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Antibiotic prophylaxis for endocarditis: time to reconsider

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Abstract

Some cardiac conditions require antibiotic prophylaxis for some types of dental treatment to reduce the risk of infective endocarditis (IE). All medical and dental practitioners are familiar with this practice but tend to use different regimens in apparently similar circumstances. Generally, the trend has been to prescribe antibiotics if in doubt. This review explores the evidence for antibiotic prophylaxis to prevent IE: does it work and is it safe? The changing nature of IE, the role of bacteraemia of oral origin and the safety of antibiotics are also reviewed. Most developed countries have national guidelines and their points of similarity and difference are discussed. One can only agree with the authority who describes antibiotic guidelines for endocarditis as being 'like the Dead Sea Scrolls, they are fragmentary, imperfect, capable of various interpretations and (mainly) missing!' Clinical case-controlled studies show that the more widely antibiotics are used, the greater the risk of adverse reactions exceeding the risk of IE. However, the consensus is that antibiotic prophylaxis is mandatory for a small number of high-risk cardiac and high-risk dental procedures. There are a large number of low-risk cardiac and dental procedures in which the risk of adverse reactions to the antibiotics exceeds the risk of IE, where prophylaxis should not be provided. There is an intermediate group of cardiac and dental procedures for which careful individual evaluation should be made to determine whether IE or antibiotics pose the greater risk. These categories are presented. All medical and dental practitioners need to reconsider their approach in light of these current findings.

Key words: Antibiotic prophylaxis, endocarditis, dental treatment.

Abbreviations and acronyms: IE = infective endocarditis.

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INTRODUCTION

Traditionally, it has been recommended that antibiotic prophylaxis should be given for some types of invasive dental treatment in patients with some types of cardiac conditions which may be susceptible to the development of infective endocarditis (IE). However, this is easier to say than it is to apply. It is a common clinical experience that various authorities, medical and dental practitioners will end up with different treatment proposals for apparently similar patients. This was evidenced by a recent survey of Australian dental practitioners who had little consensus on which were the risk procedures, which were the risk cardiac conditions and which was the appropriate antibiotic regimen.[1] National guidelines exist in most major Western countries including the United States of America,[2,3] the United Kingdom,[4] and the Netherlands.[5] Australia does not appear to have a current set of guidelines which are universally acceptable.[6-9] This has led to individual institutions developing their own guidelines.[10] As a consequence, one authority has described antibiotic guidelines for endocarditis prophylaxis as being '. . . like the Dead Sea Scrolls, they are fragmentary, imperfect, capable of various interpretations and (mainly) missing!'[11]

A scientific review was recently conducted by the Cochrane Group.[12] When they examined a large number of papers against the strict evidence-based criteria used by the Cochrane Group, they concluded that 'there is no evidence about whether penicillin prophylaxis is effective or ineffective against bacterial endocarditis in people who are at risk, and who are about to undergo invasive dental procedures'. If, however, one follows the Cochrane conclusions then a few susceptible patients would develop IE with a consequent high risk of death or significant morbidity.[13] The medical or dental practitioner who did not provide antibiotic cover may then find themselves at medico-legal risk for negligent practice.[14] Alternatively, if one takes the commonly held view that it is safer to provide antibiotic cover for just about all types of dental treatment for all types of cardiac conditions, then one places a different group of patients at risk of death from anaphylaxis. In a recent quantitative analysis it was found that three times as many would die from anaphylaxis if all were given antibiotics as would develop IE if they were not given antibiotic prophylaxis.[15]

Consequently, there is a need to carefully re-examine the evidence for under which circumstances one can best protect patients from either serious harm from IE or from antibiotics. Does prophylaxis work and is it safe? In the attempt to answer these questions it is first necessary to understand all aspects of the process. Hence, in this paper we will review the pathogenesis of IE, the clinical condition of IE, the causes and types of bacteraemia (particularly those of oral origin), the issues relating to antibiotics, current risk benefit studies of IE antibiotic prophylaxis, current international and

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national guidelines and, finally, make some current recommendations based as much as possible on the evidence.

The pathogenesis of infectious endocarditis

In a comprehensive review of the pathogenesis of IE,[16] the usual process was divided into the following steps: endocardial damage; establishment and persistence of bacteria within the endocardium; bacterial growth with local tissue damage; and the establishment of clinical IE with both cardiac and peripheral non-cardiac manifestations.

Endocardial damage

The normal endothelium is a single layer of cells derived from mesoderm which lines the cavity of the heart and lumen of all blood vessels. Its integrity is fundamental to maintaining homeostasis and normal circulatory function. The metabolic and synthetic properties of endothelial cells help to regulate inflammation, remodelling, vascular tone and coagulation. The normal endothelium is a non-thrombogenic surface and is resistant to colonization by circulating bacteria.[17,18] Endothelial cell injury or dysfunction activates metabolic and synthetic events associated with many vascular disorders.[19] The most common causes of endothelial cell damage are haemodynamic and occur in regions of extreme mechanical or shear stress.[20] These are the flow surfaces of valves along the lines of closure on the systemic side of the circulation. Thus the most common sites are the mitral and aortic valves, ventricular septal defects and complex congenital abnormalities. The assessment of haemodynamic flow disorders by echocardiography has recently been reviewed in an Australian series of dental patients who had been previously told they needed antibiotic prophylaxis for IE. It was found that 70 per cent had normal hearts and only 15 per cent required antibiotic prophylaxis.[21]

Changes in the endothelial cells are greater if there is an underlying change in the connective tissues of the valves. Scanning electron microscopy of diseased valve leaflets show abnormal morphology including alterations in shape, microvilli, discontinuity of cell borders and desquamation.[22,23] These morphological changes increase the thrombogenicity of the valve, as well as the intracellular permeability, and possibly change the cellular synthetic functions. The inflammatory activation of these endothelial cells further disrupts the endothelial cell barrier and causes thrombotic vegetations to develop on the surfaces of the valves. These vegetations further alter the haemodynamic properties of the valves, and are an ideal nidus for bacterial adherence and colonization and the source of emboli.[16]

These changes are maximal in previously damaged valves such as in patients who have had valve scarring from rheumatic fever or who have had previous bacterial endocarditis. Artificial materials as used in prosthetic heart valves and other intra-cardiac devices are particularly thrombogenic.[24]

Establishment and persistence of bacteria within the endocardium

Transient bacteraemia originating from the various bacterially-infested sites in the body (i.e., the mouth, respiratory system, gut, skin and genito-urinary system) are ubiquitous. The bacteria are usually rapidly destroyed in the blood and if they reach the heart they pass through without settling. Sometimes, however, when there is a combination of a high load of bacteria within the blood, more virulent bacteria with a greater capacity to adhere to damaged valves, or altered haemodynamics and thrombus formation on damaged valves or foreign bodies, then bacteria may settle and commence colonization. Bacteria with the greatest ability to adhere to damaged valves are *Staphylococcus aureus*, streptococcus species and enterococci. Together they are responsible for 80 per cent of IE cases.[25]

Bacterial growth

Once the valve is colonized the bacteria must survive and avoid the host defences. Maturation of the vegetation is a key event in the process, where the micro-organisms become fully enveloped and thus protected from cellular and soluble host defence systems.[26] Both staphylococci and streptococci can trigger tissue factor production from local monocytes and induce platelet aggregation. Bacterially-induced platelet activation both helps to envelop the bacteria and to release proteins which are bactericidal. Thus bacteria associated with IE need to be resistant to platelet-induced factors.

In some cases IE may occur in the presence of an intact, normal endothelium. This is seen with virulent invasive pathogens such as *Staphylococcus aureus* or micro-organisms capable of parasitising endothelium, such as *Coxiella burneti*, the agent of Q fever. This is, however, not an issue in IE of dental origin.

Clinically, IE occurs in 50 per cent of cases with no clinically identifiable history of underlying valvular damage.[27] Only 4-19 per cent of patients with IE have had a surgical procedure (including dental procedures) in the related time period.[28] Thus, the 'usual' pathogenesis of IE has been described, but it is by no means certain and is arguably an 'unusual' pathway.

Clinical infectious endocarditis

A number of clinical descriptive names have been used for IE, namely, bacterial endocarditis, acute bacterial endocarditis, subacute endocarditis and chronic endocarditis. Practically, these are evidence of the variable presentation of the clinical disease, but essentially they are the same process. The essential issue of endocarditis is that there is a microbiological infection of the endothelium of the heart.[13,16] If IE is untreated then it is invariably fatal. With intensive

modern management IE still has a significant mortality rate of the order of 25-50 per cent. Survivors commonly need surgical replacement of their damaged heart valves.

The incidence of IE in Western countries is estimated to be 1.7 to 6.2 cases per 100 000 person years.[13,29] The higher incidence is mainly associated with intravenous drug use. The incidence in this group is estimated to be 150 to 2000 per 100 000 person years, and can be higher among persons with known valvular disease. This group is also known to have a high incidence of blood-borne viral diseases which further increases their risk. There is also a higher risk associated with increasing age and greater use of prosthetic heart valves.[30] There has been a marked decrease however in rheumatic fever in Western countries. Indeed, with the ability to prevent further episodes of rheumatic fever with antibiotics, and the general reduction in rheumatic fever incidence in Western countries, the prevalence of rheumatic valvular disease is declining and is now confined to an ageing cohort of patients affected in their youth, and to specific groups such as Australian Aborigines, Pacific Islanders and certain migrant groups. Thus, the emphasis placed by most dentists on asking patients whether they have rheumatic fever is now unwarranted.[31]

The characteristic lesions of IE are valvular vegetations which are composed of collections of platelets, fibrin, micro-organisms and inflammatory cells. It most commonly occurs on damaged or prosthetic heart valves, but may also occur on normal valves, on septal defects, on chordae, tendinae or on mural endocardium.[13,16]

The clinical presentation of IE is highly variable and spans a continuum from subacute to acute and fulminating. Fever is the most common symptom. Other less common symptoms include anorexia, weight loss, malaise and night sweats. Most sufferers have a heart murmur (which may have been pre-existing), splenomegaly or petechiae of the skin, conjunctiva or oral mucosa.

The specific cardiac manifestations are heart murmurs which may be pre-existing or new regurgitant murmurs from further valvular damage or ruptured chordae. Congestive heart failure develops in 30-40 per cent of patients, usually as a consequence of valvular dysfunction, but occasionally due to endocarditis-associated myocarditis, or an intra-cardiac fistula. Progression of heart failure is variable dependent on the severity of the valvular dysfunction. Aortic valve dysfunction progresses more rapidly than mitral valve dysfunction. Pericarditis may occur from abscesses burrowing through the epicardium. Heart block may occur from interruption of the conduction system. Myocardial infarction may uncommonly occur from embolisation of a coronary artery.

The non-cardiac manifestations, particularly the non-suppurative peripheral manifestations, are less commonly seen these days due to earlier diagnosis and aggressive treatment. Arterial emboli are clinically apparent in approximately 50 per cent of patients. These are more likely in mitral valve vegetations, particularly if the vegetation is larger than 10mm. Neurologic symptoms are most often secondary to embolic strokes and occur in 40 per cent of patients. Immune complex deposition on the glomerula basement membrane causes hypocomplementemic glomerulo-nephritis and renal dysfunction.

The diagnosis of IE requires integration of clinical, laboratory and echocardiographic data. A specific and highly sensitive diagnostic schema known as the Duke criteria has been developed to assist diagnosis.[32] Treatment involves prolonged parental administration of antimicrobial agents, either singly or in combination. Antibiotic treatment either as an in-patient or, when fever and the major cardiovascular problems have resolved, as an outpatient, should continue for at least two months. Cardiac surgery is commonly required.[13] The mortality rate varies according to the virulence of the organisms involved, the presence of complications or co-existing conditions, the extent of the cardiac infection and the appropriateness of combined medical and surgical treatment. Generally, with aggressive modern treatment in a centre of cardiac excellence, the mortality rate is 20-25 per cent. Recurrence of IE may occur with a low rate (2 per cent) for penicillin susceptible *streptococci viridans*, but there is a higher relapse rate (10-15 per cent) for prosthetic valve endocarditis.

Causes of bacteraemia

All surface coverings of the body are colonized by a unique microflora. Thus, any bacteraemia may be of skin, gut, airway, genito-urinary or oral origin. Bacteria from these sources frequently enter the blood on a physiologic basis as a transient bacteraemia, and are dealt with by the host defences.

This review will only consider the bacteraemia of oral origin, although, as noted, the relative frequency of oral causes has decreased. Transient bacteraemias that follow normal physiological activities such as chewing are usually cleared by the host defences within 10 minutes.[33] With normal physiologic function of the mouth there are about 5000+ minutes of transient bacteraemia in a month (or 8 per cent of the time). Generally, the probability of this causing IE is exceedingly low, but it is greater in a patient with pre-existing valve damage, in particular a prosthetic valve.

Oral manipulations including dental treatment will produce a greater bacteraemia than physiologic function. Usually they are still relatively low grade and of short duration. A simple dental extraction with healthy gingivae produces 1 to 100 colony producing units per millilitre of blood, for less than 10 minutes.[34] Tooth extraction for patients with chronic periodontal disease results in a greater bacterial load. This association has been demonstrated in rats with induced aortic valve vegetations. Animals with experimental

Table 1. Incidence of bacteraemia following oral physiologic function, oral hygiene and dental procedures[36,37]

Procedure	
Extraction	51-85%
Periodontal surgery	88%
Periodontal scaling	8-80%
Dental prophylaxis	0-40%
Endodontic therapy (manipulation within the apex)	0%
Oral hygiene	
Tooth brushing	0-40%
Irrigating devices	7-50%
Tooth picks	20-40%
Physiologic	
Chewing	17-51%
Periodontal disease (patient resting)	11%
Periodontal disease (resting but anaerobic technique)	60-80%

gingivitis were at a greater risk of post-extraction endocarditis than those with healthy gingivae.[35]

The frequency of bacteraemia associated with various dental procedures and oral manipulations is presented in Table 1.[36,37] It should be noted that there is a wide range of values between different studies. This makes a difference as to how sophisticated the bacteriological techniques are. If anaerobic techniques are added then a wider range and greater extent of bacteraemia is demonstrated. The time at which blood is taken for analysis and the frequency in a single patient are also key values to examine when reviewing bacteraemia studies.

Traditionally, the criteria that 'significant bleeding' associates with a dental procedure has been equated with a significant bacteraemia. A recent study which involved both pre- and post-procedure bacteraemia estimations showed that bleeding is a poor predictor of odontogenic bacteraemia above usual physiologic levels.[38]

Issues in antibiotic prophylaxis

The rationale for the use of antibiotic prophylaxis for surgical, including dental, manipulations is that the procedures cause bacteraemia and the bacteraemia may cause endocarditis. As a result, the antibiotics should be given to susceptible patients before the bacteraemia is generated. These steps have been demonstrated in animal studies but it remains an unanswered question as to whether or not this reflects what occurs in humans.

Mechanism of prevention

Antibiotics may prevent endocarditis either by killing bacteria or by damaging them to an extent that the host defences can then destroy them. Therefore, the antibiotic may work before the bacteria enter the bloodstream, after they enter the bloodstream or on colonies of bacteria. The primary mechanism by which antibiotic prophylaxis could occur has not been established but a number of studies show that bacteraemia is reduced both in quantity and time in the presence of antibiotics. However it is most likely that, as they may prevent bacterial adherence, antibiotics primarily work on bacterial colonies within the endocardium.

Adverse reactions to antibiotics

All drugs carry risks, although in the past this has usually not been considered highly by medical and dental practitioners. The risks associated with antibiotics are side effects such as gastro-intestinal tract upset, colonization of resistant or fungal strains, drug interactions, allergic reactions (including anaphylaxis) and death. Mild reactions, including urticaria, occur in 0.7-10 per cent of penicillin courses, with a usual range of 1-3 per cent.[39] This rate has increased over time. Anaphylactic reactions occur in 0.011-0.04 per cent of patients receiving penicillin for prophylaxis. Ten per cent of cases of anaphylaxis result in death.[40] Thus, the most common antibiotic recommended for prophylaxis will cause harm for some patients.

Allergic reactions are rare with vancomycin[41] and gentamicin[42] but both are associated with side effects such as nephro- and oto-toxicity.

Resistant organisms

The development of resistant organisms is also a real problem. Recent indiscriminant use of antibiotics has resulted in an increase in the prevalence of penicillin-resistant *streptococcus viridans* in blood cultures. In a study of 31 Japanese children who had cardiac disease and who were at risk from IE, and thus had received a number of episodes of antibiotic prophylaxis, it was found that 61 per cent of them had resistant *streptococcus viridans* in their oral flora.[43] Overall, however, the contribution of inappropriate dental prescription is significantly less than the medical contribution, and, in turn, this is vastly less than issues relating to the use of antibiotics in agricultural animals.[44]

Clinical trials on effectiveness and safety

Randomized placebo-controlled studies have not been undertaken since the number of patients required would be large (not less than 6000 patients) and there are ethical issues related to the lethality of the disease.[45]

Case-controlled studies, when matched to patients in the community who are not at risk, are a more practical way of evaluating risk. In a large study in the USA it was found that dental treatment did not appear to be a risk factor for IE, even in patients with valvular abnormalities. There did seem to be a risk associated with dental extractions although the numbers were small. It was confirmed that cardiac valvular abnormalities were a strong risk factor for IE.[46] An extensive case-control study in The Netherlands,[47,48] which was the only study to meet the Cochrane Criteria,[12] concluded that there is no evidence to support whether penicillin prophylaxis is effective or ineffective against bacterial endocarditis in people at risk who are about to undergo an invasive dental

procedure. Similar equivocal results, although the Cochrane group excluded this study on methodological grounds, were reported by another European group.[49] There are no comparable Australian case-control studies.

In a risk benefit analysis it was indicated that if penicillin prophylaxis was given to all patients with mitral valve prolapse, irrespective of whether they had significant regurgitation or not, then three times as many deaths would occur from anaphylaxis than if no prophylaxis had been given.[15] Some patients who were given prophylaxis still developed endocarditis.[15] In a further study the annual mortality rate of IE of dental origin in the general community was compared with the incidence attributable to antibiotic prophylaxis in patients with rheumatic cardiopathy undergoing dental treatment.[50] They found that in a population of 100 million people there would be approximately 26 deaths attributed to IE associated with dental treatment. However, if 100 million people with rheumatic cardiopathy went to their dentist once per year, and were administered penicillin prophylactic cover, then there would be approximately 4000 deaths. Thus, based on these calculations (which include a number of hypothetical assumptions), the risk of prophylaxis would greatly exceed the risk of death from endocarditis. These assumptions are that all of the population would go to the dentist on an annual basis, all would receive intravenous penicillin and that resuscitation would be unsuccessful. In practical terms the risks would be much lower than that. It has also been found that if patients are assessed to determine whether they have a history of penicillin allergy there would have been no reported cases of anaphylactic allergy provoked by the administration of a single dose of 2g amoxycillin.[51] However, this is not a matter which one would routinely report. In the authors' institution, which provides dental treatment for a large number of high-risk cardiac patients, there have been a number of unreported adverse reactions.

Cost-benefit analysis

A number of studies have been conducted to look at the cost-benefit analysis of antibiotic prophylaxis. One involved a comparison of parenteral penicillin to erythromycin for patients with mitral valve prolapse.[15] This found that parenteral penicillin would cause more deaths from anaphylactic reactions than would result from endocarditis if no prophylaxis was given or if oral erythromycin was given. This study did not take into account the bacteriostatic nature of erythromycin. It is for this reason that erythromycin is no longer recommended. It also did not take into account the gastro-intestinal side effects associated with erythromycin. A further study[52] comparing penicillin prophylaxis for mitral valve prolapse patients resulted in a greater net loss of life due to death from anaphylaxis, particularly in younger patients. In older patients prophylaxis with oral penicillin may save some years of life but at a higher cost.[52] There have been no studies of a risk-benefit analysis for high-risk cardiac lesions, but the conclusions of studies to date confirm that unless the cost per intervention is very low then the cost per case prevented is extremely high.

It is on this basis that Durack, who has extensive clinical and research experience in IE, has suggested that antibiotic prophylaxis should only be given for high-risk dental procedures in high-risk cases.[53] Although this policy would result in a small but probably unmeasurable increase in the incidence of IE, it would reduce the risk of death from anaphylaxis and the cost of antibiotic treatment.

Review of current guidelines

The major international[2-5] and Australian[6-10] guidelines have been reviewed and are summarized into Tables 2, 3, 4 and 5.

The USA,[2,3] British[4] and Netherlands[5] guidelines were all formulated by high level multidisciplinary groups of experts. The principal scientific studies have been performed particularly in the Netherlands but also in the United States. The several Australian guidelines[6-10] are of variable quality. The Australian Prescriber wall chart, being old, primarily focused on antibiotic regimens, and although they are aimed to be read at a glance, they are not easy to follow.[6] Similarly, the Australian Dental Association (ADA) guidelines are not easy to follow without study and assumed knowledge.[7]

Table 2. Guideline recommendations – Cardiac conditions

High Risk	Moderate Risk	Low or No Risk

• Prosthetic cardiac valve[2-10]
  • bioprosthetic
  • homograft
• Previous bacterial[2-7,9,10] endocarditis
• Complex cyanotic[2-4] Congenital heart disease (Transposition, Tetralogy of Fallot)
• Surgically constructed[2-4,7,8,10] Systemic – pulmonary shunts
• Mitral valve prolapse with clinically significant mitral regurgitation[4,5,9]
	• Congenital cardiac malformations[2-4,7,10] other than those defined as high or low risk
	• Acquired valvular dysfunction[2-4,7] (i.e., rheumatic heart disease)
	• Hypertrophic cardiomyopathy[2-5,7,10]
	• Mitral valve prolapse[2,3,7,10] with valvular regurgitation or thickness leaflets
	• Aortic stenosis[4]
	• Mitral regurgitation[4]
	• Septal defects and patent ductus arteriosus
		• Isolated secondary atrial septal defects[2-4,7,9,10]
		• Surgical repair of septal defects[2-4,7,9,10] (arterial/ventricular and patient ductus arteriosus)
		• Previous coronary artery bypass graft[2-4,7,9,10]
		• Mitral valve prolapse[2-4,7,9,10]
		• Physiologic, functional or innocent[2-4,7,9] murmur
		• Previous Kawasaki disease[2,3,7,9,10] without valvular dysfunction
		• Previous rheumatic disease[2,3,4,9] without valvular dysfunction
		• Cardiac pacemakers[1-4,7,10]
		• Pulmonary stenosis[4]

Table 3. Guideline recommendations – dental procedures

Dental procedures requiring prophylaxis	Dental procedures not requiring prophylaxis
• Dental extraction[2-5,7,9,10] • Periodontal procedure[2-5,7,9,10] (including probing and recall)[2-4,9] • Dental implants[2-5,7,10] • Replantation of avulsed teeth[2-5,7,9,10] • Endodontic treatment beyond the apex[2-5,7,9,10] • Apicectomy[2,3,5,7,9] • Subgingival placement of a/b fibres and strips[2-4] • Initial placement of orthodontic bands[2-4,9] • Intraligamentary LA injections[2-4,7,9,10] • Prophylactic cleaning of teeth[2-4] and implants where bleeding anticipated • Rubber dam placement[4,10] • Matrix bands and wedging • Gingival retraction cord[4] • Surgical drainage abscess[9,10]	• Restorative dentistry[2,3,5,7,9,10] (with or without retraction cord) • Local anaesthetic injections[2-4,7,9,10] • Intracanal endodontics[2-4,9] • Placement of rubber dam[2,3,9] • Post-operative suture removal[2-4,10] • Placement of prosthesis[2-5,7,9,10] • Placement of orthodontic devices and brackets[2,3,5,7,9,10] • Orthodontic adjustments[7,9,10] • Impressions[2-4,9,10] • Fluoride treatment[2-4,7,9,10] • Oral radiographs[2-4,7,9,10] • Shedding primary teeth[2-5,7,9] • Dental examination[4,9] • Biopsy[4] • Drainage of an abscess[4] • Brushing and flossing[2,3,9]

Table 4. Guideline recommendations – antibiotic regimens

High-Risk Cardiac	Medium-Risk Cardiac
• Amoxycillin oral 2g[3,4] 1 hour prior to procedure	Amoxycillin oral 2g[3-5,10] 1 hour prior to procedure
• For highest risk i.e., prosthetic valve or previous endocarditis Amoxycillin 2g IV[4] and Gentamicin 1.5mg/kg IV before procedure	Amoxycillin oral 3g[5-8] 1 hour prior to procedure Amoxycillin oral 2g[10] followed by 1g 6 hours later
• Amoxycillin 1g IV[8] Gentamicin 2mg/kg IV 30 minutes before procedure followed by 500mg oral	
• Amoxycillin 2g[11] oral Gentamicin 2mg/kg IV	
For patients with penicillin hypersensitivity	
Clindamycin oral 600mg[3-6] 1 hour before procedure	Clindamycin oral 600mg[3-6,10,11] 1 hour before procedure
Cephalexin oral 2g[3,4] 1 hour before procedure (not if have immediate type hypersensitivity)	Cephalexin oral 2g[3-4] 1 hour before procedure (not if have immediate type hypersensitivity)
Vancomycin 1g slow infusion IV[7] Gentamicin 1.5mg/kg IV	Clindamycin oral 600mg[7,8] 1 hour before procedure and 300mg 6 hours later
Clindamycin 600mg IV[11] Gentamicin 2mg/kg IV	Erythromycin 800mg[8] 1 hour before procedure

The ADA pamphlet does not make recommendations but generally tends to favour the provision of antibiotics, particularly if there is uncertainty.[8] The most recent therapeutic group is appropriately multidisciplinary and simple,[9] but has been challenged as it may be too simple and possibly provides inadequate cover for high risk cases.[54] The author's institution, which is the specialist tertiary referral centre for both cardiac and oral problems in South Australia, has developed its own institutional guidelines.[10] These were produced to combat a previous circumstance of individual opinion resulting in widely variable prescribing routines for apparently identical cases. It has been only partially successful and individual variations continue to exist at all levels of experience, both medically and dentally. Sadly, this probably reflects the fate of most guidelines. They are issued, sometimes read, but variably applied.

On review of the international and national guidelines it is clear that there are many points of agreement. All agree that there is a high-risk cardiac group where the risk of endocarditis exceeds the risk of antibiotic prophylaxis from dental at-risk procedures, thus warranting antibiotic prophylaxis. There are, however, some variations as to which conditions constitute high-risk cardiac states.

All agree that there is a large group of patients with a cardiac history who are at no greater risk of endocarditis than the general population. In these patients the risk of anaphylaxis and similar adverse events from the antibiotic prophylaxis is demonstrably greater than the risk of endocarditis. Thus, in these circumstances, antibiotic prophylaxis is not warranted for any type of dental treatment.

There is then, however, an intermediate zone of moderate-risk cardiac problems which have a risk of endocarditis greater than the general population. If given antibiotic prophylaxis they also have a risk of adverse reaction to the antibiotic. The balance of risk for these patients is difficult, if not impossible, to assess as their risk to benefit is about equal.

In regard to dental interventions there is consensus that dental manipulations of either the hard or soft tissues will result in a bacteraemia. All agree that extractions and periodontal treatment do result in a significant bacteraemia and thus will present a risk of endocarditis to susceptible cases. However, there are variations as to where exactly to draw the line. The

Table 5. Guideline recommendations – antibiotic recommendations – paediatric. Note – Dosage is dependent on patient size

High	Medium
• Amoxycillin 50mg/kg[2,3,5,7] Oral up to 2g 1 hour before procedure • Amoxycillin 1.5g[4] Highest risk give 1g Amoxycillin IV /+ Gentamicin 1.5mg/kg followed by IV Amoxycillin 1g or Oral 1g	• Amoxycillin 50mg/kg[2,3,5,9] Oral up to 2g 1 hour before procedure • Amoxycillin 1.5g[4] • Amoxycillin maximum 2g[9]
Allergic to penicillin: Clindamycin 20mg/kg[2-3] Cephalosporin 50mg/kg Clindamycin 300mg[4,5] Vancomycin 20mg/kg IV[6] Gentamicin 2.5mg/kg IV per day (up to 80mg per dose maximum)	Clindamycin 20mg/kg[2,3] Cephalosporin 50mg/kg[2,3] Clindamycin 300mg[4,5] Clindamycin 10mg/kg to 2g[9]

primary examples are gingival manipulations, involving restorative dentistry such as matrix bands, placement of rubber dam and clamps or ligatures. These vary between the different guidelines.

There is also general consensus as to those procedures which have only a physiologic level of bacteraemia and thus do not require prophylaxis. Again there are some differences. One, which is difficult to understand or to accept, is that a dental abscess is not recommended for prophylaxis under the British guidelines.[4] In a patient with an abscess beyond the confines of the tooth, who also has a cardiac indication for prophylaxis, there would appear to be a clear indication for appropriate dental treatment to eliminate the cause of the abscess but also adjunctive antibiotics for both therapeutic and prophylaxis reasons.

There are some points of consensus on the choice of antibiotic dose and route for prophylaxis. If it is indicated then an appropriate antibiotic should be chosen to cover the most likely causative organisms, i.e., the oral flora. It should be administered in a sufficiently high dose prior to the commencement of the procedure in order to achieve adequate serum concentrations in the bloodstream when bacterial contamination is at its highest. There is little value from a follow-up dose on the same day. Antibiotics in the preceding days and days after the procedure are not clinically indicated as they offer no additional advantage.

There is some disagreement as to whether antibiotic prophylaxis should be different for high or medium-risk cardiac indications. The current trend is toward treating these two groups similarly with a pre-procedure dose of amoxycillin and a follow-up dose for high-risk cases. There is evidence that 2g is equivalent to 3g oral amoxicillin with less risk of nausea.[55] Practically, if one is using the single 3g oral liquid preparation, and the patient is not nauseated, then the full dose is administered. Currently, some very high-risk cardiac patients undergoing high-risk dental procedures in the Oral and Maxillofacial Surgery Unit in South Australia have intravenous antibiotic prophylaxis, usually with gentamicin and amoxycillin. These patients are usually having multiple extractions for gross oral sepsis immediately prior to valve surgery. It is accepted that the provision of intravenous antibiotics is difficult in general dental and medical practice and that gentamicin is primarily used for synergy for enterococcal infections. General practitioners treating patients in high-risk cardiac and dental categories should carefully consider whether specialist referral is in the patient's best interest. Antibiotic regimens are presented in Table 6.

CONCLUSIONS

Essentially, the decision to administer antibiotic prophylaxis is an individual matter and a careful assessment needs to be made on an evidence-based risk assessment, not on anecdote, traditional belief, or what medical and dental practitioners were taught as undergraduates. The cardiac risk should be assessed medically, preferably by a cardiologist, using current investigative technology, for example echocardiography.[21] The oral risk should be assessed dentally, both clinically and radiographically. Patients who are at

Table 6. Antibiotic regimens

Antibiotic regimen selected after careful evaluation of both the cardiac condition and the dental procedure
Standard prophylaxis
Amoxycillin 2g orally as a single dose 1 hour before procedure. For paediatric patients Amoxycillin 50mg/kg up to 2g orally as a single dose 1 hour before the procedure. Or If hypersensitive to penicillin or on long-term penicillin therapy or had a related beta-lactan antibiotic more than once in the previous month: Clindamycin 600mg orally as a single dose 1 hour before procedure. For paediatric patients clindamycin 15mg/kg up to 600mg orally as a single dose 1 hour before procedure
For high-risk cardiac having a high-risk dental procedure
Consider the addition of: Gentamicin 2mg/kg IV before procedure to either Amoxycillin 1g IV or Clindamycin 600 mg IV
For patients under general anaesthesia
Amoxycillin 1gm I/V Or Clindamycin 600mg I/V or Lincomycin 600mg IV All just before procedure

Table 7. High cardiac risk patient having a high-risk dental procedure for which antibiotic prophylaxis is mandatory

High risk cardiac conditions	High risk dental procedures

• Prosthetic cardiac valves
  • bioprosthetic
  • homograft
• Previous infectious endocarditis
• Complex cyanotic congenital heart disease (transposition, tetralogy of fallot)
• Surgically constructed
• Systemic – pulmonary shunt
• Mitral valve prolapse with clinically significant regurgitation
	• Extraction
	• Periodontal procedures
	  • deep scaling
	  • subgingival
	• Other surgical procedure
	  • implant placement
	  • apicectomy
	  • replant avulsed teeth

Table 8. Low-risk cardiac conditions having any type of dental treatment. Antibiotic prophylaxis is not indicated as the risk of IE is no greater than the general population

Low or no risk cardiac conditions	Procedure not requiring prophylaxis for any cardiac category
• Isolated secondary atrial septal defects • Surgical repair of septal defects • Previous coronary artery bypass grafts or stents • Mitral valve prolapse with regurgitation • Physiologic, functional or innocent murmur • Previous Kawasaki disease without valvular dysfunction • Cardiac pacemakers • Pulmonary stenosis • Heart/lung transplants	• Oral examination • LA injection • Restorative dentistry • Intra-dental endodontics • Rubber dam • Removal sutures • Impressions and dentures • Orthodontic bracket and adjustments • Fluoride treatment • Intra-oral radiographs • Oral hygiene • Shedding primary teeth

Table 9. Intermediate risk from both the cardiac and dental point of view. Individual decisions need to be made about the risk versus the benefit of antibiotic prophylaxis and IE. For a moderate risk cardiac patient having a high risk dental procedure, as set out in Table 8, one would more closely consider giving prophylactic antibiotics

Moderate cardiac risk	Medium risk dental procedure

• Congenital cardiac malformations other than those defined as high or low risk
• Acquired valvular dysfunction (i.e., rheumatic heart disease)
• Hypertrophic cardiomyopathy
• Significant valvular/haemodynamic dysfunction – associated with aortic/mitral and septal defects
	Key risk factors are:
	  • state of periodontal health services
	  • length and strength of the manipulation
	• Minor periodontal treatment including examination
	• Endodontics beyond the apex
	• Initial placement of orthodontic bands
	• Rubber dam placement with clamps
	• Gingival procedures
	  – wedges
	  – cords
	  – strips

cardiac risk should be made dentally fit. The at-risk dental procedures should be performed, in one, or at most two, sessions, with modification of the dental treatment plan, as necessary, to accomplish this. The patient needs to be kept dentally fit by the instruction of good oral hygiene practices and perhaps the use of antiseptic mouth rinses prior to procedures.[56] The patient who is at a cardiac risk needs to be informed of the risk both from the cardiac condition and the adverse reaction to antibiotics point of view. The patient needs to understand that they have a responsibility for their ongoing oral health maintenance. In the absence of a patient accepting responsibility, the dental treatment plan should be modified toward extractions.

On this basis all patients can be divided into one of three groups: high-risk cardiac patients having high-risk dental procedures for which antibiotic prophylaxis is mandatory (Table 7); low-risk cardiac condition having any type of dental treatment for which antibiotic prophylaxis is not indicated as the risk is no greater than for the general population (Table 8); and intermediate risk from both cardiac and the dental point of view for which individual decisions need to be made about the risk benefit of antibiotic prophylaxis (Table 9).

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