriaxone with gentamicin results in synergistic killing in animal models of VGS or *S gallolyticus (bovis)* experimental IE. In selected patients, treatment with a 2-week regimen with either penicillin or ceftriaxone combined with an aminoglycoside resulted in cure rates that are similar to those after monotherapy with penicillin or ceftriaxone administered for 4 weeks.[83,120] Studies performed in Europe, South America, and the United States demonstrated that the combination of once-daily ceftriaxone with either netilmicin or gentamicin administered once daily was equivalent in efficacy to 2 weeks of therapy with penicillin with an aminoglycoside administered in daily divided doses.[83,120] The 2-week regimen of penicillin or ceftriaxone combined with single daily-dose gentamicin is reasonable for uncomplicated cases of IE caused by highly penicillin-susceptible VGS or *S gallolyticus (bovis)* in patients at low risk for adverse events caused by gentamicin therapy (Table 7). This 2-week regimen is not recommended for patients with known extracardiac infection or those with a creatinine clearance of <20 mL/min.

Although the two, 4-week ß-lactam–containing regimens shown in Table 7 produce similar outcomes, each regimen has advantages and disadvantages. Monotherapy with either penicillin or ceftriaxone for 4 weeks avoids the use of gentamicin, which is potentially ototoxic and nephrotoxic. Compared with penicillin, the advantage of once-daily ceftriaxone is its simplicity for use in therapy administered to outpatients.[118,121] Both penicillin and ceftriaxone are overall well tolerated but, like all antimicrobials, have the potential for causing adverse drug events; some of the more common ones include rash, fever, diarrhea, and neutropenia. Liver function abnormalities can be seen with ceftriaxone use and are sometimes associated with "sludging" of drug in the gallbladder.[122]

For patients who are unable to tolerate penicillin or ceftriaxone, vancomycin is a reasonably effective alternative. Prolonged intravenous use of vancomycin may be complicated by thrombophlebitis, rash, fever, neutropenia, and rarely ototoxic reactions. The likelihood of "red man" syndrome is reduced with an infusion of vancomycin over ≥1 hour. Desired trough vancomycin levels should range between 10 and 15 μg/mL.

Recommendations

1. **Both aqueous crystalline penicillin G and ceftriaxone are reasonable options for a 4-week treatment duration (*Class IIa; Level of Evidence B*).**
2. **A 2-week treatment regimen that includes gentamicin is reasonable in patients with uncomplicated IE, rapid response to therapy, and no underlying renal disease (*Class IIa; Level of Evidence B*).**
3. **Vancomycin for a 4-week treatment duration is a reasonable alternative in patients who cannot tolerate penicillin or ceftriaxone therapy (*Class IIa; Level of Evidence B*).**
4. **The desired trough vancomycin level should range between 10 and 15 μg/mL (*Class I; Level of Evidence C*).**

VGS and *S gallolyticus (bovis)* With Penicillin (MIC >0.12–<0.5 μg/mL)

Penicillin resistance in vitro occurs among some strains of VGS and *S gallolyticus (bovis)*. To date, however, the number of IE cases that have been reported as a result of VGS or *S gallolyticus (bovis*) strains that harbor any degree of penicillin resistance is small.[123–126] Therefore, it is difficult to define the optimal treatment strategies for this group of patients.

Table 7. Therapy of NVE Caused by Highly Penicillin-Susceptible VGS and *Streptococcus gallolyticus (bovis)*

Regimen	Dose* and Route	Duration, wk	Strength of Recommendation	Comments
Aqueous crystalline penicillin G sodium	12–18 million U/24 h IV either continuously or in 4 or 6 equally divided doses	4	*Class IIa; Level of Evidence B*	Preferred in most patients >65 y or patients with impairment of eighth cranial nerve function or renal function.
Or				Ampicillin 2 g IV every 4 h is a reasonable alternative to penicillin if a penicillin shortage exists.
Ceftriaxone sodium	2 g/24 h IV/IM in 1 dose	4	*Class IIa; Level of Evidence B*	
Aqueous crystalline penicillin G sodium	12–18 million U/24 h IV either continuously or in 6 equally divided doses	2	*Class IIa; Level of Evidence B*	2-wk regimen not intended for patients with known cardiac or extracardiac abscess or for those with creatinine clearance of <20 mL/min, impaired eighth cranial nerve function, or *Abiotrophia, Granulicatella*, or *Gemella* spp infection; gentamicin dose should be adjusted to achieve peak serum concentration of 3–4 μg/mL and trough serum concentration of <1 μg/mL when 3 divided doses are used; there are no optimal drug concentrations for single daily dosing.†
Or				
Ceftriaxone sodium	2 g/24 h IV or IM in 1 dose	2	*Class IIa; Level of Evidence B*	
Plus				
Gentamicin sulfate‡	3 mg/kg per 24 h IV or IM in 1 dose	2		
Vancomycin hydrochloride§	30 mg/kg per 24 h IV in 2 equally divided doses	4	*Class IIa; Level of Evidence B*	Vancomycin therapy is reasonable only for patients unable to tolerate penicillin or ceftriaxone; vancomycin dose should be adjusted to a trough concentration range of 10–15 μg/mL.

IM indicates intramuscular; IV, intravenous; NVE, native valve infective endocarditis; and VGS, viridans group streptococci. Minimum inhibitory concentration is ≤0.12 μg/mL. The subdivisions differ from Clinical and Laboratory Standards Institute–recommended break points that are used to define penicillin susceptibility.

*Doses recommended are for patients with normal renal function.

†Data for once-daily dosing of aminoglycosides for children exist, but no data for treatment of IE exist.

‡Other potentially nephrotoxic drugs (eg, nonsteroidal anti-inflammatory drugs) should be used with caution in patients receiving gentamicin therapy. Although it is preferred that gentamicin (3 mg/kg) be given as a single daily dose to adult patients with endocarditis caused by viridans group streptococci, as a second option, gentamicin can be administered daily in 3 equally divided doses.

§Vancomycin dosages should be infused during the course of at least 1 hour to reduce the risk of histamine-release "red man" syndrome.

Table 8 shows regimens for treatment of NVE caused by relatively penicillin-resistant strains (MIC >0.12–<0.5 μg/mL). For patients with VGS or *S gallolyticus (bovis)* IE caused by these relatively resistant strains, it is reasonable to administer penicillin for 4 weeks, together with single daily-dose gentamicin for the first 2 weeks of treatment. Ampicillin is a reasonable alternative to penicillin if shortages of penicillin exist.

If the isolate is ceftriaxone susceptible, then ceftriaxone alone may be considered (Class IIb; Level of Evidence C). Vancomycin alone may be a reasonable alternative if the patient is intolerant of β-lactam therapy (Class IIb; Level of Evidence C). Consultation with an infectious diseases specialist is encouraged in both of these scenarios.

Recommendations

1. **It is reasonable to administer penicillin for 4 weeks with single daily-dose gentamicin for the first 2 weeks of therapy (*Class IIa; Level of Evidence B*).**
2. **If the isolate is ceftriaxone susceptible, then ceftriaxone alone may be considered (*Class IIb; Level of Evidence C*).**
3. **Vancomycin alone may be a reasonable alternative in patients who are intolerant of β-lactam therapy (*Class IIb; Level of Evidence C*).**

A defectiva and *Granulicatella* Species and VGS With Penicillin (MIC ≥0.5 μg/mL)

The determination of antimicrobial susceptibilities of *A defectiva* and *Granulicatella* species (both formerly known as nutritionally variant streptococci) is often technically difficult, and the results may not be accurate. Moreover, IE caused by these microorganisms is uncommon and has been more difficult to cure microbiologically compared with IE caused by a strain of non–nutritionally variant VGS.[127] For these reasons, in patients with IE caused by *A defectiva* and *Granulicatella* species, it is reasonable to administer a combination regimen that includes ampicillin (12 g/d in divided doses) or penicillin (18–30 million U/D in divided doses or by continuous infusion) plus gentamicin (3 $mg \cdot kg^{-1} \cdot d^{-1}$ in 2–3 divided doses) with infectious diseases consultation to determine length of therapy. Findings from an animal model of experimental endocarditis suggest that if vancomycin is chosen for use in patients intolerant of penicillin or ampicillin, then the addition of gentamicin is not needed.[128] Ceftriaxone combined with gentamicin may be a reasonable alternative treatment option[125,126] for VGS isolates that are susceptible to ceftriaxone on the basis of the Clinical and Laboratory Standards Institute definition and are resistant to penicillin (MIC ≥0.5 μg/mL, as defined in this statement). Currently, there is no reported clinical experience with the combination of ampicillin plus ceftriaxone for IE caused by these organisms.

Table 8. Therapy of NVE Caused by Strains of VGS and *Streptococcus gallolyticus (bovis)* Relatively Resistant to Penicillin

Regimen	Dose* and Route	Duration, wk	Strength of Recommendation	Comments
Aqueous crystalline penicillin G sodium	24 million U/24 h IV either continuously or in 4–6 equally divided doses	4	*Class IIa; Level of Evidence B*	It is reasonable to treat patients with IE caused penicillin-resistant (MIC ≥0.5 μg/mL) VGS strains with a combination of ampicillin or penicillin plus gentamicin as done for enterococcal IE with infectious diseases consultation (*Class IIa; Level of Evidence C*). Ampicillin 2 g IV every 4 h is a reasonable alternative to penicillin if a penicillin shortage exists.
Plus				
Gentamicin sulfate†	3 mg/kg per 24 h IV or IM in 1 dose	2		Ceftriaxone may be a reasonable alternative treatment option for VGS isolates that are susceptible to ceftriaxone (*Class IIb; Level of Evidence C*).
Vancomycin hydrochloride‡	30 mg/kg per 24 h IV in 2 equally divided doses	4	*Class IIa; Level of Evidence B*	Vancomycin therapy is reasonable only for patients unable to tolerate penicillin or ceftriaxone therapy.

IE indicates infective endocarditis; IM, intramuscular; IV, intravenous; MIC, minimum inhibitory concentration; NVE, native valve infective endocarditis; and VGS, viridans group streptococci. MIC is >0.12 to <0.5 μg/mL for penicillin. The subdivisions differ from Clinical and Laboratory Standards Institute–recommended break points that are used to define penicillin susceptibility.)

*Doses recommended are for patients with normal renal function.

†See Table 7 for appropriate dose of gentamicin. Although it is preferred that gentamicin (3 mg/kg) be given as a single daily dose to adult patients with endocarditis caused by viridans group streptococci, as a second option, gentamicin can be administered daily in 3 equally divided doses.

‡See Table 7 for appropriate dosage of vancomycin.

Recommendations

1. **It is reasonable to treat patients with IE caused by *A defectiva, Granulicatella* species, and VGS with a combination of ampicillin or penicillin plus gentamicin as done for enterococcal IE with infectious diseases consultation (*Class IIa; Level of Evidence C*).**
2. **If vancomycin is used in patients intolerant of ampicillin or penicillin, then the addition of gentamicin is not needed (*Class III; Level of Evidence C*).**
3. **Ceftriaxone combined with gentamicin may be a reasonable alternative treatment option for VGS isolates with a penicillin MIC ≥0.5 μg/mL that are susceptible to ceftriaxone (*Class IIb; Level of Evidence C*).**

Prosthetic Valve or Valvular Prosthetic Material

Endocarditis of Prosthetic Valves or Other Prosthetic Material Caused by VGS and *S gallolyticus (bovis)*

For patients with IE complicating prosthetic valves or other prosthetic material caused by a highly penicillin-susceptible strain (MIC ≤0.12 μg/mL), it is reasonable to administer 6 weeks of therapy with penicillin or ceftriaxone with or without gentamicin for the first 2 weeks (Table 9). It is reasonable to administer 6 weeks of therapy with a combination of penicillin or ceftriaxone and gentamicin in patients with IE caused by a strain that is relatively or highly resistant to penicillin (MIC >0.12 μg/mL). Vancomycin is useful only for patients who are unable to tolerate penicillin, ceftriaxone, or gentamicin. Ampicillin is an acceptable alternative to penicillin if shortages of penicillin exist.

Recommendations

1. **Aqueous crystalline penicillin G or ceftriaxone for 6 weeks with or without gentamicin for the first 2 weeks is reasonable (*Class IIa; Level of Evidence B*).**
2. **It is reasonable to extend gentamicin to 6 weeks if the MIC is >0.12 μg/mL for the infecting strain (*Class IIa; Level of Evidence C*).**
3. **Vancomycin can be useful in patients intolerant of penicillin, ceftriaxone, or gentamicin (*Class IIa; Level of Evidence B*).**

Streptococcus pneumoniae, *Streptococcus pyogenes*, and Groups B, C, F, and G β-Hemolytic Streptococci

IE caused by these streptococci is uncommon. There are few published reports of large case series evaluating management strategies for IE caused by these microorganisms. Results of logistic regression analysis of clinical variables from cases of pneumococcal IE demonstrated the potential value of valve replacement in preventing early death in 1 investigation.[129] For patients with NVE caused by highly penicillin-susceptible *S pneumoniae,* it is reasonable to administer 4 weeks of antimicrobial therapy with penicillin, cefazolin, or ceftriaxone. Vancomycin is reasonable only for patients who are unable to tolerate β-lactam therapy. Six weeks of therapy is reasonable for patients with prosthetic valve endocarditis (PVE).

Pneumococci with intermediate penicillin resistance (MIC >0.1–1.0 μg/mL) or high penicillin resistance (MIC ≥2.0 μg/mL) are recovered uncommonly from patients with bacteremia.[130] Moreover, cross-resistance of pneumococci to other antimicrobial agents such as cephalosporins, macrolides, fluoroquinolones, carbapenems, and even vancomycin is increasing in frequency. In 1 multicenter study[131] with a relatively large number of patients with IE caused by

Table 9. Therapy for Endocarditis Involving a Prosthetic Valve or Other Prosthetic Material Caused by VGS and *Streptococcus gallolyticus (bovis)*

Regimen	Dose* and Route	Duration, wk	Strength of Recommendation	Comments
Penicillin-susceptible strain (≤0.12 μg/mL)				
Aqueous crystalline penicillin G sodium	24 million U/24 h IV either continuously or in 4–6 equally divided doses	6	*Class IIa; Level of Evidence B*	Penicillin or ceftriaxone together with gentamicin has not demonstrated superior cure rates compared with monotherapy with penicillin or ceftriaxone for patients with highly susceptible strain; gentamicin therapy should not be administered to patients with creatinine clearance <30 mL/min.
Or				
Ceftriaxone	2 g/24 h IV or IM in 1 dose	6	*Class IIa; Level of Evidence B*	
With or without				
Gentamicin sulfate†	3 mg/kg per 24 h IV or IM in 1 dose	2		Ampicillin 2 g IV every 4 h is a reasonable alternative to penicillin if a penicillin shortage exists.
Vancomycin hydrochloride‡	30 mg/kg per 24 h IV in 2 equally divided doses	6	*Class IIa; Level of Evidence B*	Vancomycin is reasonable only for patients unable to tolerate penicillin or ceftriaxone.
Penicillin relatively or fully resistant strain (MIC >0.12 μg/mL)				
Aqueous crystalline penicillin sodium	24 million U/24 h IV either continuously or in 4–6 equally divided doses	6	*Class IIa; Level of Evidence B*	Ampicillin 2 g IV every 4 h is a reasonable alternative to penicillin if a penicillin shortage exists.
Or				
Ceftriaxone	2 g/24 h IV/IM in 1 dose	6	*Class IIa; Level of Evidence B*	
Plus				
Gentamicin sulfate	3 mg/kg per 24 h IV/IM in 1 dose	6		
Vancomycin hydrochloride	30 mg/kg per 24 h IV in 2 equally divided doses	6	*Class IIa; Level of Evidence B*	Vancomycin is reasonable only for patients unable to tolerate penicillin or ceftriaxone.

IM indicates intramuscular; IV, intravenous; MIC indicates minimum inhibitory concentration; and VGS, viridans group streptococci.

*Doses recommended are for patients with normal renal function.

†See Table 7 for appropriate dose of gentamicin. Although it is preferred that gentamicin (3 mg/kg) be given as a single daily dose to adult patients with endocarditis resulting from VGS, as a second option, gentamicin can be administered daily in 3 equally divided doses.

‡See text and Table 7 for appropriate dose of vancomycin.

S pneumoniae resistant to penicillin (MIC, 0.1–4 μg/mL), patients were evaluated and compared with 39 patients who were infected with penicillin-susceptible strains. Several key observations were made. Infection by penicillin-resistant strains did not worsen prognosis. High-dose penicillin or a third-generation cephalosporin is reasonable in patients with penicillin-resistant IE without meningitis. In patients with IE and meningitis, high doses of cefotaxime are reasonable. If the isolate is resistant (MIC ≥2 μg/mL) to cefotaxime, then the addition of vancomycin and rifampin may be considered. Ceftriaxone may be considered instead of cefotaxime in the previous recommendations. These findings are based on current levels of resistance, and increasing MICs could dictate revisions in future treatment selections. Accordingly, the treatment of patients with pneumococcal IE should be coordinated in consultation with an infectious diseases specialist.

For *S pyogenes* IE, penicillin G administered intravenously for 4 to 6 weeks is reasonable treatment on the basis of limited published data. Ceftriaxone is a reasonable alternative to penicillin. Vancomycin is reasonable only for patients who are unable to tolerate a β-lactam antibiotic.

In general, strains of group B, C, F, and G streptococci are slightly more resistant to penicillin than are strains of group A streptococci. In these patients, the addition of gentamicin to penicillin or to ceftriaxone for at least the first 2 weeks of a 4- to 6-week course of antimicrobial therapy for group B, C, and G streptococcal IE may be considered.[132,133] There is a clinical impression[134,135] that early cardiac surgical intervention has improved overall survival rates among treated patients with β-hemolytic streptococcal IE compared with patients treated decades ago. Because of the relative infrequency of IE caused by these microorganisms, consultation with an infectious diseases specialist during treatment is recommended.

Recommendations

1. **Four weeks of antimicrobial therapy with penicillin, cefazolin, or ceftriaxone is reasonable for IE caused by *S pneumoniae*; vancomycin can be useful for patients intolerant of β-lactam therapy (*Class IIa; Level of Evidence C*).**
2. **Six weeks of therapy is reasonable for PVE caused by *S pneumoniae* (*Class IIa; Level of Evidence C*).**
3. **High-dose penicillin or a third-generation cephalosporin is reasonable in patients with IE caused by penicillin-resistant *S pneumoniae* without meningitis; if meningitis is present, then high doses of**

cefotaxime (or ceftriaxone) are reasonable (*Class IIa; Level of Evidence C*).

4. **The addition of vancomycin and rifampin to cefotaxime (or ceftriaxone) may be considered in patients with IE caused by *S pneumoniae* that are resistant to cefotaxime (MIC >2 μg/mL) (*Class IIb; Level of Evidence C*).**
5. **Because of the complexities of IE caused by *S pneumoniae*, consultation with an infectious diseases specialist is recommended (*Class I; Level of Evidence C*).**
6. **For IE caused by *S pyogenes*, 4 to 6 weeks of therapy with aqueous crystalline penicillin G or ceftriaxone is reasonable; vancomycin is reasonable only in patients intolerant of β-lactam therapy (*Class IIa; Level of Evidence C*).**
7. **For IE caused by group B, C, or G streptococci, the addition of gentamicin to aqueous crystalline penicillin G or ceftriaxone for at least the first 2 weeks of a 4- to 6-week treatment course may be considered (*Class IIb; Level of Evidence C*).**
8. **Consultation with an infectious diseases specialist to guide treatment is recommended in patients with IE caused by β-hemolytic streptococci (*Class I; Level of Evidence C*).**

Staphylococci

IE may be caused by staphylococci that are coagulase positive (*S aureus*) or coagulase negative (*S epidermidis, S lugdunensis,* and various other species). Although coagulase-positive staphylococci were traditionally believed to cause primarily NVE and coagulase-negative staphylococci (CoNS) were associated with PVE, considerable overlap now exists. For example, in a multicenter, prospective, observational investigation involving >1000 consecutive patients with definite IE from >20 countries, *S aureus* was the most common cause of PVE (25.8% of 214 cases), whereas 64 cases of NVE (8%) resulted from CoNS.[136] In addition, the prevalence of CoNS NVE appears to be increasing.[137] Thus, it is important to consider both pathogen groups when a patient with suspected IE has a preliminary blood culture that suggests staphylococci by Gram stain interpretation.

S aureus

S aureus is the most common cause of IE in much of the developed world.[6–8] Data from >70 million hospitalizations in the United States suggest that rates of *S aureus* IE have increased significantly relative to other causes of IE.[3] This increase is primarily a consequence of healthcare contact (eg, intravascular catheters, surgical wounds, indwelling prosthetic devices, hemodialysis)[6,8,9] and is especially prevalent in North America.[6,138,139] Increasing rates of oxacillin-resistant *S aureus* or MRSA isolates in both hospital and community settings and the recovery of clinical *S aureus* isolates both partially and fully[138,139] resistant to vancomycin have complicated the treatment of *S aureus* IE. An increasing body of evidence suggests an association between high (but still susceptible on the basis of the Clinical and Laboratory Standards Institute definition) vancomycin MICs in *S aureus* and worse clinical outcome in both MRSA infections treated with vancomycin[140] and MRSA bacteremia treated with antistaphylococcal penicillins.[141] Importantly, this association between higher vancomycin MIC in infecting MSSA and worse clinical outcomes among patients treated with antistaphylococcal penicillins (not vancomycin) was externally validated in a large cohort of patients with MSSA IE.[142] These data suggest that host- or pathogen-specific factors, rather than higher MICs of the infecting pathogen to vancomycin, contribute to the poor outcomes in these patients (because the latter patients were not treated with a glycopeptide).

In non-IDUs, *S aureus* IE involves primarily the left side of the heart and is associated with mortality rates ranging from 25% to 40%. *S aureus* IE in IDUs often involves the tricuspid valve. Cure rates for right-sided *S aureus* IE in IDUs are high (>85%) and may be achieved with relatively short courses of either parenteral or oral treatment (2–4 weeks; see below). Complicated IE manifested, for example, by deep tissue abscesses or osteoarticular infection may require more prolonged therapy.

Coagulase-Negative Staphylococci

As noted above, in addition to their importance in PVE, CoNS now cause a significant but relatively small proportion of NVE cases.[2] Risk factors for CoNS IE are similar to those for *S aureus* and include typical risk factors associated with extensive healthcare contact. Of interest, data suggest that the overall outcomes for patients with CoNS IE and *S aureus* IE are similar.[137] Most CoNS are resistant to methicillin. These resistant organisms are particularly prominent among patients with healthcare-associated staphylococcal IE. Methicillin-resistant strains also are clinically resistant to cephalosporins and carbapenems, although this fact is not always reflected accurately in the results of standard in vitro tests.

An important subset of patients with CoNS IE has been identified: those with infection caused by *S lugdunensis*. This species of CoNS tends to cause a substantially more virulent form of IE, with a high rate of perivalvular extension of infection and metastatic infection. This organism is uniformly susceptible in vitro to most antibiotics.[143–145] Most experts believe that IE caused by this organism can be treated with standard regimens based on the in vitro susceptibility profiles of the strain. The patient also should be monitored carefully for the development of periannular extension or extracardiac spread of infection. Although microbiological differentiation of *S lugdunensis* requires specific biochemical assays, the poor outcomes associated with *S lugdunensis* underscore the importance of performing these specialized assays. Initial screening can be done with pyrrolidonyl aminopeptidase hydrolysis testing, and isolates that test positive should be further identified by a multisubstrate identification system, matrix-assisted laser desorption ionization–time of flight, or other methods, including PCR.[146,147]

Recommendation

1. **Ongoing vigilance for IE complications, including perivalvular extension of infection and extracardiac foci of infection, is reasonable (*Class IIa; Level of Evidence C*).**

IE Caused by Staphylococci in the Absence of Prosthetic Valves or Other Prosthetic Material

Right-Sided IE in IDUs

The addition of gentamicin to nafcillin or oxacillin has traditionally been a standard approach for the treatment of right-sided IE. For example, in IDUs with uncomplicated right-sided *S aureus* IE (no evidence of renal failure, extrapulmonary metastatic infections, aortic or mitral valve involvement, meningitis, or infection by MRSA), combined short-course (2 weeks) β-lactam plus aminoglycoside therapy was highly effective in several studies.[9,138–141] In 1 study, 92 patients provided such combination therapy had excellent outcomes, even HIV-infected patients and those who had large tricuspid valve vegetations (>10 mm in diameter). In contrast, short-course regimens with glycopeptides (teicoplanin or vancomycin) plus gentamicin appeared to be less effective for right-sided *S aureus* IE caused by either MSSA or MRSA strains.[91] These glycopeptides may be less effective because of limited bactericidal activity, poor penetration into vegetations, or increased drug clearance among IDUs.

A growing body of evidence suggests that the addition of adjunctive aminoglycoside therapy not only is unnecessary for patients with uncomplicated right-sided native valve *S aureus* IE but may cause harm. For example, 1 study showed that a 2-week monotherapy regimen of intravenous cloxacillin was equivalent to cloxacillin plus gentamicin administered for 2 weeks.[92] In 2006, the US Food and Drug Administration (FDA) approved the use of daptomycin ($6\ mg \cdot kg^{-1} \cdot d^{-1}$) for the treatment of *S aureus* bacteremia and right-sided *S aureus* IE.[13] In a registrational open-label, multinational, clinical trial for the treatment of *S aureus* bacteremia or right-sided IE comparing the efficacy of daptomycin monotherapy with therapy that included low-dose (1 mg/kg IV every 8 hours or adjusted on the basis of renal function) gentamicin for the first 4 days, patients did equally well in either treatment arm. In the predefined subgroup of those with MRSA bacteremia, daptomycin demonstrated a 44.4% success rate compared with 31.8% for standard therapy; this difference was not statistically significant (absolute difference, 12.6%, 95% confidence interval, −7.4 to 32.6; P=0.28). Of note, in a post hoc analysis of this landmark clinical trial,[148] the addition of even such low-dose, short-course gentamicin in 1 arm of the study was significantly associated with renal toxicity, which occurred early and often, and the clinical association between gentamicin dose and duration was minimal.

Thus, current evidence suggests that either parenteral β-lactam or daptomycin short-course therapy is adequate for the treatment of uncomplicated MSSA right-sided IE. In contrast, glycopeptide therapy for MRSA right-sided IE may require more prolonged treatment regimens. For both MSSA and MRSA infections, use of adjunctive gentamicin for the treatment of *S aureus* bacteremia or right-sided NVE is discouraged

Recommendation

1. **Gentamicin is not recommended for treatment of right-sided staphylococcal NVE (*Class III; Level of Evidence B*).**

In patients for whom parenteral antibiotic therapy is problematic, oral treatment may be a reasonable option. Two studies have evaluated the use of predominantly oral 4-week antibiotic regimens (featuring ciprofloxacin plus rifampin) for the therapy of uncomplicated right-sided MSSA IE in IDUs.[149,150] In each study, including one in which >70% of patients were HIV seropositive,[149] cure rates were >90%. However, the relatively high rate of quinolone resistance among contemporary *S aureus* strains has made this alternative treatment strategy problematic.

IE in Non-IDUs

Older anecdotal case reports in non-IDUs with *S aureus* IE suggested that the use of combined gentamicin-methicillin therapy may be of benefit in patients who fail to respond to monotherapy with methicillin.[151] This issue was addressed in a multicenter, prospective trial comparing nafcillin alone for 6 weeks with nafcillin plus gentamicin (for the initial 2 weeks) in the treatment of predominantly left-sided IE caused by *S aureus*.[152] Nafcillin-gentamicin therapy reduced the duration of bacteremia by ≈1 day compared with nafcillin monotherapy. However, combination therapy did not reduce mortality or the frequency of cardiac complications. Furthermore, combination therapy increased the frequency of gentamicin-associated nephrotoxicity. As noted above,[148] the risk of clinically significant nephrotoxicity with even short courses of adjunctive low-dose gentamicin for *S aureus* bacteremia and right-sided IE can be substantial. In addition, gentamicin should not be used with vancomycin in patients with MRSA NVE because of the nephrotoxicity risk.[13,142] In cases of brain abscess complicating MSSA IE, nafcillin is the preferred agent rather than cefazolin, which has inadequate blood-brain barrier penetrability. If the patient cannot tolerate nafcillin therapy, then vancomycin should be used.

Vancomycin is often included with cefazolin as empirical coverage for patients with IE caused by *S aureus* while awaiting susceptibility results. An analysis of the literature, however, compared the use of empirical combination of vancomycin and antistaphylococcal β-lactam therapy with vancomycin alone and demonstrated the superiority of β-lactam–containing regimens over vancomycin monotherapy for bacteremic MSSA infections, including IE.[153] This differential outcome included studies in which there was an early shift from empirical vancomycin to β-lactam therapy as soon as blood cultures yielded MSSA (not MRSA). The meta-analysis included small, retrospective studies, however, which limits support for initial combination therapy by some experts. Therefore, the usefulness of empiric combination therapy in patients with *S aureus* bacteremia until oxacillin susceptibility is known is uncertain.

Although the large majority of staphylococci are resistant to penicillin, occasional strains remain susceptible. Unfortunately, the current laboratory screening procedures for detecting penicillin susceptibility may not be reliable. Therefore, IE caused by these organisms should be treated with regimens outlined for MSSA that includes nafcillin (or equivalent antistaphylococcal penicillin) as an option rather than penicillin (Table 10).

There are no evidence-based data that demonstrate the most appropriate duration of nafcillin therapy for treatment of left-sided NVE caused by MSSA. For patients with

uncomplicated infection, 6 weeks of therapy is recommended. For patients with complications of IE such as perivalvular abscess ormation and septic metastatic complications, at least 6 weeks of nafcillin is recommended.

Currently, defining the optimal therapy for NVE attributable to MRSA is challenging. Historically, vancomycin has been used and is recommended. As outlined in the Therapy of MSSA IE in Patients Allergic to or Intolerant of β-Lactams section below, daptomycin may be a reasonable alternative to daptomycin for left-sided NVE caused by MRSA on the basis of limited data in a prospective, randomized trial; a multinational, prospective cohort investigation of the use of high-dose (≈9 mg/kg per dose) daptomycin; and a multicenter, retrospective, observational study that included daptomycin at ≥8 mg/kg per dose.[13,110,153] Selection of daptomycin dosing should be assisted by infectious diseases consultation.

At this time, additional study of ceftaroline is needed to define its role, if any, in the treatment of left-sided NVE caused by MRSA.

Recommendations

1. **Gentamicin should not be used for treatment of NVE caused by MSSA or MRSA (*Class III; Level of Evidence B*).**
2. **In cases of brain abscess resulting from MSSA IE, nafcillin should be used instead of cefazolin; vancomycin should be given in cases of nafcillin intolerance (*Class I; Level of Evidence C*).**
3. **The usefulness of empirical combination therapy with vancomycin plus an antistaphylococcal β-lactam antibiotic in patients with *S aureus* bacteremia until oxacillin susceptibility is known is uncertain (*Class IIb; Level of Evidence B*).**
4. **IE caused by staphylococci that are penicillin susceptible should be treated with antistaphylococcal β-lactam antibiotics rather than aqueous crystalline penicillin G because clinical laboratories are not able to detect penicillin susceptibility (*Class I; Level of Evidence B*).**
5. **Six weeks of nafcillin (or equivalent antistaphylococcal penicillin) is recommended for uncomplicated left-sided NVE caused by MSSA; at least 6 weeks of nafcillin (or equivalent antistaphylococcal penicillin) is recommended for complicated left-sided NVE caused by this organism (*Class I; Level of Evidence C*).**
6. **Daptomycin may be a reasonable alternative to vancomycin for treatment of left-sided IE resulting from MSSA (*Class IIb; Level of Evidence B*).**
7. **Selection of daptomycin dosing should be assisted by infectious diseases consultation (*Class I; Level of Evidence C*).**

Therapy of MSSA IE in Patients Allergic to or Intolerant of β-Lactams

Therapy for MSSA IE in patients truly unable to tolerate ß-lactams is problematic. One decision analysis study concluded that patients with a questionable history of immediate-type hypersensitivity to penicillins in the context of IE caused by MSSA should be skin tested before starting antibiotic therapy.[154] However, the limited availability of standardized skin test reagents makes testing impractical. Instead, most experts endorse one of the published standard desensitization protocols. For patients with a well-defined history of nonanaphylactoid reactions to penicillins (eg, simple skin rash), a first-generation cephalosporin such as cefazolin is reasonable. Although cefazolin may be more susceptible to β-lactamase–mediated hydrolysis than nafcillin[155] and less effective in the treatment of MSSA experimental IE,[156] the clinical significance of these observations is unknown. Many experts regularly use cefazolin for *S aureus* IE instead of nafcillin because of drug tolerability and cost, for MSSA IE in

Table 10. Therapy for NVE Caused by Staphylococci

Regimen	Dose* and Route	Duration, wk	Strength of Recommendation	Comments
Oxacillin-susceptible strains				
Nafcillin or oxacillin	12 g/24 h IV in 4–6 equally divided doses	6	*Class I; Level of Evidence C*	For complicated right-sided IE and for left-sided IE; for uncomplicated right-sided IE, 2 wk (see text).
For penicillin-allergic (nonanaphylactoid type) patients				Consider skin testing for oxacillin-susceptible staphylococci and questionable history of immediate-type hypersensitivity to penicillin.
Cefazolin*	6 g/24 h IV in 3 equally divided doses	6	*Class I; Level of Evidence B*	Cephalosporins should be avoided in patients with anaphylactoid-type hypersensitivity to β-lactams; vancomycin should be used in these cases.
Oxacillin-resistant strains				
Vancomycin§	30 mg/kg per 24 h IV in 2 equally divided doses	6	*Class I; Level of Evidence C*	Adjust vancomycin dose to achieve trough concentration of 10–20 μg/mL (see text for vancomycin alternatives).
Daptomycin	≥8 mg/kg/dose	6	*Class IIb; Level of Evidence B*	Await additional study data to define optimal dosing.

IE indicates infective endocarditis; IV, intravenous; and NVE, native valve infective endocarditis.

*Doses recommended are for patients with normal renal function.

§For specific dosing adjustment and issues concerning vancomycin, see Table 7 footnotes.

penicillin-intolerant patients, or to facilitate outpatient antibiotic administration.

Vancomycin is often recommended as an alternative to β-lactam therapy for MSSA IE. As outlined above, β-lactam allergy evaluation should be conducted in every case in which vancomycin is considered for use because poorer outcomes related to vancomycin therapy for a variety of MSSA infections are well recognized.[147]

Clindamycin has been associated with IE relapse and is not recommended.[157] For MSSA IE in patients with anaphylactoid-type β-lactam allergy who exhibit either a suboptimal response to vancomycin or vancomycin allergy, β-lactam desensitization should be considered as noted above.[158]

Daptomycin is a reasonable alternative to vancomycin for adults in the treatment of *S aureus* NVE. In the above-noted multinational trial[13] of *S aureus* bacteremia and right-sided IE, this agent (at 6 $mg \cdot kg^{-1} \cdot d^{-1}$) was noninferior to standard therapy with vancomycin or an antistaphylococcal penicillin plus low-dose, short-course gentamicin. Importantly, the small number (n=18; 9 in each arm) of patients with left-sided IE enrolled in the trial prevented meaningful conclusions on the comparative efficacy of daptomycin in this infection. For this reason, the FDA indication for daptomycin explicitly omitted left-sided IE. However, in an observational study, high-dose daptomycin (≈9 mg/kg per dose) for treatment of left-sided IE was as effective as standard-of-care therapy and cleared MRSA bacteremia significantly faster than did standard-of-care treatment.[159]

The emergence of organisms with decreased susceptibility to daptomycin was observed in ≈5% of daptomycin-treated patients. All of these patients needed but for a variety of reasons did not receive surgical intervention for debridement of deep-seated infections or left-sided IE. As indicated, the FDA-approved dose of daptomycin for *S aureus* bacteremia and right-sided IE is currently 6 mg/kg IV once daily. Some experts recommend higher doses of daptomycin at 8 to 10 mg/kg for complicated infections, including left-sided IE (these doses are not approved by the FDA).[109] This recommendation is based in part on evidence suggesting that higher-dose daptomycin may reduce the likelihood of treatment-emergent resistance, is generally well tolerated, and is not associated with excess toxicities. Whether this higher dosing strategy prevents treatment-emergent resistance of daptomycin is still not answered.

Daptomycin is inhibited by pulmonary surfactant[160] and thus is contraindicated in the treatment of *S aureus* pneumonia acquired via the aspiration route. In the registrational trial,[13] however, this agent performed as well as vancomycin or β-lactams in treating septic pulmonary emboli caused by *S aureus*, reflecting the distinct pathogenesis of this syndrome as opposed to traditional pneumonia.

Recommendations

1. **Cefazolin is reasonable in patients with a well-defined history of nonanaphylactoid reactions to penicillins (*Class IIa; Level of Evidence B*).**
2. **Allergy evaluation for tolerance to β-lactam therapy should be done in every case in which vancomycin is considered for treatment of MSSA IE (*Class I; Level of Evidence B*).**
3. **Clindamycin is not recommended as a result of an increased IE relapse rate (*Class III; Level of Evidence B*).**
4. **Daptomycin is a reasonable alternative to vancomycin for NVE caused by MSSA (*Class IIa; Level of Evidence B*).**

Additional or Adjunctive Therapies

As discussed above, combination therapy with gentamicin therapy in *S aureus* NVE is discouraged because of the relatively high rates of intrinsic gentamicin resistance, a lack of clear-cut efficacy, and documented toxicity issues.[148,152,161]

Although most staphylococci are highly susceptible to rifampin, resistance develops rapidly when this agent is used alone. The in vivo efficacy of rifampin in combination with nafcillin, oxacillin, vancomycin, trimethoprim/sulfamethoxazole, or aminoglycosides is highly variable. Moreover, use of rifampin as adjunct therapy for *S aureus* NVE has been associated with higher rates of adverse events (primarily hepatotoxicity) and a significantly lower survival rate.[162] Thus, routine use of rifampin is not recommended for treatment of staphylococcal NVE. Of note, a prospective trial in patients with IE caused by MRSA failed to demonstrate that the addition of rifampin to vancomycin either enhanced survival or reduced the duration of bacteremia compared with treatment with vancomycin alone.[163] Rifampin is often used in native valve *S aureus* IE when this infection is complicated by involvement of selected anatomic sites where rifampin penetrates effectively (eg, bone, joint, cerebrospinal fluid).[164]

No standard therapies exist for the treatment of *S aureus* IE caused by isolates that are not susceptible to vancomycin. Classification of these isolates has become complex and includes designations of reduced susceptibility (hVISA), intermediate resistance (VISA), and high-level resistance (VRSA). To date, the limited number of patients reported to have IE caused by these isolates precludes specific treatment recommendations. Thus, these infections should be managed in conjunction with an infectious diseases consultant.

Although Markowitz et al[165] showed that trimethoprim-sulfamethoxazole was inferior to vancomycin in the treatment of invasive *S aureus* infections, it is sometimes used in salvage situations. Interestingly, all treatment failures with trimethoprim-sulfamethoxazole occurred in patients infected with MSSA in that report,[165] whereas patients with MRSA infection were uniformly cured. The efficacy of trimethoprim-sulfamethoxazole and other folate antagonists may be attenuated by thymidine release from damaged host cells (eg, at sites of tissue damage such as abscesses).[166] In an in vitro study,[167] the addition of trimethoprim-sulfamethoxazole to daptomycin was rapidly bactericidal for a daptomycin-nonsusceptible strain compared with daptomycin monotherapy. The combination of daptomycin and a β-lactam antibiotic has been reported to be effective in treating a limited number of patients with persistent MRSA bacteremia.[168] The potential effectiveness of this combination may be due in part to the capacity of the β-lactam agent to alter the surface charge of the organism

in a nonbactericidal mechanism, allowing enhanced surface binding of daptomycin.[169–171] Linezolid was reported to be effective in the treatment of persistent MRSA bacteremia,[172] but this study had important study design weaknesses.[173] Patient outcomes with linezolid therapy for *S aureus* left-sided IE have generally been poor.[174–176] Quinupristin-dalfopristin[177] and telavancin[178] have been used successfully as salvage therapy in selected patients with MRSA IE who clinically failed vancomycin therapy.

Ceftaroline received FDA registrational indications for acute bacterial skin and soft tissue infections caused by both MRSA and MSSA, as well as community-acquired pneumonia caused by MSSA. Several case series suggest that it may have utility in complicated *S aureus* infections, including IE.[179–181] These promising observations should be verified with appropriately designed clinical studies before ceftaroline can be recommended for widespread use in such off-label settings.

Recommendations

1. **Routine use of rifampin is not recommended for treatment of staphylococcal NVE (*Class III; Level of Evidence B*).**
2. **IE caused by vancomycin-resistant staphylococci (hVISA, VISA, or VRSA) should be managed in conjunction with an infectious diseases consultant (*Class I; Level of Evidence C*).**

IE Caused by Staphylococci in the Presence of Prosthetic Valves or Other Prosthetic Material

Coagulase-Negative Staphylococci

CoNS that cause PVE usually are methicillin resistant, particularly when IE develops within 1 year after surgery.[182] Unless susceptibility to methicillin can be demonstrated conclusively, it should be assumed that the organism is methicillin resistant, and treatment should be planned accordingly. Experimental IE models caused by methicillin-resistant staphylococci demonstrated that vancomycin combined with rifampin and gentamicin is the optimal regimen, and limited clinical reports support this approach.[183] The dosing of rifampin is done by convention and is not based on PK data. Vancomycin and rifampin are recommended for a minimum of 6 weeks, with the use of gentamicin limited to the first 2 weeks of therapy (Table 11). If the organism is resistant to gentamicin, then an aminoglycoside to which it is susceptible should be substituted for gentamicin. Some authorities recommend delaying the initiation of rifampin therapy for several days to allow adequate penetration of vancomycin into the cardiac vegetations in an attempt to prevent treatment-emergent resistance to rifampin. If the organism is resistant to all available aminoglycosides, such adjunctive treatment should be omitted. In this situation, if the organism is susceptible to a fluoroquinolone, animal studies of therapy for foreign-body infection suggest that a fluoroquinolone can be used instead of gentamicin.[184] Thus, although clinical data are not available to support the practice, selection for fluoroquinolone resistance during treatment can occur, and prevalent fluoroquinolone resistance among CoNS will limit its use, it may reasonable to use a fluoroquinolone in this setting.

PVE, particularly when onset is within 12 months of cardiac valve implantation and an aortic valve prosthesis is involved, is frequently complicated by perivalvular or myocardial abscesses or valvular dysfunction.[136] Surgery is often required in these patients and may be lifesaving. As noted above, CoNS may become resistant to rifampin during therapy for PVE. Because of the potential for changes in the patterns of antibiotic susceptibility during therapy, organisms recovered from surgical specimens or blood from patients who have had a bacteriological relapse should be carefully retested for complete antibiotic susceptibility profiles.

Although published data on combinations of antimicrobial therapy are limited, we suggest that PVE caused by oxacillin-susceptible CoNS should be treated with nafcillin or oxacillin plus rifampin in combination with gentamicin for the first 2 weeks of therapy. A first-generation cephalosporin or vancomycin may be substituted for nafcillin/oxacillin for patients who are truly allergic to penicillin.

Recommendations

1. **Vancomycin and rifampin are recommended for a minimum of 6 weeks, with the use of gentamicin limited to the first 2 weeks of therapy (*Class I; Level of Evidence B*).**
2. **If CoNS are resistant to gentamicin, then an aminoglycoside to which they are susceptible may be considered (*Class IIb; Level of Evidence C*).**
3. **If CoNS are resistant to all aminoglycosides, then substitution with a fluoroquinolone may be considered if the isolate is susceptible to a fluoroquinolone (*Class IIb; Level of Evidence C*).**
4. **Organisms recovered from surgical specimens or blood from patients who have had a bacteriological relapse should be carefully retested for complete antibiotic susceptibility profiles (*Class I; Level of Evidence C*).**

S aureus

Because of the high mortality rate associated with *S aureus* PVE,[136] combination antimicrobial therapy is recommended (Table 11). The use of combination therapy is based not on studies of in vitro synergy but rather on the efficacy of this therapy for treatment of CoNS PVE, as well as the results of treatment of experimental IE and infected devices. In animal studies, rifampin appears to be key in the complete sterilization of foreign bodies infected by MRSA.[184,185]

For infection caused by MSSA, nafcillin or oxacillin together with rifampin is suggested; with MRSA, vancomycin and rifampin should be used. Gentamicin should be administered for the initial 2 weeks of therapy with either β-lactam or vancomycin-containing regimens. If a strain is resistant to gentamicin, then a fluoroquinolone may be used if the strain is susceptible. Early cardiac surgical interventions play an important role in maximizing outcomes in *S aureus* PVE,[186] especially in the presence of heart failure.[11]

Recommendations

1. **Combination antimicrobial therapy is recommended (*Class I; Level of Evidence C*).**

Table 11. Therapy for Endocarditis Involving a Prosthetic Valve or Other Prosthetic Material Caused by Staphylococci

Regimen	Dose* and Route	Duration, wk	Strength of Recommendation	Comments
Oxacillin-susceptible strains				
Nafcillin or oxacillin	12 g/24 h IV in 6 equally divided doses	≥6	*Class I; Level of Evidence B*	Vancomycin should be used in patients with immediate-type hypersensitivity reactions to β-lactam antibiotics (see Table 5 for dosing guidelines); cefazolin may be substituted for nafcillin or oxacillin in patients with non–immediate-type hypersensitivity reactions to penicillins.
Plus				
Rifampin	900 mg per 24 h IV or orally in 3 equally divided doses	≥6		
Plus				
Gentamicin†	3 mg/kg per 24 h IV or IM in 2 or 3 equally divided doses	2		
Oxacillin-resistant strains				
Vancomycin	30 mg/kg 24 h in 2 equally divided doses	≥6	*Class I; Level of Evidence B*	Adjust vancomycin to a trough concentration of 10–20 μg/mL. (see text for gentamicin alternatives)
Plus				
Rifampin	900 mg/24 h IV/PO in 3 equally divided doses	≥6		
Plus				
Gentamicin	3 mg/kg per 24 h IV/IM in 2 or 3 equally divided doses	2		

IM indicates intramuscular; and IV, intravenous.
*Doses recommended are for patients with normal renal function.
†Gentamicin should be administered in close proximity to vancomycin, nafcillin, or oxacillin dosing. See Table 7 for appropriate dose of gentamicin.

2. **Gentamicin should be administered for the initial 2 weeks of therapy with either β-lactam or vancomycin-containing regimens (*Class I; Level of Evidence C*).**

Enterococci

Although there are >15 species within the *Enterococcus* genus, *E faecalis* and *E faecium* are the major species isolated from clinical sources in IE patients. Enterococci are the third leading cause of IE and account for ≈10% of cases in non-IDUs. *E faecalis* causes ≈97% of cases of IE; *E faecium*, ≈1% to 2%; and other species, ≈1%.

Regimens recommended for enterococcal IE are shown in Tables 12 through 15. Enterococci should be routinely tested in vitro for susceptibility to penicillin or ampicillin and vancomycin (MIC determination) and for high-level resistance to gentamicin to predict synergistic interactions (see below). Because of the striking increase in resistance of enterococci to vancomycin, aminoglycosides, and penicillin, additional susceptibility tests may be necessary to identify alternative antimicrobial regimens. For strains of enterococci resistant to β-lactams, vancomycin, or aminoglycosides, it is reasonable to test for susceptibility in vitro to daptomycin and linezolid. Linezolid is bacteriostatic in vitro against enterococci, whereas daptomycin is bactericidal in vitro in susceptible strains. Although rarely identified, β-lactamase–producing enterococci may account for relapse of infection. Routine screening for β-lactamase production is not sensitive enough, and specialized testing will be needed for detection.

Compared with VGS and β-hemolytic streptococci, enterococci are relatively resistant to penicillin, ampicillin, and vancomycin. These streptococci usually are killed by monotherapy with these antimicrobials, whereas enterococci are inhibited but not killed. Killing of susceptible strains of enterococci requires the synergistic action of penicillin, ampicillin, or vancomycin in combination with either gentamicin or streptomycin.

Enterococci are relatively impermeable to aminoglycosides. High concentrations of aminoglycosides in the extracellular environment are required to achieve sufficient concentrations of the drug at the site of the ribosomal target within the bacterial cell for bactericidal activity. These concentrations are higher than can be achieved safely in patients; however, cell wall–active agents such as penicillin, ampicillin, and vancomycin raise the permeability of the enterococcal cell so that a bactericidal effect can be achieved by relatively low concentrations of an aminoglycoside. If an enterococcal strain is resistant to the cell wall–active agent or high concentrations of an aminoglycoside (500 μg/mL gentamicin or 1000 μg/mL streptomycin), then the combination of an aminoglycoside and the cell wall–active agent will not result in bactericidal activity in vitro or in vivo (ie, in experimental IE models), nor will it predictably produce a microbiological cure in human enterococcal IE.

Recommendations

1. **Enterococci should be tested routinely in vitro for susceptibility to penicillin and vancomycin (MIC determination) and for high-level resistance to gentamicin to predict synergistic interactions (*Class I; Level of Evidence A*).**
2. **In vitro susceptibility to daptomycin and linezolid should be obtained for strains that are resistant to β-lactams, vancomycin, or aminoglycosides (*Class I; Level of Evidence C*).**

Table 12. Therapy for Endocarditis Involving a Native or Prosthetic Valve or Other Prosthetic Material Resulting From *Enterococcus* Species Caused by Strains Susceptible to Penicillin and Gentamicin in Patients Who Can Tolerate β-Lactam Therapy*

Regimen	Dose† and Route	Duration, wk	Strength of Recommendation	Comments
Either			*Class IIa; Level of Evidence B*	Native valve: 4-wk therapy recommended for patients with symptoms of illness <3 mo; 6-wk therapy recommended for native valve symptoms >3 mo and for patients with prosthetic valve or prosthetic material. Recommended for patients with creatinine clearance >50 mL/min.
Ampicillin sodium	2 g IV every 4 h	4–6		
Or		4–6	*Class IIa; Level of Evidence B*	
Aqueous penicillin G sodium	18–30 million U/24 h IV either continuously or in 6 equally divided doses	4–6		
Plus				
Gentamicin sulfate‡	3 mg/kg ideal body weight in 2–3 equally divided doses			
Or				
Double β-lactam Ampicillin	2 g IV every 4 h	6	*Class IIa; Level of Evidence B*	Recommended for patients with initial creatinine clearance <50 mL/min or who develop creatinine clearance <50 mL/min during therapy with gentamicin-containing regimen.
Plus				
Ceftriaxone	2 g IV every 12 h	6		

IV indicates intravenous.

*For patients unable to tolerate a β-lactam, see Table 14.

†Doses recommended are for patients with normal renal and hepatic function.

‡Dose of gentamicin should be adjusted to achieve a peak serum concentration of 3 to 4 μg/mL and a trough concentration of <1 μg/mL.

Role of Aminoglycosides in the Treatment of Patients With Enterococcal IE: Special Considerations

Aminoglycoside-containing regimens have been a cornerstone of antimicrobial therapy for enterococcal IE[187] and have been recommended as standard therapy in previous (1995) AHA guidelines.[188] Since the publication of the latest (2005) AHA statement on antimicrobial therapy of patients with IE,[12] the frequency of aminoglycoside-resistant strains of enterococci has increased significantly. In addition, a number of studies have been published on the dosing of aminoglycosides, the duration of aminoglycoside therapy, and the possible role of non–aminoglycoside-containing regimens for the treatment of *E faecalis* IE.[189–191]

Approximately 97% of cases of enterococcal IE are caused by *E faecalis*, and the majority of these remain susceptible to β-lactams and vancomycin, but aminoglycoside resistance is increasing in frequency. In the study by Gavaldà et al,[190] approximately half of the patients had IE caused by high-level aminoglycoside-resistant strains of *E faecalis*. In the study by Fernández-Hidalgo et al,[191] 26% of the 272 patients had high-level aminoglycoside-resistant strains of *E faecalis*. Therefore, aminoglycoside-containing regimens would not be effective therapy for these patients.

A number of factors should be considered in the selection of aminoglycoside-containing regimens. Compared with other patients with IE, in general, patients with enterococcal IE are older; are often debilitated; may have complicated, underlying urological conditions, including pre-existing renal failure; may have healthcare-associated infections; and have significant other underlying comorbidities common in older age groups.[192] In these patients, gentamicin-associated nephrotoxicity may significantly complicate a "standard" 4- to 6-week course of therapy and could result in serious, possibly life-threatening, complications such as renal failure requiring hemodialysis. In these situations, the potential risk of attempting to complete a 4- to 6-week course of gentamicin therapy may exceed the benefit.[193]

In patients with VGS IE treated with multiple divided doses of gentamicin, single daily-dose therapy with gentamicin resulted in similar response rates and was well tolerated (see treatment of VGS IE above). Studies of single daily dosing of gentamicin compared with divided doses in enterococcal experimental IE and in humans have yielded conflicting results. These results may reflect different PK of aminoglycosides in animals compared with humans. Studies in humans of the dosing interval of gentamicin were not controlled or standardized. Dosing of gentamicin ranged from once daily to 3 times daily; therefore, the data were insufficient to compare the efficacy of once-daily doses with divided doses. Until more convincing data demonstrate that once-daily dosing of gentamicin is as effective as multiple dosing, in patients with normal renal function, gentamicin should be administered in daily multiple divided doses (total, ≈3 $mg \cdot kg^{-1} \cdot d^{-1}$) rather than a daily single dose to patients with enterococcal IE. In patients with normal renal function, it is reasonable to administer gentamicin every 8 hours with the dose adjusted to achieve a 1-hour serum concentration of ≈3 μg/mL and a trough concentration of <1 μg/mL. Increasing the dose of gentamicin in these patients did not result in enhanced efficacy but did increase the risk of nephrotoxicity.[194]

Many patients with enterococcal IE are managed in a nontertiary care facility, and the laboratory may not have the capability for rapid determination of serum gentamicin concentrations or may not have a clinical pharmacist available to assist in optimal dosing adjustments. These and other factors have prompted studies to evaluate the efficacy of non–gentamicin-containing regimens for the treatment of

enterococcal IE.[195] The decision of whether to use an aminoglycoside-containing regimen must be individualized for each patient. The rationale and recommendations for specific aminoglycoside-containing regimens for the treatment of enterococcal IE based on in vitro susceptibilities are discussed in the following groups of patients and in Tables 12 through 15.

Recommendations

1. **Gentamicin should be administered in daily multiple divided doses (total, ≈3 mg·kg^{-1}·d^{-1}) rather than a single daily dose to patients with enterococcal IE and normal renal function (*Class I; Level of Evidence B*).**
2. **It is reasonable to administer gentamicin every 8 hours with the dose adjusted to achieve a 1-hour serum concentration of ≈3 µg/mL and a trough concentration of <1 µg/mL (*Class IIa; Level of Evidence B*).**

Enterococcal Endocarditis Susceptible to Penicillin, Vancomycin, and Aminoglycosides

Antimicrobial regimens outlined in Table 12 are reasonable for treatment of patients with IE caused by these organisms. In a prospective study, the duration of antimicrobial therapy in native valve *E faecalis* IE was based on the duration of infection before diagnosis and onset of effective therapy.[196] Patients with <3 months' duration of symptoms were treated successfully with 4 weeks of antimicrobial therapy. Patients with ≥3 months' duration of symptoms were successfully treated with 6 weeks of therapy. The duration of therapy for NVE is based on this work, and the regimens that may be considered are listed in Table 12. In patients with PVE, 6 weeks of antimicrobial therapy is reasonable.

Patients with pre-existing mild (creatinine clearance, 30–50 mL/min) or severe (creatinine clearance, <30 mL/min) renal failure may not be able to safely complete a 4- to 6-week course of gentamicin therapy because of gentamicin-associated nephrotoxicity. Alternative regimens that should be considered include the use of streptomycin instead of gentamicin, short-course gentamicin therapy (2–3 weeks), and use of a non–aminoglycoside-containing double–β-lactam regimen. The risks and benefits of the alternative regimens are as follows.

Streptomycin Therapy

Although there are no published studies comparing the efficacy of regimens containing streptomycin or gentamicin, a similar cure rate was reported in a single noncomparative study.[197] The main advantage is that streptomycin is less nephrotoxic than gentamicin. There are several disadvantages of using streptomycin-containing regimens, including a lack of familiarity among clinicians with streptomycin, a higher risk of ototoxicity, which may not be reversible, and drug availability limitations. In addition, most laboratories do not routinely perform serum streptomycin assays and may not have access to a clinical pharmacist to assist in dosing adjustments. Streptomycin use should be avoided in patients with creatinine clearance <50 mL/min. If the strain of enterococcus is susceptible to both gentamicin and streptomycin, it is reasonable to use gentamicin rather than streptomycin for therapy. When gentamicin therapy is not an option, then a double–β-lactam regimen (see later section) is reasonable.

Short-Course (≈2-Week) Gentamicin Therapy

Olaison and Schadewitz[189] in Sweden reported a 5-year prospective study of 78 cases of enterococcal IE treated with a β-lactam and an aminoglycoside. The older age of these patients was a factor in their inability to tolerate prolonged aminoglycoside therapy. The median duration of aminoglycoside therapy was 15 days, and the microbiological cure and survival rates were similar to those for patients who received longer courses of gentamicin therapy. The major advantage of short-course aminoglycoside therapy is reduced risk of aminoglycoside-associated nephrotoxicity. The disadvantage is that this is a single nonrandomized, noncomparative study. The results of a Danish pilot study[185] that represented a "before and after" study, which was based on 2007 guidelines that recommended a 2-week treatment course of gentamicin for enterococcal IE in combination with β-lactam therapy for 4 to 6 weeks, confirmed the results seen in the Swedish investigation.[181]

Double–β-Lactam Regimens

Most strains of *E faecalis* are inhibited but not killed in vitro by penicillin or ampicillin, with MICs usually 2 to 4 µg/mL penicillin; ampicillin MICs are usually 1 dilution lower. Cephalosporins and antistaphylococcal penicillins (oxacillin, nafcillin) have minimal or no in vitro activity against enterococci. The in vitro activity of carbapenems is variable, with imipenem being most active.

Because there are few therapeutic alternatives to aminoglycoside-containing regimens, combinations of β-lactams were tested in vitro and in animal models of enterococcal experimental IE. The combination of ampicillin and imipenem acted synergistically in vitro and was effective therapy of multidrug-resistant enterococcal experimental IE.[198] This study led to additional studies of experimental IE that demonstrated that the combination of ampicillin-ceftriaxone was effective therapy for gentamicin-susceptible or high-level gentamicin-resistant *E faecalis* experimental IE.[199] The likely mechanism of double–β-lactam combinations against enterococci is saturation of different penicillin-binding proteins. These in vitro and in vivo studies provided the rationale for double–β-lactam therapeutic trials in humans with *E faecalis* IE caused by gentamicin-susceptible or high-level gentamicin-resistant strains. A large, multicenter study by Spanish and Italian investigators compared ampicillin-ceftriaxone with ampicillin-gentamicin therapy of *E faecalis* IE.[191] Patients with high-level aminoglycoside-resistant strains were not treated with ampicillin-gentamicin. A smaller study by this group compared ceftriaxone-ampicillin therapy of aminoglycoside-susceptible with high-level aminoglycoside-resistant *E faecalis* IE.[190] Both of these studies had significant limitations: They were observational, largely retrospective, and nonrandomized; the regimens were not standardized among the different centers; discontinuation of gentamicin therapy was at the discretion of the investigators and not always the result of gentamicin-associated nephrotoxicity; and the serum concentrations of gentamicin were not assessed or reported in all study sites.

Despite these limitations, these 2 studies provide important data. First, these are the largest series of *E faecalis* IE reported to date, 43 patients in 1 study[190] and 272 in the other study.[191] Second, high-level aminoglycoside-resistant *E faecalis* IE treated with ampicillin-ceftriaxone therapy was present in 50% of the patients in the smaller study and 33% of patients in the larger study. Third, none of the patients in either study developed nephrotoxicity with ampicillin-ceftriaxone therapy, whereas 20 of 87 (23%) ampicillin-gentamicin–treated patients developed nephrotoxicity ($P<0.001$). Fourth, in the larger study, the median age was 70 years in both treatment groups; however, patients in the ampicillin-ceftriaxone group were generally sicker and had more comorbid conditions (eg, chronic renal failure [$P=0.004$], neoplasm [$P=0.015$], and nosocomial acquisition of infection [$P=0.006$]). Fifth, in 1 study, PVE was present in 59 (37%) and 30 (34%) of patients treated with ampicillin-ceftriaxone and ampicillin-gentamicin, respectively, with similar success rates. Sixth, in the larger study, there were no significant differences between ampicillin-ceftriaxone and ampicillin-gentamicin in the need for surgery, complications (except for fewer cases of renal failure in the ampicillin-ceftriaxone group), relapse, or mortality. Finally, the overall microbiological cure and success rates for ampicillin-ceftriaxone therapy in both studies were similar to rates in previously reported studies in patients treated with aminoglycoside-containing regimens.[190,191]

The major advantages of the ampicillin-ceftriaxone regimen are the lower risk of nephrotoxicity and the lack of need for measuring aminoglycoside serum concentrations. The potential disadvantage is the possibility of hypersensitivity reactions to 2 separate β-lactams. Because it would likely not be possible to discriminate between hypersensitivities related to ampicillin or to ceftriaxone, both drugs might have to be discontinued with substitution of vancomycin-gentamicin therapy. At this time, the writing group does not have a preference for one regimen over the other but rather advocates an individualized approach to regimen selection for each patient.

Recommendations

1. **Therapy that includes either ampicillin or aqueous crystalline penicillin G plus gentamicin or ampicillin plus ceftriaxone is reasonable (*Class IIa; Level of Evidence B*).**
2. **Either 4 or 6 weeks of therapy is reasonable for NVE, depending on the duration of IE symptoms before the initiation of therapy if ampicillin or penicillin plus gentamicin is used (*Class IIa; Level of Evidence B*).**
3. **Six weeks of therapy is reasonable if ampicillin plus ceftriaxone is selected as the treatment regimen, regardless of symptom duration (*Class IIa; Level of Evidence B*).**
4. **Six weeks of antimicrobial therapy is reasonable for PVE (*Class IIa; Level of Evidence B*).**
5. **Streptomycin should be avoided in patients with creatinine clearance <50 mL/min (*Class III; Level of Evidence B*).**
6. **If the strain of *Enterococcus* is susceptible to both gentamicin and streptomycin, it is reasonable to use gentamicin rather than streptomycin for therapy (*Class IIa; Level of Evidence C*).**
7. **When gentamicin therapy is not an option, then a double–β-lactam regimen (see later section) is reasonable (*Class IIa; Level of Evidence B*).**

E faecalis IE Susceptible to Penicillin, Resistant to Aminoglycosides, or Gentamicin Resistant and Streptomycin Susceptible

Aminoglycoside resistance in enterococci is most commonly the result of the acquisition of plasmid-mediated aminoglycoside-modifying enzymes. *E faecalis* strains resistant to high levels of gentamicin are resistant to most other aminoglycosides, although some of them are susceptible to streptomycin. The regimens for *E faecalis* IE with strains that are penicillin-susceptible and aminoglycoside-resistant are shown in Table 13. Ceftriaxone-ampicillin therapy is reasonable and is given for 6 weeks. The rationale for double–β-lactam therapy is outlined above.

For gentamicin-resistant and streptomycin-susceptible *E faecalis*, ampicillin-ceftriaxone is reasonable. The 2005 AHA document[12] recommended streptomycin for patients with gentamicin-resistant strains of enterococci. The limitations of streptomycin use are summarized above. The total number of cases published in the European studies far exceeds the relatively small number of reported streptomycin-treated patients with enterococcal IE. Although there are no published data comparing ampicillin-ceftriaxone with streptomycin-containing regimens, we believe that ampicillin-ceftriaxone is reasonable for these patients. Disadvantages of streptomycin-containing regimens are outlined above.

Recommendations

1. **Ceftriaxone-ampicillin combination therapy is reasonable for IE caused by aminoglycoside-resistant enterococcal strains (*Class IIa; Level of Evidence B*).**
2. **For gentamicin-resistant and streptomycin-susceptible *Enterococcus* species, ampicillin-ceftriaxone combination therapy is reasonable (*Class IIa; Level of Evidence B*).**

Vancomycin Therapy for Enterococcal IE in Patients Unable to Tolerate β-Lactams or Patients With *E faecalis* Resistant to Penicillin

The regimens that are reasonable for these patients are shown in Table 14. Vancomycin should be administered only if a patient is unable to tolerate penicillin or ampicillin. Combinations of penicillin or ampicillin with gentamicin are preferable to combined vancomycin-gentamicin because of the potential increased risk of ototoxicity and nephrotoxicity with the vancomycin-gentamicin combination. Moreover, combinations of penicillin or ampicillin and gentamicin are more active than combinations of vancomycin and gentamicin in vitro and in animal models of experimental IE. It is reasonable that patients with NVE receive 6 weeks of vancomycin-gentamicin therapy and that patients with PVE receive at least 6 weeks of therapy.

Table 13. Therapy for Endocarditis Involving a Native or Prosthetic Valve or Other Prosthetic Material Resulting From *Enterococcus* species Caused by a Strain Susceptible to Penicillin and Resistant to Aminoglycosides or Streptomycin-Susceptible Gentamicin-Resistant in Patients Able to Tolerate β-Lactam Therapy*

Regimen	Dose† and Route	Duration, wk	Strength of Recommendation	Comments
Double β-lactam				
Ampicillin	2 g IV every 4 h	6	*Class IIa; Level of Evidence B*	Double β-lactam is reasonable for patients with normal or impaired renal function abnormal cranial nerve VIII function or if the laboratory is unable to provide rapid results of streptomycin serum concentration; native valve infection with symptoms of infection <3-mo duration may be treated for 4 wk with the streptomycin-containing regimen. PVE, NVE with symptoms >3 mo, or treatment with a double β-lactam regimen require a minimum of 6 wk of therapy.
Plus				
Ceftriaxone	2 g IV every 12 h			
Alternative for streptomycin susceptible/gentamicin resistant				
Either		4–6	*Class IIa; Level of Evidence B*	Use is reasonable only for patients with availability of rapid streptomycin serum concentrations. Patients with creatinine clearance <50 mL/min or who develop creatinine clearance <50 mL/min during treatment should be treated with double–β-lactam regimen. Patients with abnormal cranial nerve VIII function should be treated with double–β-lactam regimen.
Ampicillin sodium	2 g IV every 4 h			
Or				
Aqueous penicillin G sodium	18–30 million U/24 h IV either continuously or in 6 equally divided doses			
Plus				
Streptomycin sulfate‡	15 mg/kg ideal body weight per 24h IV or IM in 2 equally divided doses			

IM indicates intramuscular; IV, intravenous; NVE, native valve infective endocarditis; and PVE, prosthetic valve infective endocarditis.
*For patients unable to tolerate a β-lactam, see Table 14.
†Doses recommended for patients with normal renal and hepatic function.
‡Streptomycin dose should be adjusted to obtain a serum peak concentration of 20 to 35 μg/mL and a trough concentration of <10 μg/mL.

Rarely, strains of *E faecalis* produce an inducible β-lactamase. These β-lactamase–producing strains are susceptible to ampicillin-sulbactam and to vancomycin. Intrinsic penicillin resistance is uncommon in *E faecalis* but is common in *E faecium*. It is reasonable to treat patients with *E faecalis* IE caused by strains that are intrinsically resistant to penicillin with a combination of vancomycin plus gentamicin. Recommendations for treatment of IE caused by these strains are shown in Table 14.

Recommendations

1. **Vancomycin should be administered only if a patient is unable to tolerate penicillin or ampicillin (*Class I; Level of Evidence B*).**
2. **It is reasonable that patients with NVE receive 6 weeks of vancomycin-gentamicin therapy and that patients with PVE receive at least 6 weeks of therapy (*Class IIa; Level of Evidence B*).**
3. **Patients with *E faecalis* IE caused by strains that are intrinsically resistant to penicillin should be treated with a combination of vancomycin plus gentamicin (*Class I; Level of Evidence B*).**

Enterococcal Endocarditis Resistant to Penicillin, Aminoglycosides, and Vancomycin

The rapid emergence of vancomycin-resistant enterococci has become a global issue of major clinical importance. Most of these strains are *E faecium,* and as many as 95% of strains express multidrug resistance to vancomycin, aminoglycosides, and penicillins. Only about 3% of *E faecalis* strains are multidrug resistant, and many vancomycin-resistant *E faecalis* are penicillin susceptible. Fortunately, *E faecium* IE is uncommon. Most of the reports of multidrug-resistant *E faecium* IE are single case reports, reports of a small number of collected cases, or cases reported in new drug trials.[200]

Enterococci are considered to be resistant to vancomycin if MICs are >4 μg/mL. Linezolid and daptomycin are the only 2 antimicrobial agents currently available in the United States that may be useful for the treatment of multidrug-resistant *E faecium* IE. Quinupristin-dalfopristin may be active in vitro but only against strains of *E faecium* and is inactive against *E faecalis*. Quinupristin-dalfopristin is rarely used because of severe side effects, including intractable muscle pain. Tigecycline is active in vitro against some strains of multidrug-resistant enterococci, but there are minimal published data on its use clinically. The same can be said for tedizolid, which has been released.

Table 15 lists possible therapeutic options for the treatment of multidrug-resistant enterococcal IE. These patients should be managed by specialists in infectious diseases, cardiology, cardiovascular surgery, clinical pharmacy, and, if necessary, pediatrics. Antimicrobial regimens are discussed as follows.

Linezolid

Linezolid is a synthetic drug that is the first member of the oxazolidinone class. It acts by inhibiting ribosomal protein

Table 14. Vancomycin-Containing Regimens for Vancomycin- and Aminoglycoside-Susceptible Penicillin-Resistant *Enterococcus* Species for Native or Prosthetic Valve (or Other Prosthetic Material) IE in Patients Unable to Tolerate β-Lactam

Regimen	Dose* and Route	Duration, wk	Strength of Recommendation	Comments
Unable to tolerate β-lactams				
Vancomycin†	30 mg/kg per 24 h IV in 2 equally divided doses	6	*Class IIa; Level of Evidence B*	
Plus				
Gentamicin‡	3 mg/kg per 24 h IV or IM in 3 equally divided doses	6		
Penicillin resistance; intrinsic or β-lactamase producer				
Vancomycin plus aminoglycoside	30 mg/kg per 24 h IV in 2 equally divided doses	6	*Class IIb; Level of Evidence C*	For β-lactamase–producing strain, if able to tolerate a β-lactam antibiotic, ampicillin-sulbactam§ plus aminoglycoside therapy may be used.

IE indicates infective endocarditis; IM, intramuscular; and IV, intravenous.
*Doses recommended are for adults with normal renal function.
†Dose of vancomycin should be adjusted to obtain a serum trough concentration of 10 to 20 μg/mL.
‡Dose of gentamicin should be adjusted to obtain serum peak and trough concentrations of 3 to 4 and <1 μg/mL, respectively.
§Ampicillin-sulbactam dosing is 3 g/6 hour IV.

synthesis and is approved for use by the FDA in adults and children. It is not approved by the FDA for treatment of IE. Linezolid is bacteriostatic in vitro against enterococci, and susceptibility of enterococci to linezolid ranges from 97% to 99%, including strains that are multidrug resistant. Enterococci with MIC >2 μg/mL are considered to be resistant to linezolid. However, linezolid-resistant strains have developed during treatment.[201]

In a small number of patients, linezolid was effective therapy of vancomycin-resistant *E faecium* IE.[174] Birmingham et al[202] reported cure in 17 of 22 courses of therapy (77%) for *E faecium* IE. Mave et al[203] reported cure in 2 of 3 patients with *E faecium* IE with linezolid. Other case reports of cure of *E faecium* IE of native valve[204] or prosthetic valve[205] were reported. However, linezolid treatment failures of *E faecium* IE also were reported.[206]

The advantages of linezolid therapy include high bioavailability of the oral formulation, approval for pediatric patients, and a lack of many therapeutic alternatives. The disadvantages are toxicity (mild to severe neutropenia and thrombocytopenia that is reversible); peripheral and optic neuritis, which is more often seen with longer durations of therapy and may not be reversible; multidrug interactions, especially serotonin uptake inhibitors; and emergence of resistance during treatment. The previous high cost should decrease with generic availability soon. Cardiac valve replacement surgery may be necessary in patients who do not respond to linezolid therapy.

Daptomycin

Daptomycin is a cyclic lipopeptide antibiotic that has bactericidal activity in vitro against susceptible strains of enterococci. Enterococci are considered daptomycin susceptible with MIC <4 μg/mL. Although >90% of enterococci are reportedly susceptible in vitro to daptomycin, the emergence of daptomycin resistance is an increasing problem.[207] Daptomycin is FDA approved for treatment of *S aureus* infections but not for enterococcal infections. Daptomycin is not approved for use in pediatric patients.

The number of published cases of vancomycin-resistant *E faecium* IE treated with daptomycin is extremely small, so management conclusions are difficult to define, and the success rate has varied among reported cases. Levine and Lamp[208] reported daptomycin cure in 6 of 9 patients with *E faecium* IE; both daptomycin-treated patients with *E faecium* IE reported by Segreti et al[209] died. Multiple other case reports describe daptomycin failures, some as a result of emergence of daptomycin-resistance during treatment.[210,211] Other investigators have suggested that higher doses of daptomycin (8–10 $mg \cdot kg^{-1} \cdot d^{-1}$); daptomycin combined with gentamicin, ampicillin, ceftaroline, rifampin, or tigecycline; or various combinations of these should be used instead of daptomycin monotherapy.[211–217] A number of in vitro evaluations[214–216] suggested that ampicillin and ceftaroline in combination with daptomycin demonstrate the greatest synergistic activity compared with other β-lactam–daptomycin combinations.

Mave et al[203] compared daptomycin with linezolid for vancomycin-resistant *Enterococcus* bacteremia. Five patients had *E faecium* IE; 1 of 2 daptomycin-treated patients and 2 of 3 linezolid-treated patients survived. The number of cases of vancomycin-resistant *Enterococcus* bacteremia was too small to draw significant conclusions about treatment response rates.

In summary, there are insufficient data to recommend monotherapy with daptomycin for the treatment of multidrug-resistant enterococcal IE. If daptomycin therapy is selected, then doses of 10 to 12 $mg \cdot kg^{-1} \cdot 24\ h^{-1}$ may be considered. Consideration may be given to combinations of therapy with daptomycin, including ampicillin or ceftaroline, particularly in patients infected with strains with relatively high MICs to daptomycin within the susceptible range (<4 μg/mL). Other less active (in vitro) combinations with daptomycin include gentamicin, rifampin, or tigecycline.

Table 15. Therapy for Endocarditis Involving a Native or Prosthetic Valve or Other Prosthetic Material Resulting From *Enterococcus* Species Caused by Strains Resistant to Penicillin, Aminoglycosides, and Vancomycin

Regimen	Dose* and Route	Duration, wk	Strength of Recommendation	Comments
Linezolid	600 mg IV or orally every 12 h	>6	*Class IIb; Level of Evidence C*	Linezolid use may be associated with potentially severe bone marrow suppression, neuropathy, and numerous drug interactions. Patients with IE caused by these strains should be treated by a care team including specialists in infectious diseases, cardiology, cardiac surgery, clinical pharmacy, and, in children, pediatrics. Cardiac valve replacement may be necessary for cure.
Or				
Daptomycin	10–12 mg/kg per dose	>6	*Class IIb; Level of Evidence C*	

IE indicates infective endocarditis, and IV, intravenous.
*Doses recommended are for patients with normal renal and hepatic function.

Recommendations

1. **Patients with IE attributable to *Enterococcus* species resistant to penicillin, aminoglycosides, and vancomycin should be managed by specialists in infectious diseases, cardiology, cardiovascular surgery, clinical pharmacy, and, if necessary, pediatrics (*Class I; Level of Evidence C*).**
2. **If daptomycin therapy is selected, then doses of 10 to 12 mg·kg^{-1}·*24 h*$^{-1}$ may be considered (*Class IIb; Level of Evidence C*).**
3. **Combination therapy with daptomycin and ampicillin or ceftaroline may be considered, especially in patients with persistent bacteremia or enterococcal strains with high MICs (ie, 3 μg/mL) to daptomycin within the susceptible range (*Class IIb; Level of Evidence C*).**

HACEK Microorganisms

IE caused by fastidious Gram-negative bacilli of the HACEK group (HACEK indicates *Haemophilus* species, *Aggregatibacter* species, *Cardiobacterium hominis, Eikenella corrodens*, and *Kingella* species) accounts for ≈5% to 10% of community-acquired NVE in patients who are not IDUs.[218] These microorganisms grow slowly in standard blood culture media, and recovery may require prolonged incubation. Typically, only a small fraction of blood culture bottles in patients with HACEK IE demonstrate growth. Bacteremia caused by HACEK microorganisms in the absence of an obvious focus of infection is highly suggestive of IE even without typical physical findings of IE.

Previously, the HACEK group of microorganisms was uniformly susceptible to ampicillin. However, β-lactamase–producing strains of HACEK are appearing with increased frequency; rarely, resistance to ampicillin can occur in β-lactamase–negative strains.[219] Moreover, difficulty in performing antimicrobial susceptibility testing as a result of failure of growth in in vitro susceptibility testing is commonplace. In 1 survey, 60% of isolates did not grow adequately in control wells, and no valid in vitro susceptibility results were available.[219] Therefore, unless growth is adequate for in vitro screening, then HACEK microorganisms should be considered ampicillin resistant, and penicillin and ampicillin should not be used to treat patients with IE in these cases. Almost all strains of the HACEK group are susceptible to ceftriaxone (or other third- or fourth-generation cephalosporins). Ceftriaxone has commonly been used to treat HACEK IE[220] and is reasonable for treatment (Table 16). The duration of therapy for NVE of 4 weeks is reasonable; for PVE, the duration of therapy of 6 weeks is reasonable. Gentamicin is no longer recommended because of its nephrotoxicity risks.

The HACEK group is usually susceptible in vitro to fluoroquinolones.[206] On the basis of these susceptibility data, a fluoroquinolone (ciprofloxacin, levofloxacin, or moxifloxacin) may be considered as an alternative agent in patients unable to tolerate ceftriaxone (or other third- or fourth-generation cephalosporins) therapy. There are only a few case reports of HACEK IE treated with a fluoroquinolone, however. In addition, ampicillin-sulbactam may be considered a treatment option, although HACEK resistance to this agent in vitro has been described.[219] Accordingly, patients with HACEK IE who cannot tolerate ceftriaxone therapy should be treated in consultation with an infectious diseases specialist.

Recommendations

1. **Unless growth is adequate in vitro to obtain susceptibility testing results, HACEK microorganisms are considered ampicillin resistant, and penicillin and ampicillin should not be used for the treatment of patients with IE (*Class III; Level of Evidence C*).**
2. **Ceftriaxone is reasonable for treatment of HACEK IE (*Class IIa; Level of Evidence B*).**
3. **The duration of therapy for HACEK NVE of 4 weeks is reasonable (*Class IIa; Level of Evidence B*); for HACEK PVE, the duration of therapy of 6 weeks is reasonable (*Class IIa; Level of Evidence C*).**
4. **Gentamicin is not recommended because of its nephrotoxicity risks (*Class III; Level of Evidence C*).**
5. **A fluoroquinolone (ciprofloxacin, levofloxacin, or moxifloxacin) may be considered an alternative agent for patients unable to tolerate ceftriaxone (or other third- or fourth-generation cephalosporins) (*Class IIb; Level of Evidence C*).**
6. **Ampicillin-sulbactam may be considered a treatment option for HACEK IE (*Class IIb; Level of Evidence C*).**
7. **Patients with HACEK IE who do not tolerate ceftriaxone therapy should be treated in consultation with an infectious diseases specialist (*Class I; Level of Evidence C*).**

Table 16. Therapy for Endocarditis Involving a Native or Prosthetic Valve or Other Prosthetic Material Caused by HACEK Microorganisms

Regimen	Dose and Route	Duration, wk	Strength of Recommendation	Comments
Ceftriaxone sodium*	2 g/24 h IV or IM in 1 dose	4	*Class IIa; Level of Evidence B*	Preferred therapy: cefotaxime or another third- or fourth-generation cephalosporin may be substituted.
Or				
Ampicillin sodium	2 g IV every 4 h		*Class IIa; Level of Evidence B*	Ampicillin sodium may be an option if the growth of the isolate is sufficient to permit in vitro susceptibility results.
Or				
Ciprofloxacin†	1000 mg/24 h orally or 800 mg/24 h IV in 2 equally divided doses		*Class IIb; Level of Evidence C*	Fluoroquinolone therapy‡ may be considered for patients unable to tolerate cephalosporin and ampicillin therapy; levofloxacin or moxifloxacin may be substituted; fluoroquinolones generally is not recommended for patients <18 y old. Treatment for 6 wk is reasonable in patients with PVE (*Class IIa; Level of Evidence C*).

HACEK indicates *Haemophilus* species, *Aggregatibacter* species, *Cardiobacterium hominis*, *Eikenella corrodens*, and *Kingella* species; IM, intramuscular; IV, intravenous; and PVE, prosthetic valve infective endocarditis.

*Patients should be informed that intramuscular injection of ceftriaxone is painful.

†Dose recommended for patients with normal renal function.

‡Fluoroquinolones are highly active in vitro against HACEK microorganisms. Published data on the use of fluoroquinolones for endocarditis caused by HACEK are minimal.

Non-HACEK Gram-Negative Bacilli

IE caused by non-HACEK Gram-negative aerobic bacilli (*Enterobacteriaceae* and *Pseudomonas* species) is rare. In 1 large multinational database[221] that included 2761 patients seen in 61 hospitals in 28 countries, only 49 cases (1.8%) were attributable to non-HACEK Gram-negative aerobic bacilli. It is noteworthy that healthcare exposure was associated with the development of IE caused by this group of organisms in 57% of patients. In contrast, IDU, a prominent risk factor for the development of this IE syndrome in earlier years, was recognized in only 4% of cases in the multinational survey that included cases seen between 2000 and 2005. *Escherichia coli* and *Pseudomonas aeruginosa* accounted for 51% of cases, and 59% had PVE. Although management included cardiac surgery in 51% of cases, the in-hospital mortality rate was 24%.

Despite the very rare occurrence of IE caused by *Salmonella* species in North America, this syndrome deserves specific mention because it occurs with some frequency in other geographic areas.[222] *Salmonella* species have a proclivity to infect cardiovascular structures in adults. Therefore, all patients with bloodstream infection resulting from *Salmonella* species should be evaluated for complicating cardiovascular infections, including IE, myocarditis, pericarditis, and endarteritis. Although many serotypes have been implicated, most cases are caused by *S choleraesuis*, *S typhimurium*, and *S enteritidis*.[222]

Cardiac surgery in combination with prolonged courses of combined antibiotic therapy is reasonable for most patients with IE caused by non-HACEK Gram-negative aerobic bacilli, particularly in the setting of left-sided valvular involvement.

Prospective trial data are lacking to define the optimal antimicrobial regimen for the treatment of IE caused by non-HACEK Gram-negative aerobic bacilli. Input from specialists in infectious diseases who are experienced in the medical management of IE should be obtained to define an antibiotic regimen in each case. This is particularly important in IE caused by non-HACEK Gram-negative aerobic bacilli for several reasons. First, as stated previously, healthcare exposure is commonly seen in these cases; thus, multidrug resistance often characterizes these pathogens. Second, therapy may include agents with increased toxicity risks such as aminoglycosides (given in high dosages) and colistin. Third, because regimens that include >1 agent are often selected for use, the risks of drug-drug interactions and increased drug-related adverse events are problematic. Fourth, mortality is high in these infections, and medical-surgical approaches are often required for optimal management and favorable outcomes.

Combination antibiotic therapy with a β-lactam (penicillins, cephalosporins, or carbapenems) and either an aminoglycoside or fluoroquinolone for 6 weeks is reasonable.[221] Consultation with an infectious diseases expert in IE should be sought because of the various mechanisms of antibiotic resistance that can be found in the non-HACEK Gram-negative aerobic bacilli. For example, several of these bacteria may harbor "inducible β-lactamases" that could require supplemental laboratory screening, in addition to routine in vitro susceptibility testing.

Medical therapy may be successful in right-sided *P aeruginosa* IE in 50% to 75% of cases. If the disease is refractory to antibiotics, then partial tricuspid valvulectomy or "vegetectomy"[223] without valve replacement is indicated.[224] Typically, these patients have been IDUs, and because of their high recidivism risk, avoidance of placement of prosthetic valves is desirable.

Recommendations

1. **Cardiac surgery is reasonable in combination with prolonged courses of combined antibiotic therapy for most patients with IE caused by non-HACEK Gram-negative aerobic bacilli, particularly *P aeruginosa* (*Class IIb; Level of Evidence B*).**

2. **Combination antibiotic therapy with a β-lactam (penicillins, cephalosporins, or carbapenems) and either an aminoglycoside or fluoroquinolone for 6 weeks is reasonable (*Class IIa; Level of Evidence C*).**
3. **Consultation with an infectious diseases expert in IE should be sought because of the various mechanisms of antibiotic resistance that can be found in the non-HACEK Gram-negative aerobic bacilli (*Class I; Level of Evidence C*).**

Culture-Negative Endocarditis

Positive blood cultures are a major diagnostic criterion in IE and key to identifying an pathogenic agent and an optimal antimicrobial regimen.[225,226] Continuous bacteremia and a high frequency of positive blood cultures are typical hallmarks of this infection. The intensity of bacteremia may not be great, however, with <50 colony-forming units per 1 mL blood detected in the majority of patients in an investigation.[227]

Failure to culture microorganisms that cause IE can be a major problem that complicates diagnosis and timely, effective treatment. Although most previous studies have put the frequency of blood culture–negative IE at 5% to 10%, a European study of IE that included 820 cases indicated that ≈20% of patients with confirmed IE had all negative blood cultures.[228] This may be attributable to inadequate microbiological techniques, infection with highly fastidious bacteria or fungi, noncultivatable agents, or the previous administration of antimicrobial agents before blood cultures were obtained. Administration of antimicrobial agents to IE patients before blood cultures are obtained reduces the recovery rate of bacteria by 35% to 40%.[228–232] The antimicrobial susceptibility of the organism, the dose, and the duration and nature of previous antimicrobial therapy together determine the length of time that blood cultures will remain negative.[232] IE patients with blood cultures that are initially negative after only a few days of antibiotic therapy may have positive blood cultures after several days without antibiotics. The blood cultures of patients who receive longer courses of high-dose bactericidal antimicrobials may remain negative for weeks.

Selection of medical therapy for patients with culture-negative IE is difficult. On the one hand, there is a need to provide empirical antimicrobials for all likely pathogens. On the other hand, certain therapeutic agents, including aminoglycosides, have potentially toxic effects that dictate limitation or avoidance of use if at all possible. Moreover, some of the laboratory-based diagnostic techniques to define fastidious or unusual pathogens are not available in most clinical laboratories and require considerable time for completion of testing if specimens are sent to a referral laboratory.[233] During this period, patients are often treated empirically for the more common bacterial causes of IE, which can result in exposure to potentially toxic therapy that could be avoided with earlier pathogen identification.

An evaluation of epidemiological factors (Table 6), history of prior infections including cardiovascular infections, exposure to antimicrobials, clinical course, severity, and extracardiac sites of infection of the current infection should be done in all IE cases. During the period between the collection of blood cultures and the determination of a pathogen or if blood cultures are ultimately deemed culture negative, empirical therapy is generally required. Consultation with an infectious diseases specialist to define the most appropriate choice of therapy is recommended. Collection of additional clinical and laboratory data often dictates subsequent revisions in initial empirical therapy that will be administered over the treatment course.

For patients with acute (days) clinical presentations of native valve infection, coverage for *S aureus,* β-hemolytic streptococci, and aerobic Gram-negative bacilli is reasonable. Empirical coverage could include vancomycin and cefepime as an initial regimen. For patients with a subacute (weeks) presentation of NVE, empirical coverage of *S aureus*, VGS, HACEK, and enterococci is reasonable. One treatment option could include vancomycin and ampicillin-sulbactam to provide some coverage for these organisms. Subsequent regimen revision can be done when a pathogen is recovered from blood cultures.

For patients with culture-negative PVE, coverage for staphylococci, enterococci, and aerobic Gram-negative bacilli is reasonable if the onset of symptoms is within 1 year of prosthetic valve placement. A regimen could include vancomycin, rifampin, gentamicin, and cefepime. If symptom onset is >1 year after valve placement, then IE is more likely to be caused by staphylococci, VGS, and enterococci, and antibiotic therapy for these potential pathogens is reasonable. One initial treatment option could include vancomycin and ceftriaxone.

If subsequent blood culture results or other laboratory methodologies define a pathogen, then empirical therapy should be revised to focused therapy that is recommended for the specific pathogen identified.

True culture-negative IE can be caused by uncommon or rare pathogens that do not grow in routinely used blood culture systems.[234–237] The organisms that have garnered the most attention are *Bartonella* species, *Chlamydia* species, *C burnetii*, *Brucella* species, *Legionella* species, *Tropheryma whipplei*, *Candida*, and non-*Candida* fungi (particularly *Aspergillus* species). The last 2 groups of organisms are especially relevant to PV recipients. With the use of special diagnostic techniques, *Bartonella* species, *C burnetii*, and *Brucella* species have been identified in the majority of cases of culture-negative IE caused by fastidious organisms. Additional laboratory screening is required to identify the causes of culture-negative IE.[233] In some cases, serological and special blood culture techniques can be helpful. In other cases, tissue (usually valve) screening is required. Diagnostic methods for resected valve tissue include microbiological, histopathological, and molecular techniques, the last of which includes gene amplification with PCR methods. Unfortunately, most clinical laboratories do not perform molecular screening, and specimens must be sent to reference laboratories.

The most prevalent pathogen among these uncommon causes of culture-negative IE in this group has varied globally according to published data.[236] Incidence data from population-based surveys for IE caused by these organisms are lacking in the United States. In PVE cases, the timing of infection onset can also be important in defining pathogens.[235] Limitations such as referral bias and sampling bias may have affected the findings.[235–237]

Results of a large prospective analysis of referred samples from culture-negative IE performed by a well-recognized reference laboratory deserve additional comment.[236] First, there was identification of a pathogen in 62.7% of 759 cases; in 2.5%, a noninfectious origin (see below) was confirmed. Second, serological results were positive in 47.7% of cases, primarily for *Coxiella* and *Bartonella* species infection. Third, PCR identified a pathogen in two thirds of the valves studied. Fourth, no cause was defined in 35% of cases.

Treatment of the wide variety of microorganisms that cause culture-negative IE without prior antibiotic exposure has been described anecdotally, and regimens of choice are based on limited data and can be found in other publications.

Noninfectious causes of valvular vegetations can produce a syndrome similar to culture-negative IE. Perhaps the one that has received the most attention is anti-phospholipid antibody (APA) syndrome,[238] which has been described as both a primary and a secondary syndrome and is associated with the presence of APA. In its secondary form, the APA syndrome has been linked to autoimmune disorders, particularly systemic lupus erythematosus, and malignancies. Sterile valvular vegetations form and embolize, clinically mimicking in many respects culture-negative IE. The mitral valve is most often affected, and valvular regurgitation is the predominant functional abnormality seen in APA syndrome with complicating valvular involvement. To complicate matters, the APA syndrome may develop secondary to IE.[239]

Numerous other causes of noninfective vegetative endocarditis can mimic IE. These can be categorized into 4 groups[217]: neoplasia associated (atrial myxoma, marantic endocarditis, neoplastic disease, and carcinoid), autoimmune associated (rheumatic carditis, systemic lupus erythematosus, polyarteritis nodosa, and Behçet disease), postvalvular surgery (thrombus, stitch, or other postsurgery changes), and miscellaneous (eosinophilic heart disease, ruptured mitral chordae, and myxomatous degeneration).

Recommendations

1. **An evaluation of epidemiological factors, history of prior infections including cardiovascular infections, exposure to antimicrobials, clinical course, severity, and extracardiac sites of infection of the current infection should be performed in all culture-negative endocarditis cases (*Class I; Level of Evidence C*).**
2. **Consultation with an infectious diseases specialist to define the most appropriate choice of therapy in patients with culture-negative endocarditis is recommended (*Class I; Level of Evidence C*).**
3. **For patients with acute (days) clinical presentations of native valve infection, coverage for *S aureus*, β-hemolytic streptococci, and aerobic Gram-negative bacilli is reasonable (*Class IIa; Level of Evidence C*).**
4. **For patients with a subacute (weeks) presentation of NVE, coverage of *S aureus*, VGS, HACEK, and enterococci is reasonable (*Class IIa; Level of Evidence C*).**
5. **For patients with culture-negative PVE, coverage for staphylococci, enterococci, and aerobic Gram-negative bacilli is reasonable if onset of symptoms is within 1 year of prosthetic valve placement (*Class IIa; Level of Evidence C*).**
6. **If symptom onset is >1 year after valve placement, then IE is more likely to be caused by staphylococci, VGS, and enterococci, and antibiotic therapy for these potential pathogens is reasonable (*Class IIa; Level of Evidence C*).**
7. **If subsequent blood culture results or other laboratory methodologies define a pathogen, then empirical therapy should be revised to focused therapy that is recommended for the specific pathogen identified (*Class I; Level of Evidence C*).**

Fungi

Fungal IE is rare but can develop in a wide range of patients.[240,241] The well-recognized risk factors associated with fungal IE (eg, IDU and immunocompromised state) have become less prevalent compared with the presence of a cardiovascular device, including central venous catheters, permanent pacemakers and defibrillators, and prosthetic valves.[240–246]

Fungal IE has been recognized as a cause of early PVE, but a case series from a single medical center demonstrated that 43% of these cases had symptom onset >1 years after prosthetic valve placement.[242] In contrast to the expected older age predilection for the development of IE, patients with fungal IE have been younger, which was somewhat unanticipated, considering the low prevalence of IDU among the cohort. *Candida* and *Aspergillus* species account for the large majority of fungal IE, and *Candida*-related IE is much more common than *Aspergillus*-related disease.[240,241] Blood cultures are ultimately positive in most cases caused by the former pathogen, whereas they are rarely positive in cases caused by the latter fungus. Thus, *Aspergillus* is a cause of culture-negative IE, and when this occurs, it is usually in a patient with a prosthetic cardiac valve.[240] A variety of other fungi, including endemic mycoses, can rarely cause IE and can involve both native and prosthetic valves. Noncardiac sites of metastatic infection often complicate fungal IE; this can include, for example, endophthalmitis in patients with candidal IE, which may require both systemic and intraocular antifungal therapy. Further guidelines are available from the Infectious Diseases Society of America for additional management aspects of several of the fungal pathogens (http://www.idsociety.org/IDSA_Practice_Guidelines/).

Despite aggressive combined medical and surgical interventions and a younger cohort, mortality rates for fungal IE are unacceptably high. The survival rate for patients with mold-related IE is <20%. Historically, 2 treatment doctrines have prevailed in fungal IE despite the lack of prospective trials conducted to define the most appropriate therapy: Fungal IE is a "stand-alone indication" for surgical replacement of an infected valve; and amphotericin B, a fungicidal agent, is the initial drug of choice for fungal IE. Because of the alarming mortality rate associated with fungal IE and the availability of newer antifungal drugs, in particular fungicidal drugs like the echinocandins, a re-evaluation of these principles seems in order. If done, however, this will probably be based on anecdotal experience and expert opinion rather than on clinical trial data because of the rarity of the syndrome.

A 2-phase treatment of fungal IE has evolved. The initial or induction phase consists of control of infection. Treatment includes a combination of a parenteral antifungal agent, usually an amphotericin B–containing product, and valve surgery. Valve surgery should be done in most cases of fungal IE. Results of a meta-analysis that included 879 cases of *Candida* IE demonstrated a marked reduction in death (prevalence odds ratio, 0.56; 95% confidence interval, 0.16–1.99) among those who underwent adjunctive valve surgery.[244] In addition, patients who were treated with combination therapy including amphotericin B and flucytosine had reduced mortality compared with those who received antifungal monotherapy.

Antifungal therapy usually is given for >6 weeks. After completion of this initial therapy, long-term (lifelong) suppressive therapy with an oral azole is reasonable.[243,244,246] Suppressive therapy has been used in 2 populations. First, because of the high relapse rate of fungal IE and the prolonged delay (years in some cases) in relapse, oral azoles have been administered after combined medical and surgical induction therapy. In a second population with fungal IE, lifelong oral antifungal suppressive therapy has been given to patients who respond clinically to induction medical therapy but are not deemed appropriate surgical candidates for valve replacement for attempted infection cure. Anecdotal case series[243,245] indicate that IE has been successfully suppressed for months to years. A meta-analysis that included 64 reported patients with *Candida* IE who did not undergo valve surgery because they were deemed to be unacceptable surgical candidates supports the notion that fluconazole suppressive therapy is useful; 20 of 21 patients (95%) who were ultimately treated with long-term suppressive therapy survived during follow-up, which was ≥6 months.[244]

Recommendations

1. **Valve surgery should be done in most cases of fungal IE (*Class I; Level of Evidence B*).**
2. **After completion of initial parenteral therapy, lifelong suppressive therapy with an oral azole is reasonable (*Class IIa; Level of Evidence B*).**

Surgical Management

There is a prevailing opinion that valve surgery is crucial for optimal therapy in selected patients with complicated IE.[247–249] In a systematic review[5] of 15 population-based IE investigations from 7 countries, after adjustment for country, the proportion of IE cases undergoing valve surgery increased 7% per decade (95% confidence interval, −0.4% to 14%; P=0.06) between 1969 and 2000. In surveys involving population-based[1] and international multicenter cohorts,[10,11] ≈50% of both NVE and PVE patients undergo valve surgery during the active phase of IE (during initial hospitalization before completion of a full therapeutic course of antibiotics).

Although valve replacement surgery has served as an important option in the management of individual IE cases, only 1 small, randomized trial[17] has been performed to date to examine the role of valve surgery in the management of IE. In this trial, 76 patients with left-sided NVE, severe valve regurgitation without heart failure, and vegetations >10 mm were assigned to early surgery within 48 hours or to conventional treatment. Although the authors[17] report a reduction in the composite outcome of in-hospital deaths and embolic events with early surgery (3% versus 23%), the differences between the 2 groups were driven by a significant decrease in embolic events with early surgery. Thus, firm conclusions cannot be drawn from this trial on the effect of early surgery on mortality, given the small sample size of the study. In addition, patients in this trial were young and had limited comorbidity based on a EuroSCORE, a calculated risk of surgical mortality (http://www.euroscore.org), a low prevalence of *S aureus* IE, and lower mortality compared with most contemporary patient cohorts. Moreover, many patients had signs of embolization (a Class IIa indication for surgery) before randomization. Data from nonrandomized trials from a single-center experience[250] and an international collaboration[251] support the notion[252] that early valve surgery may not be beneficial in all patients with native or PVE caused by *S aureus*.

Over several decades, expert panels have relied on data from observational studies to make recommendations on the indications for early surgery. Despite the availability of new studies, the indications for surgery have not changed appreciably over time.[18] Considering that observational studies are prone to bias and confounding, researchers have used regression analysis and calculated propensity scores to adjust for prognostically important baseline differences between surgical and medical patients.[14,253] Studies[14,15,136,249,253–256] examining the association between valve surgery and outcome in left-sided IE using propensity score analysis, however, have demonstrated conflicting results, likely because of the use of different analytical approaches.

Until 2007, none of the published studies adjusted for survivor bias, which occurs because patients who live longer are more likely to undergo surgery than those who die early. A correlation between longer survival and surgery may be wrongly interpreted as evidence that surgical treatment improves survival.[257] Since 2007, at least 3 studies[15,16,258] have documented the effect of survivor bias on the association between surgery and mortality in IE patients. When adjusted for survivor bias, analyses have shown either a statistical loss of benefit of early surgery or findings indicating that the surgical intervention may actually result in harm.

Between 2007 and 2013, at least 6 observational studies[10,11,14–16,259] that adjusted for selection bias, confounding, and survivor bias were conducted. Three studies that included 2 cohorts of patients with NVE and PVE and 1 cohort with NVE showed an association between early surgery and lower mortality in IE patients in general or in specific subgroups of patients such as those with heart failure or paravalvular complications. Only 1 study examined the role of valve surgery in PVE.[259] After adjustment for differences in clinical characteristics and survival bias, early valve replacement was not associated with lower mortality compared with medical therapy in the overall cohort. Subgroup analysis indicated a lower in-hospital and 1-year mortality with early surgery only in the group of patients with the highest surgical propensity. Table 17 summarizes the characteristics of rigorously conducted observational studies that support the role of surgery in IE management.

Indications for Surgery

Decisions on surgical intervention are complex and depend on many clinical and prognostic factors[257–262] that vary among patients, including infecting organism, vegetation size, presence of perivalvular infection, presence of embolism or heart failure, age, noncardiac comorbidities, and available surgical expertise. There is a paucity of evidence available to define the optimal timing of valve surgery. Decisions on the indication and timing of surgical intervention should be determined by a multispecialty team with expertise in cardiology, imaging, cardiothoracic surgery, and infectious diseases.[261] Recommendations for early surgery in patients with recurrent emboli and persistent vegetations have generally been enacted after clinical events. Whether recurrent, asymptomatic emboli detected on advanced imaging studies should influence decision making should be considered on an individual basis. Risk stratification models such as the Society of Thoracic Surgeons Endocarditis Score are available to predict morbidity and mortality risks in IE patients after valve surgery and to assist in decision making and patient counseling.[260]

Early Valve Surgery in Left-Sided NVE: Recommendations

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 (*Class I; Level of Evidence B*).**
2. **Early surgery should be considered particularly in patients with IE caused by fungi or highly resistant organisms (eg, vancomycin-resistant *Enterococcus*, multidrug-resistant Gram-negative bacilli) (*Class I; Level of Evidence B*).**
3. **Early surgery is indicated in patients with IE complicated by heart block, annular or aortic abscess, or destructive penetrating lesions (*Class I; Level of Evidence B*).**
4. **Early surgery is indicated for evidence of persistent infection (manifested by persistent bacteremia or fever lasting >5–7 days and provided that other sites of infection and fever have been excluded) after the start of appropriate antimicrobial therapy (*Class I; Level of Evidence B*).**
5. **Early surgery is reasonable in patients who present with recurrent emboli and persistent or enlarging vegetations despite appropriate antibiotic therapy (*Class IIa; Level of Evidence B*).**
6. **Early surgery is reasonable in patients with severe valve regurgitation and mobile vegetations >10 mm (*Class IIa, Level of Evidence B*).**
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 (*Class IIb; Level of Evidence C*).**

Early Valve Surgery in PVE: Recommendations

1. **Early surgery is indicated in patients with symptoms or signs of heart failure resulting from valve dehiscence, intracardiac fistula, or severe prosthetic valve dysfunction (*Class I; Level of Evidence B*).**
2. **Early surgery should be done in patients who have persistent bacteremia despite appropriate antibiotic therapy for 5 to 7 days in whom other sites of infection have been excluded (*Class I; Level of Evidence B*).**
3. **Early surgery is indicated when IE is complicated by heart block, annular or aortic abscess, or destructive penetrating lesions (*Class I; Level of Evidence B*).**
4. **Early surgery is indicated in patients with PVE caused by fungi or highly resistant organisms (*Class I; Level of Evidence B*).**
5. **Early surgery is reasonable for patients with PVE who have recurrent emboli despite appropriate antibiotic treatment (*Class IIa; Level of Evidence B*).**
6. **Early surgery is reasonable for patients with relapsing PVE (*Class IIa; Level of Evidence C*).**
7. **Early surgery may be considered in patients with mobile vegetations >10 mm (*Class IIb; Level of Evidence C*).**

Valve Surgery in Patients With Right-Sided IE

Although outcomes are better for patients with right-sided IE compared with patients with left-sided infection, surgical intervention is occasionally considered in the former group. Because many of the patients with right-sided IE develop infection as a result of IDU (see the Right-Sided IE in IDUs section), the general approach is to treat these patients

Table 17. Direct Evidence Supporting an Association Between Valve Surgery and Lower Mortality From Observational Studies: Level of Evidence B

Study	Mortality	IE Group	PE vs SA
Lalani et al[10]	In-hospital mortality	NVE	PE
Bannay et al[15]	5-y mortality	NVE+PVE	PE
Kiefer et al[11]	In-hospital and 1-y mortality	CHF (NVE+PVE)	PE
Lalani et al[10]	In-hospital mortality	Paravalvular complications (NVE)	SA
Bannay et al[15]	5-y mortality	Intracardiac abscess (NVE+PVE)	SA
Lalani et al[10]	In-hospital mortality	Systemic embolization (NVE)	SA
Bannay et al[15]	5-y mortality	Systemic embolization (NVE+PVE)	SA
Lalani et al[10]	In-hospital mortality	*S aureus* (NVE)	SA
Bannay et al[15]	5-y mortality	CHF (NVE+PVE)	SA
Lalani et al[259]	In-hospital and 1-y mortality	PVE with the highest propensity to undergo surgery	SA

CHF indicates congestive heart failure; NVE, native valve infective endocarditis; PE, primary end point; PVE, prosthetic valve infective endocarditis; and SA, subgroup analysis.

All studies have adjusted for selection and survivor bias and confounding. Valve surgery was performed during the active phase of the disease (during initial hospitalization before completion of a full therapeutic course of antibiotics).

medically and to avoid placement of valve prostheses because of the subsequent risk of device infection with continued IDU. Surgical intervention is reasonable for patients with the following complications: right heart failure secondary to severe tricuspid regurgitation with poor response to medical therapy, sustained infection caused by difficult-to-treat organisms (ie, fungi, multidrug resistant bacteria) or lack of response to appropriate antimicrobial therapy, and tricuspid valve vegetations that are ≥20 mm in diameter and recurrent pulmonary embolism despite antimicrobial therapy. Valve repair rather than replacement should be performed when feasible. If valve replacement is performed, then an individualized choice of prosthesis by the surgeon is reasonable.[263,264]

Recommendations

1. **Surgical intervention is reasonable for patients with certain complications (*Class IIa; Level of Evidence C*).**
2. **Valve repair rather than replacement should be performed when feasible (*Class I; Level of Evidence C*).**
3. **If valve replacement is performed, then an individualized choice of prosthesis by the surgeon is reasonable (*Class IIa; Level of Evidence C*).**
4. **It is reasonable to avoid surgery when possible in patients who are IDUs (*Class IIa; Level of Evidence C*).**

Valve Surgery in Patients With Prior Emboli/ Hemorrhage/Stroke

The timing of valve surgery in IE patients with stroke remains controversial. Stroke is an independent risk factor for postoperative mortality in IE patients. After stroke, neurological deterioration can occur as a result of hemorrhagic transformation with anticoagulation during cardiopulmonary bypass or exacerbation of cerebral ischemia attributable to hypotension during cardiac surgery. The risk of intracranial hemorrhage is dependent on several factors, including extent and size of infarction, whether it is ischemic or hemorrhagic, and the exact timing of surgery.

One clinical quandary is whether early valve surgery can be safely performed within 7 days after a stroke or if it is better to postpone surgery for at least 1 week. No randomized trials have addressed this conundrum. The high rates of postoperative morbidity and mortality seen in earlier studies[265–267] have resulted in a reluctance to refer patients with IE and acute stroke for immediate valve surgery. However, these initial studies included a limited number of patients, and risk adjustments were not performed. The largest early series of operated patients with cerebral complications included 181 patients.[267] Hospital mortality rates as a function of the interval between evidence of cerebral infarction to cardiac surgery were 66.3% when surgery was performed within 24 hours of stroke and gradually decreased every week to 7.0% with surgery >4 weeks after stroke.

Investigations have suggested better outcomes for IE patients with ischemic stroke who undergo early cardiac surgery.[268–272] Ruttmann et al[270] analyzed 65 patients who underwent cardiac surgery after cardioembolic (embolic) stroke (median time, 4 days; range, 0–38 days). Surgery in this time frame was not associated with worse patient outcomes. Fifty of the 61 patients (81.9%) with CT-verified preoperative stroke survived cardiac surgery. Latency between the neurological event and cardiac surgery was not a significant factor with respect to the perioperative neurological complication rate or the postoperative neurological recovery rate. Full neurological recovery was achieved in 70% of 50 stroke patients. Other studies[6–8] suggest that the risk of neurological deterioration during cardiac surgery after a stroke is lower than previously assumed, particularly in patients with silent cerebrovascular emboli.

The first study to evaluate the timing of surgery after stroke in IE that included a risk adjustment for differences in patient characteristics comprised 198 patients.[273] Fifty-eight patients who underwent surgery within 1 week of stroke were compared with 140 patients who underwent surgery ≥8 days after stroke. Hospital mortality was numerically but not significantly higher in the early surgery group (22.4% versus 12%). After adjustment for other risk factors such as age, paravalvular abscess, and heart failure, the risk of hospital mortality remained nonsignificantly higher in the early surgery group (odds ratio, 2.308; 95% confidence interval, 0.942–5.652). Differences in 1-year mortality were less pronounced, with an adjusted hazard ratio of 1.138 (95% confidence interval, 0.802–1.650). In-hospital mortality in the early surgery group was comparable to that of the medically treated patients.

After hemorrhagic stroke, the risk of exacerbation by surgery is prohibitively high in the first month but can extend beyond 1 month in some patients, possibly because of the presence of undetected mycotic aneurysms (MAs). In a multicenter study of patients with hemorrhagic stroke, mortality was higher when surgery was performed within 4 weeks of the hemorrhagic event compared with later surgery (75% versus 40%, respectively).[274]

These data support the following recommendations: Valve surgery may be performed in IE patients with stroke or subclinical cerebral emboli without delay if intracranial hemorrhage has been excluded by imaging studies and neurological damage is not severe (ie, coma). In patients with major ischemic stroke or intracranial hemorrhage, it is reasonable to delay valve surgery for at least 4 weeks.

Recommendations

1. **Valve surgery may be considered in IE patients with stroke or subclinical cerebral emboli and residual vegetation without delay if intracranial hemorrhage has been excluded by imaging studies and neurological damage is not severe (ie, coma) (*Class IIb; Level of Evidence B*).**
2. **In patients with major ischemic stroke or intracranial hemorrhage, it is reasonable to delay valve surgery for at least 4 weeks (*Class IIa; Level of Evidence B*).**

Risk of Embolization

Systemic embolization occurs in 22% to 50% of cases of IE.[55,57,274–277] Rates can be higher if noninvasive imaging,

including MRI and CT scanning, is routinely done to detect asymptomatic (silent) emboli. Emboli often involve major arterial beds, including the brain, lungs, coronary arteries, spleen, bowel, and extremities. Up to 65% of embolic events involve the CNS, and >90% of CNS emboli lodge in the distribution of the middle cerebral artery.[277] The highest incidence of embolic complications is seen with mitral valve IE (and more with anterior rather than posterior mitral leaflet involvement) and with IE caused by *S aureus*, *Candida*, and HACEK organisms.

Emboli can occur before diagnosis, during therapy, or after therapy is completed, although most emboli occur within the first 2 to 4 weeks of antimicrobial therapy.[58,278] Of note, 2 independent studies have confirmed that the rate of embolic events decreases dramatically during and after the first 2 to 3 weeks of successful antibiotic therapy. In a study from 1991, the embolic rate dropped from 13 to <1.2 embolic events per 1000 patient-days during that time.[58] Vilacosta et al[278] confirmed the reduced frequency of embolization after 2 weeks of therapy. Moreover, the latter study reemphasized the increased risk of embolization with increasing vegetation size during therapy, mitral valve involvement, and staphylococcal pathogenesis. In a survey that included the International Collaboration on Endocarditis cohort, Dickerman and colleagues[280] focused on the incidence of stroke in a multicenter IE population and demonstrated that acute stroke rates fell significantly after initiation of antibiotic therapy regardless of valve involved or pathogen identified. Moreover, only 3.1% of the cohort suffered stroke after the first week of antimicrobial therapy; this finding has led to the opinion that stroke prevention as a sole indication for valve surgery after 1 week of appropriate antibiotic therapy is not warranted.

Prediction of individual patient risk for embolization is extremely difficult. Many studies have attempted to use echocardiography to identify a high-risk subset of IE patients who might benefit from early surgery to avoid embolization. Several studies with TTE have demonstrated a trend toward higher embolic rates with left-sided vegetations >1 cm in diameter.[55] De Castro and colleagues[276] compared TTE with multiplane TEE and found that neither technique was helpful in defining embolic risk in patients with vegetations. In a study[57] based on TEE, mitral vegetations >1 cm in diameter were associated with the greatest frequency of embolism. The association was strengthened when the analysis was limited to those patients who had not yet experienced a clinical embolic event. Another prospective TEE study, however, found no clear correlation of vegetation size with embolization.[59] Nevertheless, the same investigators later reported the results of a new prospective study of 118 patients who underwent TEE and found that, on multivariable analysis, risk factors associated with embolic risk included vegetation size >10 mm and mitral valve involvement.[56] Overall, these data are compatible with previous observations that indicate that, in general, mitral vegetations of any size are associated with a higher risk of embolization (25%) than aortic vegetations (10%). As noted above, the highest embolic risk (37%) has been seen in the subset of patients with mitral vegetations attached to the anterior rather than the posterior mitral leaflet.[59,63] This suggests that the mechanical effects of broad and abrupt leaflet excursion, occurring twice per heartbeat, may contribute to the propensity of a vegetation in this location to fragment and embolize.

In another study, the effect of vegetation size on embolic potential was dependent on the infecting organism, with large vegetations independently predicting embolic events only in the setting of streptococcal IE.[60] In contrast, as confirmed above by Vilacosta et al,[278] staphylococcal or fungal IE appears to carry a high incidence rate of embolization independently of vegetation size.

Prognosis based on echocardiographic findings was examined in a large, multicenter, prospective investigation. On the basis of TEE findings in 384 consecutive adult patients with definite IE, vegetation length >15 mm was a predictor of 1-year mortality (adjusted relative risk, 1.8; 95% confidence interval, 1.10–2.82; P=0.02) in multivariable analysis.[281]

The role of echocardiography in predicting embolic events has been controversial. In 1 survey[282] that included 4 echocardiographers who were blinded to clinical data, interobserver agreement was mixed on the characterization of vegetations. Agreement was high for the presence of vegetation (98%) and involved site (97%); interobserver agreement was considerably less for vegetation size (73%), mobility (57%), shape (37%), and attachment (40%). However, all of the series that included >100 patients who underwent TEE showed a positive relationship between embolic events and vegetation size. Moreover, the study with the largest number of patients (n=176) that assessed the value of TEE and included silent embolism detected by CT scanning demonstrated that the risk of embolic events was highly related to vegetation size and mobility but not to other known risk factors associated with embolism in IE.[283] The conflicting results on the relationship between echocardiography and embolic risk can be explained at least partially by the poor standardization of diagnostic criteria for IE in older series, inclusion or not of silent embolism, inclusion or not of previous embolism, echocardiographic method used, lack of focus on future embolic events after TEE, and sample size.

An increase in vegetation size over 4 to 8 weeks of therapy as documented by TEE appears to predict embolic events.[282] In addition, a second, albeit infrequent, peak of late embolic events has been observed to occur 15 to 30 weeks after the diagnosis of IE and has been associated with nonhealing vegetations (failure of a vegetation to stabilize or diminish in size) as defined by echocardiography.[63]

The traditional indication for valvular surgery for IE to avoid embolization has been ≥2 major embolic events.[284] This criterion is arbitrary and excludes cutaneous embolization, which is common, or embolism occurring before the institution of therapy, which is common among IE patients who develop embolic events. Because of the observed decreases in embolic risk during the first 2 weeks of antibiotic therapy, the benefit of surgery in avoiding catastrophic embolic events is greatest early in the treatment course of IE. Early surgical intervention may preclude a primary or recurrent major embolic event but exposes the patient to both immediate and lifelong risks of valve replacement if the valve cannot be primarily repaired. At this time, the strategy for surgical intervention to avoid systemic embolization in IE remains specific

to the individual patient, with benefit being greatest in the early phase of IE when embolic rates are highest and other predictors of a complicated course (ie, recurrent embolization; heart failure; aggressive, antibiotic-resistant organisms; or PVE) are present (Table 5). The benefits of early surgery were demonstrated in the prospective, randomized trial[12] that was discussed earlier in this document. Because of several limitations of that trial, additional study is needed before routine application of early surgery solely to reduce embolic risk can be strongly advocated.

Embolic events are important prognostic indicators of IE outcomes. In 1 analysis, an embolic event was 1 of 4 early predictors of in-hospital death caused by IE.[285] Other independent predictors of death by logistic regression modeling among 267 consecutive patients with definite or possible IE by modified Duke criteria were diabetes mellitus, *S aureus* infection, and Acute Physiology And Chronic Health Evaluation (APACHE) II score.

Another controversial topic is whether imaging to detect emboli should be performed in all IE patients. The current paradigm includes dedicated, anatomic imaging if there are signs or symptoms suggestive of an embolic event. There is less agreement on imaging, which can pose risks because contrast material is usually required, in patients without symptoms or signs of emboli, some of whom may have silent or subclinical events. In particular, should MRI of the brain be obtained in all IE patients because cerebral emboli are so commonplace? As previously mentioned in an earlier section (3D Echocardiography and Other Imaging Modalities), some have advocated this strategy in all patients who are to undergo valve surgery to identify those who may harbor embolic lesions that could pose a higher risk of intracranial bleeding with cardiopulmonary bypass and heparin administration used for cardiac surgery.

Anticoagulation

Anticoagulation in IE patients is controversial, particularly in mechanical valve IE.[286] Some authorities recommend continuation of anticoagulant therapy in patients with mechanical valve IE. However, the general advice is to discontinue all forms of anticoagulation in patients with mechanical valve IE who have experienced a CNS embolic event for at least 2 weeks.[287] This time should allow for thrombus organization and prevent the acute hemorrhagic transformation of embolic lesions. Reintroduction of anticoagulation in these patients should be done with great caution, beginning with intravenous unfractionated heparin titrated to an activated partial thromboplastin time range of 50 to 70 seconds and transitioning carefully to adjusted dose warfarin. The novel oral anticoagulants are not approved for use with either mechanical valves or bioprosthetic valves when risk factors for thromboembolism exist (eg, atrial fibrillation).

The benefit of therapeutic anticoagulation has never been demonstrated convincingly in patients with NVE. In part related to findings that demonstrated a salutary effect of intravenous aspirin therapy in established experimental *S aureus* IE,[288] a randomized trial compared oral aspirin 325 mg/d with placebo in 115 IE patients.[289] No significant benefit was observed in aspirin-treated patients in terms of vegetation resolution and embolic events. Moreover, there was a trend toward more bleeding episodes in the aspirin-treated patients. Aspirin levels, a critical correlate of antimicrobial efficacy in an animal model, were not monitored in this study.[290]

Retrospective, observational studies[291–296] have examined the impact, if any, of long-term antiplatelet therapy before the onset of IE on infection-related outcomes. Findings from these investigations have been mixed in terms of IE-related outcomes. Until definitive data are available, the initiation of aspirin or other antiplatelet agents as adjunctive therapy in IE is not recommended. In contrast, the continuation of long-term antiplatelet therapy at the time of development of IE with no bleeding complications may be considered.

Recommendations

1. **Discontinuation of all forms of anticoagulation in patients with mechanical valve IE who have experienced a CNS embolic event for at least 2 weeks is reasonable (*Class IIa; Level of Evidence C*).**
2. **Initiation of aspirin or other antiplatelet agents as adjunctive therapy in IE is not recommended (*Class III; Level of Evidence B*).**
3. **The continuation of long-term antiplatelet therapy at the time of development of IE with no bleeding complications may be considered (*Class IIb; Level of Evidence B*).**

Periannular Extension of Infection

Extension of IE beyond the valve annulus predicts a higher mortality rate, more frequent development of heart failure, and more frequent need for cardiac surgery.[284,297,298] Perivalvular cavities form when annular infections break through and spread into contiguous tissue. In aortic NVE, this generally occurs through the weakest portion of the annulus, which is near the membranous septum and atrioventricular node.[299] The anatomic vulnerability of this area explains both why abscesses occur in this location and why heart block is a frequent sequela.[300] Periannular extension is common, occurring in 10% to 40% of all NVE and complicating aortic IE more commonly than mitral or tricuspid IE.[301–304] Periannular infection is of even greater concern with PVE, occurring in 56% to 100% of patients.[298,302] Perivalvular abscesses are particularly common with prosthetic valves because the annulus, rather than the leaflet, is the usual primary site of infection, especially in early PVE and on bioprosthetic valves.[302]

Under the influence of systemic intravascular pressures, abscesses may progress to fistulous tracts that create intracardiac or pericardial shunts. The mortality rate was 41% in a series[304] of patients with aorto-cavitary fistulization despite surgical intervention in 87%. Multivariate analysis demonstrated that factors associated with an increased risk of death included moderate to severe heart failure, PVE, and urgent or emergency surgical intervention. In some cases, progressive periannular infection totally disrupts the ventricular-aortic continuity or the mitral-aortic trigone. Such structural lesions and intracardiac fistulas may be catastrophic; even if their hemodynamic impact is tolerated, these lesions will not heal

with medical treatment alone and require urgent operative intervention.

Clinical parameters for the diagnosis of perivalvular extension of IE are inadequate. Persistent bacteremia or fever, recurrent emboli, heart block, heart failure, or a new pathological murmur in a patient with IE on appropriate antibiotics may suggest extension.[303] Only aortic valve involvement and current IDU have been prospectively identified as independent risk factors for perivalvular abscess.[297] On ECG, new atrioventricular block has a positive predictive value of 88% for abscess formation but low (45%) sensitivity.[298]

Patients at risk for perivalvular extension of IE require prompt evaluation. The size of vegetations is not helpful for predicting perivalvular extension.[297] The sensitivity of TTE for detecting perivalvular abscess is low (18% to 63% in prospective and retrospective studies, respectively).[305,306] TEE dramatically improves the sensitivity for defining periannular extension of IE (76% to 100%) while retaining excellent specificity (95%) and positive and negative predictive values (87% and 89%, respectively).[54,307] When combined with spectral and color Doppler techniques, TEE can demonstrate the distinctive flow patterns of fistulas and pseudoaneurysms and can rule out communications from unruptured abscess cavities. Because of these combined capabilities, TEE is recommended for the initial assessment of any patient suspected of having perivalvular extension of IE.

A small number of patients with periannular extension of infection or myocardial abscess may be treated successfully without surgical intervention.[307,308] These patients potentially include those who have smaller (<1 cm) abscesses and who do not have complications such as heart block, echocardiographic evidence of progression of abscess during therapy, valvular dehiscence, or insufficiency. Such patients should be monitored closely with serial TEE; TEE should be repeated at intervals of 2, 4, and 8 weeks after completion of antimicrobial therapy.

Surgery for patients with perivalvular extension of IE is directed toward eradication of the infection and correction of hemodynamic abnormalities. Drainage of abscess cavities, excision of necrotic tissue, and closure of fistulous tracts often accompany valve replacement or repair surgery.[309] Although valve replacement is usually required, its successful performance may be compromised by extensive destruction of the periannular supporting tissues. Under these conditions, human aortic homografts, when available, can be used to replace the damaged aortic valve and to reconstruct the damaged aorta.[310,311] Homografts have a constant but low incidence rate of IE.[312] Some groups have advocated the use of stentless or mini-stented aortic valve prostheses with debridement in the same clinical scenario, particularly if homografts are not readily available.[313]

Recommendation

1. **TEE is recommended for the initial assessment of any patient suspected of having perivalvular extension of IE (*Class I; Level of Evidence B*).**

Metastatic Foci of Infection

Similar to embolic complications, metastatic foci of infection frequently occur in IE and can greatly affect management strategies, in particular timing of valve surgery, duration of antimicrobial therapy, and need for invasive interventions (usually surgical or interventional radiological drainage). Much like embolic events, metastatic foci of infection either can remain asymptomatic or may cause major clinical signs or symptoms. In the latter case, sustained fever can be a valuable clue, particularly when bloodstream infection has been cleared or in cases when bloodstream infection persists despite adequate antimicrobial coverage. In addition, distinguishing bland infarction caused by an embolus from a metastatic focus (abscess) sometimes can be difficult. In patients who are symptomatic, a diagnostic evaluation including radiological, ultrasonographic, and invasive procedures such as joint aspiration for both diagnostic and therapeutic reasons is recommended. Invasive procedures such as percutaneous drainage of soft tissue or organ abscess may be needed. Surgical intervention, as mentioned above, may be required for radical infection cure. For example, splenic abscesses generally require splenectomy or a drainage procedure because the usefulness of antimicrobial therapy is in preventing disease extension in the spleen and treating systemic infection rather than eliminating abscesses.[314] Whether percutaneous aspiration or drainage of splenic abscesses can be performed safely and effectively should be decided by an experienced team of clinicians.

Identification and management of metastatic foci of infection are critically important in patients who require valve surgery. When feasible, all invasive procedures for the initial management of metastatic foci of infection should be done before valve surgery to reduce the likelihood of infecting a placed prosthetic valve or annuloplasty ring.

Cerebrovascular imaging may be considered in all patients with left-sided IE who have no CNS signs or symptoms (see the Intracranial MAs section below). There are currently no other recommendations for routinely evaluating all patients with IE for metastatic foci of infection, although many clinicians recommend such routine screening for all cases of *S aureus* IE. Rather, a directed workup is advocated on the basis of localizing signs or symptoms. Depending on the site of interest, the choice of diagnostic procedure (eg, CT, MRI, ultrasonography) varies, and the selection should be individualized for each patient. The choice of procedure may require consultation with experts. It is strongly recommended that a discussion of which laboratory (microbiology, pathology including cytology) studies will be needed once tissue or fluid aspirate specimens are available takes place before an invasive procedure is performed.

Recommendation

1. **The choice of diagnostic procedure (eg, CT, MRI, ultrasonography) varies and the selection should be individualized for each patient (*Class I; Level of Evidence C*).**

Mycotic Aneurysms

MAs are uncommon complications of IE that result from septic embolization of vegetations to the arterial vasa vasorum or the intraluminal space, with subsequent spread of infection through the intima and outward through the vessel wall.

Arterial branching points favor the impaction of emboli and are the most common sites of development of MAs. MAs caused by IE occur most frequently in the intracranial arteries, followed by the visceral arteries and the arteries of the upper and lower extremities.

A detailed analysis of the complex management of MAs has been included in a separate AHA Scientific Statement that addresses vascular infections and is pending publication; please refer to this document for additional information.

Intracranial MAs

Intracranial MAs (ICMAs) represent a relatively small but extremely dangerous subset of neurological complications. The overall mortality rate among IE patients with ICMAs is 60%. Among patients with unruptured ICMAs, the mortality rate is 30%; in patients with ruptured ICMAs, the mortality rate approaches 80%.[315,316] The reported occurrence of ICMAs in 1.2% to 5% of cases[316–320] is probably underestimated because some ICMAs remain asymptomatic and resolve with antimicrobial therapy. Streptococci and *S aureus* account for 50% and 10% of cases, respectively,[317,318] and ICMAs are seen with increased frequency among IDUs with IE.[318] The distal middle cerebral artery branches are most often involved, especially the bifurcations. Multiple ICMAs occur in 20% of cases[319]; mortality rates are similar for multiple and single distal ICMAs. The mortality rate for patients with proximal ICMAs is >50%.[321]

The clinical presentation of patients with ICMAs is highly variable. Patients may develop severe headache, altered sensorium, or focal neurological deficits such as hemianopsia or cranial neuropathies. Neurological signs and symptoms are nonspecific and may suggest a mass lesion or an embolic event.[315,317] Some ICMAs leak slowly before rupture and produce mild meningeal irritation. Frequently, the spinal fluid in these patients is sterile, and it usually contains erythrocytes, leukocytes, and elevated protein. In other patients, there are no clinically recognized premonitory findings before sudden subarachnoid or intraventricular hemorrhage.[315]

Symptomatic cerebral emboli frequently but not invariably precede the finding of an ICMA.[315] Therefore, imaging procedures to detect ICMAs are indicated in IE patients with localized or severe headaches; "sterile" meningitis, especially if erythrocytes or xanthochromia is present; or focal neurological signs. Several imaging modalities can be used to identify ICMAs; currently, there is no preferred initial imaging study that can be recommended.[322] Techniques include cardiac (multislice) CT angiography with 3D reconstruction, digital subtraction angiography, and magnetic resonance angiography with 3D reconstruction. In cases when there is a high clinical suspicion of ICMAs and a negative initial screening with 1 of these modalities, then conventional angiography is reasonable to perform. Cerebral MRI may be considered in all patients with left-sided IE who have no CNS signs or symptoms. MRI findings may assist in subsequent medical and surgical management.[322]

Recommendations

1. **Cerebrospinal imaging should be performed to detect ICMA or CNS bleeding in all patients with IE or contiguous spread of infection who develop severe, localized headache, neurological deficits, or meningeal signs (*Class I; Level of Evidence B*).**
2. **Cerebrovascular imaging may be considered in all patients with left-sided IE who have no CNS signs or symptoms (*Class IIb; Level of Evidence C*).**
3. **CT angiography, magnetic resonance angiography, or digital subtraction angiography is reasonable as an initial imaging test for detection of ICMA (*Class IIa, Level of Evidence B*).**
4. **Conventional angiography for detection of suspected ICMA is reasonable in patients with negative CT angiography, magnetic resonance angiography, or digital subtraction angiography (*Class IIa; Level of Evidence B*).**

Extracranial MAs

Intrathoracic or intra-abdominal MAs often are asymptomatic until leakage or rupture occurs. Presumably, most extracranial MAs will rupture if not excised. The appearance of a tender, pulsatile mass in a patient with IE suggests an extracranial MA. Hematemesis, hematobilia, and jaundice suggest rupture of a hepatic artery MA; arterial hypertension and hematuria suggest rupture of a renal MA; and massive bloody diarrhea suggests the rupture of an extracranial MA into the small or large bowel. Either CT scanning or multislice CT angiography with 3D reconstruction is indicated for initial imaging. TEE is useful in identifying MAs of the sinus of Valsalva and thoracic aorta.

Recommendations

1. **Either CT scanning or multislice CT angiography with 3D reconstruction is indicated for initial imaging (*Class I; Level of Evidence B*).**
2. **TEE is useful in identifying MAs of the sinus of Valsalva and thoracic aorta (*Class I; Level of Evidence B*).**

Outpatient Therapy

Outpatient parenteral antibiotic therapy (OPAT) is efficacious, safe, and cost-effective for a variety of infections,[323–325] including IE that requires prolonged parenteral therapy in hospitalized patients who otherwise no longer require inpatient care but do require continued parenteral antimicrobial therapy. Antibiotic regimens recommended for IE vary widely and often require ≥4 weeks of therapy, generally given by the intravenous route. Absorption of orally administered antimicrobial agents may be unreliable, and such a strategy is generally not recommended as sole therapy for IE. Several other aspects of OPAT such as drug stability at room temperature; frequency of drug dosing; access to ancillary equipment, including ambulatory pumps; insurance coverage; and whether the patient has a history of IDU can all affect the ultimate use of OPAT.

The timing for transition from inpatient antibiotic therapy to OPAT and patient exclusion criteria have been critically evaluated by Andrews and von Reyn.[326] These guidelines are based on the local availability of medical care in the outpatient setting and risk factors and timing of potential adverse outcomes that would be best managed in the inpatient setting.

Before OPAT is considered, most patients with IE should first be evaluated and stabilized in the hospital; only rarely can some patients be treated entirely as outpatients. Patients selected for OPAT should be at low risk for the complications of IE, the most frequent of which are heart failure and systemic emboli. The period of greatest risk for systemic emboli is before or within the first 1 to 2 weeks of antimicrobial therapy, although serious complications such as heart failure and rupture of MAs may develop weeks to months after the initiation of antimicrobial therapy. The presence of poorly controlled heart failure, neurological findings that may result from systemic emboli or bleeding MAs, cardiac conduction abnormalities, valve ring abscesses (usually detected by TEE), persistent fever, or persistently positive blood cultures should preclude OPAT.

The risk for drug-related side effects usually increases with a prolonged drug exposure (eg, vestibular, auditory, and nephrotoxicity resulting from aminoglycosides; leukopenia caused by β-lactams and vancomycin; and nephrotoxicity resulting from the combination of vancomycin and gentamicin) and requires close monitoring by the home infusion team consisting of representatives from nursing and pharmacy and clinicians with expertise in IE management.

The following criteria are essential for an effective OPAT program:

- A reliable support system at home and easy access to a hospital for prompt re-evaluation by an experienced clinician if a complication such as recurrence of fever, symptoms of a cardiac arrhythmia, heart failure, or a neurological event develops
- Regular visits by a home infusion nurse who carefully monitors the patient for early detection of complications, failure to respond to therapy, problems with adherence to therapy, or complications (eg, catheter-related infection, catheter leakage or displacement, venous thrombosis) directly related to the antibiotics or intravenous access
- Regular visits with an experienced clinician to assess clinical status during the OPAT

Recommendations

1. **Patients with IE should first be evaluated and stabilized in the hospital before being considered for outpatient therapy (*Class I; Level of Evidence C*).**
2. **Patients selected for OPAT should be at low risk for the complications of IE, the most frequent of which are heart failure and systemic emboli (*Class I; Level of Evidence C*).**

Care at Completion of Antimicrobial Therapy

Short-Term Follow-Up

The majority of patients with IE are cured with appropriate medical and, if necessary, surgical treatment. Echocardiography is reasonable before or synchronous with completion of antimicrobial therapy to establish a new baseline for subsequent comparison (Table 18). A referral to a program to assist in the cessation of drug use should be made for IDUs. Patients should be educated about the signs of endocarditis and urged to seek immediate medical attention should they occur. If feasible, a thorough dental evaluation is reasonable, especially in patients deemed likely to require valve replacement, with all active sources of oral infection eradicated. All indwelling intravenous catheters used to infuse antimicrobial treatment should be removed promptly at the end of therapy. Routine blood cultures are no longer recommended after the completion of antimicrobial therapy because the likelihood of a positive culture result in a patient who is otherwise without evidence of active infection is low.

In the short-term follow-up, patients should be monitored for development of several complications (Table 18). A relapse of IE is a primary concern. Patients should be aware that relapses can occur and that new onset of fever, chills, or other evidence of systemic toxicity mandates immediate evaluation, including a thorough history and physical examination and ≥3 sets of blood cultures. Every effort should be made to determine the cause of signs or symptoms of infection. In addition, prescribing empirical antimicrobial therapy should be avoided for an undefined febrile illness unless the patient's clinical condition (eg, sepsis) warrants empirical therapy. It is reasonable for patients who have completed therapy to undergo an examination after completing antibiotic therapy.

Developing or worsening heart failure is a second complication that should be considered during short-term follow-up. Although new onset of heart failure caused by valvular dysfunction is unlikely during this period, valve function can deteriorate as a result of ongoing infection or mechanical stress unrelated to infection. In addition to physical examination, echocardiographic findings can support this diagnosis. If heart failure develops or worsens, the patient should be evaluated immediately for cardiac surgery.

Antibiotic toxicity still can occur after the completion of treatment and is the third complication that should be considered during short-term follow-up. Two drug-related adverse events are concerns. The first is delayed ototoxicity because of the previous use of aminoglycosides. Audiological and

Table 18. Care During and After Completion of Antimicrobial Treatment

Initiation before or at completion of therapy
Echocardiography to establish new baseline
Drug rehabilitation referral for patients who use illicit injection drugs
Education on the signs of endocarditis and need for antibiotic prophylaxis for certain dental/surgical/invasive procedures
Thorough dental evaluation and treatment if not performed earlier in evaluation
Prompt removal of intravenous catheter at completion of antimicrobial therapy
Short-term follow-up
At least 3 sets of blood cultures from separate sites for any febrile illness and before initiation of antibiotic therapy
Physical examination for evidence of heart failure
Evaluation for toxicity resulting from current/previous antimicrobial therapy
Long-term follow-up
At least 3 sets of blood cultures from separate sites for any febrile illness and before initiation of antibiotic therapy
Evaluation of valvular and ventricular function (echocardiography)
Scrupulous oral hygiene and frequent dental professional office visits

vestibular toxicity can develop despite the maintenance of appropriate serum drug concentrations during treatment. For patients receiving long-term aminoglycosides, particularly those with underlying renal or otic disorders, serial audiograms may be considered during therapy if feasible and available. No tools are routinely available for monitoring vestibular function, and patients should be told to report the onset of any symptoms of vestibular toxicity during or after treatment.

The second antibiotic-related adverse event is *Clostridium difficile* infection. Onset of diarrhea can be delayed as long as 4 weeks after the last dose of antibiotic. The hope is that prompt recognition and treatment of this infectious complication will diminish the likelihood of severe complications.

Recommendations

1. **Echocardiography is reasonable before or synchronous with completion of antimicrobial therapy to establish a new baseline for subsequent comparison (*Class IIa; Level of Evidence C*).**
2. **A referral to a program to assist in the cessation of drug use should be made for IDUs (*Class I; Level of Evidence C*).**
3. **Patients should be educated about the signs of endocarditis and urged to seek immediate medical attention should they develop (*Class I; Level of Evidence C*).**
4. **A thorough dental evaluation is reasonable, especially in patients deemed likely to require valve replacement, with all active sources of oral infection eradicated (*Class IIa; Level of Evidence C*).**
5. **Routine blood cultures are not recommended after the completion of antimicrobial therapy because the likelihood of a positive culture result in a patient who is otherwise without evidence of active infection is low (*Class III; Level of Evidence C*).**
6. **All indwelling intravenous catheters used to infuse antimicrobial treatment should be removed promptly at the end of therapy (*Class I; Level of Evidence C*).**
7. **For patients receiving long-term aminoglycosides, particularly those with underlying renal or otic disorders, serial audiograms may be considered during therapy if available (*Class IIb; Level of Evidence C*).**
8. **In the short-term follow-up, patients should be monitored for the development of several complications, including IE relapse and heart failure (*Class I; Level of Evidence C*).**
9. **Patients should be aware that relapses can occur and that new onset of fever, chills, or other evidence of systemic toxicity mandates immediate evaluation, including a thorough history and physical examination and ≥3 sets of blood cultures (*Class I; Level of Evidence C*).**
10. **Because of concerns for IE relapse, a thorough evaluation should be done to determine the cause of infection signs and symptoms (*Class I; Level of Evidence C*).**
11. **Empirical antimicrobial therapy for suspected infection should be avoided unless the patient's clinical condition (eg, sepsis) warrants it (*Class III; Level of Evidence C*).**
12. **It is reasonable to have patients who have completed therapy and do not have symptoms of systemic toxicity undergo an examination after completing antibiotic therapy (*Class IIa; Level of Evidence C*).**
13. **Developing or worsening heart failure is a common complication that should be monitored for during short-term follow-up (*Class I; Level of Evidence C*).**
14. **If heart failure develops or worsens, the patient should be evaluated immediately for cardiac surgery (*Class I; Level of Evidence B*).**
15. **Antibiotic toxicity still can occur after the completion of treatment and is a complication that should be considered during short-term follow-up (*Class I; Level of Evidence C*).**
16. **No tools are routinely available for monitoring vestibular function, and patients should be told to report the onset of any symptoms of vestibular toxicity during or after treatment (*Class I; Level of Evidence C*).**

Long-Term Follow-Up

Months to years after completion of medical therapy for IE, patients should have ongoing observation for and education about recurrent infection and delayed onset of worsening valve dysfunction (Table 18). Daily dental hygiene should be stressed, with serial evaluations by a dentist who is familiar with this patient population. Patients should be questioned about symptoms of heart failure, and a thorough physical examination should be done. Additional evaluation with echocardiography is indicated in selected patients with positive findings from history and physical examination. Patients should be instructed to seek immediate medical evaluation for persistent fever (Table 18). This is necessary because IE can mimic a variety of febrile illnesses. Blood cultures should be obtained. Antibiotic therapy should not be initiated for treatment of undefined febrile illnesses without blood cultures being obtained first. Antibiotics prescribed for nonspecific or unproved febrile syndromes are a major cause of (blood) culture-negative IE, and this practice should be strongly discouraged.

Recommendations

1. **Months to years after completion of medical therapy for IE, patients should have ongoing observation for and education about recurrent infection and delayed onset of worsening valve dysfunction (*Class I; Level of Evidence C*).**
2. **Daily dental hygiene should be stressed, with serial evaluations by a dentist who is familiar with this patient population (*Class I; Level of Evidence C*).**
3. **Patients should be questioned about symptoms of heart failure, and a thorough physical examination should be done (*Class I; Level of Evidence C*).**
4. **Additional evaluations with echocardiography should be obtained in selected patients with positive findings from history and physical examination (*Class I; Level of Evidence C*).**

5. **Patients should be instructed to seek immediate medical evaluation for fever, and blood cultures should be obtained (*Class I; Level of Evidence C*).**
6. **Antimicrobial therapy should not be initiated for the treatment of undefined febrile illnesses unless the patient's condition (eg, sepsis) warrants it (*Class III; Level of Evidence C*).**

Dental Management

A large, prospective study demonstrated a strong association between 3 indexes of oral hygiene and gingival disease and the incidence of bacteremia from IE-related species.[327] Poor oral hygiene results in gingivitis, which often leads to periodontitis, and it is likely that these 2 periodontal diseases are associated with community-acquired IE. Current evidence suggests that poor oral hygiene and periodontal diseases, not dental office procedures, are likely to be responsible for the vast majority of cases of IE that originate in the mouth.[328]

Regardless of the source of infection, inpatients with IE should be thoroughly evaluated by a dentist familiar with the potential role of the mouth in these cases. The optimal timing for this evaluation may be after the patient's cardiac status has stabilized and early enough that all invasive dental procedures can be accomplished during intravenous antibiotic therapy. The clinical examination should rule out periodontal inflammation and pocketing around the teeth and caries that will eventually result in pulpal infection. A full series of intraoral radiographs is required for the identification of caries and periodontal disease (eg, bone loss, tooth fractures). All of this is aimed at reducing the incidence and magnitude of bacteremia from any manipulation of the gingival tissues, including normal daily events such as brushing teeth and chewing food. Treatment invariably involves a thorough dental cleaning by a hygienist who will review with patients the importance of maintaining scrupulous oral hygiene.

Dental disease is almost entirely preventable if patients are compliant with 4 measures. First, the cause of both periodontal disease and caries is bacterial plaque accumulation on teeth, and prevention is dependent on keeping teeth free of plaque. Second, patients must understand that dietary measures are critically important in preventing the formation of plaque, especially in areas on the teeth that are difficult to keep clean. The degree to which sugar and other refined carbohydrates are eliminated from the diet will have a major impact on the growth of pathogenic bacterial species, some of which are responsible for IE. Third, routine follow-up with their family dentist is necessary for close monitoring of oral hygiene and the early identification and eradication of oral disease. Finally, the daily use of a high-concentration fluoridated toothpaste will help to ensure that the acid from plaque does not decalcify tooth structures and result in caries. A focus on all 4 measures should help to reduce the incidence of bacteremia and the risk for recurrent IE.

Recommendations

1. **Inpatients with IE should be thoroughly evaluated by a dentist to identify and eliminate oral diseases that predispose to bacteremia and may therefore contribute to the risk for recurrent IE (*Class I; Level of Evidence C*).**
2. **The clinical examination should focus on periodontal inflammation and pocketing around teeth and caries that may result in pulpal infection and subsequent abscess (*Class I; Level of Evidence C*).**
3. **A full series of intraoral radiographs will allow the identification of caries and periodontal disease and other disease (eg, tooth fractures) not evident from the physical examination. This should occur when the patient is able to travel to a dental facility (*Class I; Level of Evidence C*).**

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*Modest.

†Significant.

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*Modest.

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