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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—Executive Summary: Endorsed by the Infectious Diseases Society of America

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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—Executive Summary

Endorsed by the Infectious Diseases Society of America

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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 executive summary addresses the major points detailed in the larger document that contains more extensive background information and pertinent references. 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 summary 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;111:3167-3184.)

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

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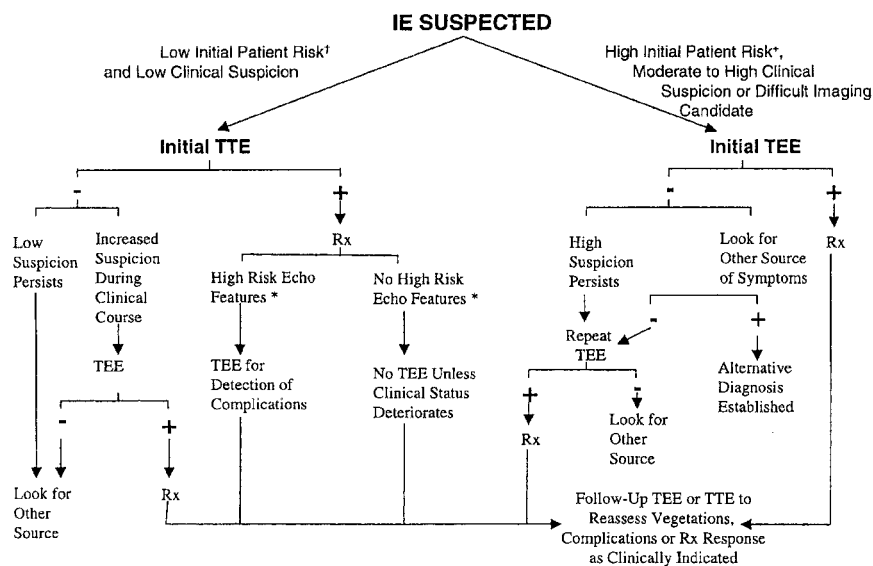
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An approach to the diagnostic use of echocardiography (echo). *High-risk echocardiographic features include large and/or mobile vegetations, valvular insufficiency, suggestion of perivalvular extension, or secondary ventricular dysfunction (see text). †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.

This statement updates and revises recommendations for the diagnosis and management of infective endocarditis (IE) published by the American Heart Association Committee on Rheumatic Fever, Endocarditis, and Kawasaki Disease in 1995. In addition, it updates and incorporates recommendations for the management of complications in IE published by the same committee in 1998. (These recommendations are available in their entirety at <http://www.americanheart.org/presenter.jhtml?identifier=3004539>.) The present Writing Committee conducted a comprehensive review of the literature published between 1990 and 2004 to assist the group in updating the previous versions 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*.

This Executive Summary highlights some of the important clinical issues in the diagnosis and management of IE. All of these issues are addressed more fully in the Web-based complete statement. The Executive Summary includes summary comments and detailed tables that focus on key aspects of patient management. A list of references is provided in the full statement.

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 American Heart Association's endo-

carditis 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

Although initially established to more accurately define cases of IE for epidemiological studies and clinical trials, the Duke criteria have been used extensively during the past decade to assist clinicians in the diagnosis of IE. The 2 key components of the criteria are persistent bacteremia resulting from typical IE organisms and evidence of cardiac valvular involvement (eg, vegetation, new murmur of valvular regurgitation, para-

TABLE 1. 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.

valvular abscess). Supporting findings include fever, risk factors for IE, vascular or immune complex phenomena, and intermittent bacteremia or fungemia.

Echocardiography

Transesophageal echocardiography is the preferred imaging technique for the diagnosis and management of IE in adults with either high risk for IE or moderate to high clinical suspicion of IE or in patients in whom imaging by transthoracic echocardiography is difficult (Figure). Transesophageal echocardiography is more sensitive than transthoracic echocardiography for detecting vegetations and cardiac abscess. Recommendations for the timing of echocardiography in diagnosis and management of IE are presented in Table 1. The echocardiographic features that suggest the potential need for surgical intervention are listed in Table 2.

Antimicrobial Therapy

Recommended antibiotic treatment regimens for IE are described in Tables 3 through 13, including drug dose, dosing frequency, route(s) of administration, duration of therapy, and strength of recommendation. Tables 3 through 5 provide regimens for IE caused by viridans group streptococci and *Streptococcus bovis*; Tables 6 and 7, staphylococci; Tables 8 through 11, enterococci; Table 12, HACEK microorganisms; and Table 13, culture-negative IE, including *Bartonella* endocarditis. With few exceptions, antibiotic treatment is

TABLE 2. 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.

prolonged, bactericidal, administered parenterally, and given in high dosages. Because complications of IE are frequent and the antimicrobial agents used to treat IE may be associated with adverse effects, patients must be monitored closely by an experienced team of clinicians.

A dramatic increase in resistance to antibiotics among the most common causes of IE is a major reason for updating these recommendations. Multidrug resistance is now commonly described among isolates of streptococcal, staphylococcal, and enterococcal species that cause IE. In addition, many of the Gram-negative bacteria that cause IE have become more drug resistant. Increasing drug resistance has occurred among “community-acquired” isolates such as HACEK (*Haemophilus*, *Actinobacillus*, *Cardiobacterium*, *Eikenella*, and *Kingella*) microorganisms, *Salmonella* species, and *Enterobacteriaceae*, as well as among nosocomial isolates such as *Pseudomonas* species. More data are needed to define the optimal treatment regimens for IE caused by multidrug-resistant *Streptococcus pneumoniae*, vancomycin-resistant strains of *Enterococcus faecium*, and multidrug-resistant *Staphylococcus aureus*. In addition, new information has prompted a reexamination of recommendations for the duration of therapy for IE. For example, data from Sweden suggest that in combination with a cell wall–active antibiotic for treatment of IE resulting from enterococci, the duration of aminoglycoside administration may be limited to only the first 2 weeks rather than the entire 4 to 6 weeks of therapy with a cell wall–active agent and no decrease in cure rates.

Despite advances in diagnostic techniques, (blood) culture–negative endocarditis remains a clinical conundrum among IE cases. Patients with culture-negative endocarditis can be divided into 2 categories: those with negative blood cultures associated with recent antibiotic therapy and those infected with microorganisms that are difficult to grow in

TABLE 3. 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 <i>or</i> Ceftriaxone sodium	12–18 million U/24 h IV either continuously or in 4 or 6 equally divided doses 2 g/24 h IV/IM in 1 dose <i>Pediatric dose</i> †: 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	4 4	IA IA	Preferred in most patients >65 y or patients with impairment of 8th cranial nerve function or renal function
Aqueous crystalline penicillin G sodium <i>or</i> Ceftriaxone sodium <i>plus</i> Gentamicin sulfate‡	12–18 million U/24 h IV either continuously or in 6 equally divided doses 2 g/24 h IV/IM in 1 dose 3 mg/kg per 24 h IV/IM in 1 dose <i>Pediatric dose</i> : 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	2 2 2	IB 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 <i>Abiotrophia</i> , <i>Granulicatella</i> , or <i>Gemella</i> 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§
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 <i>Pediatric dose</i> : 40 mg/kg per 24 h IV in 2–3 equally divided doses	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

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.

§See reference 280 in full statement.

||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.

routinely used blood culture media. The epidemiological clues listed in Table 14 may be helpful for determining the most appropriate antibiotic regimen for the individual patient with culture-negative endocarditis.

There is much room for improvement in the treatment of fungal IE. The mortality rate remains unacceptably high, particularly for IE associated with molds, and new treatment strategies are still under investigation. Many experts advocate treatment of fungal IE that involves both medical and surgical intervention in most cases. More recently, long-term suppressive therapy, usually with an oral azole agent, has been adopted for some patients who survive acute medical and surgical therapies to prevent relapse of fungal IE. Suppressive therapy also has been used for patients who are too ill to undergo valve replacement but who have responded to acute antifungal treatment.

Complications of IE

Among the complications of IE, congestive heart failure (CHF) has the greatest impact on prognosis. CHF in IE, regardless of its cause, is associated with a grave prognosis

with medical therapy alone and is the most powerful predictor of a poor outcome with surgical therapy as well. In any patient with IE and CHF, the decision to delay surgery to extend the duration of preoperative antibiotic therapy carries with it the risk of permanent ventricular dysfunction and should be discouraged. Echocardiographic evaluation helps to delineate the causes and severity of CHF.

The rate of embolic events drops dramatically during and after the first 2 to 3 weeks of successful antimicrobial therapy. The role of echocardiography in predicting embolic events has been controversial. The role of surgical intervention to prevent systemic embolization must be considered in the context of the specific patient, with the greatest benefit in the early phase of IE, when embolic rates are highest and other predictors of a complicated course (eg, recurrent embolization, CHF, aggressive antibiotic-resistant organisms, prosthetic valve IE) are present (see Table 2).

In patients with *Staphylococcus aureus* prosthetic valve IE who have experienced a recent central nervous system embolic event, discontinuation of all anticoagulation for at least the first 2 weeks of antibiotic therapy is generally advised.

TABLE 4. 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 <i>or</i> Ceftriaxone sodium <i>plus</i> Gentamicin sulfate†	24 million U/24 h IV either continuously or in 4–6 equally divided doses 2 g/24 h IV/IM in 1 dose 3 mg/kg per 24 h IV/IM in 1 dose <i>Pediatric dose‡:</i> 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	4 4 2	IB 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 8)
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 <i>Pediatric dose:</i> 40 mg/kg 24 h in 2 or 3 equally divided doses	4	IB	Vancomycin§ therapy recommended only for patients unable to tolerate penicillin or ceftriaxone therapy

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

*Dosages recommended are for patients with normal renal function.

†See Table 3 for appropriate dosage of gentamicin.

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

§See Table 3 for appropriate dosage of vancomycin.

TABLE 5. 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 $\mu\text{g/mL}$)				
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
<i>or</i>				
Ceftriaxone	2 g/24 h IV/IM in 1 dose	6	IB	
<i>with or without</i>				
Gentamicin sulfate†	3 mg/kg per 24 h IV/IM in 1 dose <i>Pediatric dose</i> ‡: 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	2		
Vancomycin hydrochloride§	30 mg/kg per 24 h IV in 2 equally divided doses <i>Pediatric dose</i> : 40 mg/kg per 24 h IV or in 2 or 3 equally divided doses	6	IB	Vancomycin therapy recommended only for patients unable to tolerate penicillin or ceftriaxone
Penicillin relatively or fully resistant strain (minimum inhibitory concentration >0.12 $\mu\text{g/mL}$)				
Aqueous crystalline penicillin sodium	24 million U/24 h IV either continuously or in 4–6 equally divided doses	6	IB	Vancomycin therapy is recommended only for patients unable to tolerate penicillin or ceftriaxone
<i>or</i>				
Ceftriaxone	2 g/24 h IV/IM in 1 dose	6	IB	
<i>plus</i>				
Gentamicin sulfate	3 mg/kg per 24 h IV/IM in 1 dose <i>Pediatric dose</i> : penicillin 300 000 U/kg per 24 h IV in 4–6 equally divided doses	6		
Vancomycin hydrochloride	30 mg/kg per 24 h IV in 2 equally divided doses <i>Pediatric dose</i> : 40 mg/kg per 24 h IV in 2 or 3 equally divided doses	6	IB	

*Dosages recommended are for patients with normal renal function.

†See Table 3 for appropriate dosage of gentamicin.

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

§See text and Table 3 for appropriate dosage of vancomycin.

TABLE 6. 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 full text)
<i>with</i>				
Optional addition of gentamicin sulfate‡	3 mg/kg per 24 h IV/IM in 2 or 3 equally divided doses <i>Pediatric dose</i> §: 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	3–5 d		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§
<i>with</i>				
Optional addition of gentamicin sulfate	3 mg/kg per 24 h IV/IM in 2 or 3 equally divided doses <i>Pediatric dose</i> : 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	3–5 d		Clinical benefit of aminoglycosides has not been established
Oxacillin-resistant strains				
Vancomycin	30 mg/kg per 24 h IV in 2 equally divided doses <i>Pediatric dose</i> : 40 mg/kg per 24 h IV in 2 or 3 equally divided doses	6 wk	IB	Adjust vancomycin dosage to achieve 1-h serum concentration of 30–45 μ g/mL and trough concentration of 10–15 μ g/mL (see full text for vancomycin alternatives)

*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 $\leq 0.1 \mu$ g/mL) and does not produce β -lactamase.

‡Gentamicin should be administered in close temporal proximity to vancomycin, nafcillin, or oxacillin dosing.

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

||For specific dosing adjustment and issues concerning vancomycin, see Table 3 footnotes.

TABLE 7. 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 <i>Pediatric dose‡:</i> 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	2		
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 full 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 <i>Pediatric dose:</i> 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	2		

*Dosages recommended are for patients with normal renal function.

†Gentamicin should be administered in close proximity to vancomycin, nafcillin, or oxacillin dosing.

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

TABLE 8. 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 \leq 3 mo; 6-wk therapy recommended for patients with symptoms $>$ 3 mo
<i>or</i>				
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
<i>plus</i>				
Gentamicin sulfate†	3 mg/kg per 24 h IV/IM in 3 equally divided doses <i>Pediatric dose</i> ‡: 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	4–6		
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
<i>plus</i>				
Gentamicin sulfate	3 mg/kg per 24 h IV/IM in 3 equally divided doses <i>Pediatric dose</i> : 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	6		6 wk of vancomycin therapy recommended because of decreased activity against enterococci

*Dosages recommended are for patients with normal renal function.

†Dosage of gentamicin should be adjusted to achieve peak serum concentration of 3–4 μ g/mL and a trough concentration of $<$ 1 μ g/mL (see full text). Patients with a creatinine clearance of $<$ 50 mL/min should be treated in consultation with an infectious diseases specialist.

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

§See full text and Table 3 for appropriate dosing of vancomycin.

TABLE 9. 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
<i>or</i>				
Aqueous crystalline penicillin G sodium	24 million U/24 h IV continuously or in 6 equally divided doses	4–6	IA	
<i>plus</i>				
Streptomycin sulfate†	15 mg/kg per 24 h IV/IM in 2 equally divided doses <i>Pediatric dose‡:</i> 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	4–6		Prosthetic valve or other prosthetic cardiac material: minimum of 6 wk of therapy recommended
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
<i>plus</i>				
Streptomycin sulfate	15 mg/kg per 24 h IV/IM in 2 equally divided doses <i>Pediatric dose:</i> 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	6		

*Dosages recommended are for patients with normal renal function. Patients with creatinine clearance of <50 mL/min should be treated in consultation with an infectious diseases specialist.

†See full text for appropriate dosing of streptomycin.

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

§See text and Table 3 for appropriate dosing of vancomycin.

TABLE 10. 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	IaC	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 <i>Pediatric dose</i> ‡: 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	6		
Vancomycin hydrochloride§	30 mg/kg per 24 h IV in 2 equally divided doses	6	IaC	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 <i>Pediatric dose</i> : 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	6		
Intrinsic penicillin resistance				
Vancomycin hydrochloride‡	30 mg/kg per 24 h IV in 2 equally divided doses	6	IaC	Consultation with a specialist in infectious diseases recommended
plus Gentamicin sulfate†	3 mg/kg per 24 h IV/IM in 3 equally divided doses <i>Pediatric dose</i> : 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	6		

*Dosages recommended are for patients with normal renal function; see Table 7 for patients with creatinine clearance of <50 mL/min.

†See full text and Table 3 for appropriate dosing of gentamicin.

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

§See Table 3 for appropriate dosing of vancomycin.

TABLE 11. 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
<i>E faecium</i>				
Linezolid	1200 mg/24 h IV/PO in 2 equally divided doses	≥8	IaC	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 <i>E faecium</i> 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
<i>or</i>				
Quinupristin-dalfopristin	22.5 mg/kg per 24 h IV in 3 equally divided doses	≥8		
<i>E faecalis</i>				
Imipenem/cilastatin	2 g/24 h IV in 4 equally divided doses	≥8	IbC	
plus				
Ampicillin sodium	12 g/24 h IV in 6 equally divided doses	≥8		
<i>or</i>				
Ceftriaxone sodium	2 g/24 h IV/IM in 1 dose	≥8	IbC	
plus				
Ampicillin sodium	12 g/24 h IV in 6 equally divided doses	≥8		
	<i>Pediatric dose†</i> : 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 once daily			

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.

TABLE 12. Therapy for Both Native and Prosthetic Valve Endocarditis Caused by HACEK* Microorganisms

Regimen	Dosage and Route	Duration, wk	Strength of Recommendation	Comments
Ceftriaxone† sodium	2 g/24 h IV/IM in 1 dose	4	IB	Cefotaxime or another third- or fourth-generation cephalosporin may be substituted
<i>or</i>				
Ampicillin- sulbactam‡	12 g/24 h IV in 4 equally divided doses	4	IIaB	
<i>or</i>				
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 Prosthetic valve: patients with endocarditis involving prosthetic cardiac valve or other prosthetic cardiac material should be treated for 6 wk
	<i>Pediatric dose</i> : 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			

**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.

TABLE 13. 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 recommended only for patients unable to tolerate penicillins
Vancomycin‡	30 mg/kg per 24 h IV in 2 equally divided doses	4–6	IIbC	
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		
	<i>Pediatric dose</i> §: 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		
	<i>Pediatric dose</i> : 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
Suspected <i>Bartonella</i>, culture negative				
Ceftriaxone sodium	2 g/24 h IV/IM in 1 dose	6	IIaB	Patients with <i>Bartonella</i> 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/kg per 24 h IV/PO in 2 equally divided doses	6		
Documented <i>Bartonella</i>, 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		
	<i>Pediatric dose</i> : 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 Table 3 for patients with creatinine clearance <50 mL/min.

†See full text and Table 3 for appropriate dosing of gentamicin.

‡See Table 3 for appropriate dosing of vancomycin.

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

TABLE 14. Epidemiological Clues in Etiological Diagnosis of Culture-Negative Endocarditis

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

In addition, the routine use of aspirin or other drugs that interfere with platelet function for established IE is not recommended.

Extension of IE beyond the valve annulus is associated with a higher mortality rate, CHF, and the need for surgical intervention. Surgery for perivalvular extension of IE is aimed at eradicating infection as well as correcting hemodynamic abnormalities.

Splenic abscess and bland infarctions both are complications of IE, and differentiating one from the other may be difficult. On CT, splenic abscess is frequently seen as a single or multiple contrast-enhancing cystic lesions, whereas infarctions (single or multiple) typically are peripheral, low-density, wedge-shaped areas. Infarctions are generally associated with clinical and radiological improvement during appropriate antimicrobial therapy. In contrast, persistent or enlarged splenic defects on CT or MRI, ongoing sepsis, and recurrent positive blood cultures suggest splenic abscess, which may respond poorly to antimicrobial therapy alone. Definitive treatment in such cases is splenectomy with appropriate antimicrobial therapy.

Mycotic aneurysms (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. The overall mortality rate among patients with IE and intracranial MAs may be as high as 60%. For patients with unruptured intracranial MAs, the mortality rate is $\approx 30\%$, but with ruptured MAs, the mortality rate approaches 80%. Conventional cerebral angiography remains the optimal imaging test for diagnosing intracranial MAs. There is no accurate way of identifying patients at risk for "imminent rupture" of an intracranial MA, and decisions about the use of surgical intervention in addition to medical therapy must be individualized. Endovascular treatment of intracranial MAs has been used as an alternative to surgical clipping or ligation. Because it is less invasive than traditional surgical approaches, endovascular therapy may be preferred for patients who are poor candidates for traditional surgical intervention.

Most extracranial MAs will rupture if not excised; therefore, surgical intervention is necessary for cure of extracranial MA and survival for most of these patients.

Care During and After Completion of Antimicrobial Treatment

Care is divided temporally into 3 phases that are highlighted in Table 15. The recommendations (Class IIb; Level of Evidence: C) focus on the importance of prompt identification of either relapse or recurrence of IE. Patients who have had previous episodes of IE and patients with prosthetic valves make up the group at highest risk for development of recurrent IE.

Summary

Despite major advances in both medical and surgical interventions, IE remains a serious illness that can be associated with considerable morbidity and mortality. More data from prospective, randomized clinical trials are needed to determine the optimal approach to IE caused by multidrug-resistant bacteria. When these data become available, the Web-

TABLE 15. 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
-

based version of these guidelines will be updated to assist clinicians in providing the most appropriate care of patients with IE.

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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—Executive Summary,” by Baddour et al (*Circulation*. 2005;111:3167–3184), the following corrections/clarifications should be made:

1. There were two errors in Table 11 on page 3178. 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 13, 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 8 and 9, 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 Table 10, the following portion of the first footnote should be deleted: ‘...see Table 7 for patients with creatinine clearance of <50 mL/min.’ In Table 13, the following portion of the first footnote should be deleted: ‘...see Table 3 for patients with creatinine clearance of <50 mL/min.’
4. In the third footnote of Table 6 and the second footnote of Table 7 (“Gentamicin should be...”), a second sentence should be added, which reads: “See Table 3 for appropriate dosage of gentamicin.” In Table 8, the second footnote should also refer the reader to Table 3 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 3 through 5).
6. Table 3, 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.

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