Prophylaxis and Treatment of Infective Endocarditis

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The incidence of infective endocarditis has not changed during the last forty years and it is probable that many susceptible patients receive no appropriate prophylaxis[1-3]. Patients with cardiac lesions who are particularly susceptible include those with (a) rheumatic and 'degenerative' valvular disease—especially mildly incompetent aortic or mitral valves; (b) congenital defects—especially patent ductus, small ventricular septal defects, and valvular disease including bicuspid aortic valves, and (c) prosthetic or graft heart valves.

Rheumatic heart disease is much less common in Britain than in the past, when it frequently affected young to middle-aged adults. Now most patients at risk of developing endocarditis are aged over 45 years. Other cardiac abnormalities may also predispose to infective endocarditis (IE)[4]. Between 30 per cent and 50 per cent of patients who develop endocarditis have no previously known cardiac abnormality and, of course, current recommendations about prophylaxis could not be expected to prevent the disease occurring in these patients. It is reasonable to advise on the prophylaxis of endocarditis for patients with known susceptible cardiac lesions but there is no direct way of determining the value of any of the prophylactic measures recommended.

The main objectives of prophylaxis in susceptible patients are the prevention or reduction of bacteraemia and the eradication of any residual organisms that may have lodged on a fibrin-platelet endothelial vegetation following bacteraemia. Between 25 and 40 per cent of patients with *Strep. viridans* endocarditis give a history of a recent dental procedure[5]. Maintenance of good oral hygiene reduces the incidence of asymptomatic bacteraemias that occur in association with diseased gums or teeth, or during daily activities such as chewing or using a toothbrush. Antibiotic prophylaxis is indicated if there is a predictable significant risk of bacteraemia occurring in a susceptible patient (Table 1).

Table 1. Some procedures predisposing to endocarditis by causing bacteraemia.

Site	Procedure	Main Bacteria in the Blood
Gums and teeth	Dental extraction Other procedures causing gingival bleeding, e.g. scaling of teeth	Viridans streptococci
Genito-urinary tract	Instrumentation Surgery Complicated vaginal delivery	Enterococci
Gastrointestinal tract	Endoscopy Surgery	Enterococci
Skin and wounds	Cardiac surgery	Staphylococci Diphtheroids Gram-negative bacilli

Antibiotic Prophylaxis for Susceptible Dental Patients

Bactericidal, rather than bacteristatic, antibiotics are required for the successful prophylaxis of endocarditis[6,7]. The majority of viridans streptococci are killed by a concentration of 0.12 mg/litre of penicillin or amoxycillin and these antibiotics are suitable for prophylaxis in patients undergoing 'at risk' procedures such as dental extraction. The first dose of antibiotic should be given just before the expected bacteraemia. There is a danger that if antibiotic prophylaxis is started too soon, endocarditis due to antibiotic-resistant organisms may follow[8]. The duration of prophylaxis should continue for the critical 'at risk period' following bacteraemia. The duration of this period is unknown in man but has been estimated as between six and nine hours in the rabbit endocarditis experimental model[6,7]. Adequate doses of bactericidal antibiotics are important for effective prophylaxis which is achieved in only a few susceptible patients in dental practice[1].

Benzylpenicillin, given to rabbits as a single high dose equivalent to 20 mega units in man, failed to prevent streptococcal endocarditis[6]. There was no serum bactericidal activity six hours after this dose and it was concluded that a high initial peak level of penicillin at the time of bacteraemia was insufficient to prevent endocarditis. Benzathine penicillin given alone was associated with inhibitory serum levels sustained for at least nine hours but was not associated with any significant 'peak level' and did not prevent endocarditis. However, a single dose of benzylpenicillin together with benzathine penicillin provided both a high early peak and sustained penicillin levels for six to nine hours, and prevented endocarditis. For optimal parenteral prophylaxis in man,

an intramuscular injection of a penicillin mixture is recommended 15 to 30 minutes before a dental manipulation (Table 2).

Table 2. Prophylaxis of endocarditis for dental procedures.

	Penidural (Wyeth)	or Triplopen (Glaxo)
Patients in hospital		
15-30 min before procedure:		
i.m. injection: 1 vial of penicillin mixture, i.e.		
Benzylpenicillin	190 mg	300 mg
Procaine penicillin	300 mg	250 mg
Benzathine/benethamine penicillin	450 mg	475 mg
If prosthetic valve present		
As above, with separate i.m. injection of streptomycin 1 g or gentamicin 80 mg		
Patients allergic to penicillin		
20 min before procedure:		
Slow i.v. injection of vancomycin 1 g		
If prosthetic valve present		
As above, with i.m. injection of gentamicin 80 mg		
Patients outside hospital		
1 hr before procedure:		
Oral amoxycillin 3 g		
Patients allergic to penicillin		
30 min before procedure:		
Erythromycin 1 g orally, then 500 mg every 6 hr for 24 hr		

Other rabbit experiments showed that a combination of penicillin and an aminoglycoside, such as streptomycin, gave more complete protection against the development of endocarditis than either drug alone, and this combination is particularly recommended in patients with a prosthetic heart valve. Excellent results were also obtained with vancomycin, and this drug is mainly recommended for hospital patients who are allergic to penicillin (Table 2).

The American Heart Association published recommendations for prophylaxis that were based largely on the data from rabbit experiments[9]. These recommendations encouraged the routine administration of injections of a penicillin mixture and streptomycin and suggested the use of oral penicillin V for 48 hours after a dental procedure. Petersdorf[10] regarded these recommendations as 'overkill' rather than 'prudent caution', and pointed out several reasons why the rabbit model should not be strictly compared with man. The comment that these experiments were mainly an exercise in the treatment of established endocarditis, rather than its prevention, has also been made[5,11].

Oral Prophylaxis

There has recently been recognition of the fact that most susceptible patients undergo dental procedures outside hospital and that when prophylaxis is offered by dentists or GPs it is usually in the oral form[1,2]. The duration of prophylaxis, too, is often reduced outside hospital, as some patients who feel well may fail to take repeat doses of antibiotic after the procedure[12].

If injections of antibiotics were impractical, the American Heart Association recommended a 2 g loading dose of oral penicillin V one hour before a dental manipulation. This was to be followed by eight further doses of 500 mg of penicillin, given six-hourly. Petersdorf subsequently suggested a similar large loading dose of penicillin V as the main method of prophylaxis, to be followed by only three doses of penicillin V after the procedure[10].

Amoxycillin is much better absorbed and has a longer half-life than penicillin V. A single 2 g oral dose of amoxycillin given one hour before dental extraction greatly reduced the incidence of bacteraemia due to both streptococci and anaerobes[12]. It was also shown that the serum antibiotic levels were much higher and more sustained following a 2 g oral dose of amoxycillin than after an equivalent dose of penicillin V. A subsequent study showed that 3 g oral amoxycillin, given as a syrup, gave serum concentrations well above the minimum bactericidal concentrations for viridans streptococci, which lasted for at least ten hours[13]. Oral high dose amoxycillin is now recommended for the routine prophylaxis of endocarditis in dental patients outside hospital[5,13,14]. The first 3 g dose is best given under supervision approximately one hour before the procedure. A second dose of 3 g can be given about eight hours afterwards, to provide serum bactericidal levels for up to 18 hours, but this is probably unnecessary.

Erythromycin is recommended for oral prophylaxis of patients allergic to penicillin, but it is important to use an adequate loading dose of 1 g one hour before the procedure (Table 2). If a prosthetic heart valve is present, the procedure should be performed in hospital and a parenteral combination of vancomycin and an aminoglycoside is recommended.

Prophylaxis for Non-Dental Procedures

Genito-urinary or Gastrointestinal Manipulations

Instrumentation or surgery on the genito-urinary or gastrointestinal tracts of susceptible patients calls for the optimal bactericidal prophylaxis that is effective against *Strep. faecalis* and other enterococci[5,9], and is best achieved by giving a parenteral combination of penicillin, ampicillin or amoxycillin together with gentamicin just before the procedure. For patients with a prosthetic heart valve who are allergic to penicillin, a combination of vancomycin and gentamicin is recommended. Other patients who are allergic to penicillin but have not had previous heart surgery may receive a prophylactic combination of erythromycin and gentamicin but this combination may not kill some enterococci as effectively as the combination of vancomycin and gentamicin[9].

Cardiac Surgery

The American Heart Association recommended that antibiotic cover for cardiac surgery should be mainly directed against staphylococci and not continued for

more than three days after the operation, otherwise infection by organisms resistant to these antibiotics might occur[9]. In Britain, a prophylactic regimen similar to that used at Papworth Hospital is recommended as providing suitable antibiotic cover against *Staph. aureus,* most strains of *Staph. epidermidis,* diphtheroids and Gram-negative bacilli[15]. This regimen includes a combination of cloxacillin, benzylpenicillin and gentamicin. It is started with the pre-medication and continued for no longer than 48 hours post-operatively.

Treatment of Infective Endocarditis

The mortality rate of IE in patients with a precise microbial diagnosis is about 15 per cent, compared with 30 per cent in those whose infecting organism is not known. Optimal treatment depends on obtaining a microbial diagnosis. The most valuable diagnostic procedure is the collection of three blood culture sets during a 24-hour period, before the start of antibiotic therapy. In the majority of cases an organism, usually a streptococcus, is isolated from more than one blood culture set within a few days of collecting the blood sample. About 20 per cent of endocarditis patients have negative blood cultures, but many of them probably have streptococci as the causative agents. Endocarditis is sometimes due to pyridoxal-dependent streptococci that are difficult to isolate from blood cultures without special techniques[16]. Brucella is a rare organism that can be detected by performing serum brucella complement fixation tests. Serology, using paired sera, is always indicated when the blood culture is negative, to look for evidence of infection by non-bacterial agents such as *Coxiella burnetii,* chlamydiae and fungi. Most patients with endocarditis have high titres of antibody to the infecting organism present in the serum, and occasionally other tests may be considered, including a serum fluorescent antibody test against viridans streptococci[17].

'Blind' Antibiotic Therapy

Antibiotic therapy is usually indicated as soon as the collection of blood for culture has been completed in patients with a firm clinical diagnosis of IE. The majority of patients have not had previous heart surgery and, in about three-quarters of them, streptococci are the causative agents. In most patients 'blind' parenteral therapy with a combination of benzylpenicillin and gentamicin is appropriate for the treatment of both viridans streptococci fully sensitive to penicillin, and streptococci such as enterococci, which have a reduced sensitivity to penicillin. Gentamicin is the synergic aminoglycoside of choice for bactericidal combination with penicillin, as it is more active than streptomycin against a wider range of enterococcal strains. Gentamicin will also have some effect on unsuspected staphylococci, but if there is clinical evidence to suggest a staphylococcal cause, such as skin sepsis, disseminated intravascular coagulation or a history of drug addiction, high dosage intravenous cloxacillin is indicated in addition to the penicillin and gentamicin combination.

Streptococci, then staphylococci, are the causative agents most often found in patients who, having undergone cardiac surgery, have developed 'late onset' endocarditis many months postoperatively. *Staph. aureus, Staph. epidermidis,* Gram-negative bacilli and diphtheroids are the bacteria most often isolated from the blood cultures of 'early onset' endocarditis. All these patients should receive initial 'blind' parenteral treatment with a combination of benzylpenicillin, gentamicin and cloxacillin. Effective 'blind' treatment of any endocarditis patient who has a definite history of penicillin allergy can be provided by a combination of vancomycin and gentamicin given intravenously.

Specific Chemotherapy when there is a Microbiological Diagnosis

Close collaboration between the clinician and the clinical microbiologist is desirable at all stages of the management of patients with suspected endocarditis. Once a microbial diagnosis has been made, the microbiologist carries out further tests to determine the best antibiotic or antibiotic combination to kill the causative organism. The patient's serum is also tested against the patient's own blood culture isolate so that peak serum bactericidal titres of at least one in eight can be achieved during antibiotic therapy. Table 3 lists the antibiotics rec-

Table 3. Chemotherapy for microbiologically diagnosed cases of infective endocarditis in which there has been no previous heart surgery.

Organism	Antibiotic	Administration	Duration
Viridans streptococci killed by 0.12 mg/litre penicillin	Benzylpenicillin or Benzylpenicillin + gentamicin followed by: Penicillin V or amoxycillin	i.v. Oral	2 weeks at least 2 to 4 weeks
Other streptococci	Bactericidal combination, guided by laboratory. *Examples* Benzylpenicillin + streptomycin Benzylpenicillin + gentamicin Ampicillin + gentamicin followed by: Amoxycillin	 i.v. Oral	 4 weeks at least 2 weeks
Staph. aureus	Bactericidal combination, guided by laboratory. *Examples* Cloxacillin (high dosage) + gentamicin Rifampicin + fusidic acid followed by: drug selected according to results of antibiotic sensitivity tests.	 i.v. Oral	 3 weeks at least 3 weeks at least

ommended for treating microbiologically diagnosed endocarditis cases.

The use of benzylpenicillin combined with an aminoglycoside to treat a penicillin-sensitive viridans streptococcus (MBC less than 0.24 mg/litre) is still controversial[18]. Good clinical results have been obtained with benzylpenicillin used alone and with combined treatment, and the method of treatment chosen is largely a matter of personal preference. One possible advantage of combined treatment over penicillin used alone is that the streptococcus may be killed more rapidly. This is suggested by the data from rabbit endocarditis experiments. If penicillin has to be stopped after three weeks of treatment because of the development of severe hypersensitivity, the patient would still have received at least two weeks of optimal bactericidal therapy.

During the first two weeks of parenteral therapy the intravenous bolus administration of antibiotics may be preferred to a continuous infusion. Amoxycillin is better absorbed than penicillin V but whatever oral drug is selected, it is desirable to check during therapy that adequate serum bactericidal titres are achieved against the patient's own streptococcal isolate.

Effective chemotherapy is often difficult to provide if a prosthetic valve is present or if there is polymicrobial, Q fever or fungal endocarditis. In these circumstances, cardiac surgery is frequently indicated in addition to appropriate chemotherapy[19]. Further details of the treatment of IE are given elsewhere[20-23].

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References

1. Durack, D. T. (1975) *British Heart Journal,* **37,** 478.
2. McGowen, D. A. (1979) *Dental Update,* **7,** 195.
3. Oakley, C. M. (1979) *Thorax,* **34,** 711.
4. Rodbard, S. (1963) *Circulation,* **27,** 18.
5. Oakley, C. M. (1980) *British Journal of Hospital Medicine,* **24,** 232.
6. Durack, D. T. and Petersdorf, R. G. (1973) *Journal of Clinical Investigation,* **52,** 592.
7. Pelletier, L. L., Durack, D. T. and Petersdorf, R. G. (1975) *Journal of Clinical Investigation,* **56,** 319.
8. Garrod, L. P. and Waterworth, P. M. (1962) *British Heart Journal,* **24,** 39.
9. American Heart Association (1977) *Circulation,* **56,** 139a.
10. Petersdorf, R. G. (1978) *American Journal of Medicine,* **65,** 220.
11. Shanson, D. C. (1978) *Journal of Antimicrobial Chemotherapy,* **4,** 2.
12. Shanson, D. C., Cannon, P. and Wilks, M. (1978) Ibid., p. 431.
13. Shanson, D. C., Ashford, R. F. U. and Singh, J. (1980) *British Medical Journal,* **280,** 446.
14. Editorial (1979) *British Medical Journal,* **1,** 290.
15. Newsom, S. W. B. (1978) *Journal of Antimicrobial Chemotherapy,* **4,** 389.
16. Roberts, R. B., Krieger, A. G., Schiller, N. L. and Gross, K. G. (1979) *Reviews of Infectious Diseases* (University of Chicago), **1,** 955.
17. Shanson, D. C. and Hince, C. (1978) *Journal of Clinical Pathology,* **31,** 292.
18. Newsom, S. W. B. (1980) *Thorax,* **35,** 321.
19. English, T. A. H. and Ross, J. K. (1972) *British Medical Journal,* **4,** 598.
20. Hamer, J. and O'Grady, F. W. (1977) In *Recent Advances in Cardiology.* (ed J. Hamer.) London: Churchill Livingstone.
21. Shanson, D. C. (1980) In *Antibiotic and Chemotherapy: Current Topics.* (ed R. N. Gruneberg.) Lancaster: MTP Press.
22. Hook, G. W. and Johnson, W. D. (1978) *American Journal of Medicine,* **65,** 411.
23. Oakley, C. M. and Darrell, J. H. (1980) *Prescribers' Journal,* **20,** 98.