

GUIDELINES

Antibiotic treatment of streptococcal, enterococcal, and staphylococcal endocarditis

Working Party of the British Society for Antimicrobial Chemotherapy

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The Endocarditis Working Party of the British Society for Antimicrobial Chemotherapy first issued recommendations for the treatment of streptococcal and staphylococcal endocarditis in 1985.¹ Since then numerous reports have been published of the results of treatment with the recommended regimens and with other antibiotics, some of which were not available in 1985, and the American Heart Association has recently reviewed its guidelines for antibiotic treatment.² Revised diagnostic criteria^{3,4} and new therapeutic procedures have also become available and many more patients have had prosthetic valves implanted. We have reviewed our recommendations in light of these developments and our wish to have simplified up to date guidelines that are most appropriate for use in the UK. They are intended to cover more than 90% of the cases of infective endocarditis seen in the UK, which are caused by streptococci, enterococci and staphylococci.

In endocarditis the heart valves may be damaged at an early stage thus prompt treatment is essential. Patients with a fever and a heart murmur should have blood cultures taken without delay before any antibiotic treatment is given. Patients with prosthetic valves who become feverish should be referred to a hospital with cardiology and, ideally, cardiothoracic surgery facilities and they should also have blood cultures taken before antibiotics are given.

A combination of a penicillin and an aminoglycoside, usually gentamicin, is still the most suitable first line treatment for streptococcal and most enterococcal and staphylococcal endocarditis. The type of penicillin, the dose, and the duration of treatment depend on the infecting organism and its in vitro antibiotic sensitivity, and this should be established as soon as possible. In patients who are allergic to penicillins one of the glycopeptide antibiotics, vancomycin or teicoplanin, should be used. We recommend similar treatment for native and prosthetic valve infections except where stated. Important changes from our previous guidelines include endorsement of a two week treatment regimen for cases of uncomplicated penicillin sensitive viridans streptococcal native valve endocarditis, and the abandonment of routine minimum bactericidal concentrations and serum bactericidal titres.

The early stage

Treatment should be started before the results of blood cultures are known. For most patients we recommend the same combination of antibiotics in the same dosage as for the treatment of endocarditis caused by penicillin sensitive viridans streptococci, namely benzylpenicillin and gentamicin (table 1). If there is a strong possibility of staphylococcal infection—for example, in intravenous drug users and patients on haemodialysis, vancomycin should be used instead of penicillin (table 1, regimen C for staphylococci). Community acquired native valve *Staphylococcus aureus* endocarditis is rarely caused by methicillin resistant strains and prosthetic valve endocarditis is frequently caused by methicillin resistant staphylococci, but the Working Party preferred to recommend only one set of treatment guidelines to cover both situations for the brief period while waiting for the results of culture and antibiotic sensitivities. When the results of blood cultures are known and the antibiotic sensitivity of any organism found has been determined, the treatment can be modified and decisions made about its duration.

If the patient's haemodynamic condition deteriorates despite appropriate antibiotic treatment, the opinion of a cardiac surgeon should be sought. Delay in valve replacement may prove fatal.

Streptococcal endocarditis

VIRIDANS STREPTOCOCCI AND *STREP BOVIS*

The viridans streptococci are responsible for about 40% cases of endocarditis. They are a heterogeneous group that includes *Strep oralis*, *Strep mitis*, *Strep sanguis*, *Strep mutans*, *Strep salivarius*, and other oral streptococci. *Strep bovis*, a normal inhabitant of the intestinal tract, is similar to the viridans streptococci in respect to its sensitivity to penicillin. Their precise penicillin sensitivity, on which our recommendations for the duration of treatment are based, cannot be predicted and must be determined in each case by in vitro tests.

We previously recommended that viridans streptococci should be divided into those fully sensitive to penicillin and those with reduced sensitivity as determined by the minimum bactericidal concentration (MBC). We now believe that the routine determination of the minimum inhibitory concentration (MIC),

Table 1 Treatment regimens for adults not allergic to the penicillins

<i>Viridans streptococci and Streptococcus bovis</i>	
(A) Fully sensitive to penicillin (MIC \leq 0.1 mg/l)	Benzylpenicillin 7.2 g daily in six divided doses by intravenous bolus injection for two weeks plus intravenous gentamicin 80 mg twice daily for two weeks* (table 2)
(B) Reduced sensitivity to penicillin (MIC > 0.1 mg/l)	Benzylpenicillin 7.2 g daily in six divided doses by intravenous bolus injection for four weeks plus intravenous gentamicin 80 mg twice daily for four weeks*
<i>Enterococci</i>	
(A) Gentamicin sensitive or low level resistant (MIC < 100 mg/l)	Ampicillin or amoxycillin 12 g daily in six divided doses by intravenous bolus injection for four weeks plus intravenous gentamicin 80 mg twice daily for four weeks*
(B) Gentamicin highly resistant (MIC \geq 2000 mg/l)	Ampicillin or amoxycillin 12 g daily in six divided doses by intravenous bolus injection for a minimum of six weeks. Streptomycin can be given if strain is sensitive
<i>Staphylococci</i>	
(A) Penicillin sensitive	Benzylpenicillin 7.2 g daily in six divided doses by intravenous bolus injection for four weeks plus intravenous gentamicin 80–120 mg three times daily for one week*
(B) Penicillin resistant, methicillin sensitive	Flucloxacillin 12 g daily in six divided doses by intravenous bolus injection for four weeks plus intravenous gentamicin 80–120 mg three times daily for one week*
(C) Penicillin and methicillin resistant	Vancomycin initially 1 g by intravenous infusion given over at least 100 minutes twice daily. Determine blood concentration and adjust dose to achieve one hour postinfusion concentrations of about 30 mg/l and trough levels of 5–10 mg/l. Give for four weeks plus intravenous gentamicin 80–120 mg three times daily for one week*

*Gentamicin levels must be monitored.

which is a simpler and more reproducible test, is adequate. Similar to the American Heart Association,² we could find no data to show that the MBC is better than the MIC for this purpose.

In the past we have recommended that treatment should be given for a minimum of four weeks. However, if all the conditions listed in table 2 are met, we believe that two weeks of treatment with penicillin and gentamicin is adequate for endocarditis caused by fully sensitive viridans streptococci or *Strep bovis*, as combination treatment for two weeks has been shown to be highly effective in selected cases.⁵ If the streptococci are less sensitive or the other conditions are not met, treatment must be given for one month. If complications develop, surgery may be required at an early stage. Streptococci are seldom sensitive to gentamicin alone, but it usually acts synergistically

Table 2 Conditions to be met for a two week treatment regimen for viridans streptococcal and *Strep bovis* endocarditis

<i>Penicillin sensitive viridans streptococcus or Strep bovis</i> (penicillin MIC \leq 0.1 mg/l)
No cardiovascular risk factors such as heart failure, aortic insufficiency or conduction abnormalities
No evidence of thromboembolic disease
Native valve infection
No vegetations more than 5 mm diameter on echocardiogram
Clinical response within seven days. Temperature should return to normal, patient should feel well and appetite return

Table 3 Treatment regimens for adults allergic to the penicillins

<i>Viridans streptococci, Strep bovis, and enterococci</i>	
Initially either vancomycin 1 g by intravenous infusion given over at least 100 minutes twice daily. Determine blood concentrations and adjust dose to achieve one hour postinfusion concentrations of about 30 mg/l and trough concentrations of 5–10 mg/l or teicoplanin 400 mg by intravenous bolus injection 12 hourly for three doses and then a maintenance intravenous dose of 400 mg daily	Give vancomycin or teicoplanin for four weeks plus intravenous gentamicin 80 mg twice daily. Viridans streptococcal and <i>Strep bovis</i> endocarditis should be treated with gentamicin for two weeks and enterococcal endocarditis for four weeks*
<i>Staphylococci</i>	
Vancomycin initially 1g by intravenous infusion given over at least 100 minutes twice daily	Blood concentrations should be monitored as above. Give for four weeks plus intravenous gentamicin 80–120 mg three times daily for one week*

*Gentamicin blood levels must be monitored.

with penicillin, and the proposed low dose of 80 mg twice daily is sufficient to achieve that effect. If serum creatinine concentration is within normal limits, serum gentamicin concentrations should be determined twice a week. If serum creatinine is raised, serum gentamicin concentrations should be determined more often. It is possible to reduce post-dose concentration of gentamicin by reducing the dose and to reduce trough concentrations by extending the time interval between the doses. Post-dose concentration in blood taken one hour after intravenous bolus injections should be 3–5 mg/l, and trough concentrations in blood taken just before the next dose should be less than 1 mg/l.

In the past, we have recommended that titrations of serum bactericidal activity against the infecting organism should be used to monitor antibiotic treatment, but we have found great variation in the monitoring methods used and the interpretation of results.⁶ We are no longer convinced of their predictive value and do not now recommend them.

Enterococci

Enterococcus faecalis and *E faecium* account for about 10% of cases of endocarditis, and are most often encountered in elderly patients. These organisms are more resistant to penicillin (median MIC 2 mg/l) than the viridans streptococci. Although they may be marginally more sensitive to amoxycillin and ampicillin, they are difficult to kill in vitro with a penicillin alone. Most strains are killed by a combination of either ampicillin or amoxycillin plus gentamicin and the recommended regimens are given in table 3. Serum gentamicin concentrations should be monitored and maintained at the same levels as those recommended for viridans streptococci. Some strains exhibit high level gentamicin resistance and cannot be killed with the combination. Some high level gentamicin resistant enterococci may be sensitive to streptomycin, therefore streptomycin sensitivity should be determined for these strains. Streptomycin may be used instead of gentamicin if the organism is sensitive. We recommend treatment of endocarditis caused by highly gentamicin and streptomycin resistant strains with high dose ampicillin or amoxycillin alone for a minimum of six weeks.

ALLERGY TO PENICILLINS

Penicillins are fundamental to the antibiotic treatment of endocarditis and hypersensitivity to them may occasionally be associated with hypersensitivity to cephalosporins and other β lactams; thus penicillin hypersensitivity seriously compromises the range of antibiotics that can be used. For this reason, patients who claim to be allergic to penicillins should be closely questioned about the nature of any penicillin hypersensitivity reaction. Where the alleged allergic manifestations of penicillin hypersensitivity are of a vague and minor nature—for example, gastrointestinal disturbances, and do not indicate that the patient has immediate-type hypersensitivity, treatment with a penicillin is justified. Treatment with a

penicillin, cephalosporin or other β lactam antibiotic of a patient with a history of an immediate-type (IgE mediated) hypersensitivity reaction, including urticarial rashes, is unjustifiable. In these circumstances, vancomycin or teicoplanin should be substituted for the penicillin, and given with gentamicin. Vancomycin should initially be given in a dose of 1 g infused intravenously over at least 100 minutes twice a day and blood concentrations determined twice a week. The dose should be adjusted to achieve one hour postinfusion serum concentrations of about 30 mg/l and trough concentrations of 5–10 mg/l.

Our recommended regimen for teicoplanin is 400 mg 12 hourly by intravenous bolus injection for the first three doses and then a daily maintenance dose of 400 mg administered as a single intravenous injection.⁷

Gentamicin should be given in the same dosage as that recommended for patients not hypersensitive to the penicillins.

HOME TREATMENT

Home treatment with ceftriaxone has recently been advocated for selected patients with penicillin sensitive streptococcal endocarditis when close home support can be made available.⁸ Patients should be initially assessed in hospital where they should meet all the other criteria listed in table 3, and must respond satisfactorily to treatment within seven days. These patients are identical to those for whom we now recommend treatment for just 14 days with benzylpenicillin and gentamicin. Therefore, in most situations, little would be gained from recommending home treatment in the United Kingdom.

Staphylococcal endocarditis

Endocarditis caused by coagulase negative staphylococci, particularly *Staph lugdunensis*, may be just as severe as that caused by *Staph aureus*, and our recommended regimens are similar for both. Staphylococci may be penicillin sensitive non- β lactamase producers, β lactamase producers resistant to penicillin but sensitive to methicillin (and flucloxacillin), or penicillin and methicillin resistant. If staphylococci are isolated from blood cultures of a patient with suspected endocarditis, treatment should be started with vancomycin and gentamicin until the sensitivity is known when it can be modified (table 1).

We know of no evidence that the addition of gentamicin improves cure rates when the staphylococcus is sensitive to this antibiotic, but combination treatment with gentamicin may result in a more rapid defervescence and clearance of bacteraemia.⁹ Therefore, for gentamicin sensitive staphylococci we recommend the addition of gentamicin in a dose of 80–120 mg three times daily for the first week only, when blood concentrations must be monitored two to three times. The objective is to achieve one hour post-dose blood concentrations above 5 mg/l and not more than 10 mg/l, and trough concentrations of less than 2 mg/l. Oral fusidic acid may be considered as an alternative to gentamicin for combination

treatment for fusidic acid sensitive strains. For patients hypersensitive to penicillin we prefer the regimen recommended for methicillin resistant staphylococcal infections—vancomycin and gentamicin. We are not yet convinced that teicoplanin can be substituted for vancomycin for the treatment of staphylococcal endocarditis.

As with streptococcal endocarditis we are not convinced of the value of serum bactericidal titrations and do not recommend them.

We recommend the same choice of antibiotics for native and prosthetic valve infections; however, while the duration of treatment rarely needs to be longer than four weeks for native valve infection, four to six weeks may be preferable for treating prosthetic valve endocarditis.

Coagulase negative staphylococci and *Staph aureus* are usually sensitive to rifampicin and in difficult cases addition of this agent may be effective. However, resistance to rifampicin develops rapidly and it should never be given alone. In endocarditis it is usually given with vancomycin. Rifampicin is a potent hepatic enzyme inducer and interacts with other drugs, notably reducing the activity of anticoagulants and oral contraceptives.

Persistent or recurrent fever during treatment

The fever associated with infective endocarditis usually resolves within two to three days of the start of antibiotic treatment. However, sometimes it persists and sometimes, having settled, it recurs. The most common cause of persistent fever is extensive infection of the valve ring.¹⁰

Penicillin hypersensitivity is a relatively common cause of recurrent fever; even more common is penicillin toxicity. Rash and eosinophilia are indicative of hypersensitivity, but neutropenia and impairment of renal function suggest toxicity associated with overdose. In both cases, the fever usually disappears promptly after drug withdrawal.

Other causes of persistent or recurrent fever include embolism and infection of venous access sites. The emergence of antibiotic resistance in the infecting organism is seldom a cause, and if the infecting bacteria have been cultured and the patient given appropriate bactericidal antibiotics, the temptation to change the treatment should be resisted.

Evidence of drug hypersensitivity, another infection or embolism should be sought, and if not found, the advice of a cardiac surgeon should be taken as prompt surgical intervention may be needed and delay may prove fatal.

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