

Antibiotic Treatment of Adults With Infective Endocarditis Due to Streptococci, Enterococci, Staphylococci, and HACEK Microorganisms

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Objective. To provide guidelines for the treatment of endocarditis in adults caused by the following microorganisms: viridans streptococci and other streptococci, enterococci, staphylococci, and fastidious gram-negative bacilli of the HACEK group.

Participants. An ad hoc writing group appointed by the American Heart Association under the auspices of the Committee on Rheumatic Fever, Endocarditis, and Kawasaki Disease, Council on Cardiovascular Disease in the Young.

Evidence. Published studies of the treatment of patients with endocarditis and the collective clinical experience of this group of experts.

Consensus Process. The recommendations were formulated during meetings of the working group and were prepared by a writing committee after the group had agreed on the specific therapeutic regimens. The consensus statement was subsequently reviewed by standing committees of the American Heart Association and by a group of experts not affiliated with the working group.

Conclusions. Sufficient evidence has been published that recommendations regarding treatment of the most common microbiological causes of endocarditis (viridans streptococci, enterococci, *Streptococcus bovis*, staphylococci, and the HACEK organisms) are justified. There are insufficient published data to make a strong statement regarding the efficacy of specific therapeutic regimens for cases of endocarditis due to microorganisms that uncommonly cause endocarditis. As a useful aid to the practicing clinician, the writing group developed a consensus opinion regarding management of endocarditis caused by the most commonly encountered microorganisms and regarding those cases due to infrequent causes of endocarditis.

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ORGANISMS that commonly cause infective endocarditis are gram-positive cocci: viridans streptococci, enterococci, *Streptococcus bovis*, staphylococci, and the HACEK group of microorganisms (*Haemophilus parainfluenzae*, *Haemophilus aphrophilus*, *Actinobacillus actinomycetemcomitans*, *Cardiobacterium hominis*, *Eikenella corrodens*, and *Kingella kingae*). This report provides recommendations for the treatment of infective endocarditis caused by these microorganisms. The recommendations are the consensus of the American Heart Association writing group that analyzed current clinical and experimental data. The group recognizes that these data are incomplete or inconclusive for some subgroups of patients and for certain etiologic agents. This article updates an earlier article written by the American Heart Association.¹

VIRIDANS STREPTOCOCCI AND *S BOVIS*

Although the taxonomy is currently unresolved, the viridans group includes a variety of streptococcal species, including *Streptococcus sanguis*, *Streptococcus oralis* (mitis), *Streptococcus salivarius*, *Streptococcus mutans*, and others. Viridans streptococci are the most common etiologic agents in subacute infective endocarditis occurring on native heart valves in patients with congenital cardiac abnormalities and in patients who are not injection drug users (IDUs). The following recommendations are intended to assist the clinician in selecting an appropriate antimicrobial regimen(s) for a particular patient and also apply to infection with *S bovis*, a nonenterococcal, penicillin-susceptible group D streptococcus.

Certain viridans streptococci have biological characteristics that may complicate diagnosis and/or therapy. Some strains, for example, 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 streptococci may exhibit a laboratory phenomenon termed "penicillin tolerance." For tolerant strains, the minimum bactericidal concentration (MBC) of penicillin greatly exceeds the minimum inhibitory concentration (MIC) (usually by more than 32-fold). These strains are killed more slowly by penicillin in animal models of endocarditis.² However, there are no data for humans, and we believe that laboratory demonstration of tolerance has no implication for selection of antimicrobial therapy for endocarditis due to viridans streptococci. Accordingly, determination of MBC for these microorganisms is not routinely recommended.

HIGHLY PENICILLIN-SUSCEPTIBLE VIRIDANS STREPTOCOCCI OR *S BOVIS* (MIC ≤ 0.1 µG/ML) (TABLE 1)

Table 1. Suggested Regimens for Therapy of Native Valve Endocarditis Due to Penicillin-Susceptible Viridans Streptococci and *Streptococcus bovis* (Minimum Inhibitory Concentration ≤ 0.1µg/mL)*

Antibiotic	Dosage and Route	Duration, wk	Comments
Aqueous crystalline penicillin G sodium or Ceftriaxone sodium	12-18 million U/24 h IV either continuously or in six equally divided doses 2 g once daily IV or IM†	4 4	Preferred in most patients older than 65 y and in those with impairment of the eighth nerve or renal function
Aqueous crystalline penicillin G sodium With gentamicin sulfate‡	12-18 million U/24 h IV either continuously or in six equally divided doses 1 mg/kg IM or IV every 8 h	2 2	When obtained 1 h after a 20-30 min IV infusion or IM injection, serum concentration of gentamicin of approximately 3 µg/mL is desirable; trough concentration should be <1 µg/mL
Vancomycin hydrochloride §	30 mg/kg per 24 h IV in two equally divided doses, not to exceed 2 g/24 h unless serum levels are monitored	4	Vancomycin therapy is recommended for patients allergic to β-lactams (see text); peak serum concentrations of vancomycin should be obtained 1 h after completion of the infusion and should be in the range of 30-45 µg/mL for twice-daily dosing

*Dosages recommended are for patients with normal renal function. For nutritionally variant streptococci, see Table 3. IV indicates intravenous; IM, intramuscular.

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

‡Dosing of gentamicin on a mg/kg basis will produce higher serum concentrations in obese patients than in lean patients. Therefore, in obese patients, dosing should be based on ideal body weight. (Ideal body weight for men is 50 kg + 2.3 kg per inch over 5 feet, and ideal body weight for women is 45.5 kg + 2.3 kg per inch over 5 feet.) Relative contraindications to the use of gentamicin are age >65 y, renal impairment, or impairment of the eighth nerve. Other potentially nephrotoxic agents (eg, nonsteroidal anti-inflammatory drugs) should be used cautiously in patients receiving gentamicin.

§Vancomycin dosage should be reduced in patients with impaired renal function. Vancomycin given on a mg/kg basis will produce higher serum concentrations in obese patients than in lean patients. Therefore, in obese patients, dosing should be based on ideal body weight. Each dose of vancomycin should be infused over at least 1 h to reduce the risk of the histamine-release "red man" syndrome.

High cure rates can be anticipated for patients who complete therapy for endocarditis caused by highly penicillin-susceptible viridans streptococci or *S bovis*. Treatment for 4 weeks with parenteral penicillin in doses of 12 to 18 million U/24 h or 2 g of ceftriaxone sodium in a single daily dose can be expected to achieve bacteriologic cure in up to 98% of patients.³⁻⁵ The addition of gentamicin sulfate to penicillin therapy exerts a synergistic killing effect on viridans streptococci in vitro. Moreover, in an animal model of endocarditis, the addition of gentamicin to penicillin results in more rapid sterilization of cardiac vegetations.⁶ On the other hand, the cure rate in endocarditis due to viridans streptococci achieved with penicillin-gentamicin combination therapy has not been established as superior to 4 weeks of penicillin or ceftriaxone therapy alone.⁷

Considerable experience in the use of short-course (2-week) combination therapy with penicillin and an aminoglycoside has been accumulated. The use of the 2-week regimen results in bacteriologic cure rates as high as 98% in selected cases.⁷ Recent studies in Europe and South America confirm that 2 weeks of therapy with the combination of once-daily ceftriaxone and once-daily netilmicin may be equivalent to those following 2 weeks of treatment with penicillin and an aminoglycoside in daily divided doses.⁸ The 2-week regimen is appropriate for uncomplicated cases of endocarditis due to highly penicillin-susceptible viridans streptococci or *S bovis* occurring in patients at low risk for adverse events caused by gentamicin therapy. The 2-week regimen is not recommended for patients with complications such as extracardiac foci of infection or intracardiac abscesses.⁷ For patients infected with nutritionally variant viridans streptococci, most authorities suggest treatment with the regimen advised for treatment of enterococcal endocarditis⁹ (see "Enterococci"). In patients whose infection involves prosthetic valves or other prosthetic materials, a 6-week regimen of penicillin is recommended together with gentamicin for at least the first 2 weeks.¹⁰

Although most reported clinical experience with two-drug regimens involves penicillin and streptomycin, in vitro and animal model data suggest that penicillin and gentamicin also exert a synergistic effect in treatment of endocarditis due to viridans streptococci.^{10,11} Gentamicin currently is used more widely in clinical practice than streptomycin, determinations of gentamicin serum levels are more readily available, and in contrast to streptomycin, gentamicin can be administered either intravenously (IV) or intramuscularly (IM). Thus, it seems reasonable to consider gentamicin as interchangeable with and preferable to streptomycin in combination treatment regimens.¹² Additionally, strains of viridans streptococci and *S bovis* that exhibit high-level resistance (MIC >1000 µg/mL) to streptomycin have been recovered from patients with endocarditis.¹³ However, such strains remain relatively rare at this time. If streptomycin therapy is preferred, strains should be screened for high-level streptomycin resistance. (For a more detailed explanation of the significance of high-level aminoglycoside resistance by streptococci, see "Enterococci.")

Specific recommendations for treatment of endocarditis due to highly penicillin-susceptible viridans streptococci or *S bovis* in patients who are not allergic to penicillin are presented in Table 1. While all four regimens are acceptable, each has advantages and disadvantages. Compared with 4 weeks of penicillin therapy, the 2-week regimen may appreciably shorten the period of hospitalization, while the use of penicillin or

ceftriaxone alone avoids the use of gentamicin, which is potentially ototoxic and nephrotoxic. The advantage of the once-daily ceftriaxone regimen is its simplicity for use in therapy administered to outpatients^{4,5} (see "Outpatient Therapy").

PATIENTS ALLERGIC TO β -LACTAM

Vancomycin hydrochloride is an effective alternative and the drug of choice in patients with immediate-type hypersensitivity to penicillins and other β -lactam antibiotics. Prolonged IV use of this drug may be complicated by occurrence of thrombophlebitis, rash, fever, anemia, thrombocytopenia, and (rarely) ototoxic reactions. This agent should be infused over at least 1 hour to reduce the risk of the histamine-release "red man" syndrome.

VIRIDANS STREPTOCOCCI WITH PENICILLIN MIC > 0.1 μ G/ML AND NUTRITIONALLY VARIANT VIRIDANS STREPTOCOCCI (TABLE 2)

Table 2. Therapy for Native Valve Endocarditis Due to Strains of Viridans Streptococci and *Streptococcus bovis* Relatively Resistant to Penicillin G (Minimum Inhibitory Concentration >0.1 μ g/mL and <0.5 μ g/mL)*

Antibiotic	Dosage and Route	Duration, wk	Comments
Aqueous crystalline penicillin G sodium	18 million U/24 h IV either continuously or in six equally divided doses	4	Cefazolin or other first-generation cephalosporins may be substituted for penicillin in patients whose penicillin hypersensitivity is not of the immediate type
With gentamicin sulfate†	1 mg/kg IM or IV every 8 h	2	
Vancomycin hydrochloride‡	30 mg/kg per 24 h IV in two equally divided doses, not to exceed 2 g/24 h unless serum levels are monitored	4	Vancomycin therapy is recommended for patients allergic to β -lactams

*Dosages recommended are for patients with normal renal function. IV indicates intravenous; IM, intramuscular.

†For specific dosing adjustment and issues concerning gentamicin (obese patients, relative contraindications), see Table 1 footnotes.

‡For specific dosing adjustment and issues concerning vancomycin (obese patients, length of infusion), see Table 1 footnotes.

When endocarditis is due to viridans streptococci requiring more than 0.1 µg/mL of penicillin for inhibition, combination therapy with penicillin and gentamicin is indicated. Although published data for viridans streptococci with an MIC for penicillin of greater than 0.1 but less than 0.5 µg/mL are limited, it is recommended that gentamicin be given for the first 2 weeks of the 4-week course of penicillin therapy. When endocarditis is due to viridans streptococci requiring 0.5 µg/mL or more of penicillin for inhibition, a standard regimen for endocarditis caused by enterococci is recommended (Table 3). When vancomycin is the chosen antibiotic, the addition of gentamicin is not necessary.

Determination of antimicrobial susceptibility of nutritionally variant streptococci may be technically difficult. Moreover, endocardial infections due to such organisms often have been difficult to eradicate. For these reasons, these infections should be treated with a standard regimen recommended for enterococcal endocarditis (Table 3).

***STREPTOCOCCUS PNEUMONIAE*, *STREPTOCOCCUS PYOGENES*, AND GROUPS B, C, AND G STREPTOCOCCI**

Endocarditis caused by these streptococci is relatively uncommon. There are no published reports of large series of cases evaluating therapeutic regimens for endocarditis caused by these organisms. When *S pneumoniae* is recovered from a patient with endocarditis, the organism should be tested for penicillin susceptibility. An increasing number of intermediately penicillin-resistant pneumococci (MIC=0.1 to 1.0 µg/mL) and highly penicillin-resistant pneumococci (MIC ≥2.0 µg/mL) are now recognized. Furthermore, pneumococcal resistance to other antimicrobial agents such as cephalosporins, macrolides, and trimethoprim-sulfamethoxazole is also increasing.¹⁴ Therefore, treatment of a patient with pneumococcal endocarditis should be coordinated in consultation with an infectious diseases specialist.

Based on limited published data for the treatment of endocarditis caused by *S pyogenes*, aqueous crystalline penicillin G potassium given IV is recommended. A first-generation cephalosporin (cefazolin or cephalothin) is an acceptable alternative. In general, strains of group B, C, and G streptococci are slightly more resistant to penicillin than are strains of group A streptococci (*S pyogenes*). Some authorities recommend the addition of gentamicin to penicillin (or cephalosporin) therapy for at least the first 2 weeks of a 4- to 6-week course of antimicrobial therapy.

Because of the rarity of endocarditis caused by these organisms, consultation with an infectious diseases specialist for the treatment of these patients is recommended.

ENTEROCOCCI (TABLE 3)

Table 3. Standard Therapy for Endocarditis Due to Enterococci*

Antibiotic	Dosage and Route	Duration, wk	Comments
Aqueous crystalline penicillin G sodium	18-30 million U/24 h IV either continuously or in six equally divided doses	4-6	
With gentamicin sulfate†	1 mg/kg IM or IV every 8 h	4-6	4-wk therapy recommended for patients with symptoms <3 mo in duration; 6-wk therapy recommended for patients with symptoms >3 mo in duration
Ampicillin sodium	12 g/24 h IV either continuously or in six equally divided doses	4-6	
With gentamicin sulfate†	1 mg/kg IM or IV every 8 h	4-6	
Vancomycin hydrochloride†‡	30 mg/kg per 24 h IV in two equally divided doses, not to exceed 2 g/24 h unless serum levels are monitored	4-6	Vancomycin therapy is recommended for patients allergic to β -lactams; cephalosporins are not acceptable alternatives for patients allergic to penicillin
With gentamicin sulfate†	1 mg/kg IM or IV every 8 h	4-6	

*All enterococci causing endocarditis must be tested for antimicrobial susceptibility in order to select optimal therapy (see text). This table is for endocarditis due to gentamicin- or vancomycin-susceptible enterococci, viridans streptococci with a minimum inhibitory concentration of >0.5 μ g/mL, nutritionally variant viridans streptococci, or prosthetic valve endocarditis caused by viridans streptococci or *Streptococcus bovis*. Antibiotic dosages are for patients with normal renal function. IV indicates intravenous; IM, intramuscular.

†For specific dosing adjustment and issues concerning gentamicin (obese patients, relative contraindications), see Table 1 footnotes.

‡For specific dosing adjustment and issues concerning vancomycin (obese patients, length of infusion), see Table 1 footnotes.

Enterococci are a major gram-positive component of the gastrointestinal tract flora. These organisms, which belong to Lancefield's serogroup D, are no longer considered members of the genus *Streptococcus*. They have been accorded their own genus, *Enterococcus*. Although according to standard taxonomy there are at least 12 species within the genus *Enterococcus*, *Enterococcus faecalis* and *Enterococcus faecium* are the major enterococci isolated from clinical sources. Several organisms may be confused with enterococci. In particular, *S bovis* manifests the group D antigen but can be distinguished from enterococci by appropriate biochemical tests. *Streptococcus bovis* endocarditis frequently is associated with pathological conditions of the gastrointestinal tract, especially carcinoma of the colon.¹⁵ *Streptococcus mutans*, a common inhabitant of the oral cavity, also may be confused with enterococci on the basis of certain biochemical characteristics, although it is not a group D streptococcus. The penicillin susceptibility of an organism may also be helpful in suggesting errors in identification. The great majority of viridans streptococci and *S bovis* are inhibited by 0.1 µg or less of penicillin G per milliliter, while enterococci are uniformly resistant to this low concentration of penicillin G. Distinguishing these organisms from enterococci is important because both *S bovis* and *S mutans* are usually readily killed by penicillin alone and, thus, can be treated with regimens recommended for endocarditis due to viridans streptococci.

Treatment of enterococcal endocarditis is complicated because the organisms are relatively resistant to penicillin (median MIC, 2 µg/mL), expanded-spectrum penicillins, or vancomycin. In fact, most enterococci are inhibited but not killed by clinically relevant concentrations of these antibiotics.^{16,17} Furthermore, enterococci are uniformly resistant to cephalosporins. Enterococci are generally resistant to standard therapeutic concentrations of aminoglycosides. Nevertheless, penicillin, ampicillin, or vancomycin in combination with certain aminoglycoside antibiotics exert a synergistic bactericidal effect on these organisms.^{16,17}

The degree of resistance of enterococci to aminoglycosides is highly variable. An MIC greater than or equal to 2000 µg of streptomycin per milliliter or 500 to 2000 µg of gentamicin per milliliter is considered the dividing point between low-level and high-level resistance of enterococci to these agents.^{16,17} Enterococci that are highly resistant to an aminoglycoside are not killed synergistically when that aminoglycoside is combined with either a penicillin or vancomycin. For enterococci that do not exhibit high-level resistance to streptomycin or gentamicin, either aminoglycoside provides synergistic killing when combined with an effective penicillin or vancomycin. When treating endocarditis caused by these strains of enterococci, either streptomycin or gentamicin can be used. Consideration of the nature of the toxicity associated with each aminoglycoside and the ease of monitoring therapy should be weighed in making the choice (discussed herein). Other aminoglycosides cannot routinely be substituted for streptomycin or gentamicin, nor do the MICs of other aminoglycosides reliably predict their utility in effecting bactericidal synergy. For example, the combination of penicillin and tobramycin does not provide synergistic killing of *E faecium* even in the absence of demonstrable high-level resistance to tobramycin.^{16,17}

For many years, a high proportion of enterococci have exhibited high-level resistance to

streptomycin and were not killed by the combination of penicillin and streptomycin. Until recently, enterococci in general were not highly resistant to gentamicin and were predictably killed by the combination of penicillin and gentamicin. Consequently, penicillin plus gentamicin became the preferred therapy for enterococcal endocarditis in order to treat infections caused not only by strains with high-level streptomycin resistance, but also by strains whose aminoglycoside resistance had not been established. The regimens in Table 3 remain the standard for treatment of enterococcal endocarditis caused by strains for which synergistic therapy can be achieved. Recent reports indicate that 10% to 25% of *E faecalis* and 45% to 50% of *E faecium* demonstrate high-level resistance to gentamicin.¹⁷ Aminoglycoside resistance in a strain causing endocarditis must be carefully evaluated when selecting therapy.

Currently in many geographic locales, a substantial proportion of enterococcal strains are resistant to penicillin, vancomycin, or both. Intrinsic resistance to penicillin and ampicillin has increased in frequency, and β -lactamase production has been noted in *E faecalis* since 1983.¹⁸ This form of resistance to penicillins will not be detected by MIC tests using standard inocula of enterococci; detection requires testing with the chromogenic cephalosporin, nitrocefim. Most recently, resistance to vancomycin has been recognized with increasing frequency in strains of *E faecalis* and *E faecium*.^{17,19} In some strains, resistance to vancomycin is modest (MICs=16 to 32 $\mu\text{g}/\text{mL}$). These organisms may remain susceptible to teicoplanin, an investigational glycopeptide antibiotic. (Physicians can get information on attaining teicoplanin by contacting the US manufacturer, Marion Merrell Dow, Kansas City, Kan.) Other strains possess very high MICs (>256 $\mu\text{g}/\text{mL}$) to vancomycin and are highly resistant to teicoplanin as well. Enterococci with one or more of these forms of resistance to penicillins or vancomycin are not killed synergistically when these drugs are combined with an aminoglycoside.

Because of the increasing frequency of these highly resistant enterococci among clinical isolates, it is no longer reasonable to expect that routine use of the previously standard recommendations for therapy of enterococcal endocarditis will provide optimal therapy. In fact, all enterococcal strains causing endocarditis must be screened to define antimicrobial resistance patterns. For organisms with intrinsic high-level resistance to penicillins (MICs >16 $\mu\text{g}/\text{mL}$), vancomycin is the agent of choice for synergistic therapy; whereas for organisms that are resistant to penicillins by virtue of β -lactamase production, either ampicillin-sulbactam sodium or vancomycin may be combined with an aminoglycoside for bactericidal synergistic therapy. For organisms resistant to both penicillin and vancomycin, teicoplanin may be useful. High-level aminoglycoside resistance represents the most common and grave obstacle to optimal therapy for enterococcal endocarditis. Because high-level resistance to gentamicin and streptomycin is encoded by separate genes, strains of enterococci causing endocarditis should be screened with both compounds, and an aminoglycoside to which the strain is not highly resistant should be used. If endocarditis is caused by a strain that exhibits high-level resistance to both gentamicin and streptomycin, the addition of an aminoglycoside to a cell wall active agent will not be beneficial. Rather, prolonged therapy (8 to 12 weeks) with high doses of a penicillin or ampicillin may cure approximately one half of these patients. Those failing therapy should be considered for surgical treatment. In order to select the best antimicrobial regimen to treat endocarditis caused by a strain of

enterococcus that possesses high-level resistance to all aminoglycosides and penicillins or vancomycin, special microbial susceptibility tests using other antibiotics and combinations of antibiotics and infectious disease consultative assistance should be sought.

Prolonged therapy with an aminoglycoside may be complicated by ototoxic and/or nephrotoxic effects, which are less frequent in children than adults. Streptomycin is primarily ototoxic and gentamicin is primarily nephrotoxic; while nephrotoxicity is potentially reversible, ototoxicity often is not. Serum levels of the aminoglycoside should be monitored during therapy of enterococcal endocarditis to avoid levels associated with toxic reactions. The recommended dosage of gentamicin (Table 3) has been chosen in an effort to minimize toxicity while preserving synergistic therapy. Peak serum levels of gentamicin used for synergistic killing of enterococci need not be as high as those conventionally achieved in treatment of systemic gram-negative bacillary infections. With such lower dose regimens, serum concentrations of gentamicin obtained 1 hour after a 20- to 30-minute IV infusion or IM injection should be approximately 3 $\mu\text{g/mL}$ with a trough of less than 1 $\mu\text{g/mL}$.²⁰ While most of the published data concerning gentamicin therapy for enterococcal endocarditis used this lower dosage (1 mg/kg per dose), some authorities recommend a higher dosage (1.5 mg/kg every 8 hours), which results in a higher peak concentration in serum of approximately 5 $\mu\text{g/mL}$. The suggested initial dosage of streptomycin is 7.5 mg/kg IM every 12 hours (not to exceed 500 mg per dose). Serum levels of streptomycin 1 hour after IM injection should be approximately 20 $\mu\text{g/mL}$.²⁰

Standard therapy for enterococcal endocarditis should continue for a minimum of 4 weeks. Patients whose symptoms of infection have existed for more than 3 months before institution of appropriate therapy and patients with prosthetic valve endocarditis should receive at least 6 weeks of combined antimicrobial therapy.^{20,21}

In patients allergic to penicillin, physicians must choose between risking penicillin or ampicillin treatment and using vancomycin as an alternative agent. Clinical experience with penicillin or ampicillin in treating life-threatening enterococcal infections is much greater than that with vancomycin. Thus, when faced with a patient whose history of penicillin allergy is equivocal or consists only of a mild skin rash, the physician might consider cautious treatment with a penicillin. Details of precautions to be observed when treating a penicillin-allergic patient are beyond the scope of this statement. The reader should consult standard medical texts for risk/benefit considerations and protocols for penicillin desensitization. In patients with a clear-cut history of an anaphylactic-type reaction to penicillin therapy, vancomycin treatment, in most instances, should be used as an alternative. Vancomycin use may enhance the nephrotoxic potential of gentamicin.

STAPHYLOCOCCI

Infective endocarditis may be caused by staphylococci that are coagulase-positive (*Staphylococcus aureus*) or coagulase-negative (*Staphylococcus epidermidis* and various other species). Although coagulase-positive and coagulase-negative staphylococci may

infect either native or prosthetic valves, most cases of endocarditis due to coagulase-negative organisms occur in patients with valvular prostheses.^{22,23}

Endocarditis due to *S aureus* occurring in nonaddicts primarily involves valves on the left side of the heart and is associated with mortality rates ranging from 25% to 40%. *Staphylococcus aureus* endocarditis in IDUs often involves the tricuspid valve. Cure rates of at least 85% have been reported for right-sided staphylococcal endocarditis in IDUs. These patients may at times be cured by relatively short courses of treatment (<4 weeks).^{24,25}

The great majority of staphylococci, acquired either in the hospital or in the community, produce β -lactamase, and they are highly resistant to penicillin G. The drugs of choice in this situation are semisynthetic, penicillinase-resistant penicillins such as nafcillin sodium or oxacillin sodium.

Treatment regimens for staphylococcal endocarditis that occurs on native cardiac valves differ from those required for treatment of staphylococcal endocarditis that occurs on prosthetic valves or on other prosthetic materials. They will be discussed separately.

STAPHYLOCOCCAL ENDOCARDITIS IN THE ABSENCE OF PROSTHETIC MATERIALS (TABLE 4)

Killing of methicillin-susceptible staphylococci in vitro and in experimentally induced cardiac vegetations is accelerated by adding gentamicin to nafcillin. In a multicenter collaborative study of *S aureus* endocarditis, however, addition of gentamicin for the first 2 weeks of a 6-week course of IV nafcillin therapy failed to improve cure rates or any other significant clinical outcome but was associated with an increased incidence of renal dysfunction.²⁶ However, because the combination was associated with more rapid clearing of bacteremia, a case can be made for the addition of gentamicin for the first 3 to 5 days of therapy in the hope of minimizing damage to the heart valve and extracardiac abscess formation, while avoiding toxic reactions associated with more prolonged courses of aminoglycosides. Recommended regimens are detailed in Table 4. Those few patients infected with a penicillin-susceptible staphylococcus may be treated with aqueous crystalline penicillin G in doses at the higher end of the range recommended for viridans streptococci, with or without a brief course of aminoglycosides. Limited data suggest that IDUs with methicillin-susceptible *S aureus* endocarditis that is limited to right heart valves may be treated effectively with a 2-week course of nafcillin or oxacillin plus an aminoglycoside.^{24,25} The substitution of vancomycin for nafcillin in this regimen was ineffective.^{27,28} Injection drug users with evidence of metastatic infection or left-sided endocarditis (mitral or aortic murmur, systemic emboli or cutaneous stigmata, or echocardiographically demonstrated vegetations on the mitral or aortic valve) should not be treated with this abbreviated regimen. It is also unclear whether IDUs with right-sided *S aureus* endocarditis and echocardiographically demonstrated vegetations (tricuspid or pulmonic valve), underlying acquired immunodeficiency syndrome (AIDS), or extensive pulmonary complications of right-sided endocarditis (lung abscess) are appropriate candidates for

the 2-week antimicrobial regimen. One recent study of 10 IDUs with right-sided *S aureus* endocarditis suggested that a predominantly oral regimen of ciprofloxacin plus rifampin is efficacious when given over a 4-week course.²⁹ The high frequency of fluoroquinolone resistance may limit the usefulness of this approach.³⁰

Table 4. Therapy for Endocarditis Due to Staphylococcus in the Absence of Prosthetic Material*

Antibiotic	Dosage and Route	Duration	Comments
Methicillin-Susceptible Staphylococci			
Regimens for non- β -lactam-allergic patients			
Nafcillin sodium or oxacillin sodium	2 g IV every 4 h	4-6 wk	Benefit of additional aminoglycosides has not been established
With optional addition of gentamicin sulfate [†]	1 mg/kg IM or IV every 8 h	3-5 d	
Regimens for β -lactam-allergic patients			
Cefazolin (or other first-generation cephalosporins in equivalent dosages)	2 g IV every 8 h	4-6 wk	Cephalosporins should be avoided in patients with immediate type hypersensitivity to penicillin
With optional addition of gentamicin [†]	1 mg/kg IM or IV every 8 h	3-5 d	
Vancomycin hydrochloride [‡]	30 mg/kg per 24 h IV in two equally divided doses, not to exceed 2 g/24 h unless serum levels are monitored	4-6 wk	Recommended for patients allergic to penicillin

Methicillin-Resistant Staphylococci

Vancomycin hydrochloride [‡]	30 mg/kg per 24 h IV in two equally divided doses, not to exceed 2 g/24 h unless serum levels are monitored	4-6 wk
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*For treatment of endocarditis due to penicillin-susceptible staphylococci (minimum inhibitory concentration $\leq 0.1 \mu\text{g/mL}$), aqueous crystalline penicillin G sodium (Table 1, first regimen) can be used for 4 to 6 wk instead of nafcillin or oxacillin. Shorter antibiotic courses have been effective in some drug addicts with right-sided endocarditis due to *Staphylococcus aureus* (see text). See text for comments on use of rifampin. IV indicates intravenous; IM, intramuscular.

[†]For specific dosing adjustment and issues concerning gentamicin (obese patients, relative contraindications), see Table 1 footnotes.

[‡]For specific dosing adjustment and issues concerning vancomycin (obese patients, length of infusion), see Table 1 footnotes.

β -Lactam-allergic individuals infected with methicillin-susceptible staphylococci may be treated with a first-generation cephalosporin or vancomycin (Table 4). Recent clinical experience and in vitro studies have suggested that vancomycin may be a less effective anti-staphylococcal agent than nafcillin or oxacillin.^{31,32} Accordingly, caution is advised when considering treatment of *S aureus* endocarditis with vancomycin purely for reasons of convenience related to pharmacokinetics.

A high percentage of coagulase-negative staphylococci and an increasing percentage of coagulase-positive strains are resistant to nafcillin and oxacillin (methicillin-resistant staphylococci). These resistant organisms are particularly prominent in IDUs with endocarditis and among patients with nosocomial staphylococcal endocarditis. Caution must be exercised in interpreting results of antimicrobial susceptibility testing because some systems fail to detect methicillin resistance. Methicillin-resistant strains are also resistant to cephalosporins and imipenem, although this fact is not always reflected by an in vitro test of antimicrobial susceptibility.

Endocarditis due to methicillin-resistant staphylococci should be treated with IV vancomycin (Table 4 and Table 5). Treatment options for this entity in patients who cannot tolerate vancomycin are limited. Teicoplanin, an investigational glycopeptide antibiotic, is active against methicillin-resistant staphylococci and has been tolerated by some patients who are allergic to vancomycin. However, suboptimal outcomes have been reported with staphylococcal endocarditis in patients receiving teicoplanin.^{32,33} The role of supplemental gentamicin in native valve endocarditis due to methicillin-resistant staphylococci is similar to that described herein for methicillin-sensitive staphylococci. Although aminoglycosides have been added to the vancomycin regimen, there is evidence of synergistic nephrotoxic effects without clinical evidence of enhanced efficacy. Furthermore, many strains of methicillin-resistant *S aureus* are also resistant to aminoglycosides. Thus, addition of an aminoglycoside should be restricted to endocarditis caused by aminoglycoside-susceptible strains and the duration of aminoglycoside administration should be limited to 3 to 5 days.

Although most staphylococci are highly susceptible to rifampin, resistance develops rapidly when this agent is used as a single drug. The in vivo effect of rifampin in combination with nafcillin, oxacillin, vancomycin, or aminoglycosides is highly variable. Routine use of rifampin is not recommended for the treatment of native valve staphylococcal endocarditis. It has been used, however, as supplemental therapy in patients who do not respond adequately to conventional antimicrobial therapy. Of note, in patients with endocarditis caused by methicillin-resistant *S aureus*, a prospective trial failed to demonstrate that the addition of rifampin to vancomycin either enhanced survival or reduced the duration of bacteremia in comparison with treatment with vancomycin alone.³⁴

Tolerance to β -lactam antibiotics and vancomycin has been reported widely among staphylococci; however, tolerance has no clear clinical implication for selection of antimicrobial therapy.

STAPHYLOCOCCAL ENDOCARDITIS IN THE PRESENCE OF INTRACARDIAC PROSTHETIC MATERIAL (TABLE 5)

Table 5. Treatment of Staphylococcal Endocarditis in the Presence of a Prosthetic Valve or Other Prosthetic Material*

Antibiotic	Dosage and Route	Duration, wk	Comments
Regimen for Methicillin-Resistant Staphylococci			
Vancomycin hydrochloride†	30 mg/kg per 24 h IV in 2 or 4 equally divided doses, not to exceed 2 g/24 h unless serum levels are monitored	≥6	
With rifampin‡	300 mg orally every 8 h	≥6	
And with gentamicin sulfate§//	1.0 mg/kg IM or IV every 8 h	2	Rifampin increases the amount of warfarin sodium required for antithrombotic therapy.
Regimen for Methicillin-Susceptible Staphylococci			
Nafcillin sodium or oxacillin sodium	2 g IV every 4 h	≥6	
With rifampin‡	300 mg orally every 8 h	≥6	First-generation cephalosporins or vancomycin should be used in patients allergic to β-lactam. Cephalosporins should be avoided in patients with immediate-type hypersensitivity to penicillin or with methicillin-resistant staphylococci.
And with gentamicin sulfate§//	1.0 mg/kg IM or IV every 8 h	2	

*Dosages recommended are for patients with normal renal function. IV indicates intravenous; IM, intramuscular.

†For specific dosing adjustment and issues concerning vancomycin (obese patients, length of infusion), see Table 1 footnotes.

‡Rifampin plays a unique role in the eradication of staphylococcal infection involving prosthetic material (see text); combination therapy is essential to prevent emergence of rifampin resistance.

§For specific dosing adjustment and issues concerning gentamicin (obese patients, relative contraindications), see Table 1 footnotes.

//Use during initial 2 wk.

Coagulase-negative staphylococci. Coagulase-negative staphylococci causing prosthetic valve endocarditis are usually methicillin-resistant, particularly when endocarditis develops within 1 year after surgery.^{10,35} Unless susceptibility to methicillin can be conclusively demonstrated, coagulase-negative staphylococci causing prosthetic valve endocarditis should be assumed to be methicillin-resistant, and treatment should be designed accordingly. Evidence from experimental models of endocarditis due to methicillin-resistant coagulase-negative staphylococci and clinical experience in treating prosthetic valve endocarditis caused by these organisms suggest that optimal antibiotic therapy is vancomycin combined with rifampin and gentamicin^{10,35} (Table 5). Vancomycin and rifampin are administered for a minimum of 6 weeks, with gentamicin use limited to the initial 2 weeks of therapy. If the coagulase-negative staphylococcus is resistant to gentamicin, an aminoglycoside to which it is susceptible is 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 model studies of therapy for foreign body infections suggest that a fluoroquinolone may be used instead of the aminoglycoside.³⁵ Because one important role of the nonrifampin components of the multidrug regimen is to prevent the emergence of rifampin-resistant staphylococci, it may be prudent to delay initiation of rifampin until therapy with two effective anti-staphylococcal drugs has been initiated.

Prosthetic valve infections, particularly when onset occurs within 12 months of cardiac valve implantation or when an aortic valve prosthesis is involved, are complicated frequently by perivalvular and myocardial abscesses and valvular dysfunction.³⁶ Surgery is commonly required in this setting and is often lifesaving. Coagulase-negative staphylococci may become resistant to rifampin during combination therapy of prosthetic valve endocarditis. Because of the potential for changes in antibiotic susceptibility patterns, organisms recovered from surgical specimens or blood at relapse should be studied for antibiotic sensitivity, and therapeutic regimens should be reassessed.

Although data on combination therapy are extremely limited, it is our consensus that prosthetic valve endocarditis caused by methicillin-susceptible coagulase-negative staphylococci should be treated with nafcillin or oxacillin in combination with rifampin and gentamicin (Table 5). In patients who are allergic to penicillin, a first-generation cephalosporin or vancomycin can be substituted for nafcillin or oxacillin.

Staphylococcus aureus. Considering the high mortality rate associated with prosthetic valve endocarditis caused by coagulase-positive staphylococci, combination therapy seems prudent (Table 5). The use of combination therapy is not based on traditional studies of in vitro synergy in broth culture but rather on the favorable experience using this therapy for treatment of endocarditis caused by coagulase-negative staphylococci and involving prosthetic devices as well as on animal studies. In animal studies, rifampin has been shown to play a unique role in the complete sterilization of foreign bodies infected by *S aureus*.³⁷ If infecting strains are methicillin-susceptible, nafcillin or oxacillin is used; however, when methicillin-resistant organisms are encountered, regimens containing vancomycin must be used. Gentamicin should be given for the initial 2 weeks of therapy. If strains are resistant to gentamicin, an alternative agent

should be selected as outlined in the discussion of therapy for prosthetic valve endocarditis caused by coagulase-negative staphylococci. Appropriate adjustments must be made for patients who are allergic to penicillin.

HACEK MICROORGANISMS (TABLE 6)

Table 6. Therapy for Endocarditis Due to HACEK Microorganisms (*Haemophilus parainfluenzae*, *Haemophilus aphrophilus*, *Actinobacillus actinomycetemcomitans*, *Cardiobacterium hominis*, *Eikenella corrodens*, and *Kingella kingae*)*

Antibiotic	Dosage and Route	Duration, wk	Comments
Ceftriaxone sodium†	2 g once daily IV or IM†	4	Cefotaxime sodium or other third-generation cephalosporins may be substituted
Ampicillin sodium‡	12 g/24 h IV either continuously or in six equally divided doses	4	
With gentamicin sulfate§	1 mg/kg IM or IV every 8 h	4	

*Antibiotic dosages are for patients with normal renal function. IV indicates intravenous; IM, intramuscular.

†Patients should be informed that IM injection of ceftriaxone is painful. For patients unable to tolerate β -lactam therapy, consult text.

‡Ampicillin should not be used if laboratory tests show β -lactamase production.

§For specific dosing adjustment and issues concerning gentamicin (obese patients, relative contraindications), see Table 1 footnotes.

Endocarditis caused by slow-growing fastidious gram-negative bacilli of the HACEK group accounts for approximately 5% to 10% of native valve endocarditis in patients who are not IDUs.³⁸ These microorganisms grow slowly in standard blood culture media, and recovery may require prolonged incubation. Typically, only a fraction of the blood culture bottles from patients with HACEK endocarditis demonstrate growth. The

microbiology laboratory should be notified to retain blood cultures for 2 weeks or longer in patients who have a clinical illness suggestive of endocarditis but whose blood cultures are initially negative. Conversely, 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.

Until recently, the HACEK group of organisms were uniformly susceptible to ampicillin. Recently, however, β -lactamase-producing strains of HACEK have been identified. Because of the difficulty in performing antimicrobial susceptibility testing, HACEK microorganisms should be considered ampicillin-resistant. Although earlier studies demonstrated that ampicillin administered alone for 3 weeks was effective therapy for HACEK endocarditis,³⁸ monotherapy with ampicillin is no longer recommended. Both β -lactamase-producing and non- β -lactamase-producing strains of the HACEK group are susceptible to third-generation cephalosporins. While limited clinical data are published demonstrating their efficacy, the third-generation cephalosporins cefotaxime sodium or ceftriaxone should be considered the drugs of choice for treatment of HACEK endocarditis³⁹ (Table 6). The duration of therapy for native valve infection should be 3 to 4 weeks, and the duration of therapy for prosthetic valve endocarditis should be 6 weeks.

The HACEK group are susceptible *in vitro* to trimethoprim-sulfamethoxazole, fluoroquinolones, and aztreonam. Based on these susceptibility data, these antimicrobial agents could be considered as alternative regimens in patients unable to tolerate β -lactam therapy. There are only a few case reports of HACEK endocarditis treated with alternative regimens. Accordingly, patients with HACEK endocarditis who cannot tolerate β -lactam therapy should be treated in consultation with an infectious diseases specialist.

OUTPATIENT TREATMENT FOR ENDOCARDITIS

Considerations of cost have made outpatient treatment of endocarditis in selected patients an increasingly attractive option. Single daily dose regimens (eg, ceftriaxone treatment for endocarditis caused by penicillin-susceptible viridans streptococci) are particularly suited for outpatient therapy.^{4,39} The availability of small, portable computerized pumps allows practical outpatient use of multiple-dose or continuous-infusion therapy. Use of a dual-lumen central catheter and two portable pumps allows outpatient administration of combination therapy. The range of devices available to facilitate outpatient therapy makes it unacceptable to use a less-than-optimal regimen for reasons of convenience alone. Patients and families should be appraised of the risk of embolic complications during therapy and advised that inpatient treatment does not prevent these risks and outpatient treatment does not increase these risks. Clarification of such risks is particularly important in settings where the risk of emboli is possibly increased, such as in HACEK endocarditis. Importantly, patients selected for outpatient therapy must be hemodynamically stable, compliant, and capable of managing the technical and unanticipated aspects of outpatient therapy, and they must receive careful medical monitoring and have prompt access to medical care, including cardiac surgery, in the event of complications.

ENDOCARDITIS IN HIV-SEROPOSITIVE PATIENTS

Human immunodeficiency virus (HIV)-positive patients acquire endocarditis by two main mechanisms: (1) as a complication of injection drug use, or (2) as a complication of indwelling central catheters placed for long-term administration of medications. In either situation, *S aureus* is the most frequent pathogen recovered from blood cultures. In IDUs who are HIV-positive, the infection primarily involves the tricuspid valve, while in patients who are HIV-positive but do not use injection drugs, endocarditis is equally distributed on right-sided and left-sided valves.⁴⁰ In comparing IDUs who are HIV-positive with their counterparts who are HIV-negative, the following observations have been made: (1) the frequency of vegetations demonstrable by transthoracic echocardiography is similar (approximately 60%); (2) the proportion of cases caused by *S aureus* is similar (approximately 80%); (3) the endocarditis-related morbidity and mortality rates among IDUs who do not have an AIDS-defining illness or criteria are similar to those in their HIV-negative counterparts; and (4) the endocarditis-related morbidity and mortality rates of patients with AIDS exceed those of HIV-positive patients without AIDS.⁴⁰ Currently, it seems prudent to treat endocarditis in patients with AIDS with maximal antibiotic regimens; such patients should probably not be given short-course regimens.

MONITORING ADEQUACY OF ANTIBIOTIC THERAPY

Careful clinical observation is the most important aspect of monitoring adequacy of therapy. Persistent or recurrent fever may be a manifestation of therapeutic failure but also may be due to a variety of other causes, including hypersensitivity reactions to drugs, thrombophlebitis, or sterile embolization.

The serum bactericidal titer is the highest dilution of the patient's serum (obtained while he or she is receiving antibiotic therapy) that kills a standard inoculum of the patient's organism in vitro. The test has not been validated fully under clinical circumstances, and results vary from one laboratory to another according to the methods used; therefore, it is not routinely recommended.⁴¹ Rarely, the serum bactericidal titer may be useful when response to therapy is suboptimal, when endocarditis is due to an unusual organism, or when an unconventional treatment regimen is used.⁴¹

All patients with infective endocarditis should be followed assiduously. Blood cultures should be obtained during therapy of staphylococcal endocarditis to assure eradication of the organism. This is particularly important in patients with prolonged or recurrent febrile states. Additional blood cultures should be performed once or twice in the 8 weeks after completion of antibiotic treatment to ensure cure. Relapses, should they occur, usually manifest themselves clinically within 4 weeks and then can be detected promptly by blood cultures. Relapses usually respond to retreatment in patients with native valve endocarditis. Surgery should be considered for patients who experience a relapse for prosthetic valve endocarditis after appropriate antimicrobial treatment and for patients with resistant enterococcal endocarditis. Among patients with *S aureus* or coagulase-negative staphylococcal endocarditis, if blood cultures remain persistently positive, perivalvular abscess or metastatic infection should be considered.

The major causes of death among patients with infective endocarditis include congestive heart failure, which is usually secondary to valvular dysfunction, and emboli. Surgical intervention may be lifesaving in patients with infective endocarditis. A detailed consideration of indications for surgery in infective endocarditis is beyond the scope of this article. For further information on this subject, the reader is referred to other sources.^{10,42,43}

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