AHA Scientific Statement

Infective Endocarditis

Diagnosis, Antimicrobial Therapy, and Management of Complications

A Statement for Healthcare Professionals From the Committee on Rheumatic Fever, Endocarditis, and Kawasaki Disease, Council on Cardiovascular Disease in the Young, and the Councils on Clinical Cardiology, Stroke, and Cardiovascular Surgery and Anesthesia, American Heart Association

Endorsed by the Infectious Diseases Society of America

Larry M. Baddour, MD, Chair; Walter R. Wilson, MD; Arnold S. Bayer, MD;
Vance G. Fowler, Jr, MD, MHS; Ann F. Bolger, MD; Matthew E. Levison, MD*; Patricia Ferrieri, MD;
Michael A. Gerber, MD; Lloyd Y. Tani, MD; Michael H. Gewitz, MD; David C. Tong, MD;
James M. Steckelberg, MD; Robert S. Baltimore, MD†; Stanford T. Shulman, MD; Jane C. Burns, MD;
Donald A. Falace, DMD‡; Jane W. Newburger, MD, MPH; Thomas J. Pallasch, DDS, MS;
Masato Takahashi, MD; Kathryn A. Taubert, PhD

Background—Despite advances in medical, surgical, and critical care interventions, infective endocarditis remains a disease that is associated with considerable morbidity and mortality. The continuing evolution of antimicrobial resistance among common pathogens that cause infective endocarditis creates additional therapeutic issues for physicians to manage in this potentially life-threatening illness.

Methods and Results—This work represents the third iteration of an infective endocarditis "treatment" document 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 updates recommendations for diagnosis, treatment, and management of complications of infective endocarditis. A multidisciplinary committee of experts drafted this document to assist physicians in the evolving care of patients with infective endocarditis in the new millennium. This extensive document is accompanied by an executive summary that covers the key points of the diagnosis, antimicrobial therapy, and management of infective endocarditis. For the first time, an evidence-based scoring system that is used by the American College of Cardiology and the American Heart Association was applied to treatment recommendations. Tables also have been included that provide input on the use of echocardiography during diagnosis and treatment of infective endocarditis, evaluation and treatment of culture-negative endocarditis, and short-term and long-term management of patients during and after completion of antimicrobial treatment. To assist physicians who care for children, pediatric dosing was added to each treatment regimen.

Conclusions—The recommendations outlined in this update should assist physicians in all aspects of patient care in the diagnosis, medical and surgical treatment, and follow-up of infective endocarditis, as well as management of associated complications. Clinical variability and complexity in infective endocarditis, however, dictate that these guidelines be used to support and not supplant physician-directed decisions in individual patient management. (***Circulation.*** **2005; 111:e394-e433.**)

Key Words: AHA Scientific Statements ■ endocardium ■ drugs ■ echocardiography ■ infection

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Infective endocarditis (IE), like most other syndromes of bacterial infection, has not escaped the impact of burgeoning antibiotic resistance among common pathogens. Since the most recent version of the American Heart Association (AHA) statement addressing treatment of IE was published in 1995,[1] unparalleled changes have occurred in antibiotic susceptibility among the 3 major bacterial causes of IE: streptococci, staphylococci, and enterococci. Reports from different patient populations indicate that multidrug resistance among viridans group streptococci is now characteristic of many colonizing and infecting strains.[2–4] Oxacillin resistance among *Staphylococcus aureus* (ORSA) isolates is at an all-time high at many tertiary care institutions. In addition, reports[5–7] from several areas of the United States indicate that community-acquired infection resulting from ORSA is frequently seen. Perhaps the most alarming event for *S aureus* is the development of intermediate- and high-level resistance to vancomycin, which was first described in Japan in 1997[8] and subsequently reported in several other areas, including the United States.[9–11] Vancomycin resistance among enterococci is characteristic of many of the nosocomial isolates. Increasing aminoglycoside resistance among enterococci has been reported[12] and has potential serious ramifications for treatment efficacy if it becomes more prevalent among enterococcal isolates causing IE.

Coupled with the recent deterioration of antibiotic susceptibility among these groups of Gram-positive cocci is the observation that *S aureus* has surpassed viridans group streptococci as the leading cause of IE in several recent case series.[13–15] This has resulted in an overall worsening of the average clinical course of patients with endocarditis and has been associated with an increased number of serious complications and higher mortality rates.

The AHA's recommendations for the treatment of IE have therefore been updated in this statement to better address these microbiological changes. The present Writing Committee conducted a comprehensive review of the literature published between 1990 and 2004 to assist the group in updating 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, congestive heart failure, emboli, stroke, conduction abnormalities, survival, pathogens, organisms, treatment, surgery, indications, valve replacement, valve repair, ambulatory care, trials, and *prevention.*

In addition, the present statement includes and updates sections of a separate statement[16] that addressed diagnostic and management issues, so that all aspects of endocarditis diagnosis and treatment would be more conveniently presented in a single citation. This work primarily addresses IE in adults; a more detailed review of the unique features of IE in children is available in another statement[17] from the AHA Committee on Rheumatic Fever, Endocarditis, and Kawasaki Disease. The Committee has also published a statement[18] on endocarditis that complicates electrophysiological (pacemakers, intracardiac defibrillators), ventricular assist, and other nonvalvular cardiac devices.

Evidence-Based Scoring System

This is the first time that the American College of Cardiology/American Heart Association evidence-based scoring system (see http://circ.ahajournals.org/manual/manual_IIstep6.shtml) has been incorporated into the AHA's endocarditis treatment guidelines. The purpose of the scoring system is to assist the clinician in interpreting these recommendations and formulating treatment decisions. The system is based on both a classification of recommendations and the level of evidence. Each treatment recommendation has been assigned a class and a level of evidence. The use of this system should support but not supplant the clinician's decision making in the management of individual patients' cases.

Classification of Recommendations

Class I: Conditions for which there is evidence, general agreement, or both that a given procedure or treatment is useful and effective.

Class II: Conditions for which there is conflicting evidence, a divergence of opinion, or both about the usefulness/efficacy of a procedure or treatment.

    Class IIa: Weight of evidence/opinion is in favor of usefulness/efficacy.

    Class IIb: Usefulness/efficacy is less well established by evidence/opinion.

Class III: Conditions for which there is evidence, general agreement, or both that the procedure/treatment is not useful/effective and in some cases may be harmful.

Level of Evidence

Level of Evidence A: Data derived from multiple randomized clinical trials

Level of Evidence B: Data derived from a single randomized trial or nonrandomized studies

Level of Evidence C: Consensus opinion of experts

Diagnosis

The diagnosis of IE is straightforward in patients with classic Oslerian manifestations: bacteremia or fungemia, evidence of active valvulitis, peripheral emboli, and immunologic vascular phenomena. In other patients, however, the classic peripheral stigmata may be few or absent. This may occur during acute courses of IE, particularly among patients who are injection drug users (IDUs), in whom IE is often the result of *S aureus* infection of right-sided heart valves. Acute IE may evolve too quickly for the development of immunologic vascular phenomena, which are more characteristic of subacute IE. In addition, valve lesions in acute right-sided IE usually do not create the peripheral emboli and immunologic vascular phenomena that can result from left-sided valvular involvement. Right-sided IE can cause septic pulmonary emboli, however.

The variability in clinical presentation of IE requires 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[19] from Duke University Medical Center proposed a diagnostic schema termed *the Duke criteria*, which stratified patients with suspected IE into 3 categories: "definite" cases, identified either clinically or pathologically (IE proved at surgery or autopsy); "possible" cases (not meeting the criteria for definite IE); and "rejected" cases (no pathological evidence of IE at autopsy or surgery, rapid resolution of the clinical syndrome with either no treatment or short-term antibiotic therapy, or a firm alternative diagnosis).

A diagnosis of IE is based on the presence of either major or minor clinical criteria. Major criteria in the Duke strategy included IE documented by data obtained at the time of open heart surgery or autopsy (pathologically definite) or by well-defined microbiological criteria (high-grade bacteremia or fungemia) plus echocardiographic data (clinically definite). To maintain the high specificity of blood culture results for IE, the Duke criteria required that some patients with high-grade bacteremia with common IE pathogens also fulfill secondary criteria. For example, bacteremia resulting from viridans streptococci and members of the HACEK group of fastidious Gram-negative rods, which are classic IE pathogens but uncommonly seen in patients without IE, are given primary diagnostic weight. In contrast, *S aureus* and *Enterococcus faecalis* commonly cause both IE and non-IE bacteremias. The Duke criteria therefore gave diagnostic weight to bacteremia with staphylococci or enterococci only when they were community acquired and without an apparent primary focus; these latter types of bacteremia have the highest risk of being associated with IE.[19,20]

The Duke criteria incorporated echocardiographic findings in the diagnostic strategy. Major diagnostic weight was given to only 3 typical echocardiographic findings: mobile, echodense masses attached to valvular leaflets or mural endocardium; periannular abscesses; or new dehiscence of a valvular prosthesis (see Echocardiography).

Six common but less specific findings of IE also were included as minor criteria in the original Duke schema: intermittent bacteremia or fungemia, fever, major embolic events, nonembolic vascular phenomena, underlying valvular

TABLE 1A. Definition of Infective Endocarditis According to the Modified Duke Criteria

Definite infective endocarditis

  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; or

    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 days; or

    No pathological evidence of IE at surgery or autopsy, with antibiotic therapy for ≤4 days; or

    Does not meet criteria for possible IE as above

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TABLE 1B. Definition of Terms Used in the Modified Duke Criteria for the Diagnosis of Infective Endocarditis

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 of 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; or abscess; or new partial dehiscence of prosthetic valve; new valvular regurgitation (worsening or changing or preexisting 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's lesions

  Immunologic phenomena: glomerulonephritis, Osler's nodes, Roth's spots, and rheumatoid factor

  Microbiological evidence: positive blood culture but does not meet a major criterion as noted above* or serological evidence of active infection with organism consistent with IE

  Echocardiographic minor criteria eliminated

Modifications shown in boldface.
*Excludes single positive cultures for coagulase-negative staphylococci and organisms that do not cause endocarditis.
TEE indicates transesophageal echocardiography; TTE, transthoracic echocardiography.
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disease or injection drug use, and echocardiographic abnormalities that fell short of typical valvular vegetations, abscesses, or dehiscence. Clinically definite IE by the Duke criteria required the presence of 2 major criteria, 1 major criterion and 3 minor criteria, or 5 minor criteria. In the mid- to late 1990s, direct analyses of the Duke criteria were made in 11 major studies,[21–32] including nearly 1700 patients composed of geographically and clinically diverse groups (adult, pediatric, older adult [>60 years old], patients from the community, patients with and without injection drug use, and patients with both native and prosthetic valves). These studies[21–32] 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% to 90%) between the Duke criteria and clinical assessment by infectious disease experts blinded to underlying IE risk factors.[33]

Several refinements have been made recently to both the major and minor Duke criteria. As noted above, in the original Duke criteria, bacteremia resulting from *S aureus* was considered to fulfill a major criterion only if it was community acquired because ample literature has suggested that this parameter is an important surrogate marker for underlying IE.[20] An increasing number of contemporary studies, however, have documented IE in patients experiencing nosocomial staphylococcal bacteremia. For example, of 59 consecutive patients with *S aureus* IE, 45.8% had nosocomially acquired infections and 50.8% had a removable focus of infection.[34] In a more recent analysis of 262 patients at 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 1A and 1B) recommend the inclusion of *S aureus* bacteremia as a major criterion, regardless of whether the infection is nosocomially acquired (with or without a removable source of infection) or community acquired.[35]

Specific serological data have now been included to more precisely establish the etiologic agents of "culture-negative" endocarditis (as a surrogate for positive blood cultures). Such serological criteria would be applied in circumstances in which the etiologic organism is slow growing or requires special culture media (eg, *Brucella*) or in which the organism is not readily cultivated in most clinical microbiology laboratories (eg, *Coxiella burnetii*). For example, in the original Duke criteria, a positive serology for Q fever was considered a minor microbiological criterion. Subsequently, Fournier et al[36] 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. An anti–phase I immunoglobulin G antibody titer ≥1:800 or a single blood culture positive for *C burnetii* should be major criteria in the modified Duke schema.

Serological tests and polymerase chain reaction (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 and uncertainties for proposing antibody titers that are positive for *Bartonella* and *Chlamydia* species or for PCR-based testing for *T whippelii* as major criteria in the Duke schema. For example, endocarditis infections caused by *Bartonella* and *Chlamydia* species often are indistinguishable in serological test results because of cross-reactions.[37] PCR-based tests have low sensitivity unless the tests are performed directly on cardiac valvular tissue.[38–40] Moreover, few centers provide timely PCR-based testing for these rare causes of IE. Therefore, the inclusion of such 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, 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. These additional parameters have not been formally integrated into the modified Duke criteria, however.[41]
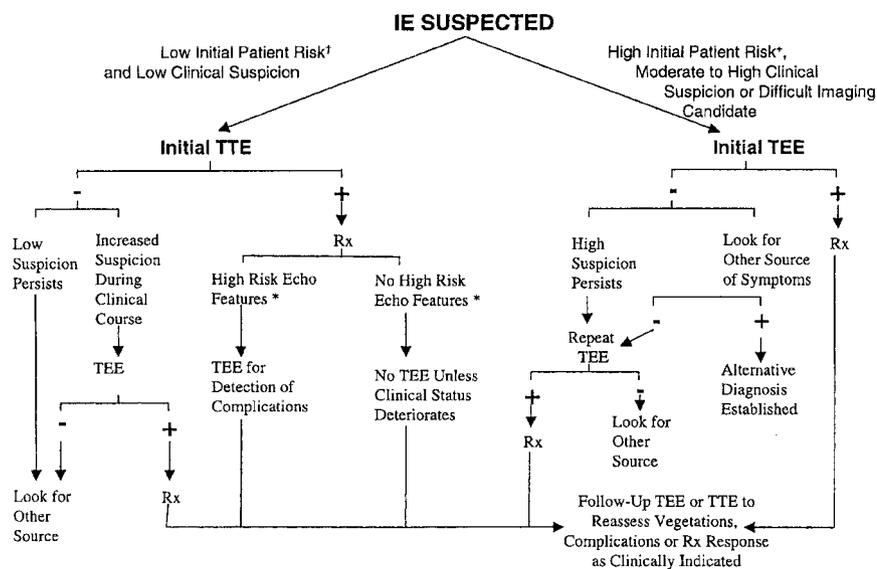
One minor criterion from the original Duke schema, "echocardiogram consistent with IE but not meeting major criterion," has been reevaluated. This criterion originally was used in cases in which nonspecific valvular thickening was detected by transthoracic echocardiography (TTE). In a reanalysis of patients 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.

Finally, adjustment of the Duke criteria to require a minimum of 1 major and 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 that category. This approach was used in a series of patients initially categorized as possible IE by the original Duke criteria. With the guidance of the "diagnostic floor," a number of these cases were reclassified as "rejected" for IE.[35] Follow-up in these reclassified patients documented the specificity of this diagnostic schema because no patients developed IE during the subsequent 12 weeks.

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 primarily 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. Because IE is a heterogeneous disease with highly variable clinical presentations, the use of 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 clinical guide for diagnosing IE and must not replace clinical judgment. Clinicians may appropriately and wisely decide whether to treat or not treat an individual patient, regardless of whether they meet or fail to meet the criteria for definite or possible IE by the Duke schema. We believe, however, that the modifications of the Duke criteria (Tables 1A and 1B) 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 endocarditis must be made as soon as possible to initiate therapy and identify patients at high risk for complications who may be best managed by early surgery. In cases with a high suspicion of endocarditis, based on either the clinical picture or the patient's risk factor profile, such as injection drug use or a history of previous endocarditis, the presumption of endocarditis 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 duration of therapy. Although the use of case definitions to establish a diagnosis of IE should not replace clinical judgment,[42] the recently modified Duke criteria[35] have been useful in both epidemiological and clinical trials and in individual patient management. Clinical, echocardiographic, and microbiological criteria (Tables 1A and 1B) are used routinely to support a diagnosis of IE, and they do not rely on histopathologic confirmation of resected valvular material or arterial embolus. If suggestive features are absent, then a negative echocardiogram may prompt a more thorough search for alternative sources of fever and sepsis. In light of these important functions, echocardiography should be performed urgently in patients suspected of having endocarditis.

IE SUSPECTED

An approach to the diagnostic use of echocardiography (echo). *High-risk echocardiographic features include large and/or mobile vegetations, valvular insufficiency, suggestion of perivalvular extension, or secondary ventricular dysfunction (see text). †For example, a patient with fever and a previously known heart murmur and no other stigmata of IE. +High initial patient risks include prosthetic heart valves, many congenital heart diseases, previous endocarditis, new murmur, heart failure, or other stigmata of endocarditis. Rx indicates antibiotic treatment for endocarditis. Reproduced with permission from: Bayer AS, Bolger AF, Taubert KA, Wilson W, Steckelberg J, Karchmer AW, Levison M, Chambers HF, Dajani AS, Gewitz MH, Newburger JW, Gerber MA, Shulman ST, Pallasch TJ, Gage TW, Ferrieri P. Diagnosis and Management of Infective Endocarditis and Its Complications. *Circulation*. 1998;98:2936–2948.

Echocardiography

Echocardiography is central to the diagnosis and management of patients with IE. As previously stated, 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.

Echocardiography should be performed in all cases of suspected IE (Class I, Level of Evidence: A). Whether TTE or TEE should be performed first depends on the clinical scenario (Figure). If the clinical suspicion is relatively low or imaging is likely to be of good quality (many children), then it is reasonable to perform TTE. When imaging is difficult or poor, TEE should be considered. If any circumstances preclude securing optimal echocardiographic windows, including chronic obstructive lung disease, previous thoracic surgery, morbid obesity, or other conditions, then TEE should be performed instead of TTE. If 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 (prosthetic valve, staphylococcal bacteremia, or new atrioventricular block), then 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 more sensitive than TTE for the detection of vegetations and abscesses.[43] In addition, 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 perivalvar area where those infections often start.[44] Although cost-effectiveness calculations suggest that TEE should be the first examination in adults with suspected IE (Table 2), particularly in the setting of staphylococcal bacteremia,[45,46] many patients are not candidates for immediate TEE because of oral intake during 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.

Many findings identified by TEE also can be detected on transthoracic views. 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. Some findings, such as tricuspid vegetations or abnormalities of the right ventricular outflow tract, may occasionally be better visualized with TTE than with TEE.[47]

Both TEE and TTE may produce false-negative results if vegetations are small or have already embolized.[48] Even TEE may miss initial perivalvular abscesses, particularly when the study is performed early in the patient's illness.[49] In such cases, the incipient abscess may be seen only as nonspecific perivalvular thickening, which on repeat imaging across several days may become recognizable as it expands and cavitates. Similarly, perivalvular fistulae 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's excrescences may be indistinguishable from active changes on the valves. As echocardiographic technology improves, with higher frequencies and refined beam-forming technology, more subtle findings continue to be recognized and may add to the category of indeterminate findings. One approach to minimizing confusion from these structures is to exploit the high frame rates that are often available with current equipment to improve temporal resolution and clearly visualize rapidly moving structures such as microcavitations 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 2. 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 7–10 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; TTE, transthoracic echocardiography.

(Table 3). These features include large vegetations, severe valvular insufficiency, abscess cavities or pseudoaneurysms, valvular perforation or dehiscence, and evidence of decompensated heart failure.[16] The ability of echocardiographic features to predict embolic events is limited.[50–52] The greatest risk appears to occur with large vegetations (>10 mm in diameter) on the anterior mitral leaflet.[53] Vegetation size and mobility must be taken into account, along with bacteriologic factors and other indications for surgery, when considering early surgery to avoid embolization.[54]

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 2; Class I, Level of Evidence: A). Among patients with an initial positive TTE and a high risk for cardiac complications including perivalvular extension of infection, TEE should be obtained as soon as possible (Class I, Level of Evidence: A). Repeating TEE 7 to 10 days after an initial "negative" result is often advisable (Class I, Level of Evidence: B) when clinical suspicion of IE persists.[55] In some cases, vegetations may reach detectable size in the interval, or abscess cavities or fistulous tracts may become clear. 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.[55]

Repeat TEE also may be useful when a patient with an initially positive TEE develops worrisome clinical features during antibiotic therapy (Class I, Level of Evidence: A). Unexplained progression of heart failure symptoms, change in cardiac murmurs, and new atrioventricular block or arrhythmia should prompt emergent evaluation by TEE if possible or by TTE if necessary to minimize delay.

Intraoperative Echocardiography

Preoperative surgical planning for patients with IE will benefit from echocardiographic delineation of the mechanisms of valvular dysfunction or regions of myocardial disruption (Table 3). The use of aortic homografts is facilitated by preoperative estimates of annular size, which allow the selection of appropriately sized donor tissues.[56,57] Intraoperatively, echocardiographic goals include assessment of not only 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 recognized and documented to avoid later confusion about whether the 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 have been closed.[58] Afterload augmentation, however, may not mimic actual awake physiology and may still lead occasionally to an inaccurate evaluation of the awake postoperative state.

Echocardiography at Completion of Therapy

All patients who have experienced an episode of endocarditis remain at high risk for recurrent infection indefinitely. It is extremely important for the future care of these patients to establish a new baseline for valvular morphology, including the presence of vegetations, ventricular function, 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 2). TTE is preferable (Class IIb, Level of Evidence: C) for this because measurements of vegetation size are more reproducible and spectral Doppler interrogation often 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 valvular dysfunction at the end of otherwise successful treatment; clearly, they will require eventual surgery. Posttreatment echocardiography can guide both medical management and the discussion of the appropriate timing of the intervention.

Antimicrobial Therapy

Antimicrobial Treatment Perspectives

Results of clinical efficacy studies support the use of most treatment regimens described in these guidelines (Class I,

Level of Evidence: A). Other recommendations (Class IIa, Level of Evidence: C) listed herein are based largely on in vitro data and consensus opinion and include the following 3 criteria. First, the counting of days of recommended duration of therapy should begin on the first day on which blood cultures were negative in cases in which blood cultures were initially positive. At least 2 sets of blood cultures should be obtained every 24 to 48 hours until bloodstream infection is cleared. Second, for patients with native valve endocarditis who undergo valve resection with prosthetic valve replacement, the postoperative treatment regimen should be one that is recommended for prosthetic valve treatment rather than one that is recommended for native valve treatment. If the resected tissue is culture positive, then an entire course of antimicrobial therapy is recommended after valve resection. If the resected tissue is culture negative, then the recommended duration of prosthetic valve treatment should be given less the number of days of treatment administered for native valve infection before valve replacement. Third, in regimens that contain combination antimicrobial therapy, it is important to administer agents at the same time or temporally close together to maximize the synergistic killing effect on an infecting pathogen.

Overview of Viridans Group Streptococci, *Streptococcus bovis*, *Abiotrophia defectiva*, *Granulicatella* Species, and *Gemella* Species

Viridans group streptococci, or α-hemolytic streptococci, are common etiologic agents that are the cause of community-acquired native valve endocarditis in patients who are not intravenous drug users (IDUs). The taxonomy of viridans group streptococci is evolving. The species that most commonly cause endocarditis 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 cause hematogenously disseminated infection (eg, myocardial and visceral abscesses, septic arthritis, vertebral osteomyelitis). Consequently, the duration of antimicrobial treatment of endocarditis caused by these organisms may need to be longer than that for endocarditis caused by other α-hemolytic streptococci. In addition, although the *S intermedius* group usually is sensitive to penicillin, some strains may exhibit variable penicillin resistance. Species of *Gemella* (*morbillorum*, *bergeriae*, *sanguinis*, and *hemolysans*) share some physiological characteristics with nutritionally variant streptococci, and endocarditis caused by these organisms should be treated with more aggressive combination therapy such as that used for nutritionally variant streptococcal endocarditis (see below). The recommendations that follow are intended to assist clinicians in selecting appropriate antimicrobial therapy for patients with endocarditis caused by viridans group streptococci and *S bovis* (a nonenterococcal penicillin-susceptible group D streptococcus). *S bovis* expresses the group D antigen, but it can be distinguished from group D *Enterococcus* by appropriate biochemical tests.

TABLE 3. 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 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.

Patients with either *S bovis* bacteremia or endocarditis should undergo colonoscopy to determine whether malignancy or other mucosal lesions are present.

Certain viridans group streptococci have biological characteristics that may complicate diagnosis and therapy. Some strains, such as the newly named *Abiotrophia defectiva* and *Granulicatella* species (*G elegans*, *G adiacens*, *G paraadiacens*, and *G balaenopterae*; formerly known as nutritionally variant streptococci), have nutritional deficiencies that hinder their growth in routine laboratory culture media. Such organisms may require broth supplemented with pyridoxal hydrochloride or cysteine. In addition, some strains of viridans group streptococci may exhibit a laboratory phenomenon called "penicillin tolerance." For tolerant strains, the minimum bactericidal concentration (MBC) of penicillin greatly exceeds the minimum inhibitory concentration (MIC) (usually by >32-fold). These strains are killed more slowly by penicillin in animal models of endocarditis.[59] There are no published data on the influence of tolerance on the outcome of endocarditis in humans, however, and we believe that laboratory demonstration of tolerance has no implication for the selection of antimicrobial therapy for endocarditis resulting from viridans group streptococci. Accordingly, the determination of MBC for these microorganisms is not routinely recommended (Class IIa, Level of Evidence: C).

It should be noted that treatment regimens outlined for viridans group streptococci, *S bovis*, *A defectiva*, *Granulicatella* species, and *Gemella* species are subdivided into categories based on penicillin MIC data. These subdivisions are not based on Clinical and Laboratory Standards Institute (CLIS, formally known as the National Committee for Clinical Laboratory Standards, or NCCLS) recommended break points that are used to define penicillin susceptibility.

TABLE 4.   Therapy of Native Valve Endocarditis Caused by Highly Penicillin-Susceptible Viridans Group Streptococci and *Streptococcus bovis*

Regimen	Dosage* and Route	Duration, wk	Strength of Recommendation	Comments
Aqueous crystalline penicillin G sodium **or**	12–18 million U/24 h IV either continuously or in 4 or 6 equally divided doses	4	IA	Preferred in most patients >65 y or patients with impairment of 8th cranial nerve function or renal function
Ceftriaxone sodium	2 g/24 h IV/IM in 1 dose	4	IA	
	Pediatric dose†: penicillin 200 000 U/kg per 24 h IV in 4–6 equally divided doses; ceftriaxone 100 mg/kg per 24 h IV/IM in 1 dose			
Aqueous crystalline penicillin G sodium **or**	12–18 million U/24 h IV either continuously or in 6 equally divided doses	2	IB	2-wk regimen not intended for patients with known cardiac or extracardiac abscess or for those with creatinine clearance of <20 mL/min, impaired 8th cranial nerve function, or *Abiotrophia, Granulicatella,* or *Gemella* spp infection; gentamicin dosage 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; nomogram used for single daily dosing§
Ceftriaxone sodium **plus**	2 g/24 h IV/IM in 1 dose	2	IB	
Gentamicin sulfate‡	3 mg/kg per 24 h IV/IM in 1 dose	2		
	Pediatric dose: penicillin 200 000 U/kg per 24 h IV in 4–6 equally divided doses; ceftriaxone 100 mg/kg per 24 h IV/IM in 1 dose; gentamicin 3 mg/kg per 24 h IV/IM in 1 dose or 3 equally divided doses‖			
Vancomycin hydrochloride¶	30 mg/kg per 24 h IV in 2 equally divided doses not to exceed 2 g/24 h unless concentrations in serum are inappropriately low	4	IB	Vancomycin therapy recommended only for patients unable to tolerate penicillin or ceftriaxone; vancomycin dosage should be adjusted to obtain peak (1 h after infusion completed) serum concentration of 30–45 μg/mL and a trough concentration range of 10–15 μg/mL
	Pediatric dose: 40 mg/kg per 24 h IV in 2–3 equally divided doses			

Minimum inhibitory concentration ≤0.12 μg/mL.

*Dosages recommended are for patients with normal renal function.

†Pediatric dose should not exceed that of a normal adult.

‡Other potentially nephrotoxic drugs (eg, nonsteroidal antiinflammatory 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 due to viridans group streptococci, as a second option, gentamicin can be administered daily in 3 equally divided doses.

§See reference 280 in full statement. Although this reference outlines dosing for gentamicin use at 7 mg/kg/dose for treatment in other types of infection syndromes, the nomogram was selected as an example for use with gentamicin dosing of 3 mg/kg/dose in this table to direct dosing in patients with underlying renal dysfunction. Currently, there is no other formal address of drug concentration monitoring with this gentamicin dosage.

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

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

Highly Penicillin-Susceptible Viridans Group Streptococci and *S bovis* (MIC ≤0.12 μg/mL)

Bacteriologic cure rates ≥98% may be anticipated in patients who complete 4 weeks of therapy with parenteral penicillin or ceftriaxone for endocarditis caused by highly penicillin-susceptible viridans group streptococci or *S bovis*.[60,61] Ampicillin is an 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 viridans group streptococci and *S bovis*. The combination of penicillin or ceftriaxone together with gentamicin results in synergistic killing in vivo in animal models of viridans group streptococcal or *S bovis* experimental endocarditis.

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.[61,62] 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 together with an aminoglycoside administered in daily divided doses.[62,63] The 2-week regimen of penicillin or ceftriaxone combined with single daily-dose gentamicin is appropriate for uncomplicated cases of endocarditis caused by highly penicillin-susceptible viridans group streptococci or *S bovis* in patients at low risk for adverse events caused by gentamicin therapy (Table 4). 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 β-lactam–containing regimens shown in Table 4 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.[60,64]

TABLE 5.   Therapy of Native Valve Endocarditis Caused by Strains of Viridans Group Streptococci and *Streptococcus bovis* Relatively Resistant to Penicillin

Regimen	Dosage* 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	IB	Patients with endocarditis caused by penicillin-resistant (MIC >0.5 μg/mL) strains should be treated with regimen recommended for enterococcal endocarditis (see Table 9)
or				
Ceftriaxone sodium	2 g/24 h IV/IM in 1 dose	4	IB	
plus				
Gentamicin sulfate†	3 mg/kg per 24 h IV/IM in 1 dose	2		
	Pediatric dose‡: penicillin 300 000 U/24 h IV in 4–6 equally divided doses; ceftriaxone 100 mg/kg per 24 h IV/IM in 1 dose; gentamicin 3 mg/kg per 24 h IV/IM in 1 dose or 3 equally divided doses			
Vancomycin hydrochloride‡	30 mg/kg per 24 h IV in 2 equally divided doses not to exceed 2 g/24 h, unless serum concentrations are inappropriately low	4	IB	Vancomycin§ therapy recommended only for patients unable to tolerate penicillin or ceftriaxone therapy
	Pediatric dose: 40 mg/kg 24 h in 2 or 3 equally divided doses			

Minimum inhibitory concentration (MIC) >0.12 μg/mL–≤0.5 μg/mL.

*Dosages recommended are for patients with normal renal function.

†See Table 4 for appropriate dosage of gentamicin. Although it is preferred that gentamicin (3 mg/kg) be given as a single daily dose to adult patients with endocarditis due to viridans group streptococci, as a second option, gentamicin can be administered daily in 3 equally divided doses.

‡Pediatric dose should not exceed that of a normal adult.

§See Table 4 for appropriate dosage of vancomycin.

For patients who are unable to tolerate penicillin or ceftriaxone, vancomycin is the most effective alternative. Prolonged intravenous use of vancomycin may be complicated by thrombophlebitis, rash, fever, anemia, thrombocytopenia, and, rarely, ototoxic reactions. Vancomycin should be infused for ≥1 hour to reduce the risk of the histamine release–associated "red man" syndrome.

Viridans Group Streptococci and *S bovis* With Penicillin MIC >0.12 to ≤0.5 μg/mL

Penicillin resistance in vitro is increasing in frequency among strains of viridans group streptococci and *S bovis*. Table 5 shows regimens recommended for native valve endocarditis caused by relatively penicillin-resistant strains (MIC >0.12 to ≤0.5 μg/mL). For patients with viridans group streptococcal or *S bovis* endocarditis, penicillin or ceftriaxone should be administered for 4 weeks together with single daily-dose gentamicin for the first 2 weeks of treatment.

Abiotrophia defectiva and *Granulicatella* Species, *Gemella* Species, and Viridans Group Streptococci With Penicillin MIC >0.5 μg/mL

The determination of antimicrobial susceptibilities of *A defectiva*, *Granulicatella* species (formerly known as nutritionally variant streptococci), and *Gemella* species is often technically difficult, and the results may not be accurate. Moreover, endocarditis caused by these microorganisms has been more difficult to cure microbiologically than has endocarditis caused by a strain of non-nutritionally variant group viridans streptococci.[65] For these reasons, patients with endocarditis caused by *A defectiva*, *Granulicatella* species, and *Gemella* species should be treated with a regimen that is recommended for enterococcal endocarditis (Table 9). Patients with endocar-

ditis caused by a microorganism with an MIC to penicillin >0.5 μg/mL should be treated with a regimen recommended for enterococcal endocarditis (Table 9). When vancomycin is the chosen antibiotic, the addition of gentamicin is not necessary.

Endocarditis of Prosthetic Valves or Other Prosthetic Material Caused by Viridans Group Streptococci and *S bovis*

Patients with endocarditis complicating prosthetic valves or other prosthetic material caused by a highly penicillin-susceptible strain (MIC ≤0.12 μg/mL) should receive 6 weeks of therapy with penicillin or ceftriaxone with or without gentamicin for the first 2 weeks (Table 6). Endocarditis caused by a strain that is relatively or highly resistant to penicillin (MIC >0.12 μg/mL) should receive 6 weeks of therapy with a combination of penicillin or ceftriaxone together with gentamicin. Vancomycin therapy is recommended only for patients who are unable to tolerate penicillin or ceftriaxone.

S pneumoniae, *S pyogenes*, and Groups B, C, and G Streptococci

Endocarditis caused by these streptococci is relatively uncommon. There are few published reports of large series of cases evaluating therapeutic regimens for endocarditis caused by these microorganisms. When *S pneumoniae* is recovered from a patient with endocarditis, the organism should be tested for penicillin susceptibility. Patients with endocarditis caused by highly penicillin-susceptible *S pneumoniae* should receive 4 weeks of antimicrobial therapy with penicillin, cefazolin, or ceftriaxone. Vancomycin should be administered only to patients who are unable to tolerate β-lactam therapy. Increasingly, *S pneumoniae* with intermediate peni-

cillin resistance (MIC >0.1 to 1.0 μg/mL) or high penicillin resistance (MIC ≥2.0 μg/mL) is being recovered from patients with bacteremia.[66] Moreover, cross-resistance of pneumococci to other antimicrobial agents, such as cephalosporins, macrolides, fluoroquinolones, carbapenems, and even vancomycin, is increasing in frequency. In one multicenter study[67] with a relatively large (n=24) number of patients with IE caused by *S pneumoniae* resistant to penicillin (MIC 0.1 to 4 μg/mL), patients were evaluated and compared with 39 patients who were infected with penicillin-susceptible strains. Several observations were made. Infection by penicillin-resistant strains did not worsen prognosis. High-dose penicillin or a third-generation cephalosporin can be used in patients with penicillin-resistant infection and without meningitis. In patients with IE and meningitis, high doses of cefotaxime may be used. If the isolate is resistant (MIC ≥2 μg/mL) to cefotaxime, then the addition of vancomycin and rifampin should be considered. Of course, 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 endocarditis should be coordinated in consultation with an infectious diseases specialist.

Results of logistic regression analysis of clinical variables from cases of pneumococcal endocarditis demonstrate the potential value of valve replacement in preventing early death. The increased number of patients undergoing valve replacement surgery surveyed in a multicenter study from France[68] may account in part for the improved outcome in recent years.

Aqueous crystalline penicillin G administered intravenously (IV) for 4 weeks is the recommended treatment, based on limited published data for the treatment of endocarditis caused by *S pyogenes*. Cefazolin or ceftriaxone is an acceptable alternative to penicillin. Vancomycin therapy should be administered only to patients who are unable to tolerate a β-lactam antibiotic. In general, strains of group B, C, and G streptococci are slightly more resistant to penicillin than are strains of group A streptococci. Some authorities recommend the addition of gentamicin to penicillin or a cephalosporin 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.[69,70] There is a clinical impression[71,72] that early cardiac surgery intervention has improved overall survival rates among more recently treated patients with β-hemolytic streptococcal endocarditis as compared with patients treated decades ago. Because of the relative infrequency of endocarditis caused by these microorganisms, consultation with an infectious diseases specialist for the treatment of these patients is recommended.

Staphylococci

IE may be caused by staphylococci that are coagulase positive (*S aureus*) or coagulase negative (*S epidermidis* and various other species). Traditionally, it has been believed that coagulase-positive staphylococci cause primarily native valve endocarditis, whereas coagulase-negative staphylococci (CoNS) are thought to cause primarily prosthetic valve endocarditis, but considerable overlap exists. For example, in

a recent multicenter, prospective, observational investigation involving >1000 consecutive patients with definite IE from >20 countries, *S aureus* was the most common cause of prosthetic valve IE (25.8% of 214 cases), whereas 64 (8%) cases of native valve endocarditis resulted from CoNS.[73] Thus, it is important to consider both pathogens when a patient with suspected endocarditis has a preliminary blood culture that suggests staphylococci by Gram's stain interpretation.

S aureus

S aureus is the most common cause of IE in much of the developed world.[74] This increase is primarily a consequence of healthcare contact (eg, intravascular catheters, surgical wounds, indwelling prosthetic devices).[73–76] Increasing rates of oxacillin resistance in both hospital and community settings and the recovery of clinical *S aureus* isolates both partially[77] and fully[78] resistant to vancomycin have complicated the treatment of *S aureus* endocarditis. In nonaddicts, endocarditis arising from *S aureus* primarily involves the left side of the heart and is associated with mortality rates ranging from 25% to 40%. *S aureus* endocarditis in IDUs often involves the tricuspid valve. Cure rates for right-sided *S aureus* endocarditis in IDUs are high (>85%) and may be achieved with relatively short courses of treatment (<4 weeks; see below).

Coagulase-Negative Staphylococci

Although CoNS are one of the most common causes of prosthetic valve endocarditis,[79] the role of CoNS as pathogens on native valves is well documented.[80–82] Most of the patients with native valve endocarditis had documented underlying valvular abnormalities, particularly mitral valve prolapse. Their clinical course is typically indolent with a satisfactory response to medical or surgical therapy.

An important subset of patients with CoNS IE has been identified recently: 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.[83–89] Most experts recommend that endocarditis caused by this organism 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. The microbiological differentiation of *S lugdunensis* from other CoNS may be difficult,[89] and many laboratories do not have the capability to assign species identification to CoNS isolates.

Endocarditis Caused by Staphylococci in the Absence of Prosthetic Valves

Right-Sided Endocarditis in IDUs

The addition of gentamicin to nafcillin accelerates the killing of methicillin-susceptible staphylococci in vitro. In experimentally induced cardiac vegetations, the data support the use of combined gentamicin-nafcillin therapy in humans with right-sided IE. For example, in IDUs with uncomplicated right-sided *S aureus* endocarditis (no evidence of renal

failure, extrapulmonary metastatic infections, aortic or mitral valve involvement, meningitis, or infection by oxacillin-resistant *S aureus*, or ORSA), combined β-lactam-aminoglycoside short-course (2 weeks) therapy was effective in several studies.[90–94] In one study,[92] such combination therapy had excellent efficacy in HIV-infected patients (most with CD4 counts >300 ×10^{6} cells) and in those who had large tricuspid valve vegetations (>10 mm in diameter). A more recent study showed that a 2-week monotherapy regimen of cloxacillin was equivalent to that of cloxacillin plus gentamicin administered for 2 weeks.[93] By contrast, glycopeptide (teicoplanin or vancomycin) plus gentamicin-based short-course regimens appeared to be less effective for right-sided *S aureus* IE caused by either oxacillin-susceptible *S aureus* (OSSA) or ORSA strains.[92] These glycopeptides may be less effective because of limited bactericidal activity, poor penetration into vegetations, and increased drug clearance among IDUs.[95] Thus, the weight of evidence suggests that parenteral β-lactam short-course therapy, with or without aminoglycoside, is adequate for the treatment of uncomplicated OSSA right-sided IE. In contrast, glycopeptide therapy (with or without adjunctive gentamicin) often requires more prolonged treatment regimens.

In patients who will not comply with a course of parenteral antibiotic therapy, oral treatment may be an option. Two studies have evaluated the use of predominantly oral 4-week antibiotic regimens (ciprofloxacin plus rifampin) for the therapy of uncomplicated right-sided *S aureus* endocarditis in IDUs.[96,97] In each study, including one in which >70% of patients were HIV-seropositive,[97] cure rates were >90%.

Endocarditis in Non-IDUs
Anecdotal case reports in nonaddicts with staphylococcal endocarditis suggest that the use of gentamicin-nafcillin therapy may be of benefit in patients who fail to respond to monotherapy with nafcillin.[98] 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 endocarditis caused by *S aureus*.[99] Nafcillin-gentamicin therapy reduced the duration of bacteremia by ≈1 day as compared with nafcillin monotherapy. The combination therapy did not reduce mortality or the frequency of cardiac complications, however, but it did result in an increased frequency of gentamicin-associated nephrotoxicity. Many authorities thus recommend the use of combination therapy for the first 3 to 5 days of therapy for left-sided *S aureus* endocarditis, especially in fulminant cases (Table 7). Experience to date with gentamicin in the treatment of left-sided native valve *S aureus* endocarditis has involved multiple daily-dosing schedules. Thus, pending further clinical data, when gentamicin is used for this indication, it should be administered whenever possible in a 2- or 3-times-daily dosing schedule, with a total daily gentamicin dose not to exceed 3 mg/kg in patients with normal renal function. Gentamicin therapy should be discontinued after the first 3 to 5 days of therapy.

Thus, in summary, for both right- and left-sided *S aureus* endocarditis, there is little compelling evidence that adjunctive gentamicin therapy, especially beyond 3 to 5 days,

confers additional clinical benefit[100] and is optional. Rarely, staphylococci are susceptible to penicillin and do not produce β-lactamase; these patients may be treated with penicillin.

There are no evidence-based data that demonstrate the most appropriate duration of nafcillin therapy for treatment of left-sided native valve IE caused by OSSA. For patients with uncomplicated infection, 4 weeks of therapy should be sufficient. For patients with complications of IE, such as perivalvular abscess formation and septic metastatic complications, 6 weeks of nafcillin should be administered.

Therapy for staphylococcal endocarditis in patients truly unable to tolerate a β-lactam is problematic. A recent decision analysis concluded that patients with a questionable history of immediate-type hypersensitivity to penicillin and endocarditis caused by oxacillin-sensitive *S aureus* should be skin tested before starting antibiotic therapy.[101] A first-generation cephalosporin is recommended in patients with nonanaphylactoid penicillin allergies (eg, simple skin rash). Although cefazolin may be more susceptible to β-lactamase–mediated hydrolysis than nafcillin[102] and less effective in the treatment of OSSA experimental endocarditis,[103] the clinical significance of these observations is unknown, and many experts regularly use cefazolin in *S aureus* IE. Vancomycin therapy is recommended for *S aureus* endocarditis in patients with anaphylactoid β-lactam allergies; however, recent studies reported suboptimal outcomes with vancomycin therapy for serious *S aureus* infections.[104–107] Clindamycin was used to treat >60 cases of staphylococcal endocarditis in 1 study but was associated with an unacceptable rate of relapse, and its use is not routinely recommended (Class III, Level of Evidence: B).[108] For OSSA endocarditis 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.[109]

Most CoNS and an increasing percentage of *S aureus* strains are resistant to oxacillin. These resistant organisms are particularly prominent among patients with healthcare-associated staphylococcal endocarditis. Caution must be exercised in interpreting the results of antimicrobial susceptibility testing because some systems fail to detect oxacillin resistance, particularly among CoNS. Oxacillin-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.

Endocarditis caused by oxacillin-resistant staphylococci should be treated with vancomycin. With the burgeoning frequency of serious community-onset ORSA infections,[110,111] it is anticipated that the incidence of endocarditis caused by such strains also will rapidly increase. Skin and soft-tissue infections caused by such strains have excellent clinical outcomes when treated with trimethoprim-sulfamethoxazole; however, clinical experiences with this agent (with or without rifampin) for endocarditis caused by such strains are limited to date. Moreover, increasing drug resistance to agents other than oxacillin has been witnessed recently among community-acquired ORSA strains. Therapeutic options for patients who cannot tolerate vancomycin are limited. At present, trimethoprim-sulfamethoxazole, doxycycline or minocycline (either with or without rifampin),

TABLE 6.   Therapy for Endocarditis of Prosthetic Valves or Other Prosthetic Material Caused by Viridans Group Streptococci and *Streptococcus bovis*

Regimen	Dosage* and Route	Duration, wk	Strength of Recommendation	Comments
Penicillin-susceptible strain (minimum inhibitory concentration ≤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	IB	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 of <30 mL/min
or				
Ceftriaxone	2 g/24 h IV/IM in 1 dose	6	IB	
with or without				
Gentamicin sulfate†	3 mg/kg per 24 h IV/IM in 1 dose	2		
	Pediatric dose‡: penicillin 300 000 U/kg per 24 h IV in 4–6 equally divided doses; ceftriaxone 100 mg/kg IV/IM once daily; gentamicin 3 mg/kg per 24 h IV/IM, in 1 dose or 3 equally divided doses			
Vancomycin hydrochloride§	30 mg/kg per 24 h IV in 2 equally divided doses	6	IB	Vancomycin therapy recommended only for patients unable to tolerate penicillin or ceftriaxone
	Pediatric dose: 40 mg/kg per 24 h IV or in 2 or 3 equally divided doses			
Penicillin relatively or fully resistant strain (minimum inhibitory concentration >0.12 μg/mL)				
Aqueous crystalline penicillin sodium	24 million U/24 h IV either continuously or in 4–6 equally divided doses	6	IB	
or				
Ceftriaxone	2 g/24 h IV/IM in 1 dose	6	IB	
plus				
Gentamicin sulfate	3 mg/kg per 24 h IV/IM in 1 dose	6		
	Pediatric dose: penicillin 300 000 U/kg per 24 h IV in 4–6 equally divided doses			
Vancomycin hydrochloride	30 mg/kg per 24 h IV in 2 equally divided doses	6	IB	Vancomycin therapy is recommended only for patients unable to tolerate penicillin or ceftriaxone
	Pediatric dose: 40 mg/kg per 24 h IV in 2 or 3 equally divided doses			

*Dosages recommended are for patients with normal renal function.

†See Table 4 for appropriate dosage of gentamicin. Although it is preferred that gentamicin (3 mg/kg) be given as a single daily dose to adult patients with endocarditis due to viridans group streptococci, as a second option, gentamicin can be administered daily in 3 equally divided doses.

‡Pediatric dose should not exceed that of a normal adult.

§See text and Table 4 for appropriate dosage of vancomycin.

and linezolid are reasonable alternatives for susceptible strains in this difficult clinical situation. Limited experimental data[112] and published clinical experience[113] exist for doxycycline-minocycline. Markowitz et al[114] have reported the efficacy of trimethoprim-sulfamethoxazole in invasive ORSA infections. Treatment failures of *S aureus* with linezolid have been described in both animal models[115] and patients,[116–118] and the risk for linezolid-induced myelosuppression increases with prolonged (>2 weeks) administration.[119] The roles of quinupristin-dalfopristin and daptomycin in the treatment of staphylococcal endocarditis are not clearly defined. The putative role of supplemental gentamicin therapy in native valve endocarditis caused by oxacillin-resistant staphylococci is similar to that outlined earlier for oxacillin-sensitive staphylococci. Many strains of ORSA also are resistant to aminoglycosides. In addition, there is a potential for the development of synergistic nephrotoxic and ototoxic effects of vancomycin-aminoglycoside combination without bona fide clinical evidence of enhanced efficacy.[120] Thus, if gentamicin is used, its use should be limited to no more than the initial 3 to 5 days of therapy and restricted to patients with endocarditis caused by aminoglycoside-susceptible strains.

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. Routine use of rifampin is not recommended for treatment of native valve staphylococcal endocarditis (Class IIa, Level of Evidence: C). Rifampin has been suggested as supplemental therapy in patients who do not respond adequately to conventional antimicrobial therapy. Of note, a prospective trial in patients with endocarditis caused by ORSA failed to demonstrate that the addition of rifampin to vancomycin either enhanced survival or reduced the duration of bacteremia as compared with treatment with vancomycin alone.[106]

"Tolerance" of β-lactam antibiotics and vancomycin (MBC $\geq 32 \times$ MIC) among staphylococci has been widely reported; however, tolerance has no clear clinical implication for selection of antimicrobial therapy.

The recent descriptions of *S aureus* clinical isolates with partial[77,121] or complete[78] resistance to vancomycin have underscored the intense clinical need for new therapies for *S aureus*. No standard therapies exist for the treatment of IE caused by *S aureus* isolates that are not susceptible to vancomycin. Classification of these isolates has become complex and includes designations of "reduced susceptibility," "intermediate resistance," and "high-level resistance." 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.

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

Coagulase-Negative Staphylococci

The CoNS that cause prosthetic valve endocarditis usually are oxacillin resistant, particularly when endocarditis develops within 1 year after surgery.[79,122] Unless susceptibility to oxacillin can be demonstrated conclusively, it should be assumed that the organism is oxacillin resistant, and treatment should be planned accordingly. Evidence from models of experimental endocarditis caused by oxacillin-resistant staphylococci and limited clinical experience in treating prosthetic valve endocarditis caused by CoNS suggest that the optimal antibiotic therapy is vancomycin combined with rifampin and gentamicin.[79,122] Vancomycin and rifampin are administered for a minimum of 6 weeks, with the use of gentamicin limited to the first 2 weeks of therapy (Table 8). If the organism is resistant to gentamicin, then an aminoglycoside to which it is susceptible should be substituted for gentamicin. If the organism is resistant to all available aminoglycosides, aminoglycoside 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 may be used instead of gentamicin.[122]

Prosthetic valve infections, particularly when onset is within 12 months of cardiac valve implantation or when an aortic valve prosthesis is involved, are frequently complicated by perivalvular and myocardial abscesses and valvular dysfunction.[123] Surgery frequently is required in these patients and may be lifesaving. CoNS may become resistant to rifampin during therapy for prosthetic valve endocarditis. 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 relapse should be retested for antibiotic susceptibility (Class IIa, Level of Evidence: C).

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

S aureus

Because of the high mortality rate associated with *S aureus* prosthetic valve endocarditis,[124] combination antimicrobial therapy is recommended (Table 8). The use of combination therapy is not based on studies of in vitro synergy but rather on the efficacy of this therapy for treatment of CoNS prosthetic valve endocarditis and the results of treatment of experimental endocarditis and infected devices. In animal studies, rifampin played a unique role in the complete sterilization of foreign bodies infected by *S aureus*.[125] For infection caused by an oxacillin-susceptible strain, nafcillin or oxacillin together with rifampin is suggested; with oxacillin-resistant staphylococci, 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 the strains are resistant to gentamicin, then a fluoroquinolone may be used if the strain is susceptible. It appears that cardiac surgical interventions play an important role in maximizing outcomes in *S aureus* prosthetic valve endocarditis.[124]

In summary, a 2-week regimen of aminoglycoside is recommended for staphylococcal prosthetic valve endocarditis because of the associated high morbidity and mortality rates for such infections. It should be emphasized that this recommendation is based on limited clinical data.

Enterococci

Enterococci, which belong to Lancefield's group D, are no longer designated as part of the *Streptococcus* genus but have a separate genus, *Enterococcus*. Although there are >15 species within the *Enterococcus* genus, *E faecalis* and *E faecium* are the major species isolated from clinical sources.

Suggested regimens recommended for enterococcal endocarditis are shown in Tables 9 though 12. Enterococci should be routinely tested in vitro for susceptibility to penicillin and vancomycin (MIC determination) and for high-level resistance to gentamicin and streptomycin (Class I, Level of Evidence: A). Although rarely identified, β-lactamase–producing enterococci may account for relapsing infection, and screening the isolate for β-lactamase production should be done in these cases.

In comparison with streptococci, enterococci are relatively resistant to penicillin, ampicillin, and vancomycin. Streptococci usually are killed by these antimicrobials alone, 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 milieu 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 concentration of an aminoglycoside that is readily achieved in patients without excessive toxicity. If an enterococcus strain is resistant to the cell

TABLE 7. Therapy for Endocarditis Caused by Staphylococci in the Absence of Prosthetic Materials

Regimen	Dosage* and Route	Duration	Strength of Recommendation	Comments
Oxacillin-susceptible strains				
Nafcillin or oxacillin†	12 g/24 h IV in 4–6 equally divided doses	6 wk	IA	For complicated right-sided IE and for left-sided IE; for uncomplicated right-sided IE, 2 wk (see text)
with				
Optional addition of gentamicin sulfate‡	3 mg/kg per 24 h IV/IM in 2 or 3 equally divided doses	3–5 d		
	Pediatric dose§: Nafcillin or oxacillin 200 mg/kg per 24 h IV in 4–6 equally divided doses; gentamicin 3 mg/kg per 24 h IV/IM in 3 equally divided doses			Clinical benefit of aminoglycosides has not been established
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 wk	IB	Cephalosporins should be avoided in patients with anaphylactoid-type hypersensitivity to β-lactams; vancomycin should be used in these cases§
with				
Optional addition of gentamicin sulfate	3 mg/kg per 24 h IV/IM in 2 or 3 equally divided doses	3–5 d		Clinical benefit of aminoglycosides has not been established
	Pediatric dose: cefazolin 100 mg/kg per 24 h IV in 3 equally divided doses; gentamicin 3 mg/kg per 24 h IV/IM in 3 equally divided doses			
Oxacillin-resistant strains				
Vancomycin‖	30 mg/kg per 24 h IV in 2 equally divided doses	6 wk	IB	Adjust vancomycin dosage to achieve 1-h serum concentration of 30–45 μg/mL and trough concentration of 10–15 μg/mL (see text for vancomycin alternatives)
	Pediatric dose: 40 mg/kg per 24 h IV in 2 or 3 equally divided doses			

*Dosages recommended are for patients with normal renal function.

†Penicillin G 24 million U/24 h IV in 4 to 6 equally divided doses may be used in place of nafcillin or oxacillin if strain is penicillin susceptible (minimum inhibitory concentration ≤0.1 μg/mL) and does not produce β-lactamase.

‡Gentamicin should be administered in close temporal proximity to vancomycin, nafcillin, or oxacillin dosing. See Table 4 for appropriate dosage of gentamicin.

§Pediatric dose should not exceed that of a normal adult.

‖For specific dosing adjustment and issues concerning vancomycin, see Table 4 footnotes.

wall–active agent or high concentrations of an aminoglycoside (500 μg/mL of gentamicin or 1000 μg/mL of streptomycin), then the combination of an aminoglycoside with the cell wall–active agent will not result in bactericidal activity in vitro or in vivo (animal model of endocarditis), nor will it predictably produce a microbiological cure in human enterococcal endocarditis.

Results of studies of experimental enterococcal endocarditis suggest that an in vivo postantibiotic effect does not occur with penicillin, ampicillin, or vancomycin. Accordingly, the trough antibiotic concentration in serum must be maintained above the MIC. Some animal model data suggest that continuous infusion of a β-lactam is more effective than is intermittent infusion, whereas other studies suggest an equiv-

alent effect. In these studies, the serum trough concentrations were greater than the MIC with either intermittent or continuous administration.

Enterococci Susceptible to Penicillin, Vancomycin, and Aminoglycosides

The regimens suggested for antimicrobial therapy are shown in Table 9. When combined with penicillin or ampicillin, streptomycin and gentamicin therapy had similar microbiological cure rates for enterococcal endocarditis.[126] The choice of a specific aminoglycoside for therapy should be based on gentamicin and streptomycin in vitro susceptibility testing. If the strain is susceptible to both gentamicin and streptomycin, then gentamicin is preferred because the determination of

TABLE 8.   Therapy for Prosthetic Valve Endocarditis Caused by Staphylococci

Regimen	Dosage* and Route	Duration, wk	Strength of Recommendation	Comments
Oxacillin-susceptible strains				
Nafcillin or oxacillin *plus*	12 g/24 h IV in 6 equally divided doses	≥6	IB	Penicillin G 24 million U/24 h IV in 4 to 6 equally divided doses may be used in place of nafcillin or oxacillin if strain is penicillin susceptible (minimum inhibitory concentration ≤0.1 μg/mL) and does not produce β-lactamase; vancomycin should be used in patients with immediate-type hypersensitivity reactions to β-lactam antibiotics (see Table 3 for dosing guidelines); cefazolin may be substituted for nafcillin or oxacillin in patients with non–immediate-type hypersensitivity reactions to penicillins
Rifampin *plus*	900 mg per 24 h IV/PO in 3 equally divided doses	≥6		
Gentamicin†	3 mg/kg per 24 h IV/IM in 2 or 3 equally divided doses	2		
	Pediatric dose‡: nafcillin or oxacillin 200 mg/kg per 24 h IV in 4–6 equally divided doses; rifampin 20 mg/kg per 24 h IV/PO in 3 equally divided doses; gentamicin 3 mg/kg per 24 h IV/IM in 3 equally divided doses			
Oxacillin-resistant strains				
Vancomycin *plus*	30 mg/kg 24 h in 2 equally divided doses	≥6	IB	Adjust vancomycin to achieve 1-h serum concentration of 30–45 μg/mL and trough concentration of 10–15 μg/mL (see text for gentamicin alternatives)
Rifampin *plus*	900 mg/24 h IV/PO in 3 equally divided doses	≥6		
Gentamicin	3 mg/kg per 24 h IV/IM in 2 or 3 equally divided doses	2		
	Pediatric dose: vancomycin 40 mg/kg per 24 h IV in 2 or 3 equally divided doses; rifampin 20 mg/kg per 24 h IV/PO in 3 equally divided doses (up to adult dose); gentamicin 3 mg/kg per 24 h IV or IM in 3 equally divided doses			

*Dosages recommended are for patients with normal renal function.

†Gentamicin should be administered in close proximity to vancomycin, nafcillin, or oxacillin dosing. See Table 4 for appropriate dosage of gentamicin.

‡Pediatric dose should not exceed that of a normal adult.

serum gentamicin concentrations may be performed in most laboratories, whereas streptomycin serum concentrations require special laboratory testing. Studies of single daily dosing of aminoglycosides compared with dosing every 8 hours in animal models of enterococcal endocarditis have yielded conflicting results. These results may reflect different pharmacokinetics of aminoglycosides in animals as compared with humans. Until more data demonstrate that once-daily dosing of an aminoglycoside is as effective as multiple dosing, gentamicin or streptomycin should be administered in daily multiple divided doses rather than a daily single dose to patients with enterococcal endocarditis.

In patients with normal renal function, gentamicin should be administered every 8 hours and the dosage adjusted to achieve a 1-hour serum concentration of ≈3 μg/mL and a trough concentration of <1 μg/mL. Increasing the dosage of gentamicin in these patients did not result in enhanced efficacy but did increase the risk of nephrotoxicity.[127] In patients with mildly abnormal renal function (creatinine clearance ≥50 mL/min), the dosage of gentamicin should be adjusted and the serum concentrations closely monitored to achieve the target concentrations above. In patients with more severely reduced renal function (creatinine clearance <50 mL/min), treatment should be in consultation with an infectious diseases specialist.

The duration of antimicrobial therapy in native valve endocarditis depends on the duration of infection before diagnosis and onset of effective therapy. Patients with <3 months' duration of symptoms may be treated successfully with 4 weeks of antimicrobial therapy, whereas patients with ≥3 months' duration of symptoms require 6 weeks of therapy.[128,129] Patients with prosthetic valve endocarditis should receive at least 6 weeks of antimicrobial therapy.

Vancomycin therapy 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 endocarditis. Patients with native valve endocarditis should receive 6 weeks of vancomycin-gentamicin therapy; patients with prosthetic valve infection also should receive at least 6 weeks of therapy.

Findings from a 5-year, nationwide, prospective study of 93 episodes of definite enterococcal endocarditis are noteworthy because they suggest that the duration of aminoglycoside therapy could be shortened to 2 to 3 weeks.[130] These patients, who were managed in Sweden between 1995 and 1999, represent the largest series of enterococcal endocarditis cases published to date. The age of these patients, who were

TABLE 9. Therapy for Native Valve or Prosthetic Valve Enterococcal Endocarditis Caused by Strains Susceptible to Penicillin, Gentamicin, and Vancomycin

Regimen	Dosage* and Route	Duration, wk	Strength of Recommendation	Comments
Ampicillin sodium	12 g/24 h IV in 6 equally divided doses	4–6	IA	Native valve: 4-wk therapy recommended for patients with symptoms of illness ≤3 mo; 6-wk therapy recommended for patients with symptoms >3 mo
or				
Aqueous crystalline penicillin G sodium	18–30 million U/24 h IV either continuously or in 6 equally divided doses	4–6	IA	Prosthetic valve or other prosthetic cardiac material: minimum of 6 wk of therapy recommended
plus				
Gentamicin sulfate†	3 mg/kg per 24 h IV/IM in 3 equally divided doses	4–6		
	Pediatric dose‡: ampicillin 300 mg/kg per 24 h IV in 4–6 equally divided doses; penicillin 300 000 U/kg per 24 h IV in 4–6 equally divided doses; gentamicin 3 mg/kg per 24 h IV/IM in 3 equally divided doses			
Vancomycin hydrochloride§	30 mg/kg per 24 h IV in 2 equally divided doses	6	IB	Vancomycin therapy recommended only for patients unable to tolerate penicillin or ampicillin
plus				
Gentamicin sulfate	3 mg/kg per 24 h IV/IM in 3 equally divided doses	6		6 wk of vancomycin therapy recommended because of decreased activity against enterococci
	Pediatric dose: vancomycin 40 mg/kg per 24 h IV in 2 or 3 equally divided doses; gentamicin 3 mg/kg per 24 h IV/IM in 3 equally divided doses			

*Dosages recommended are for patients with normal renal function.

†Dosage of gentamicin should be adjusted to achieve peak serum concentration of 3–4 μg/mL and a trough concentration of <1 μg/mL (see text). See Table 4 for appropriate dosage of gentamicin.

‡Pediatric dose should not exceed that of a normal adult.

§See text and Table 4 for appropriate dosing of vancomycin.

older than patients with other types of endocarditis, was a factor in their ability to tolerate prolonged aminoglycoside therapy in combination with cell wall–active agents and prompted an abbreviated aminoglycoside course. Despite limiting the duration of aminoglycosides (median treatment time was 15 days), the overall cure rate was comparable to that of longer courses of combined therapy. The implications of this work are extremely practical and deserve further study before routine use of shortened aminoglycoside therapy in combination regimens for treatment of enterococcal endocarditis can be recommended.

Enterococci Susceptible to Penicillin, Streptomycin, and Vancomycin and Resistant to Gentamicin

Aminoglycoside resistance in enterococci is most commonly the result of the acquisition of plasmid-mediated aminoglycoside-modifying enzymes. Strains that are resistant to high levels of gentamicin are resistant to other aminoglycosides, but some of these strains are susceptible to streptomycin. All *E faecium* are intrinsically resistant to amikacin, kanamycin, netilmicin, and tobramycin, and *E faecalis* are often resistant to kanamycin and amikacin. Infecting strains of enterococci recovered from patients with endocarditis should be tested for susceptibility to both gentamicin and streptomycin but not other aminoglycosides.

The suggested regimens for antimicrobial therapy are shown in Table 10. The duration of therapy is the same whether gentamicin or streptomycin is used and whether the patient has native or prosthetic valve endocarditis.

In patients with normal renal function, streptomycin should be administered every 12 hours and the dosage adjusted to achieve a 1-hour serum concentration of 20 to 35 μg/mL and a trough concentration of <10 μg/mL. Patients with a creatinine clearance of <50 mL/min should be treated in consultation with an infectious diseases specialist.

Enterococci Resistant to Penicillin and Susceptible to Aminoglycosides and Vancomycin

Table 11 presents the antimicrobial regimens suggested for the treatment of endocarditis caused by enterococci susceptible to vancomycin and aminoglycosides and resistant to penicillin. *E faecium* are more resistant to penicillin, with MICs usually >16 μg/mL as compared with *E faecalis*, with MICs usually 2 to 4 μg/mL of penicillin. Ampicillin MICs usually are 1 dilution lower than those of penicillin. The activity of piperacillin is similar to that of penicillin, but ticarcillin, aztreonam, antistaphylococcal penicillins (nafcillin and methicillin), cephalosporins, cephamycins, and meropenem have limited or no activity against enterococci. Imipenem has some activity against enterococci.

TABLE 10. Therapy for Native or Prosthetic Valve Enterococcal Endocarditis Caused by Strains Susceptible to Penicillin, Streptomycin, and Vancomycin and Resistant to Gentamicin

Regimen	Dosage* and Route	Duration, wk	Strength of Recommendation	Comments
Ampicillin sodium	12 g/24 h IV in 6 equally divided doses	4–6	IA	Native valve: 4-wk therapy recommended for patients with symptoms of illness <3 mo; 6-wk therapy recommended for patients with symptoms >3 mo
or				
Aqueous crystalline penicillin G sodium	24 million U/24 h IV continuously or in 6 equally divided doses	4–6	IA	
plus				
Streptomycin sulfate†	15 mg/kg per 24 h IV/IM in 2 equally divided doses	4–6		Prosthetic valve or other prosthetic cardiac material: minimum of 6 wk of therapy recommended
	Pediatric dose‡: ampicillin 300 mg/kg per 24 h IV in 4–6 equally divided doses; penicillin 300 000 U/kg per 24 h IV in 4–6 equally divided doses; streptomycin 20–30 mg/kg per 24 h IV/IM in 2 equally divided doses			
Vancomycin hydrochloride§	30 mg/kg per 24 h IV in 2 equally divided doses	6	IB	Vancomycin therapy recommended only for patients unable to tolerate penicillin or ampicillin
plus				
Streptomycin sulfate	15 mg/kg per 24 h IV/IM in 2 equally divided doses	6		
	Pediatric dose: vancomycin 40 mg/kg per 24 h IV in 2 or 3 equally divided doses; streptomycin 20–30 mg/kg per 24 h IV/IM in 2 equally divided doses			

*Dosages recommended are for patients with normal renal function.
†See text for appropriate dosing of streptomycin.
‡Pediatric dose should not exceed that of a normal adult.
§See text and Table 4 for appropriate dosing of vancomycin.

Some strains of *E faecalis* produce an inducible β-lactamase that can be detected only by testing against an inoculum that is 100-fold greater than that routinely used to detect β-lactamase production by other microorganisms. At the lower inoculum, the MICs of β-lactamase-positive and negative strains of enterococci are the same. The β-lactamase produced by enterococci is inhibited by the β-lactamase inhibitors sulbactam and clavulanic acid, and these β-lactamase-positive strains are susceptible to ampicillin/sulbactam or amoxicillin/clavulanate, as well as to vancomycin.

Enterococci Resistant to Penicillin, Aminoglycosides, and Vancomycin

Enterococci are considered susceptible to vancomycin if MICs are ≤4 μg/mL; they are thought to have intermediate-level resistance to vancomycin if MICs are 8 to 16 μg/mL and have full resistance to vancomycin if MICs are >16 μg/mL. Five phenotypes of vancomycin resistance (*vanA* through *E*) in enterococci have been described.[131] IE cases are most often caused by enterococci with the phenotypes *vanA*, *B*, or *C*. The *vanA* phenotype is characterized by high-level vancomycin resistance (MIC >64 μg/mL), *vanB* by intermediate- to high-level resistance (MIC 16 to 512 μg/mL), and *vanC* by low- to intermediate-level resistance (MIC 2 to 32 μg/mL).

The genes encoding *vanA* and *vanB* are found primarily in *E faecium* and some strains of *E faecalis*, and the gene encoding *vanC* is found intrinsically in all *E casseliflavus* and *E gallinarum*, the only 2 motile enterococcal species.

Vancomycin-resistant (MIC >4 μg/mL) enterococci, in particular *E faecium*, are often multidrug-resistant; however, vancomycin-resistant *E faecalis* and *E gallinarum/casseliflavus* usually are penicillin susceptible. Linezolid inhibits the growth of both *E faecalis* and *E faecium*, but quinupristin-dalfopristin (Synercid) inhibits growth only in *E faecium* because *E faecalis* are intrinsically resistant to quinupristin-dalfopristin.

Few therapeutic options are available for antimicrobial therapy of enterococcal endocarditis caused by multiply resistant enterococci (Table 12); linezolid therapy resulted in the cure of 77% of 22 courses of therapy in patients with vancomycin-resistant enterococci endocarditis.[132] Synercid therapy was effective in 4 of 9 patients with endocarditis caused by vancomycin-resistant *E faecium*. Synergistic bactericidal activity in vitro and in vivo for *E faecalis* strains has been demonstrated with double β-lactam combinations of imipenem and ampicillin or cephalosporins plus ampicillin, probably as a result of the saturation of different penicillin-binding protein targets. These double β-lactam combinations have been used to treat endocarditis caused by high-level

TABLE 11. Therapy for Native or Prosthetic Valve Enterococcal Endocarditis Caused by Strains Resistant to Penicillin and Susceptible to Aminoglycoside and Vancomycin

Regimen	Dosage* and Route	Duration, wk	Strength of Recommendation	Comments
β-Lactamase–producing strain				
Ampicillin-sulbactam	12 g/24 h IV in 4 equally divided doses	6	IIaC	Unlikely that the strain will be susceptible to gentamicin; if strain is gentamicin resistant, then >6 wk of ampicillin-sulbactam therapy will be needed
plus				
Gentamicin sulfate†	3 mg/kg per 24 h IV/IM in 3 equally divided doses	6		
	Pediatric dose‡: ampicillin-sulbactam 300 mg/kg per 24 h IV in 4 equally divided doses; gentamicin 3 mg/kg per 24 h IV/IM in 3 equally divided doses			
Vancomycin hydrochloride§	30 mg/kg per 24 h IV in 2 equally divided doses	6	IIaC	Vancomycin therapy recommended only for patients unable to tolerate ampicillin-sulbactam
plus				
Gentamicin sulfate†	3 mg/kg per 24 h IV/IM in 3 equally divided doses	6		
	Pediatric dose: vancomycin 40 mg/kg per 24 h in 2 or 3 equally divided doses; gentamicin 3 mg/kg per 24 h IV/IM in 3 equally divided doses			
Intrinsic penicillin resistance				
Vancomycin hydrochloride‡	30 mg/kg per 24 h IV in 2 equally divided doses	6	IIaC	Consultation with a specialist in infectious diseases recommended
plus				
Gentamicin sulfate†	3 mg/kg per 24 h IV/IM in 3 equally divided doses	6		
	Pediatric dose: vancomycin 40 mg/kg per 24 h IV in 2 or 3 equally divided doses; gentamicin 3 mg/kg per 24 h IV/IM in 3 equally divided doses			

*Dosages recommended are for patients with normal renal function.
†See text and Table 4 for appropriate dosing of gentamicin.
‡Pediatric dose should not exceed that of a normal adult.
§See Table 4 for appropriate dosing of vancomycin.

aminoglycoside-resistant strains in experimental enterococcal endocarditis and in a small number of patients with endocarditis caused by a strain of multidrug-resistant *E faecalis*.[132–136] Clinical results of daptomycin therapy are needed for vancomycin-resistant enterococci endocarditis treatment.

Surgery may be indicated for endocarditis resulting from enterococci for which there is no synergistic bactericidal combination, and cardiac valve replacement may be the only chance of cure in some patients. Because of the high complexity of treating patients with vancomycin-resistant enterococci or multiple antibiotic-resistant enterococcal endocarditis, therapy should be done in consultation with specialists in infectious diseases, cardiology, cardiac surgery, and microbiology.

HACEK Microorganisms

Endocarditis caused by fastidious Gram-negative bacilli of the HACEK group (*Haemophilus parainfluenzae*, *H aphrophilus*, *H paraphrophilus*, *H influenzae*, *Actinobacillus actinomycetemcomitans*, *Cardiobacterium hominis*, *Eikenella corrodens*, *Kingella kingae*, and *K denitrificans*) accounts for ≈5% to 10% of native valve community-acquired endocar-

ditis in patients who are not IDUs.[137] These microorganisms grow slowly in standard blood culture media, and recovery may require prolonged incubation. Typically, only a small portion of the blood culture bottles in patients with HACEK endocarditis demonstrate growth. In cases in which blood cultures are initially negative, the microbiology laboratory should be asked to retain blood cultures for ≥2 weeks in all patients suspected of having IE. Bacteremia caused by HACEK microorganisms in the absence of an obvious focus of infection is highly suggestive of endocarditis even in the absence of typical physical findings.

Previously, the HACEK group of microorganisms was uniformly susceptible to ampicillin; however, β-lactamase–producing strains of HACEK are appearing with increased frequency. Because of the difficulty in performing antimicrobial susceptibility testing, HACEK microorganisms should be considered ampicillin resistant, and ampicillin should not be used for the treatment of patients with HACEK endocarditis. Both β-lactamase–producing and non–β-lactamase–producing strains of the HACEK group are susceptible to ceftriaxone (or other third- or fourth-generation cephalosporins),

TABLE 12.   Therapy for Native or Prosthetic Valve Enterococcal Endocarditis Caused by Strains Resistant to Penicillin, Aminoglycoside, and Vancomycin

Regimen	Dosage* and Route	Duration, wk	Strength of Recommendation	Comments
E faecium				
Linezolid	1200 mg/24 h IV/PO in 2 equally divided doses	≥8	IIaC	Patients with endocarditis caused by these strains should be treated in consultation with an infectious diseases specialist; cardiac valve replacement may be necessary for bacteriologic cure; cure with antimicrobial therapy alone may be <50%; severe, usually reversible thrombocytopenia may occur with use of linezolid, especially after 2 wk of therapy; quinupristin-dalfopristin only effective against *E faecium* and can cause severe myalgias, which may require discontinuation of therapy; only small no. of patients have reportedly been treated with imipenem/cilastatin-ampicillin or ceftriaxone + ampicillin
or				
Quinupristin-dalfopristin	22.5 mg/kg per 24 h IV in 3 equally divided doses	≥8		
E faecalis				
Imipenem/cilastatin	2 g/24 h IV in 4 equally divided doses	≥8	IIbC	
plus				
Ampicillin sodium	12 g/24 h IV in 6 equally divided doses	≥8		
or				
Ceftriaxone sodium	4 g/24 h IV/IM in 2 equally divided doses	≥8	IIbC	
plus				
Ampicillin sodium	12 g/24 h IV in 6 equally divided doses	≥8		
	Pediatric dose†: Linezolid 30 mg/kg per 24 h IV/PO in 3 equally divided doses; quinupristin-dalfopristin 22.5 mg/kg per 24 h IV in 3 equally divided doses; imipenem/cilastatin 60–100 mg/kg per 24 h IV in 4 equally divided doses; ampicillin 300 mg/kg per 24 h IV in 4–6 equally divided doses; ceftriaxone 100 mg/kg per 24 h IV/IM in 2 equally divided doses			

Decreasing order of preference based on published data.
*Dosages recommended are for patients with normal renal function.
†Pediatric dose should not exceed that of a normal adult.

ampicillin-sulbactam, and fluoroquinolones. Although there are limited published clinical data demonstrating the efficacy of ceftriaxone or ampicillin-sulbactam therapy, these drugs should be considered the regimens of choice for the treatment of patients with HACEK endocarditis[64] (Table 13). The duration of therapy for native valve infection should be 4 weeks; for prosthetic valve endocarditis, the duration of therapy should be 6 weeks. Gentamicin is no longer recommended because of its nephrotoxicity risks.

The HACEK group is susceptible in vitro to fluoroquinolones. On the basis of these susceptibility data, a fluoroquinolone (ciprofloxacin, levofloxacin, gatifloxacin, or moxifloxacin) should be considered as an alternative agent for patients unable to tolerate β-lactam therapy. There are only a few case reports of HACEK endocarditis treated with a fluoroquinolone, however. Accordingly, patients with HACEK endocarditis who cannot tolerate β-lactam therapy should be treated in consultation with an infectious diseases specialist.

Non-HACEK Gram-Negative Bacilli

Although Gram-negative aerobic bacilli have traditionally been reported to cause up to 10% of endocarditis cases,[138–140] this proportion has been considerably lower in recent series. For example, in a prospective cohort study involving 34 centers in 15 countries, only 21 (2.1%) of the 1024 cases of definite IE were caused by Gram-negative bacteria.[73] Some studies have suggested that the incidence of endocarditis resulting from Gram-negative bacteria may be increasing.[138,141] IDUs, recipients of prosthetic valves, and patients with cirrhosis[142] appear to be at increased risk for developing Gram-negative bacillary endocarditis. The duration of illness before presentation usually is <6

weeks; most patients are 40 to 50 years of age, and men and women are affected equally.[143] Congestive heart failure (CHF) is common, and mortality rates range from ≈60% to 80%.[137,139,144]

Enterobacteriaceae

Among Enterobacteriaceae, *Salmonella* species were the most common causes in early reports. These organisms have an affinity for abnormal cardiac valves, usually on the left side of the heart.[139,145] Although many serotypes have been implicated, most cases are caused by *S choleraesuis*, *S typhimurium*, and *S enteritidis*. Valvular perforation or destruction, atrial thrombi, myocarditis, and pericarditis are common, and the outlook is grave. *Salmonellae* also may produce endarteritis in aneurysms of major vessels. Other Enterobacteriaceae, including *E coli* and *Serratia marcescens*, may rarely cause endocarditis.[144] *S marcescens* endocarditis typically develops in IDUs. Left-sided disease, large vegetations, and involvement of architecturally normal valves are common features, and mortality rates are ≈70%.[146,147] Valve replacement after ≈7 to 10 days of antibiotic therapy has been recommended for these difficult infections.

Cardiac surgery in combination with prolonged courses of combined antibiotic therapy is a cornerstone of treatment (Class IIa, Level of Evidence: B) for most patients with endocarditis caused by Gram-negative bacilli, particularly in the setting of left-sided involvement.[139,147] Certain combinations of penicillins or cephalosporins and aminoglycosides have been shown to be synergistic against many of these strains and usually are recommended. For IE caused by susceptible strains of *Escherichia coli* or *Proteus mirabilis*, a combination of either a penicillin—either ampicillin (2 g IV every 4 hours) or penicillin (20 million U IV daily)—or a broad-spectrum cephalosporin with an aminoglycoside, usually gentamicin (1.7 mg/kg every 8 hours), is recommended. Third-generation cephalosporins are extremely active against *E coli* in vitro, and some (eg, ceftriaxone) have proved effective in experimental models of *E coli* endocarditis in animals.[148] This group of agents deserves further evaluation in humans for IE caused by susceptible Gram-negative bacilli. Endovascular *Salmonella* infections, including IE, also may respond to third-generation cephalosporins.[149] A combination of a third-generation cephalosporin and an aminoglycoside (either gentamicin or amikacin) is recommended for *Klebsiella* endocarditis. Certain β-lactam/β-lactamase inhibitor combinations (eg, piperacillin-tazobactam[150] but not ceftriaxone-sulbactam[151]) are active in vivo in experimental models of *Klebsiella* endocarditis induced by TEM-3–producing isolates in animals and deserve further evaluation in combination with an aminoglycoside in humans with this disease. The specific aminoglycoside used is a critical variable and cannot be totally predicted from MIC data alone because pharmacodynamic characteristics differ markedly in animal models of IE caused by Gram-negative aerobic bacilli.[152,153] Thus, determinations of tube-dilution MBC often are necessary to guide therapy (Class IIb, Level of Evidence: C).

Pseudomonas Species

More than 200 cases of *P aeruginosa* endocarditis have been reported.[142,143,154–158] Most (95%) patients have abused intravenous drugs, and nearly all IDUs have abused tripelennamine and pentazocine ("T's and blues").[143,154,158] The male:female ratio is 2.5:1, and the mean age is 30 years. The organism affects normal valves in most cases. Major embolic phenomena, inability to sterilize valves, neurological complications (53%), ring and annular abscesses, splenic abscesses, bacteremic relapses, and rapidly progressive CHF are common. Ecthyma gangrenosum, the necrotizing cutaneous lesion characteristic of *Pseudomonas* bacteremia, has occasionally been noted, especially in cases of IE caused by *P (Burkholderia) cepacia*.[159] The disease carries the highest mortality rate in patients >30 years of age (73% versus 33% in younger patients) when the duration of illness is <5 days (which increases mortality from 41% to 76%) and when there is left-sided cardiac involvement.[154,157] Because of the gloomy outlook and frequent complications,[155] many authorities recommend early surgery for left-sided *Pseudomonas* endocarditis.[143,158] In contrast, high-dose regimens of antipseudomonal penicillins combined with aminoglycosides have had a salutary effect in a majority of patents with isolated right-sided pseudomonal IE.

Medical therapy may be successful in *P aeruginosa* IE involving the right side of the heart in 50% to 75% of cases. If the disease is refractory to antibiotics, then partial tricuspid valvulectomy or "vegetectomy"[160] without valve replacement is indicated.[161] Although valve replacement often is necessary for curing left-sided IE caused by *P aeruginosa*,[162] results in a series of 10 patients (7 with left-sided involvement alone or in combination with tricuspid disease) suggest that medical therapy alone is occasionally curative.[149] Studies in animals with experimental *Pseudomonas* endocarditis[163] offer a potential explanation for these disparate results: The penetration into vegetations and the time during which antibiotic concentrations exceeded the MBC were both significantly greater with tricuspid than with aortic vegetations for both ceftazidime and tobramycin.

Problems have emerged with all potential regimens in animal models of *P aeruginosa* IE, including failure of β-lactam (eg, ceftazadime) therapy as a result of constitutive hyperproduction of type Id β-lactamase by isolates within valve vegetations in animal models[163] and clinically[164]; isolates demonstrating aminoglycoside resistance caused by permeability defects that emerge during therapy[165]; absence of a postantibiotic effect of β-lactams against *P aeruginosa* in vivo,[166] thus necessitating frequent (or continuous) drug administration; and reduced host-mediated clearance of mucoid strains from the valvular vegetation resulting from alginate exopolysaccharide.[167]

On the basis of clinical experience,[154,156,157] however, the preferred regimen for IE caused by *P aeruginosa* is high-dose tobramycin (8 mg/kg per day IV or intramuscularly in once-daily doses) with maintenance of peak and trough concentrations of 15 to 20 μg/mL and ≤2 μg/mL, respectively, in combination with either an extended-spectrum penicillin (eg, ticarcillin, piperacillin, azlocillin) or ceftazidime or cefepime in full doses (Class IIa, Level of Evidence: B). The toxicity associated with this regimen is surprisingly low; combination treatment should be given for a minimum of 6 weeks. The use of quinolones (in combination with an

aminoglycoside) for the treatment of *Pseudomonas* endocarditis appears promising, based on favorable results in animal models[163] and humans,[168] but the development of stepwise resistance during therapy may limit the efficacy of this class of drugs in the future. On the basis of limited experimental data,[169] ceftazidime-tobramycin is preferred over aztreonam-tobramycin for this disease. Approximately 7 cases of *P aeruginosa* endocarditis have been successfully treated with imipenem plus an aminoglycoside,[170] but the potential for the development of resistance exists with any of these regimens.

Unusual Gram-Negative Bacteria

Neisseria gonorrhoeae was responsible for at least 5% to 10% of IE cases before the introduction of penicillin but is now rarely implicated. Of the cases of gonococcal endocarditis reported since 1949,[171–173] most occurred in young men. Skin manifestations consistent with the gonococcal arthritis-dermatitis syndrome or endocarditis are documented in only 20% of cases. Most cases of gonococcal endocarditis now follow an indolent course in contrast to the often fulminant progression in the preantibiotic era. Aortic valve involvement, large vegetations seen on TTE, associated valve ring abscesses, CHF, and nephritis are common. Recently,[171] a high frequency of late-complement component deficiencies has been noted in patients with gonococcal endocarditis. Sudden hemodynamic deterioration despite appropriate therapy may occur,[171–173] and the mortality rate remains ≈20%. "Nonpathogenic" *Neisseria* species (*N perflava*, *N flava*, *N pharyngis*, *N mucosa*, *N sicca*, *N flavescens*, and especially *N elongata* subspecies *nitroreducens* [Centers for Disease Control and Prevention group M-6]) and *Moraxella [Branhamella] catarrhalis* are now isolated more frequently in IE than gonococci, but they usually produce infection on abnormal or prosthetic heart valves.[174–176]

The gonococci that cause systemic infection usually are susceptible to penicillin.[177] IE caused by these organisms as well as by meningococci can be effectively treated with the same penicillin regimen recommended for pneumococcal endocarditis. There are several reasons why infectious disease consultation should be obtained in cases in which gonococci are resistant to penicillin. These include limited clinical experience,[178] various mechanisms of penicillin resistance, and resistance to other potential therapies, including ceftriaxone and ciprofloxacin.

Culture-Negative Endocarditis

Positive blood cultures are a major diagnostic criterion for IE and key to identifying the etiologic agent and the optimal antimicrobial regmen.[19,179,180] Continuous bacteremia and a high frequency of positive blood cultures are typical of this infection. In a study of 206 patients with blood culture–positive endocarditis, 95% of 789 blood cultures yielded the causative microorganism, and in 91% of cases, all of the cultures were positive.[181] The intensity of bacteremia may not be great, however; <50 colony-forming units per milliliter of blood were detected in the majority of patients.[181]

Blood cultures are negative in up to 20% of patients with IE diagnosed by strict diagnostic criteria.[182] Failure to culture the microorganism causing endocarditis may result from inadequate microbiological techniques, infection with highly fastidious bacteria or nonbacterial pathogens, or previous administration of antimicrobial agents before blood cultures were obtained. The last of these 3 factors is an important cause of culture-negative endocarditis because it is so prevalent. Administration of antimicrobial agents to IE patients before blood cultures are obtained reduces the recovery rate of bacteria by 35% to 40%.[180,181,183–185] The antimicrobial susceptibility of the organism and the duration and nature of previous antimicrobial therapy together determine the length of time that blood cultures will remain negative.[186] Endocarditis 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 the most appropriate medical therapy for patients with culture-negative endocarditis is difficult. On the one hand, there is a need to provide empiric 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 pathogens that are not usually encountered are not available in many clinical laboratories and require considerable time for completion of testing. 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 may not have been necessary had a pathogen been identified.

Selection of an empirical treatment regimen (Table 14) should include consideration of epidemiological features (Table 15) and the clinical course of infection. Consultation with an infectious diseases specialist to define the most appropriate choice of therapy is recommended.

Patients should be classified into 1 of 2 groups (provided the reason for negative blood cultures is determined not to be inadequate laboratory techniques) when choice of empirical therapy is considered. One group includes patients who received antibiotic therapy before collection of blood cultures. For those with acute clinical presentations of native valve infection, coverage for *S aureus* should be provided as outlined in the section on the treatment of proven staphylococcal disease. For patients with a subacute presentation, coverage of *S aureus*, viridans group streptococci, and enterococci should be given. Therapy for the HACEK group of organisms also should be considered. One treatment option could include 3 g IV ampicillin-sulbactam every 6 hours combined with gentamicin 1 mg/kg IV or intramuscularly every 8 hours.

Patients with culture-negative prosthetic valve infection should receive vancomycin if onset of symptoms begins within 1 year of prosthetic valve placement to provide coverage of oxacillin-resistant staphylococci. Coverage for aerobic Gram-negative bacilli with cefepime 2 g IV every 8 hours could be considered for onset of infection within 2 months of valve replacement. If symptom onset is 1 year after valve placement, then infection is more likely to be caused by

TABLE 13.   Therapy for Both Native and Prosthetic Valve Endocarditis Caused by HACEK* Microorganisms

Regimen	Dosage and Route	Duration, wk	Strength of Recommendation	Comments
Ceftriaxone† sodium *or*	2 g/24 h IV/IM in 1 dose	4	IB	Cefotaxime or another third- or fourth-generation cephalosporin may be substituted
Ampicillin- sulbactam‡ *or*	12 g/24 h IV in 4 equally divided doses	4	IIaB	
Ciprofloxacin‡§	1000 mg/24 h PO or 800 mg/24 h IV in 2 equally divided doses	4	IIbC	Fluoroquinolone therapy recommended only for patients unable to tolerate cephalosporin and ampicillin therapy; levofloxacin, gatifloxacin, or moxifloxacin may be substituted; fluoroquinolones generally not recommended for patients <18 y old
	Pediatric dose‖: Ceftriaxone 100 mg/kg per 24 h IV/IM once daily; ampicillin-sulbactam 300 mg/kg per 24 h IV divided into 4 or 6 equally divided doses; ciprofloxacin 20–30 mg/kg per 24 h IV/PO in 2 equally divided doses			Prosthetic valve: patients with endocarditis involving prosthetic cardiac valve or other prosthetic cardiac material should be treated for 6 wk

Haemophilus parainfluenzae, H aphrophilus, Actinobacillus actinomycetemcomitans, Cardiobacterium hominis, Eikenella corrodens, and *Kingella kingae.*

†Patients should be informed that IM injection of ceftriaxone is painful.

‡Dosage recommended for patients with normal renal function.

§Fluoroquinolones are highly active in vitro against HACEK microorganisms. Published data on use of fluoroquinolone therapy for endocarditis caused by HACEK are minimal.

‖Pediatric dose should not exceed that of a normal adult.

oxacillin-susceptible staphylococci, viridans group streptococci, and enterococci, and antibiotic therapy for these potential pathogens should be administered for at least 6 weeks.

The second group of patients with culture-negative endocarditis has infection caused by uncommon or rare endocarditis pathogens that do not grow in routinely used blood culture systems.[184,187] The organisms that have garnered the most attention are *Bartonella* species, *Chlamydia* species, *Coxiella burnetii, Brucella* species, *Legionella* species, *Tropheryma whippleii,* and non-*Candida* fungi. *Bartonella* species, *Coxiella burnetii,* and *Brucella* species have been the most commonly identified in most series of culture-negative endocarditis caused by fastidious organisms. *Bartonella* may be more common than the other 2 and has been reported as a cause of IE in 3% of cases in 3 different countries.[187] *Bartonella quintana* is the most commonly identified species, followed by *B henselae.* Treatment of this wide variety of microorganisms has been described anecdotally, and regimens of choice are based on limited data and can be found in other publications. Treatment choices for *Bartonella* endocarditis are included in Table 14 because it may be the most commonly seen form of endocarditis among those caused by fastidious organisms. Antibiotic regimens should include at least 2 weeks of aminoglycoside therapy.[187]

Noninfectious causes of valvular vegetations can produce a syndrome similar to culture-negative endocarditis. Perhaps the one that has received the most attention is antiphospholipid syndrome.[188] This syndrome has been described as both a primary and a secondary syndrome and is associated with the presence of antiphospholipid antibodies. In its secondary form, antiphospholipid 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 endocarditis. The mitral valve is most often affected, and valvular regurgitation is the predominant functional abnormality seen.

Numerous other causes of noninfective vegetative endocarditis can mimic IE. These can be categorized into 4 groups[184]: neoplasia associated (atrial myxoma, marantic endocarditis, neoplastic disease, and carcinoid); autoimmune associated (rheumatic carditis, systemic lupus erythematosus, polyarteritis nodosa, and Behçet's disease); postvalvular surgery (thrombus, stitch, or other postsurgery changes); and miscellaneous (eosinophilic heart disease, ruptured mitral chordae, and myxomatous degeneration).

Fungi

Fungal endocarditis is a relatively new syndrome and is often a complication of medical and surgical advances.[189,190] Patients who develop this illness usually have multiple predisposing conditions that often include the use of cardiovascular devices, in particular, prosthetic cardiac valves and central venous catheters. Despite aggressive combined medical and surgical interventions, mortality rates for fungal endocarditis are unacceptably high. The survival rate for patients with mold-related endocarditis is <20%.

Candida and *Aspergillus* species account for the large majority of fungal endocardial infections, and *Candida*-related endocarditis is much more common than *Aspergillus*-related disease.[189,190] Blood cultures are usually positive in 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 endocarditis, and when this occurs, it is usually in a patient with recent placement of a prosthetic cardiac valve.[189]

Historically, 2 treatment doctrines have prevailed in fungal endocarditis despite the lack of prospective trials conducted to define the most appropriate therapy. One doctrine is that

TABLE 14.   Therapy for Culture-Negative Endocarditis Including *Bartonella* Endocarditis

Regimen	Dosage* and Route	Duration, wk	Strength of Recommendation	Comments
Native valve				
Ampicillin-sulbactam	12 g/24 h IV in 4 equally divided doses	4–6	IIbC	Patients with culture-negative endocarditis should be treated with consultation with an infectious diseases specialist
plus				
Gentamicin sulfate†	3 mg/kg per 24 h IV/IM in 3 equally divided doses	4–6		
Vancomycin‡	30 mg/kg per 24 h IV in 2 equally divided doses	4–6	IIbC	Vancomycin recommended only for patients unable to tolerate penicillins
plus				
Gentamicin sulfate	3 mg/kg per 24 h IV/IM in 3 equally divided doses	4–6		
plus				
Ciprofloxacin	1000 mg/24 h PO or 800 mg/24 h IV in 2 equally divided doses	4–6		
	Pediatric dose§: ampicillin-sulbactam 300 mg/kg per 24 h IV in 4–6 equally divided doses; gentamicin 3 mg/kg per 24 h IV/IM in 3 equally divided doses; vancomycin 40 mg/kg per 24 h in 2 or 3 equally divided doses; ciprofloxacin 20–30 mg/kg per 24 h IV/PO in 2 equally divided doses			
Prosthetic valve (early, ≤1 y)				
Vancomycin	30 mg/kg per 24 h IV in 2 equally divided doses	6	IIbC	
plus				
Gentamicin sulfate	3 mg/kg per 24 h IV/IM in 3 equally divided doses	2		
plus				
Cefepime	6 g/24 h IV in 3 equally divided doses	6		
plus				
Rifampin	900 mg/24 h PO/IV in 3 equally divided doses	6		
	Pediatric dose: vancomycin 40 mg/kg per 24 h IV in 2 or 3 equally divided doses; gentamicin 3 mg/kg per 24 h IV/IM in 3 equally divided doses; cefepime 150 mg/kg per 24 h IV in 3 equally divided doses; rifampin 20 mg/kg per 24 h PO/IV in 3 equally divided doses			
Prosthetic valve (late, >1 y)		6	IIbC	Same regimens as listed above for native valve endocarditis with the addition of rifampin
Suspected *Bartonella*, culture negative				
Ceftriaxone sodium	2 g/24 h IV/IM in 1 dose	6	IIaB	Patients with *Bartonella* endocarditis should be treated in consultation with an infectious diseases specialist
plus				
Gentamicin sulfate	3 mg/kg per 24 h IV/IM in 3 equally divided doses	2		
with/without				
Doxycycline	200 mg/24 h IV or PO in 2 equally divided doses	6		
Documented *Bartonella*, culture positive				
Doxycycline	200 mg/24 h IV or PO in 2 equally divided doses	6	IIaB	If gentamicin cannot be given, then replace with rifampin, 600 mg/24 h PO/IV in 2 equally divided doses (see reference 187 in full statement)
plus				
Gentamicin sulfate	3 mg/kg per 24 h IV/IM in 3 equally divided doses	2		
	Pediatric dose: ceftriaxone 100 mg/kg per 24 h IV/IM once daily; gentamicin 3 mg/kg per 24 h IV/IM in 3 equally divided doses; doxycycline 2–4 mg/kg per 24 h IV/PO in 2 equally divided doses; rifampin 20 mg/kg per 24 h PO/IV in 2 equally divided doses			

*Dosages recommended are for patients with normal renal function.
†See text and Table 4 for appropriate dosing of gentamicin.
‡See Table 4 for appropriate dosing of vancomycin.
§Pediatric dose should not exceed that of a normal adult.

fungal endocarditis is a stand-alone indication for surgical replacement of an infected valve. The second is that amphotericin B, a fungicidal agent, is the drug of choice for fungal endocarditis. Because of the alarming mortality rate associated with fungal endocarditis and the availability of newer antifungal drugs, a reevaluation of these principles seems in order. If done, however, it will be based on anecdotal experience and expert opinion rather than on clinical trial data because of the rarity of the syndrome.

A 2-phase therapy has evolved in recent years. The initial or induction phase consists of control of infection. Treatment is a combination of a parenteral antifungal agent, usually an amphotericin B–containing product, and valve replacement. Most authorities agree that valve replacement is mandatory for prosthetic valve infection, regardless of fungal causes. If the patient survives, then antifungal therapy usually is given for ≥6 weeks.

After a clinical response to initial induction therapy, long-term (lifelong) suppressive therapy with an oral azole has been used.[191,192] Suppressive therapy has been used in 2 populations. First, because of the high relapse rate of fungal endocarditis 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 endocarditis, 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[191,192] indicate that infection has been successfully suppressed for months to years.

Endocarditis in IDUs

Acute infection accounts for ≈60% of hospital admissions among IDUs; IE is implicated in 5% to 15% of these episodes.[155] The exact incidence of IE in IDUs is unknown. A conservative estimate is 1.5 to 3.3 cases per 1000 person-years,[193,194] although 1 nested case-control study demonstrated that IE incidence was higher among HIV-seropositive IDUs than among HIV-seronegative IDUs (13.8 versus 3.3 cases per 1000 person-years) after accounting for IDU behaviors.[195] Injection drug use is the most common risk factor for development of recurrent native valve IE; 43% of 281 patients with this syndrome surveyed from 1975 to 1986 were IDUs.[196]

Mortality associated with IE among HIV-infected patients is affected by degree of immunosuppression. Patients who have severe immunosuppression and who meet the criteria for a diagnosis of AIDS have a higher mortality rate than do patients who are more immunocompetent.[197] HIV infection is not a contraindication for cardiac surgery, and postoperative complications, including mortality, are not increased in the HIV-infected population.[198]

It has proved difficult to accurately predict the presence of IE in febrile IDUs,[199] especially from history and physical examination findings alone,[200] although cocaine use by IDUs should heighten the suspicion of IE.[201] The most reliable predictors of IE in febrile IDUs are visualization of vegetations by echocardiography[200,202] and the presence of embolic

phenomena.[200] Although the clinical manifestations of IE are seen in IDUs, several distinctions are worthy of emphasis. Two thirds of these patients have no clinical evidence of underlying heart disease, and there is a predilection for the infection to affect the tricuspid valve. Only 35% of IDUs with IE demonstrate heart murmurs on admission.[155]

From 1977 to 1993, among 1529 episodes of IE in IDUs in Spain, the frequency of valvular involvement was as follows: tricuspid alone or in combination with others, 73%; aortic alone, 7%; mitral alone, 6%; and aortic plus mitral, 1.5%.[95] Left-sided involvement among IDUs has been more frequent in some series,[203] however, and may be increasing.[204] Biventricular and multiple-valve infections occur most commonly in *Pseudomonas* endocarditis[205] (see section on non-HACEK Gram-negative endocarditis). Recent analyses have demonstrated that although *S aureus* remains the most common cause of right-sided IE in IDUs, cases of left-sided IE in the population are caused equally by viridans group streptococci and *S aureus*.[204]

In patients with tricuspid valve infection, 30% have pleuritic chest pain; pulmonary findings may dominate the clinical picture, and the chest roentgenogram will document abnormalities (eg, infiltrates, effusion) in 75% to 85%.[206] Roentgenographic evidence of septic pulmonary emboli is eventually present in 87% of cases.[95,197] Signs of tricuspid insufficiency (systolic regurgitant murmur louder with inspiration, large V waves, or a pulsatile liver) are present in only one third of cases. Most (80%) of these patients are 20 to 40 years old and men (4 to 6:1). Almost two thirds have extravalvular sites of infection, which are helpful in diagnosis.[95,207]

Etiology of Endocarditis in IDUs

The organisms responsible for IE in IDUs require separate consideration because the distribution differs from that in other patients with IE. Although IE in IDUs usually is caused by *S aureus*[95] (see section on treatment of staphylococcal endocarditis), these patients also are at an increased risk for endocarditis resulting from unusual pathogens, including Gram-negative bacilli (see section on non-HACEK Gram-negative endocarditis), polymicrobial infections,[95] fungi,[189] group B streptococci,[208] and *S mitis*.[209] For example, the frequencies of the etiologic agents isolated before 1977 in 7 major series were as follows[210]: *S aureus*, 38%; *P aeruginosa*, 14.2%; *Candida* species, 13.8%; enterococci, 8.2%; viridans streptococci, 6.0%; *S epidermidis*, 1.7%; Gram-negative aerobic bacilli, 1.7% to 15%; other bacteria, 2.2%; mixed infections, 1.3%; and culture-negative, 12.9%. In addition, there appears to be an unexplained geographic variation in the causal agents of IDU-associated IE. *S aureus* predominated in New York City, Washington, DC, Chicago, and Cincinnati, Ohio. *P aeruginosa* was commonly isolated in Detroit, Mich, but ORSA now predominates. In the most recent compilation from Detroit, the distribution of causative agents in IDUs with IE (n=74) was *S aureus*, 60.8%; streptococci, 16.2%; *P aeruginosa*, 13.5%; polymicrobial, 8.1%; and *Corynebacterium* JK, 1.4%.[155] Polymicrobial endocarditis (up to 8 different pathogens have been recovered from blood cultures from

an individual patient) is fairly common among IDUs, occurring in 3% of 1529 episodes of endocarditis in Spain.[95]

The emergence of ORSA in IDUs with staphylococcal IE, first documented in the Detroit area, is disturbing.[154,155,211] Among 180 IDUs with bacteremia who were admitted to the Detroit Medical Center in 1 year, 24% developed ORSA, and 41% of patients overall had IE. Previous hospitalizations, long-term addiction (particularly in men), and use of nonprescribed antibiotics were predictive of ORSA acquisition (odds ratio 8.6:1).[154]

Complications and Their Treatment

Surgical Therapy

Decisions regarding surgical intervention in patients with IE should be individualized, with input from both the cardiologist and the cardiovascular surgeon. If a patient with IE is receiving long-term oral anticoagulation, coumadin therapy should be discontinued and replaced by heparin immediately after the diagnosis of IE has been established in the event that surgical intervention is required.

Patients with IE and CHF, irrespective of the mechanism, should be immediately evaluated for possible surgical therapy (Class I, Level of Evidence: B). Despite a higher operative mortality rate in patients with CHF than in those without CHF, patients with IE who have CHF and undergo valve surgery have a substantially reduced mortality rate compared with those treated with medical therapy alone.[212] The incidence of reinfection of newly implanted valves in patients with active IE is ≈2% to 3%[213,214] and is far less than the mortality rate for IE and CHF without surgical therapy, which can be as high as 51%.[212] Surgical approaches to CHF caused by different mechanisms are discussed in the section on CHF.

Other clinical situations in which surgical intervention should be considered are fungal IE, infection with aggressive antibiotic-resistant bacteria or bacteria that respond poorly to antibiotics, left-sided IE caused by Gram-negative bacteria such as *S marcescens* and *Pseudomonas* species, persistent infection with positive blood cultures after 1 week of antibiotic therapy, or 1 or more embolic events during the first 2 weeks of antimicrobial therapy (Class I, Level of Evidence: B).

Consideration of surgical intervention also is warranted when there is echocardiographic evidence of valve dehiscence, perforation, rupture, or fistula, or a large perivalvular abscess (Class I, Level of Evidence: B). Other echocardiographic findings that indicate the possible need for surgery are anterior mitral leaflet vegetation (particularly with size >10 mm) or persistent vegetation after systemic embolization (Class IIa, Level of Evidence: B) and an increase in vegetation size despite appropriate antimicrobial therapy (Class IIb, Level of Evidence: C; Table 3). Decision making regarding the role of surgical intervention to prevent systemic embolization is complex and must be individualized to the patient. Benefit is greatest in the early phase of IE, when embolic rates are highest and other predictors of a complicated course (eg, recurrent embolization and prosthetic valve endocarditis) are present.[54] The greatest risk of embolization appears to occur with vegetations >10 mm in diameter occurring on the anterior mitral leaflet[51,52] and during the first 1 to 2 weeks of therapy.[53]

Prosthetic valve IE, particularly early prosthetic valve IE (<12 months after valve replacement), often is caused by infection by *Staphylococcus* species and may be particularly severe, with perivalvular abscess and valve dehiscence. For these reasons, surgical intervention is more commonly indicated in prosthetic valve endocarditis than in native valve infection. Even in patients with prosthetic valve IE, however, decisions regarding surgical intervention are complex and depend on many individual factors that vary among patients, including infective organism, vegetation size, presence of perivalvular infection, presence of embolism or heart failure, age, and noncardiac morbidities.

Congestive Heart Failure

Many studies during the past 3 decades have demonstrated that among the complications of IE, CHF has the greatest impact on prognosis.[212–215] Moderate to severe CHF was identified as 1 of 5 baseline features that were independently associated with 6-month mortality in an investigation[216] to validate a prognostic classification system for adults with complicated left-sided native valve IE. In native valve IE, acute CHF occurs more frequently in aortic valve infections (29%) than with mitral (20%) or tricuspid disease (8%).[212] In addition, the degree of tolerance of CHF is valve dependent, with acute aortic regurgitation being least tolerant and acute tricuspid regurgitation most tolerant. The tolerance for acute mitral regurgitation is intermediate. CHF may develop acutely from perforation of a native or bioprosthetic valve leaflet, rupture of infected mitral chordae, valve obstruction by bulky vegetations, or sudden intracardiac shunts from fistulous tracts or prosthetic dehiscence. Mitral valve preclosure that can be detected by both physical examination and echocardiography should be screened for in each case.

CHF also may develop more insidiously despite administration of appropriate antibiotics as a result of progressive worsening of valvular insufficiency and ventricular dysfunction. Patients who have normal ventricular function or only mild CHF when IE is initially diagnosed may progress to severe CHF during treatment, and two thirds of these patients will do so within the first month of therapy.[212] CHF in IE, irrespective of the course or mechanism, portends a grave prognosis with medical therapy alone and also is the most powerful predictor of poor outcome with surgical therapy.[214]

Echocardiographic evaluation of IE patients delineates the causes and severity of CHF. Ventricular size, wall motion, and dynamic function can be readily defined and valve insufficiency quantified. Progressive chamber enlargement, elevation of pulmonary arterial pressures, and increasing wall stress on serial evaluation all indicate a trend toward decompensation. Medical and surgical treatment decisions can be guided by echocardiographic detection of fistulae, prosthetic dehiscence, obstructive vegetations, or flail leaflets, none of which will resolve with medical therapy alone. In addition, detection of myocardial abscess is important because many will not resolve without surgical intervention. Table 3 lists the echocardiographic features that suggest the potential need for surgical intervention.[217]

The decision to operate on patients with IE is driven primarily by severity of CHF. Poor surgical outcome is predicted by preoperative New York Heart Association Class III or IV CHF, renal insufficiency, and advanced age. In any patient, a decision to delay surgery to extend preoperative antibiotic treatment carries the risk of permanent ventricular dysfunction and should be discouraged. The incidence of reinfection of newly implanted valves in patients with active IE has been estimated to be 2% to 3%,[218,219] far less than the mortality rate for uncontrolled CHF.

Surgical approaches to IE patients with CHF must take into account the distortion of the valve and its surrounding structures. Severe valvular disruption usually will require prosthetic replacement. Ruptured mitral chordae may sometimes be repaired with a combination of leaflet resection, chordal reattachment or transposition, and annular support. Leaflet perforations may be repaired with small pericardial patches if the surrounding leaflet tissue is well preserved and valve motion can be maintained. Similarly, in selected cases, discrete vegetations on aortic or mitral leaflets have been excised along with underlying leaflet tissue ("vegetectomy") and repaired with a patch. To date, clinical experience with vegetation excision has been predominantly limited to mitral valve IE. Recent experiences in Europe have emphasized the potential for early valve repairs when feasible, especially in patients with anterior mitral valve IE and even in the absence of other conventional indicators for surgical interventions.[220–222] This approach has a 2-fold potential benefit: Because >50% of patients with left-sided native valve IE will require valve replacement surgery within 10 to 15 years of the IE episode,[223] this "preemptive" repair strategy has the advantage of earlier-age intervention; and this approach may circumvent ultimate valve replacement requirements, with the attendant risks of long-term anticoagulation.

Risk of Embolization

Systemic embolization occurs in 22% to 50% of cases of IE.[50,52,224–226] Emboli often involve major arterial beds, including the lungs, coronary arteries, spleen, bowel, and extremities. Up to 65% of embolic events involve the central nervous system, and >90% of central nervous system emboli lodge in the distribution of the middle cerebral artery.[226] The highest incidence of embolic complications is seen with aortic and mitral valve infections and in IE caused by *S aureus*, *Candida*, HACEK, and *Abiotrophia* 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.[227] Of note, 2 independent studies have confirmed that the rate of embolic events drops dramatically during or 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.[52] In a more recent study, Vilacosta et al[227] 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 causes.

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.[50] DeCastro and colleagues[225] compared TTE with multiplane TEE and found that neither technique was helpful in defining embolic risk in patients with vegetations. In a study[52] based on TEE, mitral vegetations >1 cm in diameter were associated with the greatest frequency of embolism. The association was strengthened when 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.[54] 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.[54,58] This suggests that the mechanical effects of broad and abrupt leaflet excursion, occurring twice per heartbeat, may contribute to the propensity of a vegetation 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.[54] In contrast, as confirmed above by Vilacosta et al,[227] staphylococcal or fungal IE appears to carry a high incidence rate of embolization independent of vegetation size.

The role of echocardiography in predicting embolic events has been controversial. In 1 survey[228] 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%).

An increase in vegetation size over 4 to 8 weeks of therapy as documented by TEE does appear to predict embolic events. 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.[58]

The traditional indications for valvular surgery for IE to avoid embolization have been ≥2 major embolic events.[229] These criteria are arbitrary and exclude cutaneous embolization, which is common, or embolism occurring before the institution of therapy.[229] 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 the immediate and lifelong risks of valve replacement. At this time, the strategy for surgical intervention to avoid systemic emboli-

zation 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; CHF; aggressive, antibiotic-resistant organisms; or prosthetic valve IE) are present (Table 3).

In one analysis, an embolic event was 1 of 4 early predictors of in-hospital death caused by IE.[230] 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.

Anticoagulation

Anticoagulation in IE patients is controversial, particularly in mechanical valve endocarditis.[231] In general, in patients with native valve disease, the benefit of anticoagulation has never been demonstrated convincingly. In contrast, some authorities recommend continuation of therapy in patients with mechanical prosthetic valve IE; however, the general advice is to discontinue all anticoagulation in patients with *S aureus* prosthetic valve IE who have experienced a recent central nervous system embolic event for at least the first 2 weeks of antibiotic therapy.[232] 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 caution, and prothrombin times should be monitored carefully.

In a follow-up to experimental data that demonstrated a salutary effect of intravenous aspirin therapy in established experimental *S aureus* endocarditis,[233] a recent randomized trial in Canada compared oral aspirin 325 mg/d with placebo in 115 endocarditis patients. No compelling benefit was observed, however, in aspirin-treated patients in terms of vegetation resolution and embolic events.[234] Moreover, there was a trend toward more bleeding episodes in the aspirin-treated patients. Aspirin levels, a critical correlate of antimicrobial efficacy, were not monitored in this study, however.[235] Until further definitive data are available, the routine use of aspirin for established endocarditis is not recommended (Class III, Level of Evidence: B).

Periannular Extension of Infection

Extension of IE beyond the valve annulus predicts a higher mortality rate, more frequent development of CHF, and more frequent cardiac surgery.[229,236,237] Perivalvular cavities form when annular infections break through and spread into contiguous tissue. In native aortic valve IE, this generally occurs through the weakest portion of the annulus, which is near the membranous septum and atrioventricular node.[238] The anatomic vulnerability of this area explains both why abscesses occur in this location and why heart block is a frequent sequela.[237] Periannular extension is common, occurring in 10% to 40% of all native valve IE and complicating aortic IE more commonly than mitral or tricuspid IE.[239–242] Periannular infection is of even greater concern with prosthetic valve IE, occurring in 56% to 100% of patients.[237,241] Perivalvular abscesses are particularly common with prosthetic valves because the annulus, rather than the leaflet, is the

usual primary site of infection.[241] Most periannular infections involving the mitral area are associated with prosthetic mitral valves.

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 1 series[243] 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, prosthetic valve involvement, 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 fistulae may be catastrophic; even if their hemodynamic impact is tolerated, such 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, CHF, or a new pathological murmur in a patient with IE on appropriate antibiotics may suggest extension.[242] Only aortic valve involvement and recent injection drug use have been prospectively identified as independent risk factors for perivalvular abscess.[236] On ECG, new atrioventricular block has a positive predictive value of 88% for abscess formation but low (45%) sensitivity.[237]

Patients at risk for perivalvular extension of IE require prompt evaluation. The size of vegetations is not helpful for predicting perivalvular extension.[236] The sensitivity of TTE for detecting perivalvular abscess is low (18% to 63% in prospective and retrospective studies, respectively).[244,245] TEE dramatically improves 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).[49,246] When combined with spectral and color Doppler techniques, TEE can demonstrate the distinctive flow patterns of fistulae and pseudoaneurysms and can rule out communications from unruptured abscess cavities. Because of these combined capabilities, TEE is the modality of choice for the initial assessment of any patient suspected of having perivalvular extension of IE (Class I, Level of Evidence: A).

A small number of patients with periannular extension of infection or myocardial abscess may be treated successfully without surgical intervention.[247,248] 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, as well as correction of hemodynamic abnormalities. Drainage of abscess cavities, excision of necrotic tissue, and closure of fistulous tracts often accompany valve replacement surgery.[249] Although valve replacement is usually required, it

may be complicated in the face of extensive destruction of the periannular supporting tissues. Under these conditions, human aortic homografts, when available, can be used to replace the damaged aortic valve, as well as to reconstruct the damaged aorta.[250,251] Homografts have a constant but low incidence rate of development of sewing-ring infections and mural IE, possibly related to the improved penetration of antibiotics.[252] Some groups have recently advocated the use of "stentless" or "ministented" aortic valve prostheses with debridement in the same clinical scenario, particularly if homografts are not readily available.[253]

Splenic Abscess

Splenic abscess is a well-described but rare complication of IE. This infection develops by 1 of 2 mechanisms: bacteremic seeding of a bland infarction, created via splenic arterial occlusion by embolized vegetations, or direct seeding of the spleen by an infected embolus also originating from an infected valvular vegetation. Although splenic infarction is a common complication of left-sided IE ($\approx$40% of cases), it is estimated that only $\approx$5% of patients with splenic infarction will develop splenic abscess.[254–256] Reflecting their overall high frequencies in IE, viridans streptococci and *S aureus* each account for $\approx$40% of cases in which splenic abscess cultures are positive, whereas enterococci account for 15% of cases. Aerobic Gram-negative bacilli and fungi are isolated in <5% of cases. Clinical splenomegaly, which is present in up to 30% of cases of IE, is not a reliable sign of splenic infarction or abscess. Splenic infarction delineated by imaging techniques often is asymptomatic[256]; pain in the back, left flank, or left upper quadrant, or abdominal tenderness may be associated with either splenic infarction or abscess.[257,258] Splenic rupture with hemorrhage is a rare complication of infarction. Persistent or recurrent bacteremia, persistent fever, or other signs of sepsis are suggestive of splenic abscess, and patients with these findings should be evaluated via one or more of the imaging studies discussed below.

Abdominal CT and MRI appear to be the best tests for diagnosing splenic abscess, with both sensitivities and specificities ranging from 90% to 95%. On CT, splenic abscess is frequently seen as single or multiple contrast-enhancing cystic lesions, whereas infarcts typically are peripheral low-density, wedge-shaped areas. On ultrasonography, a sonolucent lesion suggests abscess. ^{99m}Tc liver-spleen scans, labeled white blood cell scans, and gallium scans have become obsolete in the diagnosis of splenic abscess.

Differentiation of splenic abscess from bland infarction may be difficult. Infarcts generally are associated with clinical and radiographic improvement during appropriate antibiotic therapy. Ongoing sepsis, recurrent positive blood cultures, and persistence or enlargement of splenic defects on CT or MRI suggest splenic abscess, which responds poorly to antibiotic therapy alone. Definitive treatment is splenectomy with appropriate antibiotics, and this should be performed immediately unless urgent valve surgery also is planned. Percutaneous drainage or aspiration of splenic abscess has been performed successfully,[259,260] and this procedure may be an alternative to splenectomy for the patient who is a poor surgical candidate. A recent report emphasized the use of laparoscopic splenectomy as an alternative to formal laparotomy approaches.[261] If possible, splenectomy should be performed before valve replacement surgery to mitigate the risk of infection of the valve prosthesis as a result of the bacteremia from the abscess.

Mycotic Aneurysms

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.[262,263]

Intracranial MAs

Neurological complications develop in 20% to 40% of patients with IE.[226,263] Intracranial MAs (ICMAs) represent a relatively small but extremely dangerous subset of these 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%.[264,265] The reported occurrence of ICMAs in 1.2% to 5% of cases[265–268] is probably underestimated because some ICMAs remain asymptomatic and resolve with antimicrobial therapy. Streptococci and *S aureus* account for $\approx$50% and $\approx$10% of cases, respectively,[256,268] and are seen with increased frequency among IDUs with IE.[268] The distal middle cerebral artery branches are most often involved, especially the bifurcations. ICMAs occur multiply in 20% of cases[267]; mortality rates are similar for multiple or single distal ICMAs. The mortality rate for patients with proximal ICMAs is >50%.[269]

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.[264,267] 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.[264]

In the absence of clinical signs or symptoms of ICMAs, routine screening with imaging studies is not warranted. Symptomatic cerebral emboli frequently but not invariably precede the finding of an ICMA.[269] Accordingly, 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.

Noncontrast CT may provide useful initial information in patients who are suspected of having an ICMA.[270] This technique has a sensitivity of 90% to 95% for intracerebral bleeding and may indirectly identify the location of the MA.

Magnetic resonance angiography (MRA; noncontrast or contrast enhanced) and contrast-enhanced computed tomography angiography (CTA) are noninvasive methods used to detect ICMAs. Although these methods may someday replace conventional catheter angiography, at present they should be considered screening techniques. CTA can be performed more rapidly than MRA, although the contrast load may be substantial, which is a significant concern in patients with renal insufficiency and/or CHF. These methods have similar sensitivity and specificity (90% to 95%) for detecting ICMAs, although rapid improvements in technology continue to advance both techniques. Both techniques also are far less accurate in identification of small (<5 mm) aneurysms.[270,271]

Conventional cerebral angiography remains the diagnostic imaging test for diagnosing ICMAs.[266] The accuracy of this method recently has been enhanced by the use of a 3-dimensional rotation technique that improves spatial resolution in comparison with conventional 2-dimensional technology.[272] In most cases, MRI/MRA or CT/CTA can provide sufficient information to identify and monitor intracranial aneurysms. Conventional angiography is required when suspicion remains and the results of less-invasive studies are negative, particularly in the context of small (≤5 mm) ICMAs.

ICMAs may heal with medical therapy. Bingham[273] reported that ICMAs resolved between initial and follow-up angiography in 52% of patients treated with effective antibiotic therapy. A decrease in ICMA size was observed in an additional 29% of patients. In 19% of patients, however, ICMA increased in size by the time of the second angiogram, and in 10%, a new ICMA was discovered. Although it is clear that in many patients, ICMAs treated with antibiotics alone will heal, in others, rupture may lead to significant morbidity or death. The risk of intervention is affected by the patient's age, underlying comorbid conditions, and the location of the ICMA. Currently, no data precisely identify patients at risk for "imminent rupture," and decisions concerning medical versus surgical therapy must be individualized. It is generally believed that a single ICMA distal to the first bifurcation of a major artery (eg, middle cerebral artery) should be monitored with frequent serial imaging (CTA, MRA, or conventional angiography) and treated promptly if the aneurysm enlarges or bleeds.[265] Multiple ICMAs present a complex problem and should be monitored closely. ICMAs that occur proximal to the first bifurcation are less amenable to surgical excision. Such ICMAs frequently arise from major vessels, and ligation may result in severe neurological deficits. As with distal aneurysms, proximal lesions should be monitored with serial neuroimaging, and if signs of enlargement or leakage develop, intervention should be strongly considered. Occasionally, proximal ICMAs stabilize and form a thrombus with antimicrobial therapy.

More recently, endovascular treatment of ICMAs has been used as an alternative to surgical clipping or ligation. The less-invasive nature of endovascular treatment is an advantage, permitting the treatment of patients who might otherwise be poor candidates for intervention. Several recent case series have reported that this treatment can be used successfully in IE-related aneurysms. For example, Chapot et al[274]

recently reviewed their experiences with endovascular treatment in 18 ICMAs among 14 IE patients in France; most ICMAs were located within the distal cerebral circulation. Late follow-up cerebral angiography with cyanoacrylate, autologous clots, and detachable or fibered coils showed stable aneurysm occlusion, and 10 of 14 patients experienced a normal long-term neurological outcome.

Some patients with IE require both cardiac valve replacement and ICMA ligation. Although data are limited in this situation, an approach that uses staged procedures, with the more severe problem dictating the procedure to be performed first, has been suggested. A bioprosthetic valve, which does not require that the patient receive anticoagulant therapy, may be preferable to a mechanical valve under this circumstance. To prevent hemorrhagic complications, it has been suggested that valve surgery be delayed for a minimum of 2 weeks after either a central nervous system embolic event or bleed or repair of ICMAs.

Extracranial MAs

Intrathoracic or intra-abdominal MAs often are asymptomatic until leakage or rupture occurs. Presumably, most extracranial MAs (ECMAs) will rupture if not excised. The appearance of a tender, pulsatile mass in a patient with IE should suggest an ECMA. 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 ECMA into the small or large bowel.

Proximal and distal ligation with excision of all infected material is ideal but generally not feasible. Moreover, the risk of reinfection and rupture of interposed vascular grafts is high. Revascularization usually is established via extra-anatomic routes through uninfected tissue planes. Autologous venous grafts have a lower risk of recurrent infection than do synthetic materials.[275,276] Long-term suppressive oral antimicrobial therapy may be desirable in patients at high risk of recurrence of infection, such as those with interposed vascular grafts in infected areas.

Despite improved diagnostic techniques and more aggressive surgical therapy, the mortality rate among patients with IE and ECMA is high and is attributable to suture-line infection with vessel or graft rupture. For most patients, however, surgical intervention represents the only hope for radical cure of ECMAs and an improved chance of survival.

Outpatient Therapy

Outpatient parenteral antibiotic therapy (OPAT) has been shown to be efficacious, safe, and cost-effective for a variety of chronic infections that require prolonged parenteral therapy in selected patients who otherwise do not require hospitalization. Antibiotic regimens recommended for endocarditis require ≥2 weeks of therapy, usually by the intravenous route. Absorption of orally administered antimicrobial agents may be unreliable and is generally not recommended for the treatment of endocarditis, especially during the initial phase of therapy. Economic pressures have encouraged shorter hospital stays for endocarditis patients either by use of shorter courses of intravenous antimicrobial therapy for selected

indications or outpatient administration of intravenous antibiotic therapy. Indeed, in a review of the experience from the OPAT Outcome Registry of 7800 patients treated at 24 US medical centers since 1966, Tice[277] reported in 2001 that 198 patients received a diagnosis of endocarditis. At present, however, there is no controlled experience comparing outcomes of inpatient versus outpatient parenteral antimicrobial therapy for endocarditis.

Monteiro and Cobbs[278] reviewed 14 studies of OPAT for endocarditis published in the English-language medical literature; of a total of 277 patients, 223 were available for clinical assessment at the end of therapy. The authors concluded that patients with penicillin-susceptible viridans streptococcal endocarditis (penicillin MIC <0.1 μg/mL) whose disease was apparent for <3 months and who had no important complications at the time of admission generally did well with outpatient intravenous therapy (ie, 2 weeks of β-lactam plus an aminoglycoside or 4 weeks of a β-lactam such as ceftriaxone) alone.

The timing for transition from inpatient intravenous antibiotic therapy to OPAT and patient exclusions have been critically evaluated by Andrews and von Reyn[279] after 2 of their patients died while receiving OPAT. The guidelines they developed 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 considering outpatient therapy, 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 the administration of parenteral therapy at home should be at low risk for the complications of endocarditis, the most frequent of which are CHF and systemic emboli. The period of greatest risk for systemic emboli is before or within the first 1 to 2 weeks of antimicrobial therapy. CHF and rupture of an MA may develop weeks to months after antimicrobial therapy, however. The presence of poorly controlled CHF, neurological findings that may result from systemic emboli or bleeding MAs, cardiac conduction abnormalities, valve ring abscesses (usually detected by TEE), persistent fever, positive blood cultures, and (usually) prosthetic valve endocarditis should preclude home intravenous therapy.

Although the risk for embolic events usually wanes after 2 weeks of antimicrobial therapy, the risk for drug-related side effects usually increases with increased time of drug exposure (eg, vestibular, auditory, and nephrotoxicity from aminoglycosides,[280] leukopenia and thrombocytopenia from β-lactams and vancomycin, and nephrotoxicity from the combination of vancomycin and gentamicin) and requires close observation by the home infusion team and experienced physicians.

Although a 2-week inpatient regimen of nafcillin plus gentamicin for uncomplicated *S aureus* right-sided endocarditis, which usually occurs in IDUs, has been shown to be effective, outpatient therapy for IDUs may be problematic because of compliance difficulties and misuse of intravenous access in this population.

The following criteria are essential for an effective OPAT program:

- A reliable support system at home and easy access to a hospital for prompt reevaluation by an experienced physician should a complication develop, such as recurrence of fever, symptoms of a cardiac arrhythmia, CHF, or a neurological event
- 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, infection, leakage, displacement) directly related to the antibiotics or intravenous access
- Regular visits (eg, on a weekly basis) with an experienced physician to assess clinical status while receiving OPAT

Other criteria that should be considered when treating patients with OPAT are outlined elsewhere.[281]

Care at Completion of Treatment

Short-Term Follow-Up

The majority of patients with IE are cured with appropriate medical and, if necessary, surgical treatment. Before completing antimicrobial therapy, the patient should receive TTE (Class IIb, Level of Evidence: C) to establish a new baseline for subsequent comparison (Table 16). A referral to a program to assist in cessation of drug use should be made for IDU patients. Patients should be educated about the signs of endocarditis and urged to seek immediate medical attention should they occur. A thorough dental evaluation should be obtained and all active sources of oral infection should be eradicated. All catheters used to infuse antimicrobial treatment should be promptly removed at the end of therapy.

In the short-term follow-up, patients should be monitored for development of several complications (Table 16). A relapse of endocardial infection 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 obtaining ≥ 3 sets of blood cultures from different phlebotomy sites after a thorough history and physical examination. Every effort should be made to determine the cause of relapsing symptoms of systemic toxicity and to avoid prescribing empiric antibiotic therapy for an undefined febrile illness. Other patients who have completed therapy and do not have symptoms of systemic toxicity should undergo an examination during the first month after completing antibiotic therapy.

Developing or worsening CHF is a second complication that must be considered during short-term follow-up. Although new onset of CHF caused by valvular dysfunction is unlikely during this period, valvular competency can deteriorate and may result from ongoing infection or stress unrelated to infection on a malfunctioning dynamic cardiac structure. In addition to physical examination, echocardiographic findings can support this diagnosis. If CHF develops or worsens, the patient should be evaluated immediately for cardiac and cardiothoracic surgery.

Antibiotic toxicity can occur after completing treatment and is the third complication that must be considered during short-term follow-up. Two drug-related adverse events are concerns. The first is delayed toxicity because of the previous use of aminoglycosides. Audiological and vestibular toxicity can develop despite the maintenance of

TABLE 15.   Epidemiological Clues in Etiological Diagnosis of Culture-Negative Endocarditis

Epidemiological Feature	Common Microorganism(s)
Injection drug use	*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, 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	Viridans group streptococci "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 patients	*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–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 transplant	*S aureus* *Aspergillus fumigatus* *Enterococcus* sp *Candida* sp
Gastrointestinal lesions	*S bovis* *Enterococcus* sp *Clostridium septicum*

TABLE 16.   Care During and After Completion of Antimicrobial Treatment

Initiate before or at completion of therapy

Obtain transthoracic echocardiogram to establish new baseline

Drug rehabilitation referral for patients who use illicit injection drugs

Educate regarding signs of endocarditis, need for antibiotic prophylaxis for certain dental/surgical/invasive procedures

Thorough dental evaluation and treatment if not performed earlier in evaluation

Prompt removal of IV catheter at completion of antimicrobial therapy

Short-term follow-up

Obtain 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 congestive heart failure

Evaluate for toxicity resulting from current/previous antimicrobial therapy

Long-term follow-up

Obtain 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

appropriate serum drug concentrations during treatment. Serial audiograms should be performed during therapy (Class IIb, Level of Evidence: C). 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 diarrhea and colitis caused by the overgrowth of *Clostridium difficile* and toxin. Onset of diarrhea can be delayed as long as 4 weeks after the last dose of antibiotic. Early treatment of *C difficile* colitis can prevent the development of colitis-related complications.

Long-Term Follow-Up

Months to years after completion of medical therapy for IE, patients need ongoing observation and education regarding recurrent infection and delayed onset of worsening valvular dysfunction (Table 16). Ongoing daily dental hygiene should be stressed, with serial evaluations by a dentist who is familiar with this patient population. Patients should be questioned about the symptoms of decreased cardiac output and CHF. A thorough cardiac examination will be needed. Additional evaluations with TTE will be necessary in selected patients with positive findings from history and physical examination. Patients must be reminded to seek immediate medical evaluation for fever (Table 16). This is necessary because IE can mimic a panoply of febrile illnesses. Antibiotic therapy should not be initiated for treatment of undefined febrile illnesses without obtaining previous blood cultures. Antibiotics prescribed for nonspecific or unproved febrile syndromes are the major cause of (blood) culture-negative endocarditis and should be strongly discouraged.

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Writing Group Member	Employment	Research Grant/Other Research Support	Speakers Bureau/Honoraria	Ownership Interest	Consultant/Advisory Board	Other
Larry M. Baddour	Mayo Clinic	None	None	None	None	None
Walter R. Wilson	Mayo Clinic	None	None	None	None	None
Arnold S. Bayer	University of California-Los Angeles	Pfizer, Inhibitex, Catalyst Pharmaceuticals	None	None	Pfizer, Inhibitex, Catalyst Pharmaceuticals	None
Vance G. Fowler, Jr	Duke University Medical Center	Cubist, Inhibitex, Merck, Nabi Biopharmaceuticals, Theravance, NIH, Vicuron Pharmaceuticals	Cubist, Pfizer	None	Cubist, Elusys, Inhibitex, Merck, Nabi Biopharmaceuticals	None
Ann F. Bolger	University of California-San Francisco	None	None	None	None	None
Matthew E. Levison	Drexel University College of Medicine	None	Wyeth Laboratories	None	None	None
Patricia Ferrieri	University of Minnesota Medical School	None	None	None	None	None
Michael A. Gerber	Cincinnati Children's Hospital Medical Center	None	None	None	None	None
Lloyd Y. Tani	University of Utah School of Medicine	None	None	None	S.T.A.B.L.E Program	None
Michael H. Gewitz	Children's Hospital of Westchester, New York Medical College	None	None	None	None	None
David C. Tong	Stanford University	None	Boerhinger-Ingelheim, Sanofi, Bristol-Myers Squibb, Wyeth Laboratories	None	None	None
James M. Steckelberg	Mayo Foundation	None	None	None	None	None
Robert S. Baltimore	Yale University School of Medicine	None	None	None	None	None
Stanford T. Shulman	Children's Memorial Hospital, Chicago	None	None	None	None	None
Jane C. Burns	University of California-San Diego	Centocor	None	None	Bristol-Myers Squibb	None
Donald A. Falace	University of Kentucky	None	None	None	None	None
Jane W. Newburger	Boston Children's Heart Foundation	Philips	None	None	None	None
Thomas J. Pallasch	None	None	None	None	None	None
Masato Takahashi	Children's Hospital Los Angeles; University of Southern California School of Medicine	None	None	None	None	None
Kathryn A. Taubert	American Heart Association	None	None	None	None	None

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Blase A. Carabello	Veterans Affairs Medical Center	None	None	None	None	None
David L. Longworth	Tufts University School of Medicine	None	None	None	None	Drug and Safety Monitoring committee member of a pharmaceutical trial sponsored by Cubist
Patrick O'Gara	Harvard Medical School	None	None	None	None	None
Neal Kon	Wake Forest University School of Medicine	None	None	None	None	None
Bruce Lytle	The Cleveland Clinic Foundation	None	None	None	None	None

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Larry M. Baddour, Walter R. Wilson, Arnold S. Bayer, Vance G. Fowler, Jr, Ann F. Bolger, Matthew E. Levison, Patricia Ferrieri, Michael A. Gerber, Lloyd Y. Tani, Michael H. Gewitz, David C. Tong, James M. Steckelberg, Robert S. Baltimore, Stanford T. Shulman, Jane C. Burns, Donald A. Falace, Jane W. Newburger, Thomas J. Pallasch, Masato Takahashi and Kathryn A. Taubert

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Correction

In the AHA Scientific Statement, "Infective Endocarditis: Diagnosis, Antimicrobial Therapy, and Management of Complications: A Statement for Healthcare Professionals From the Committee on Rheumatic Fever, Endocarditis, and Kawasaki Disease, Council on Cardiovascular Disease in the Young, and the Councils on Clinical Cardiology, Stroke, and Cardiovascular Surgery and Anesthesia, American Heart Association," by Baddour et al (*Circulation*. 2005;111:e394–e434), the following corrections/clarifications should be made:

1. There were two errors in Table 12 on page e413. In the "Ceftriaxone sodium" row, the entry in the "Dosage and Route" column originally read "2 g/24 h IV/IM in 1 dose" but should have read "4 g/24 h IV/IM in 2 equally divided doses." In the "Pediatric dose" entry in the "Dosage and Route" column, the entry originally gave the dosage of ceftriaxone as "100 mg/kg per 24 h IV/IM once daily" but should have read "100 mg/kg per 24 h IV/IM in 2 equally divided doses."

   Although an every-24-hour dosing of ceftriaxone has never been formally studied in human trials in combination with ampicillin for the treatment of multidrug-resistant *Enterococcus faecalis*, unpublished animal model data indicate that every-12-hour dosing of ceftriaxone in combination with ampicillin is more efficacious in reducing the bacterial concentration in infected vegetations as compared with every-24-hour dosing of ceftriaxone with ampicillin. Therefore, the recommendation was changed to 2 equally divided doses per 24 hours.

2. In Table 14, for the section "Prosthetic valve (late, >1 y)," the Comments section should read: "Same regimens as listed above for native valve endocarditis with the addition of rifampin."

3. In Tables 9 and 10, the following sentence should be deleted from the footnotes: "Patients with creatinine clearance of <50 mL/min should be treated in consultation with an infectious diseases specialist." In Tables 11 and 14, the following portion of the first footnote should be deleted: "...see Table 9 for patients with creatinine clearance of <50 mL/min."

4. In the third footnote of Table 7 and the second footnote of Table 8 ("Gentamicin should be..."), a second sentence should be added, which reads: "See Table 4 for appropriate dosage of gentamicin." In Table 9, the second footnote should also refer the reader to Table 4 for appropriate dosage of gentamicin.

5. Although it is preferred that gentamicin (3 mg/kg) be given as a single daily dose to adult patients with endocarditis due to viridans group streptococci, as a second option, gentamicin can be administered daily in 3 equally divided doses (see Tables 4 through 6).

6. Table 4, titled "Therapy of Native Valve Endocarditis Caused by Highly Penicillin-Susceptible Viridans Group Streptococci and *Streptococcus bovis*," lists reference No. 280 that refers to a nomogram for dosing gentamicin. Although this reference outlines dosing for gentamicin use at 7 mg/kg/dose for treatment in other types of infection syndromes, the nomogram was selected as an example for use with gentamicin dosing of 3 mg/kg/dose in this table to direct dosing in patients with underlying renal dysfunction. Currently, there is no other formal address of drug concentration monitoring with this gentamicin dosage.

7. On page e403, in the section on "*Abiotrophia defectiva* and *Granulicatella* Species, *Gemella* Species, and Viridans Group Streptococci With Penicillin MIC >0.5 μg/mL," the following should be added as the last sentence of the section: "When vancomycin is the chosen antibiotic, the addition of gentamicin is not necessary."