Abstract
Oral commensal microorganisms are commonly associated with the pathogenesis of infective endocarditis. Despite modern antimicrobial and surgical treatment, infective endocarditis continues to cause substantial morbidity and mortality. Although dentistry is no longer considered a major risk factor for infective endocarditis, it is current standard of practice that dental procedures likely to produce significant bacteraemia in patients who are susceptible to this disease be prophylactically covered with an antimicrobial agent. The concepts of antimicrobial prophylaxis prior to invasive dental procedures are outlined in this review, with particular reference to the latest recommendations of the Australian Dental Association.

Key words: Infective endocarditis, antimicrobial prophylaxis, dental procedures, review.

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INTRODUCTION
Infective endocarditis (IE) is a rare, potentially fatal disease where susceptible endocardium or a prosthetic heart valve is colonised by microorganisms such as streptococci, staphylococci and candida. As oral (viridans) streptococci are found in many cases of IE, it is postulated that certain dental procedures produce bacteraemias which may subsequently cause this disease. Based on animal studies showing the efficacy of prophylactic antimicrobials in preventing IE, it has been generally accepted that at-risk patients undergoing at-risk dental procedures be given antimicrobial cover. The many different guidelines on antimicrobial cover can be a potential source of confusion. This review examines the evidence that links dental procedures with IE and considers various current dental guidelines, with particular emphasis on the latest recommendations made by the Australian Dental Association (ADA) in 2000.
Pathogenesis

Infective endocarditis is a disease where a susceptible heart structure is colonised by microorganisms. Although its pathogenesis is not fully understood, it is postulated that viridans streptococcal IE requires endothelial damage as an initiating factor, as normal endocardium is resistant to colonisation by all but the most virulent microorganisms. Damage to the endocardium exposes collagen, which thereafter accumulates platelets and fibrin, to give rise to a non-infected thrombotic vegetation. Subsequent circulating microorganisms from a bacteraemia may then adhere to the thrombotic vegetation, aggregating more platelets and fibrin. In this environment, protected from phagocytosis, the microorganisms are able to multiply, causing the vegetation to increase in size. It appears that the non-infected thrombotic vegetation is dynamic, in that its susceptibility to colonisation by microorganisms varies momentarily.

Once established, an IE lesion may progress in four ways: constant bacteraemia; local infiltration of bacteria giving rise to conduction abnormalities, abscess or valve incompetence; peripheral embolisation of dislodged vegetation fragments; or circulating immune complexes.

It is generally accepted that streptococcal IE has an incubation period of less than two weeks before any non-specific clinical symptoms arise. This is significant in that many retrospective studies putatively linking IE with dental treatment made this association despite dental treatment having been performed more than several months before the onset of symptoms.

Microbiology

Infective endocarditis can be caused by a wide variety of microorganisms. Despite the reduced prevalence of streptococcal IE, oral streptococci are still the most common pathogens found in IE cases acquired outside of a hospital environment, accounting for 33-50 per cent of all cases of IE. The virulence of these organisms, with respect to IE, is possibly related to their ability to produce dextran, which aids in attachment, as well as to their ability to aggregate platelets. Staphylococcus aureus is a common causative organism in intravenous drug users and appears to be able to induce IE upon intact endocardium.

Dental procedures

It is well recognised that most dental procedures, as well as normal oral function, produce a transient bacteraemia lasting up to 30 minutes after the cessation of the procedure. Furthermore, it has long been general consensus that dental procedures which induce a bacteraemia of substantial magnitude have an increased potential to induce IE in susceptible hearts. However, the significance, if any, of the size, frequency or makeup of the bacteraemia still remains unclear. A recent cohort study has found no definitive link between IE and dental procedures, even in patients with valvular abnormalities.

Antimicrobial prophylaxis

Rationale

Antimicrobial prophylaxis may be defined as the use of an antimicrobial agent before any infection has occurred for the purpose of preventing a subsequent infection. As the prevention of IE is desirable, due to its high rates of morbidity and mortality, there is general consensus that all patients with predisposing heart conditions be given appropriate antimicrobials prior to operative procedures that may give rise to IE. This is based on the fact that IE may follow a bacteraemia and that certain dental procedures can produce bacteraemia with organisms having the potential to cause IE. Despite this, there is no direct evidence that antimicrobial cover in humans actually works.

Current regimes are primarily based on animal studies which use inoculum doses much larger than would occur with a typical bacteraemia in a human. As antimicrobial cover is effective in preventing IE in animals, it has been extrapolated that prophylaxis is effective in humans. However, despite microbial cover, some patients do contract IE. It should be stated that most, but not all, such failures occurred after inappropriate timing and/or dosaging.

The aim of all prophylactic regimes is to provide adequate plasma levels of an effective antimicrobial agent for the entire duration of the bacteraemia and, most probably, for the initial phases of bacterial adherence and colonisation of the thrombus when the microorganisms are still accessible. Although bactericidal mechanisms may play a role, there is now substantial evidence that bacteriostatic levels of antimicrobials are effective in preventing IE. The primary mechanism by which antimicrobials prevent IE is unknown and the minimum antimicrobial levels to provide this protection in humans have not been established.

If an at-risk patient has inadvertently undergone a dental procedure liable to cause significant bacteraemia, data from animal studies suggest that antimicrobial prophylaxis given within two hours of the bacteraemia might still provide useful prophylaxis.

In 1943, antimicrobial agents were first used as an adjunct in the treatment of IE arising from dental procedures. This work led to the publication of the initial prophylactic regime by the American Heart Association (AHA) in 1955. Following this original protocol, not only has the AHA revised its guidelines on nine occasions but many other advisory bodies have devised and revised alternate guidelines. As new evidence has been uncovered, these protocols have been modified and it seems likely that such regimes will continue to evolve.
Antimicrobial agents

In 2000, with the intention of producing a simpler and more effective regime with less undesirable side-effects, the ADA published its latest recommendations on the prevention of IE (Table 1). These guidelines are based largely on the 1997 recommendations of the AHA. Both the ADA and the American Heart Association (AHA) recommend amoxycillin as the drug of first choice in penicillin-tolerant patients. Although no more effective against viridans streptococci than penicillin V, amoxycillin is favoured for its superior absorption and prolonged serum levels. Irrespective of the type of underlying cardiac condition, both associations recommend that amoxycillin be taken orally one hour before the procedure. This move toward oral administration may result in a reduction in both cost and risk of anaphylactic reaction while increasing compliance and efficacy. Although the solution made from the powder form is more rapidly absorbed and provides higher initial serum levels than the capsule form, both forms of amoxycillin give comparable and effective levels over four-six hours.

In an attempt to reduce the adverse gastrointestinal effects of high-dose amoxycillin while still maintaining effective plasma levels, the ADA has revised its recommended oral dose of amoxycillin from 3g to 2g (Fig 1). As a single oral dose provides plasma levels above the minimum inhibitory concentrations of most oral streptococci and prolonged inhibitory activity against such strains, a second dose of amoxycillin, given six hours post-operatively, has been eliminated by both the ADA and the AHA. This change will reduce cost, the risk of allergic reaction and the potential of microbial resistance associated with the administration of a second dose. Where amoxycillin is not available for parenteral administration, 2g ampicillin is equally effective.

If the patient is unable to take amoxycillin due to allergic reaction or recent administration of β-lactam antimicrobials, the ADA recommends the use of clindamycin at a dose of 600mg. Clindamycin, the only oral non-β-lactam agent recommended by the ADA, is an effective bacteriostatic agent against viridans streptococci and also acts as a bactericidal (Fig 1). Clindamycin is very well absorbed and has less gastrointestinal side-effects than erythromycin. While clindamycin is associated with pseudo-membranous colitis more frequently than other antimicrobials, no cases of pseudo-membranous colitis have been reported with single 600mg doses of clindamycin. Clindamycin potentiates phagocytosis of microbial organisms as well as inhibiting bacterial adhesion to host cells.

High rates of gastrointestinal problems, bacterial resistance and significantly reduced efficacy in preventing experimental IE have led to erythromycin being no longer recommended by either the ADA or the AHA. The AHA now recommends two oral macrolide agents, clarithromycin and azithromycin, as amoxycillin alternatives. These agents are effective against oral streptococci for the prophylaxis of IE and are also better intestinally tolerated than erythromycin.

The ADA has included cephalexin, a first generation cephalosporin, as an alternate agent to amoxycillin. Although this agent is effective against oral streptococci, 5-10 per cent of penicillin-allergic patients will also be allergic to first generation cephalosporins.
Cephalosporins should not be given to patients with histories of immediate type I hypersensitivity to penicillins and it should be noted that patients who have undergone recent penicillin treatment may possess \(-\text{lactamase producing microorganisms.}\)

The combination of the synergistically acting agent gentamycin with amoxycillin is recommended, in several guidelines, for patients deemed to be at high risk of contracting IE. Although there are different levels of risk for contracting IE, a recommended antimicrobial regime should protect all susceptible patients. Oral amoxycillin is effective in preventing IE. The use of gentamycin in combination with amoxycillin is more costly, less convenient and offers no proven significant benefit over oral amoxycillin. For these reasons, the ADA and the AHA no longer recommend the use of gentamycin with amoxycillin.

Vancomycin was once recommended by the AHA and many other protocols for high-risk penicillin-allergic patients. The AHA no longer makes distinctions between high and low risk patients when recommending a treatment regime and, consequently, does not recommend vancomycin for dental procedures. However, the ADA recommends vancomycin for penicillin-allergic patients who cannot take oral medication. The disadvantages of vancomycin include toxicity, thrombophlebitis and the hour-long infusion period. On the positive side, vancomycin is one of the few antimicrobials effective against methicillin-resistant staphylococci. An alternate parenteral agent recommended by the ADA – clindamycin, lincomycin or teicoplanin – should be considered instead of vancomycin.

Within hours of administration, oral streptococci can acquire resistance to an antimicrobial and such resistant microorganisms may predominate for many days. Any subsequent dose of a similar antimicrobial agent within this time may result in the loss of antimicrobial efficacy and/or the development of a more pathogenic bacteraemia. To avoid this situation, as much dental work as possible should be done in one appointment and the same class of antimicrobial should not be used twice in a nine to 14 day period.

At-risk patients and procedures

As well as modifying the antimicrobial regimes, the ADA now recognises only one risk category as opposed to the previous two categories of high risk and low risk (Table 2). Australian Dental Association guidelines make a clear distinction between patients who are at risk of contracting IE and those who are considered to be at no greater risk of developing IE than the general population. Hence, a patient is either at risk or not at risk of contracting IE. Furthermore, in determining which procedures require antibiotic prophylaxis, the ADA has separated dental procedures causing significant bacteraemia from those causing any bacteraemia (Table 3).

**Adjunctive measures**

The revised recommendations of the AHA also make mention of the efficacy of chlorhexidine and povidone iodine rinses in eliminating or reducing the size of the bacteraemia. The potential for these agents as adjuncts or even as alternatives for antimicrobial cover has not been extensively evaluated. The AHA, in a long-

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Table 2. ADA risk categories.

<table>
<thead>
<tr>
<th>At-risk patient</th>
<th>Non-risk patient</th>
</tr>
</thead>
<tbody>
<tr>
<td>All acquired valvular heart diseases</td>
<td>Coronary bypass</td>
</tr>
<tr>
<td>Hypertrophic cardiomyopathy</td>
<td>Isolated atrio-ventricular defects</td>
</tr>
<tr>
<td>Mitral valve prolapse with regurgitation</td>
<td>Kawasaki disease without valvular dysfunction</td>
</tr>
<tr>
<td>Most congenital heart diseases</td>
<td>Mitral valve prolapse without regurgitation</td>
</tr>
<tr>
<td>Prosthetic heart valve</td>
<td>Pacemakers and implanted defibrillators</td>
</tr>
<tr>
<td>Previous episode of IE</td>
<td>Physiological/innocent heart murmurs</td>
</tr>
<tr>
<td>Surgically constructed shunts</td>
<td>Rheumatic fever without valvular dysfunction</td>
</tr>
</tbody>
</table>

Adapted from Spicer, 2000.

Table 3. ADA risk procedures.

<table>
<thead>
<tr>
<th>Risk procedures</th>
<th>Non-risk procedures</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dental prophylaxis</td>
<td>Exfoliation of deciduous teeth</td>
</tr>
<tr>
<td>Endodontic surgery</td>
<td>Intra-canal instrumentation</td>
</tr>
<tr>
<td>Extractions</td>
<td>Local anaesthesia (except intra-ligamentary)</td>
</tr>
<tr>
<td>Implant placement</td>
<td>Orthodontic adjustments</td>
</tr>
<tr>
<td>Instrumentation beyond the apex</td>
<td>Radiographs</td>
</tr>
<tr>
<td>Intra-ligamentary injections</td>
<td>Removal of sutures</td>
</tr>
<tr>
<td>Osteotomy</td>
<td>Restorative dental procedures</td>
</tr>
<tr>
<td>Periodontal procedures</td>
<td>Rubber dam placement</td>
</tr>
<tr>
<td>Placing orthodontic bands</td>
<td>Taking impressions</td>
</tr>
<tr>
<td>Reimplantation of avulsed teeth</td>
<td>Surgical drainage of abscess</td>
</tr>
<tr>
<td>Surgical repair of jaw fracture</td>
<td>Surgical repair of heart defects after six months</td>
</tr>
</tbody>
</table>

Adapted from Spicer, 2000.
term effort to reduce the microbial burden of bacteraemias, also advocates the employment of good oral hygiene measures.

Adverse effects
The administration of prophylactic antimicrobials may result in gastrointestinal upset, cross-reaction with other medications, emergence of resistant micro-organisms, hypersensitivity and death.6,7,8

Type I hypersensitivity to penicillins occurs in approximately one in 10,000 doses of penicillin, with 10 per cent of these being fatal (one death per 100,000 doses of penicillin).9 Of these fatalities, 96 per cent occur within 60 minutes of administration (usually parenteral administration) and the most serious reactions have occurred in those with no previous history of allergy.10,11 Given that one in one million people die from IE,12 it becomes apparent that the administration of antimicrobial agents for the prevention of IE is not without associated risks.

DISCUSSION
Of the many different guidelines in use around the world, no two are identical and no one regime has proven superior to another. It must be realised that such regimes are only guidelines and are not intended to cover all possible clinical situations. Hence, in order to exercise a reasonable standard of care where the benefits outweigh the risks, the clinician needs to consider several factors for each individual case (Table 4). So long as the clinician takes these factors into account and bases their decision on current accepted scientific evidence, they will be providing a reasonable standard of care.

CONCLUSION
Infective endocarditis is a serious disease which may arise as a result of dental treatment. As such, it is the general consensus that patients at risk of contracting IE be given appropriate antimicrobial cover prior to any at-risk dental procedure. To ensure that the potential benefits outweigh the potential risk, the decision to adopt a treatment regime must take into account several factors. Unfortunately, there is no international consensus on one particular regime.

REFERENCES
37. Guntheroth WG. How important are dental procedures as a cause of infective endocarditis? Am J Cardiol 1984;54:797-801.