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New guidelines for the antibiotic treatment of streptococcal, enterococcal and staphylococcal endocarditis

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Revised guidelines for the treatment of bacterial endocarditis have recently been issued by the BSAC Working Party,[1] complementing previous recommendations from the American Heart Association (AHA).[2] The AHA guidelines do not include empirical treatment recommendations, perhaps implying that the results of blood cultures should be awaited, which is not usually the policy in the UK. Apart from these differences, the two reports, which were initiated by independent working groups, include broadly similar recommendations. In both publications, antibiotic treatment is indicated for patients with a diagnosis of infective endocarditis based on the Duke diagnostic criteria,[3,4] and early surgical intervention is emphasized for some patients, especially if their haemodynamic condition deteriorates. The main purpose of this article is to discuss important changes in the latest BSAC Working Party recommendations on antibiotic treatment compared with those in previous guidelines.[5]

The main recommendations of the 1998 BSAC Working Party Report for the treatment of streptocccal, enterococcal and staphylococcal endocarditis are summarized in Tables I and II. The most important differences from the previous guidelines concern the abandonment of routine MBC testing and the adoption of a 2-week treatment regimen for uncomplicated endocarditis caused by penicillin-susceptible viridans streptococci and *Streptococcus bovis*. Streptococci are now defined as penicillin susceptible if their MIC of penicillin is $\leqslant$0.1 mg/L. There are many more technical pitfalls with MBC determinations than with MIC determinations, including the use of suboptimal inocula, difficulties with interpreting a 99.9% bactericidal endpoint that involves both a baseline surface viable count and counting any persisting colonies, and uncertainties over the efficiency of the methods used to prevent carryover of antibiotics from the broths to the subculture plates. There has also been a problem over the lack of standardization of the techniques used. The BSAC Working Party, like the AHA Committee, could not find any advantage for the patient in carrying out routine MBC determinations.

Two-week treatment regimens have been recommended in the USA during the last 20 years but were not previously advocated in the UK.[2,6] Many reports indicate that a combination of penicillin plus an aminoglycoside kills penicillin-sensitive viridans streptococci more rapidly than penicillin alone, and that a 2-week course of penicillin plus streptomycin is effective clinically.[2,6] Gentamicin is, however, generally the preferred aminoglycoside as it is much more often used in general clinical practice than streptomycin, convenient to give by the intravenous route, and more readily assayed than streptomycin. In-vitro and in-vivo experimental data support the use of gentamicin as an alternative to streptomycin for short-course treatment;[2,7] there is a relative lack of clinical reports on 2-week treatment courses using gentamicin instead of streptomycin. High-level aminoglycoside resistance is uncommon in viridans streptococci but is more frequently reported with streptomycin than gentamicin, and gentamicin is now preferable to streptomycin as a synergic drug for combination treatment with penicillin.[8,9] Excellent clinical and bacteriological outcomes have been reported with the 2-week penicillin plus gentamicin regimen for treating selected patients with penicillin-susceptible viridans streptococcal endocarditis.[9] This regimen is widely used in the USA and should become 'standard' therapy for patients in the UK who fulfil the criteria listed in Table II. A 2-week treatment regimen with ceftriaxone plus netilmicin has also been found effective in Switzerland and some other countries.[10] Short-course treatment is as effective as the traditional 4-week treatment courses previously recommended, is more convenient for appropriately selected patients (Table II) and saves on hospital costs.

The choice of antibiotics recommended in the 1998 BSAC report is the same for both native and prosthetic valve endocarditis, although a longer course of treatment (4–6 weeks) may be required for treating prosthetic valve endocarditis caused by staphylococci. The latest BSAC report does not differentiate between endocarditis caused by *Staphylococcus aureus* and that due to coagulase-negative staphylococci (CNS), since similar principles apply concerning the use of flucloxacillin or vancomycin,

Table I. BSAC antibiotic treatment recommendations for adults with endocarditis[1]

Blood culture isolate	Not allergic to penicillin	Allergic to penicillin
Viridans streptococci and *S. bovis*		
(a) Fully sensitive to penicillin (MIC ≤ 0.1 mg/L)	Benzylpenicillin 7.2 g daily in six divided doses by iv bolus injection for 2 weeks plus iv gentamicin 80 mg bd[a] for 2 weeks[b]	Either (i) teicoplanin 400 mg by iv bolus injection bd for three doses and then 400 mg daily for 4 weeks or (ii) vancomycin 1 g by iv infusion bd (details as for staphylococcal treatment—see below) for 4 weeks plus gentamicin, 80 mg bd iv[a] given for initial 2 weeks
(b) Less sensitive to penicillin (MIC > 0.1 mg/L)	As above, but given for 4 weeks	
Enterococci		
(a) Gentamicin-sensitive or low-level resistant (MIC < 100 mg/L)	Ampicillin or amoxycillin, 12 g daily in six divided iv bolus doses, plus iv gentamicin 80 mg bd[a] for 4 weeks	Teicoplanin or vancomycin, plus gentamicin[a] given as above for 4 weeks
(b) Highly resistant to gentamicin (MIC ≥ 2000 mg/L)	Ampicillin or amoxycillin, as above but given for 6 weeks. Streptomycin 1 g daily for 6 weeks, added if strain is sensitive	
Staphylococci (*S. aureus* or CNS)		
(a) Penicillin-sensitive	Benzylpenicillin 7.2 g daily in six divided doses by iv bolus injection for 4 weeks plus iv gentamicin 80–120 mg tds[c] for 1 week	Vancomycin, 1 g iv infusion given over at least 100 min bd (details as in (c) opposite), plus iv gentamicin, 80–120 mg tds[c] for 1 week
(b) Penicillin-resistant, methicillin-sensitive	Flucloxacillin 12 g daily in six divided doses by iv bolus injection for 4 weeks plus gentamicin 80–120 mg tds for 1 week	
(c) Penicillin- and methicillin-resistant	Vancomycin, initially 1 g by iv infusion given over at least 100 min bd. Determine serum vancomycin concentration and adjust dose to achieve 1 h post-infusion concentration of about 30 mg/L and trough concentration of 5–10 mg/L. Give for 4 weeks plus iv gentamicin 80–120 mg tds[c] for 1 week if the strain is sensitive to gentamicin	

[a] Serum gentamicin assays regularly monitored before and after bolus doses so that 1 h post-dose concentrations of 3–5 mg/L and trough concentrations <1 mg/L are achieved.
[b] See Table II for selection of cases.
[c] Gentamicin concentrations of 5–10 mg/L at 1 h post-dose and trough concentrations <2 mg/L should be obtained.

Table II. Conditions for 2-week treatment regimen for penicillin-sensitive streptococcal endocarditis[1]

1. Penicillin-sensitive viridans streptococcus or *S. bovis* (penicillin MIC ≤ 0.1 mg/L).
2. No cardiovascular risk factors such as heart failure, aortic insufficiency or conduction abnormalities.
3. No evidence of thromboembolic disease.
4. Native valve infection.
5. No vegetation of >5 mm diameter on ECHO.
6. Clinical response within 7 days. The temperature should return to normal, the patient should feel well and the appetite return.

based on the results of antibiotic sensitivity tests, and also concerning the initial combination with gentamicin (Table I). Oral fusidic acid can be given in place of gentamicin when the latter is contraindicated or when the strain is resistant to gentamicin but sensitive to fusidic acid.

The addition of rifampicin and the possible need for cardiac surgery should be considered for cases of staphylococcal endocarditis that do not respond to the above antibiotic therapy.[11] However, the value of adding rifampicin for the treatment of MRSA endocarditis has been questioned since no enhanced survival or shortened duration of bacteraemia occurred in patients receiving a combination of rifampicin plus vancomycin compared with vancomycin alone in a recent study.[12] Rifampicin plus vancomycin and gentamicin has provided optimal antibiotic therapy for treating endocarditis due to methicillin-resistant CNS both in experimental animal models and clinically.[13]

The recommended treatment of enterococcal endocarditis is with a combination of ampicillin or amoxycillin plus gentamicin, with different regimens depending whether the MIC of gentamicin is <100 mg/L or >2000 mg/L (Table I). Streptomycin susceptibility should be tested for in highly gentamicin-resistant strains since occasional strains are sensitive to streptomycin.[14] The BSAC Working Party report does not give recommendations for enterococci with gentamicin MICs between 100 and 2000 mg/L. It may be desirable to send the occasional strains in this category to a reference laboratory for an antibiotic combination test to ascertain if bactericidal synergy between ampicillin and gentamicin can be detected. If synergy is shown then this combination should be used for treatment.

Empirical therapy of bacterial endocarditis is outlined in the British but not the American guidelines.[2] In the former, penicillin plus gentamicin is recommended for most patients but, when staphylococcal infection is suspected, vancomycin plus gentamicin is now recommended rather than the penicillin plus flucloxacillin plus gentamicin combination advocated in the 1985 report.[5] MRSA is an uncommon cause of community-acquired native valve endocarditis, except in intravenous drug abusers, whereas MRSA or CNS are increasingly prevalent causes of prosthetic heart valve endocarditis. The BSAC Working Party preferred to make simplified recommendations, involving vancomycin plus gentamicin for empirical therapy, rather than have two sets of guidelines for different circumstances. In any event this empirical treatment is usually only needed for a few days since the results of blood cultures and antibiotic sensitivity tests will soon allow treatment to be modified.

Serum bactericidal assays to monitor treatment are no longer routinely recommended by either the BSAC or AHA because of the great variety of monitoring methods used and the interpretation of the results.[15,16] A recent report[17] suggested that, although more than 100 laboratories in the UK continue to use this test for most patients with infective endocarditis, possibly because of the previous recommendations of the BSAC Working Party, only 25% of the laboratories would consider changing therapy on the basis of the results obtained. This survey also showed considerable variation in the interpretation of the results as well as in the methods used.[17] Although there may be a general correlation between the results of assay and bacteriological outcome, there is now a consensus that these assays are of no benefit for managing the individual patient.

Patients with a definite history of immediate-type penicillin hypersensitivity should not be given a β-lactam antibiotic and the BSAC Working Party recommends that a glycopeptide should be substituted (Table I). Cephalosporins are not recommended in the BSAC report but are considered by the AHA for some patients with doubtful penicillin-allergy. Teicoplanin is recommended as an alternative to vancomycin for treating penicillin-allergic patients with streptococcal endocarditis.[1,18] It has the advantage of a more convenient intravenous administration (as a bolus) than vancomycin, which needs to be infused over at least 100 min, and teicoplanin is relatively non-toxic. However, vancomycin is recommended, rather than teicoplanin, for the treatment of staphylococcal endocarditis in patients allergic to β-lactams, as unsatisfactory outcomes have been reported in some patients treated with teicoplanin for staphylococcal infection.[19,20] Some of the high failure rates in early reports of teicoplanin treatment of *S. aureus* endocarditis can be

attributed to inadequate dosage (e.g. 6 mg/kg/day in adult cases).[19] Improved efficacy was subsequently reported with higher doses that produced trough serum concentrations >20 mg/L.[20] However, the optimal dosage of teicoplanin in endocarditis is still the subject of controversy as unsatisfactory outcomes of teicoplanin treatment with higher doses have also been reported in *S. aureus* endocarditis in intravenous drug abusers.[21,22] Teicoplanin is less active than vancomycin against some strains of CNS,[23,24] including *Staphylococcus haemolyticus* and *Staphylococcus epidermidis*, and teicoplanin might be less effective than vancomycin for treating CNS endocarditis caused by such strains. Further work is needed comparing the clinical efficacy of teicoplanin with vancomycin for the treatment of CNS endocarditis.

The 1998 BSAC Working Party report does not attempt to be a comprehensive treatise on the treatment of infective endocarditis. It concentrates on streptococcal, enterococcal and staphylococcal endocarditis since these will be relevant in >90% of cases of endocarditis seen in the UK. The AHA guidelines are longer than the BSAC recommendations and include a brief discussion about staphylococcal endocarditis in patients with HIV[25] as well as endocarditis caused by the HACEK (*Haemophilus, Actinobacillus, Cardiobacterium, Eikenella* and *Kingella* spp.) group of organisms. The AHA recommends a cephalosporin, such as ceftriaxone,[26] in combination with gentamicin, for treating HACEK endocarditis.

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