Endodontic Topics 2003, 4, 46–59
Printed in Denmark. All rights reserved

ENDODONTIC TOPICS 2003
1601-1538

Antibiotic prophylaxis

THOMAS J. PALLASCH

The age of antibiotic prophylaxis began shortly after World War II with the introduction of penicillin to the general population and received significant impetus from the introduction of the first American Heart Association (AHA) recommendations for the prevention of bacterial endocarditis (BE) in 1955. Since that time, considerable effort has been expended to prove its efficacy, develop the appropriate drugs and dosages and determine its clinical indications. It was not until the mid-1980s that any attention was directed towards its potential adverse effects, particularly regarding penicillin allergy. Currently, one of the major concerns with antibiotic prophylaxis is its use in large populations and how this might contribute to the global problems with microbial resistance to antibiotics.

The potential value of antibiotic prophylaxis is based upon an assumption that if antibiotics aid host defenses to eliminate infections and restore homeostasis, then they must prevent infections. That these are very different microbiological processes has essentially gone unappreciated. On the one hand, antibiotics kill or prevent the growth of microbes that will be eliminated eventually by the patient's immune system, while on the other, the antibiotic is expected to prevent the colonization of any or all microbes of varied virulence, adhesion factors, nutritional requirements and antibiotic sensitivity in any or all organ systems. One ends microbial virulence, while the other anticipates it.

Antibiotic prophylaxis as a public health measure has a serious fault. In most public health prevention measures (sanitation, fluoridation, immunization), it is required that the benefits greatly outweigh the risks. Generally, the risk must be minimal and the benefit great as millions will receive the proposed preventive measure. With antibiotic prophylaxis, just the opposite occurs: virtually, no one will benefit except for a few. This also assumes that prophylaxis is effective, although there are limited experimental and clinical data to support this assumption. Great care should be taken to document the efficacy of a procedure that will be applied to many in the hope that a few will benefit.

Antibiotics have also been termed 'societal drugs' (1) in that they not only affect the microbial flora of those to whom they are administered, but also those close to them (the transfer of antibiotic resistance genes among family members) and society as a whole (2). The world epidemic of antibiotic-resistant *Streptococcus pneumoniae*, *Enterococcus*, *Staphylococcus aureus* and *S. epidermidis*, *Pseudomonas aeruginosa*, *Klebsiella pneumoniae* and the oral pathogens, viridans group streptococci (VGS) and *Prevotella* and *Porphyromonas*, did not happen by chance, but by the massive application of antibiotics in health care and agriculture. Each dentist or physician on any given day likely feels that only they are prescribing the antibiotic, when in reality, millions of their colleagues are doing the very same thing. After only a short time, the millions become billions and the microbes decide to rebel against those trying to extinguish them as a life form. Microorganisms will always be with us and ahead of us (2).

In a best case scenario, antibiotic prophylaxis may prevent 10% of all cases of BE (3). Studies in the Netherlands indicate that antibiotic prophylaxis may prevent 5.7% of all native valve endocarditis and 3.8% of all prosthetic valve endocarditis which, if it is assumed that the prophylaxis were 49% effective, would prevent five endocarditis cases annually in a population of 14.5 million (4, 5). In the United States, it has been estimated that optimal antibiotic prophylaxis could prevent 240–280 of the annual 11 200 cases of infective endocarditis (IE) (6). If VGS accounts for 25% of all endocarditis cases in the United States and dental procedures are responsible for 1% of these cases (28 episodes), then it is important that proper risk– and cost–benefit appraisals be made. It should also be appreciated that VGS-induced BE is less than 10% fatal

(two to three cases annually in the United States). As a final caveat, the absolute risk rate for BE from a single dental treatment procedure may range from 1/14 million for the general population to a high of 1/95 000 for the highest risk patient (previous endocarditis) (7, 8).

It is not for the individual dental practitioner to use these data to modify or eliminate antibiotic prophylaxis regimens that have been established by expert groups, such as the AHA for endocarditis prevention (9) and the American Dental Association/American Academy of Orthopaedic Surgeons for dental patients with orthopedic prosthetic joints (10). In time, these concerns will be addressed and recommendations modified. This review will concentrate on two aspects of antibiotic prophylaxis: the biological principles that guide its use and various clinical situations where its use has been suggested and need to be judged according to the present data. This effort will be evidence-based and not authority-based. The history of antibiotic prophylaxis is one of substantial ignorance and profound abuse.

Principles of antibiotic prophylaxis

Antibiotic prophylaxis is the use of antibiotics to prevent infections that in the vast majority of situations would never have occurred anyway. Therefore, its use should be restricted to the prevention of infections that are rare, but carry a high mortality rate or those that are common, but not fatal (11). The only clinical situations where antibiotic prophylaxis has been proven successful is in the prevention of recurrent rheumatic fever with continuous penicillin therapy (the causative beta-hemolytic streptococcus has yet to demonstrate resistance to penicillin), sulfonamide prophylaxis for the prevention of bacterial meningitis and in clean–clean and clean–contaminated surgical procedures, where the infection rate is commonly reduced from 2% to 1% and possibly in neutropenic patients undergoing bone marrow transplants.

The principles of antibiotic prophylaxis are listed in Table 1 and were developed 30–40 years ago and updated with current clinical research (7, 11–16). Risk– and cost–benefit analyses should be performed, the antibiotic must be in the tissue or blood before the invasive procedure begins (to be at the target site before the onset of the surgery or bacteremia), a loading dose (two to four times the maintenance dose) is required to establish high blood or tissue concentrations, the antibiotic to be employed must be targeted only at the single most likely microorganism to cause the infection (antibiotic prophylaxis is ineffective against polymicrobial infections) and the antibiotic is maintained only as long as the microbial contamination of or from the invasive site continues (7, 11–16).

The adverse effects of antibiotic prophylaxis must be seriously considered: antibiotic allergy and toxicity, risk of superinfection (onset of a new infection while treating a previous infection), selection of resistant microorganisms and the induction of antibiotic resistance gene expression or transfer in drug-susceptible microorganisms (2). Contraindications for antibiotic prophylaxis include: lack of documented efficacy or poor risk/cost–benefit, the inability to adequately define the segment of the population at risk for the infection and prophylaxis directed at any/all microbes that could conceivably cause the infection.

Antibiotic prophylaxis is employed for three reasons: (1) to prevent surgical infections or their postoperative sequelae, (2) to prevent metastatic bacteremias (microorganisms moving from one region of the body to another) and (3) as 'drugs of fear' (17) to 'prevent' any possible accusation that 'all was not done for the patient'. It is suspected, but difficult to prove, that most antibiotic prophylaxis is employed as malpractice prevention 'insurance'. This is unfortunate as then lawyers dictate much of the use (and abuse) of antibiotics with no shared legal responsibility for its untoward sequelae of multiply antibiotic-resistant microorganisms and the increasing inability to treat these pathogens.

The unresolved difficulties with antibiotic prophylaxis as they pertain to dentistry have recently been reviewed: (1) the lack of evidence that surgical antibiotic 'prophylaxis' as employed in dentistry (begun after the procedure is terminated) is efficacious, (2) the high financial costs of antibiotic prophylaxis (literally hundreds of thousands to a million dollars to prevent a single case of endocarditis), (3) documentation that the risk of an orally induced bacteremia is thousands of times greater from normal daily living activities (tooth brushing, flossing, mastication) than from dental treatment procedures, (4) the extreme rarity of endocarditis caused by periodontal pathogens (less than 150 cases in the literature and most of these

Table 1. Principles of antibiotic prophylaxis (7, 11–16).

General indications	The infection to be prevented is common but not fatal or is rare, but carries an unacceptably high morbidity or mortality rate.
Basic criteria	(1) The risk– and cost–benefit ratios must be acceptable
	(2) The antibiotic must be in the blood or target tissue before the onset of the surgery or bacteremia
	(3) An antibiotic loading dose must be employed for high blood/tissue concentrations
	(4) The antibiotic must be chosen on the basis of the single most likely microorganism to cause the infection or bacteremia
	(5) The antibiotic should be continued only as long as the microbial contamination of or from the operative site continues
Surgical prophylaxis	(1) Clean–clean surgery where the risk of infection is remote, but its potential consequences grave or in clean–contaminated surgery, where the likelihood of infection is great but seldom fatal
	(2) Where infection is unlikely, but is associated with major morbidity/mortality
	(3) In surgical procedures with high infection rates
	(4) To prevent contamination of a sterile area
	(5) During implantation of prosthetic material
Adverse effects of antibiotic prophylaxis	(1) Risk of antibiotic toxicity or allergy
	(2) Promotion of superinfections
	(3) Selection of antibiotic-resistant microbes
	(4) Induction of antibiotic-resistant gene expression and/or transfer
Contraindications to antibiotic prophylaxis	(1) The at-risk group to be given prophylaxis cannot be narrowly defined to prevent antibiotic abuse/overuse
	(2) In the clinical situation, prophylaxis is too random in efficacy or proof of efficacy is too limited or nonexistent
	(3) The bacteremia to be prevented is very seldom the cause of disease
	(4) Prophylaxis is directed at any or all potential pathogens rather than the colonization of the single most likely pathogen

caused by a single microorganism, *Actinobacillus actinomycetemcomitans*), (5) the extremely low absolute risk rates of acquiring endocarditis from dental treatment, (6) the probability that antibiotic prophylaxis does not reduce bacteremias significantly, making it either ineffective or having another mechanism of action, (7) the contribution of antibiotic prophylaxis misuse to the global epidemic in antibiotic-resistant bacteria and (8) the possibility that deaths from penicillin anaphylaxis may be greater than the lives saved by penicillin prophylaxis against VGS (7).

The ensuing discussion will address these deficiencies of antibiotic prophylaxis in the light of current evidence to arrive at clinical decisions that are reasonable and prudent. In some situations, reasonable people can reasonably disagree. In others, there is simply no evidence that antibiotic prophylaxis is safe and effective. Hopefully, this discussion will reduce antibiotics as 'drugs of fear'.

Surgical antibiotic prophylaxis

Antibiotics are misused in dentistry in primarily three ways: (1) given for too long a duration of time, (2) as a substitute for incision and drainage ('the sun should never set on undrained pus') and (3) as 'antibiotic prophylaxis' to prevent or mitigate surgical infections or postoperative sequelae (18). The common practice of providing an antibiotic to an otherwise healthy non-risk patient with no signs or symptoms of active infection after the completion of various dental procedures has not been proven effective in preventing infections, and in most cases does not reduce sequelae such as trismus, pain and edema (12, 18).

This use of antibiotics violates several of the principles of antibiotic prophylaxis: the antibiotic is not in the system before the invasive procedure begins; very often a loading dose is not employed; the antibiotic is directed against all potential pathogens instead of the one most likely to produce an infection; and in many cases the drug is continued well beyond the time of infectivity. Antibiotic pharmacokinetics dictates that an antibiotic given without a loading dose and with the first dose taken hours after the surgery (usually at bedtime after the spouse has returned from the pharmacy with the antibiotic) will achieve a steady-state blood level 6–12 h after the first several doses, which will likely be the next day or later when the issue of whether an infection will occur has already been decided (18).

As stated in Table 1, surgical antibiotic prophylaxis is only indicated to prevent contamination of a sterile area, where an infection is associated with high morbidity and mortality, in surgical procedures with high infection rates and during implantation of prosthetic material (15). The Medical Letter only recommends surgical antibiotic prophylaxis for procedures with high infection rates, implantation of prosthetic materials and devices and in head and neck surgery only when the surgery extends through the pharyngeal mucosa (19).

Surgical prophylaxis has been documented as being effective only for clean–clean surgery (open heart, major vascular reconstruction, prosthetic joint, central nervous system) where the risk of infection is remote but its consequences grave, or in clean–contaminated surgery (elective biliary, gastric or clonic), where the risk of infection is great but seldom fatal (14). In these hospital situations, the antibiotic is begun intravenously 1–2 h before the surgery and is terminated no longer than 24–28 h after the surgery is completed (14, 15, 20). Ideally, this perioperative use of antibiotic prophylaxis should be ended with the placement of the last suture, but this is rarely carried out as our medical colleagues cannot resist the illogical adage: 'the patient is doing well, let's continue the antibiotic'. The infection rate increases if the antibiotic is given for longer than 24–48 h after the surgery (15).

There are no adequate studies in dentistry to test the hypothesis that perioperative use of antibiotic prophylaxis will prevent postoperative infections. Virtually all studies performed in dentistry regarding surgical antibiotic prophylaxis have not looked at infection rates, but rather only at the surrogate markers of edema, trismus and pain (12). The oral cavity is one of the most heavily contaminated areas of the body, in no sense can surgery in the oral cavity be considered clean–clean or clean–contaminated; the risk for serious postoperative sequelae is very low and there are no adequate clinical studies that assess risk– or cost–benefit. All we presently know regarding oral surgical antibiotic prophylaxis is that it does not work very well and is associated with significant individual and societal risks.

Prevention of metastatic bacteremias

The primary goal of the prevention of infections by antibiotics due to blood-borne bacteria (bacteremias) is to kill the bacteria in the blood before colonization of an organ or tissue can occur. Animal studies indicate that the antibiotic must be in the tissue before the bacteria enter the blood, which makes biological sense (11, 13, 14). What does not make sense is the purported ability of antibiotics to quickly kill microorganisms upon entrance into blood. Many studies have reported a substantial decline in the bacterial colony-forming units (cfus) in blood seconds to minutes after initiation of the bacteremia if antibiotic blood concentrations are above the minimal inhibitory concentration for that organism (12). No explanation has ever emerged as to how drugs that act so slowly (minutes to hours) can reduce these bacteremias so quickly (seconds to minutes).

The beta-lactam antibiotics (penicillins and cephalosporins) prevent the final transpeptidation reaction necessary for the formation of the rigid bacterial cell

wall. In order to accomplish this the microorganism must be in the process of cell division. A fully formed and non-dividing cell wall cannot be affected by the beta-lactams. This concept underlies the current dosing schedule recommendations for the beta-lactams: their concentration in the blood must be above the MIC for the organism for at least 60% of the interval between doses (18). Unless the antibiotics are present for most of the time between doses, the requisite number of microorganisms will not be dividing and the drug will be unable to prevent substantial microorganism multiplication or growth during the dosing interval, thus leading to potential antibiotic failure. When beta-lactam antibiotic prophylaxis is employed for bacteremia prevention, it must then be assumed that all pathogenic bacteria will choose to divide when the bacteremia begins. As soon as the dentist places the forceps on the tooth, instruments the canal or employs the curette, all VGS then placed into the blood must magically receive a signal to begin cell division. It strains all credulity to believe that this actually occurs, yet it must for the theory of bacteremic killing by antibiotics to be true.

Studies in Sweden using sophisticated microbial culturing techniques document that neither the beta-lactams, erythromycin nor clindamycin given 1.0–1.5 h before dental extractions significantly reduce bacteremias minutes after the dental procedure (21–23). These studies and others (12) along with the biologic implausibility of antibiotic reduction of bacteremias in seconds to minutes has led to the hypotheses that antibiotic prophylaxis reduces metastatic infections by either preventing the adhesion of bacteria to surfaces (i.e. damaged cardiac valve endothelium) or by killing or inhibiting the growth of bacteria once attached to these surfaces (24). While a beta-lactam effect on bacteria to produce cell wall-deficient microorganisms could reduce or eliminate their ability to use various adhesins to stick to surfaces, this would not apply to bacteriostatic antibiotics (macrolides, clindamycin) that act by inhibiting ribosomal protein synthesis. It is also difficult to rationalize how bacteria once incorporated into the cardiac valve vegetation (a successive layering of platelets and fibrin) could be seriously affected by short-lived blood concentrations of prophylactic antibiotics when the antibiotic treatment of BE commonly requires 4–6 weeks of treatment. The mechanism by which antibiotics prevent metastatic infections awaits elucidation and verification.

Further difficulties with antibiotic prophylaxis include risk– and cost–benefit considerations. Until the 1980s, it was simply assumed that the benefit from antibiotic prophylaxis greatly outweighed its risks and that it was also cost effective. In one later calculation, it appeared that the mortality rate from endocarditis exceeded that from penicillin used for its prophylaxis only in the highest incidence rate of endocarditis (50/million population) with the highest death rate (40%) (25). In many other situations, particularly endocarditis due to VGS with its low mortality rate ($<10\%$), a net loss of life might occur with penicillin since more deaths might result from the drug than the disease (an ethically untenable position). Tzukert et al. (26) determined that 1.36 persons per million population were likely to die from penicillin anaphylaxis during endocarditis prevention, while only 0.26 deaths per million population would die as a result of dental treatment-induced endocarditis. This would then be a five times greater risk of death from penicillin anaphylaxis than from dental treatment-induced endocarditis.

Antibiotic prophylaxis is very expensive as the drug must be given to so many persons to prevent only a few infections. In a companion paper in this volume, it has been calculated that the absolute risk rate for endocarditis from a dental procedure may vary from 1/95 000 for a patient with previous endocarditis to 1/1.1 million for a patient with mitral valve prolapse (MVP) with regurgitation (8). As there is no possible way to determine which of these 95 000 to 1.1 million will acquire endocarditis, all must receive antibiotic prophylaxis. It has been calculated that using the 1990 AHA guideline dosages for prophylaxis (3 g then 1.5 g of penicillin), the cost would be 96 million dollars to attempt prevention of 32 fatal cases of endocarditis due to VGS (3 million dollars a case) or $300 000 for each non-fatal case (assuming that endocarditis from VGS is 10% fatal) (12). The 1997 AHA guidelines (2 g dose) have significantly reduced these antibiotic costs but they are still substantial. Others have made similar calculations: (1) 20 million dollars to attempt prevention of 35 cases of BE with erythromycin in patients with MVP and (2) 1 million dollars per life saved with penicillin prophylaxis for patients with MVP (12).

The studies of Guntheroth (27) and Roberts (28) have amply documented that the risk of bacteremias

from daily living activities, particularly those associated with oral hygiene and mastication, is 1000–8000 times greater than that associated with dental treatment. The incidence of these bacteremias can approximate those seen with dental treatment (8). Periodontal pathogens *per se* are very rarely a cause of endocarditis, with only 102 reported cases due to *Actinobacillus actinomycetemcomitans*, two due to *Prevotella oralis*, one due to *Prevotella bivia*, one due to *Bacteroides melaninogenicus*, five due to *Veillonella* and none due to *Prophyromonas* species (7). Only 50 cases due to *Lactobacillus* and 10 due to *Actinomyces* have been reported with *Peptostreptococcus*, also a very rare cause of BE (7). It is unlikely that anaerobic bacteria survive well in the oxygen-risk atmosphere of the cardiovascular system and also probably do not possess the varied adhesion abilities of streptococci and staphylococci.

A final difficulty with antibiotic prophylaxis to prevent orally induced bacteremias with virtually all antibiotics is the increasing resistance to oral pathogens to these agents (2). In a cohort of Japanese children at high risk for BE, 31.7% of oral VGS were penicillin resistant at MICs ranging from 4 to 16 μg/mL (high penicillin resistance) (29). In the United States, 40–50% of sampled VGS were resistant to penicillin at MICs ≥0.25 μg/mL (30) and in a 1993–1994 survey of 43 United States Medical Centers, 352 blood cultures of VGS had a resistance rate of 13.4% at MICs ≥4 μg/mL and 42.9% at MICs of 0.25–2.0 μg/mL (31). In 139 VGS cultures isolated from orofacial infections, 23% were resistant to penicillin G, 43% to erythromycin and 46% to clindamycin (32). Now it appears that we face two difficulties with antibiotic-resistant oral microbial pathogens: a reduction in our ability to treat acute infections as well as to prevent metastatic bacteremias.

Antibiotic prophylaxis and varied clinical situations

The principal use of antibiotic prophylaxis is the attempt to eliminate metastatic infections and thereby prevent BE. Table 2 is a comprehensive list of various medical conditions where antibiotic prophylaxis may or may not be indicated with the majority of indications for persons with increased risk for BE over the general population due to the presence of various forms of cardiac valve pathology primarily of the mitral and aortic valves (33, 34).

The preponderance of evidence at this moment indicates that such a prophylaxis may be beneficial, but Table 2 is a dynamic listing that may change with the addition of new scientific evidence. The risk for endocarditis in these patients has been discussed in the companion paper in this issue. Some of the other disorders listed have varying degrees of risk to which reasonable people can agree or disagree. Some have very minimal risk such as Kawasaki disease, which is an acute febrile vasculitis commonly seen in children between ages 3 and 5 years and carrying a 1% chance of cardiac valve pathology predisposing to endocarditis. Most would likely agree that dental patients with white cell counts below 1000 should only have emergency dental treatment and then receive antibiotic prophylaxis, although there are no case–control studies to document the efficacy of such a prophylaxis.

Patients with collagen disorders (particularly systemic lupus erythematosus), certain myeloproliferative disorders and solid organ transplants are prone to acquire marantic or Libman–Sacks endocarditis, which is a sterile deposition of platelets and fibrin (vegetations) on cardiac valves that carries a risk of microbial attachment similar to that seen with BE (34). There are no established guidelines for antibiotic prophylaxis for such patients but they are at definite risk for endocarditis (34). Calcific aortic stenosis is becoming a major finding in the elderly and may pose a risk for endocarditis, but as yet no authoritative group has addressed this issue. Likewise there are no guidelines for antibiotic prophylaxis prior to dental treatment for patients who have had head and neck radiation (34).

The issue of intravenous drug abusers (IVDA) has also not been adequately addressed, yet these individuals have a risk for IE of 2–5% per year and between 20% and 40% have cardiac valvular damage, suggesting that endocarditis antibiotic prophylaxis may be indicated (35) even though most of the endocarditis is right-sided (tricuspid valve) and caused by staphylococci.

Bacterial endocarditis

The most common use for antibiotic prophylaxis is to prevent metastatic bacteremias that may be responsible for infection of altered cardiac valves that are prone to non-bacterial thrombotic endocarditis or vegetations

Table 2. Antibiotic prophylaxis for various medical situations (7, 12, 33, 34).

Antibiotic prophylaxis indicated	*Antibiotic prophylaxis not indicated*
Previous infective endocarditis	Isolated secundum atrial septal defect
Cardiac valve prosthesis	Coronary bypass surgery
Rheumatic heart disease	Previous rheumatic fever without RHD
MVP with regurgitation	MVP without regurgitation
Hypertrophic cardiomyopathy	Coronary artery disease
Solid organ transplants with valvulopathy	Solid organ transplants without valvulopathy
Congenital heart disease (CHD)*	Cardiac pacemakers/implanted defibrillators
Kawasaki disease with valvulopathy	Kawasaki disease without valvulopathy
VA shunts for hydrocephaly	Arterial grafts
Collagen disorders with valvulopathy†	Peripheral and coronary stents
Indwelling catheter (right heart)	Physiological, functional heart murmurs
Myeloproliferative disorders with valvulopathy‡	HIV-AIDS
Idiopathic hypertrophic aortic stenosis	Asplenia
Mitral and aortic valve stenosis/regurgitation§	Diabetes
Surgically repaired intracardiac CHD with residual hemodynamic defects	Surgically repaired intracardiac CHD without residual hemodynamic defects
WBC count less than 500–1000	Orthopedic pins and screws
Anorectic drug-induced valvulopathy	Orthopedic prosthetic joints¶
	Breast and penile implants
	Dacron carotid patches
	Left ventricular assist devices
	Artificial hearts
	Hemodialysis
Antibiotic prophylaxis undecided	
Calcific aortic stenosis	
Congenital pulmonary stenosis	
Head and neck radiation	
Intravenous drug abusers	
Libman–Sacks (marantic) endocarditis‖	

*Includes: ventricular septal defect, atrial septal defect, bicuspid/unicuspid aortic valves, coarctation of the aorta, complex cyanotic heart disease, tetralogy of Fallot, transposition of the great vessels, systemic pulmonary artery shunt.
†Includes: systemic lupus erythematosus, rheumatoid arthritis, Marfan's syndrome, osteogenesis imperfecta, Hurler's syndrome, Ehlers–Danlos syndrome, pseudoxanthoma elasticum who may have valvulopathy or Libman–Sacks endocarditis.
‡Includes: polycythemia vera, essential thrombocytopenia, anogenic myeloid dysplasia who may have valvulopathy or Libman–Sacks endocarditis
§Depends upon severity; physician consultation may be advisable.
¶Should be considered, but not mandatory for patients with inflammatory arthropathies (systemic lupus erythematosus, rheumatoid arthritis); disease, drug or radiation-induced immunosuppression; type I diabetes, hemophilia, malnourishment; previous joint infection; up to 2 years following joint surgery.
‖Includes patients with: heart and other solid organ transplants, cancer, collagen and myeloproliferative disorders and primary phospholipid syndrome; valvulopathy may or may not be present, physician consultation may be appropriate.

(NBTE, NBTV). BE addresses only the disease caused by bacteria, whereas the term IE entails all possible infecting microorganisms (bacteria, fungi, rickettsia and others). The cardiac valvular abnormalities that predispose to endocarditis are generally of two types: congenital heart disease and acquired heart disease. Congenital heart disease includes atrial and ventricular septal defects, patent ductus arteriosus, coarctation of the aorta, bicuspid or unicuspid aortic valves, complex cyanotic heart disease and transposition of the great vessels. Acquired valvular heart disease includes rheumatic heart disease, MVP, previous IE and varying degrees of mitral and aortic valve stenosis, calcification and regurgitation.

Most acquired valvular heart disease is the result of high-velocity turbulent blood flow (jet streams) that over the time damage the endothelial surfaces of the heart ('wear and tear') and promote the deposition of successive layers of fibrin and platelets to form NBTE or NBTV. This turbulent blood flow is detected on auscultation as various types of cardiac murmurs and on the echocardiogram as altered intracardiac blood flow patterns.

The classic indications for the use of antibiotic prophylaxis to prevent endocarditis is based upon certain observations that: (1) various cardiac defects predispose to endocarditis, (2) the majority of infecting microbes are routinely susceptible to antibiotics, (3) the risk of bacteremia is increased by invasive medical and dental procedures, (4) antibiotic prophylaxis reduces the incidence and magnitude of such bacteremias and (5) antibiotics may prevent the attachment of bacteria of the damaged cardiac endothelium or inhibit their multiplication once attached (36). Some of these tenets are no longer true: most endocarditis is now caused by highly antibiotic-resistant microorganisms (staphylococci, enterococci and fungi), most endocarditis is not caused by invasive medical or dental procedures and antibiotic prophylaxis probably does not function by reducing bacteremias at least in the early stages of bacteremia. It remains true that cardiac valvular defects predispose to IE and that antibiotics may prevent attachment of microorganisms to this altered endothelium.

There is no dispute that dental treatment and oral hygiene procedures and mastication produce bacteremias of the low-level and transient type of commonly 1–12 cfus/mL (37) that may last 15–30 min, but probably much less in many situations due to the remarkable efficiency of the lungs, liver, spleen and reticuloendothelial system to clear the blood of microorganisms (34). It is commonly assumed that the blood is sterile before invasive procedures, but at least two studies have documented that a 31% and 80% incidence of bacteremia may be present immediately prior to dental extractions (37,38).

The aim of the AHA prevention of BE guidelines as they pertain to dentistry is to prevent or reduce bacteremias only due to VGS: *Streptococcus mitis, S. mutans, S. sanguis, S. parasanguis, S. oralis, S. crista, S. gordonii, S. anginosus, S. constellatus, S. intermedius, S. salivarius* and *S. vestibularis*. Although dentists have been accused of causing endocarditis due to other microorganisms (*Haemophilus, S. aureus* and *S. epidermidis, A. actinomycetemcomitans*), none of these are commonly susceptible to the amoxicillin recommended by the AHA. The propensity of streptococci and staphylococci to cause endocarditis (up to 80% of cases) is due to their remarkable ability to attach to surfaces via various adhesins and their ecological niches of easily traumatized skin and mucosal surfaces of the body. Not all VGS have the same adhesive abilities, possibly due to variations in adhesin gene expression even within the same subspecies (not all *S. sanguis* have an equal ability to cause endocarditis). The most likely to cause BE are *S. mitis*, *S. mutans*. *S. sanguis* and the *S. milleri* group (*S. intermedius, S. anginosus, S. constellatus*). It often goes unappreciated that VGS are ubiquitous in the body as they are found on the skin, conjunctiva, oropharynx, gastrointestinal and genitourinary tracts as well as the oral cavity. The risk for IE increases by a factor of 100–200 times in persons with previous endocarditis, cardiac valve prostheses and rheumatic heart disease and complex cyanotic heart disease with lesser, but significant risks for persons with congenital heart disease whether or not surgically corrected (39). The individual risk for MVP with regurgitation is relatively low, but patients with MVP may constitute up to 20% of all IE cases.

One of the highest risks for IE is the patient with a prosthetic heart valve that carries a lifetime IE risk of 1–4% and accounts for 9.5–16% of all annual IE cases (34). The incidence of IE is similar with either the bioprosthetic or mechanical valve with a mortality from VGS of 5% and 65% from *S. aureus*. It appears that about 15% of prosthetic valve endocarditis is caused by VGS (40).

MVP has posed several problems since its definition as the 'cardiac disease of the 70s'. Initially, it was vastly overdiagnosed by employing improper echocardiographic techniques that failed to account for the saddle shape of the mitral valve, which deceptively placed the ends of the saddle into the left atrium resulting in early estimates of a 20–50% incidence of MVP in the general population. Recent agreement on case definitions for MVP has led to an estimated incidence in the general population of 1.6–2.4% with an equal prevalence in males and females (41,42). Importantly, MVP is much more serious in males than females as the risk for severe valve degeneration and the need for valve repair or replacement is two to four times higher in males (43).

MVP is characterized by a mid-systolic click and/or a late systolic murmur with the 'classic' form diagnosed as a greater than 2 mm displacement of the mitral leaflet(s) into the atrial cavity during systole and more than a 5-mm leaflet thickness or the 'non-classic' type with the same 2 mm or greater superior leaflet displacement, but less than a 5-mm valve thickness. The severity of regurgitation associated with MVP can only be determined by a 2D color flow Doppler echocardiogram (44). The majority of persons with MVP have a normal lifespan with no significant disability and do not acquire IE. A small subset gradually (usually over a period of 25 years) develops billowing mitral leaflets, myxomatous degeneration, floppy mitral valves and flail leaflets that requires correction with valve surgery or replacement (45).

In 1997, reports began to appear of cardiac valve damage in persons taking certain serotonergic anorectic drugs (fenfluramine and dexfenfluramine) and led to guidelines for the management of such patients by the Department of Human Services and the American College of Cardiology/AHA (46). These recommendations remain in effect and have yet to be rescinded or modified.

All persons who have taken these drugs are to have a medical physical examination and an echocardiogram if deemed appropriate. These patients should be identified with a written and/or dialogue medical history, be advised to seek a medical consultation and have any elective dental treatment deferred until a determination of any valvulopathy is made (46). If emergency dental treatment is required before this determination, then the 1997 AHA endocarditis prevention guidelines should be employed.

Current evidence indicates that: (1) virtually all clinical studies have detected some degree of valve pathology dependent upon dose and duration of drug use (commonly but not always greater than 60 mg per day and longer than 90 days of duration), (2) some valvular lesions regress, some stay the same and some progress over time, (3) histological valve examination reveals chordae tendineae fusion, myxoid stroma and dense fibroblastic tissue with leaflets and chordae encased in whitish plaque adherent to the valve and (4) no data presently exist regarding the risk for IE (34). The prevalence of valvulopathy has been estimated to be from 4.4% to 13.7% with some likely to resolve over time and others likely to remain the same or to progress (47–49). Long-term studies beyond 2 years are not yet available.

One of the more perplexing questions on the health history entails the 'childhood murmur' or the 'physiologic/non-organic/functional murmur' of adulthood. In this time of managed care, it may be very difficult for the patient to get a diagnostic echocardiogram and it is possible that many internists and medical residents have not and likely will not develop the adequate stethoscope skills required to properly identify cardiac murmurs and to differentiate between those that are pathologic and those that are functional (50). An astute pediatric or adult cardiologist can readily make this distinction, but referral to the specialist may be restricted with 2 g of amoxicillin for antibiotic prophylaxis much preferred for its economics. Most cardiac murmurs in children are not pathologic and are merely the result of the changing hemodynamics of the heart during growth and maturation (51). Between 32% and 95% of children have a detectable heart murmur at some time, depending on the skill of the listener and how often the child is examined (52). The incidence of cardiac malformations at birth is 6.0–9.3 per 1000 live births.

Common innocent childhood murmurs include: pulmonary flow murmur, vibratory Still's murmur, peripheral pulmonary arterial stenosis murmur, aortic systolic murmur, normal continuous murmur and supraclavicular murmurs. Adult non-pathologic murmurs have certain characteristics: a systolic murmur of short duration with a 1 or 2 grade intensity heard at the left sternal border, normal intensity and a splitting of the second heart sound, no other abnormal sounds or murmurs, no evidence of ventricular dysfunction, no thrills and no increase in intensity with the Valsalva

maneuver (53). Because of the inability of the dentist to frequently obtain confirmation of the precise diagnosis of a given patient's heart murmur, it is likely that antibiotic prophylaxis will be employed in a significant number of patients who do not require it.

The 1997 AHA guidelines for the prevention of BE are reasonable and prudent at this time and, as with past recommendations, will likely undergo revision in the near future incorporating new data and addressing the questions contained herein. Since the publication of these 1997 recommendations, a number of questions have arisen and have been addressed (54). The two major questions were: if the patient forgets to take the antibiotic 1 h prior to the appointment, is it permissible to give it to them in the office and immediately begin treatment and the other question pertained to confusion regarding what constitutes significant bleeding. The guidelines allow for the dentist to administer the antibiotic if at first he/she anticipated no significant bleeding, but during treatment such was to occur as there are some data to support the contention that antibiotic prophylaxis may be effective up to 2 h after the onset of the bacteremia. However, the principles of antibiotic prophylaxis clearly state that it is most effective if the drug is in the system prior to the onset of the invasive procedure. Therefore, the answer to this question is no; the patient must be reappointed or wait for an hour after the drug is given in the office. On a pragmatic note, it would be very difficult to defend a dentist if it could be established that the antibiotic was given and then treatment immediately begun to save the economic loss of the canceled appointment.

One of the major goals of the 1997 AHA recommendations was the desire to reduce antibiotic prophylaxis in order to mitigate its role in promoting microbial resistance to antibiotics. To this end, the committee decided to forgo the previous guidelines recommendations that *all* invasive procedures associated with *any* bleeding whatsoever and restrict antibiotic prophylaxis only to those dental and medical procedures associated with *significant* bleeding. The rarely read text of the guidelines clearly states what is meant by significant bleeding and is portrayed in a chart that classifies dental procedures as to which should receive antibiotic prophylaxis and which need not (significant vs. insignificant bleeding). Significant bleeding may commonly (but not always) be associated with dental extractions, periodontal surgery, scaling and root planing, implant placement, reimplantation of avulsed teeth, subgingival placement of antibiotic fibers or strips, initial placement of orthodontic bands, intraligamentary injections, periodontal prophylaxis where bleeding is anticipated and endodontic instrumentation or surgery only beyond the tooth apex. All other dental procedures were considered to be a minor risk for significant bleeding, including rubber dam placement, suture removal, restorative dentistry and oral impressions.

Inherent in all reasonable guidelines is the provision that the clinical judgment of the practitioner in applying these recommendations to a given clinical situation is important and can result in occasional deviation from the guidelines. This is not likely to occur often, but might result from an unusual medical or drug history or uncommon clinical circumstances or difficulty in determining if 'significant bleeding' is to occur. This may be particularly true with endodontics, where it may be impossible with any degree of certainty to determine whether the instrumentation has passed beyond the tooth apex. In this case, the dentist should use her/his 'best clinical judgment' as stated in the guidelines and proceed accordingly. It is certainly reasonable that endodontists may opt for antibiotic prophylaxis in most cases because of this uncertainty, while others choose differently with the realization that the least likely dental treatment procedure to be associated with significant bacteremia is root canal therapy.

As in all clinical situations where clarity is not present, the best guide is the simplest rule of ethics: if you would do this on your parents, siblings, spouse and children, then by all means proceed for you are very likely to be correct in your decision. If you would do this on a patient but not those you love, then cease and desist because you have a double standard and your ethics are in serious question. Your guide should not include an ex-spouse or an in-law as this may cloud your judgment. In all clinical situations where *post facto* judgment of your treatment may occur (malpractice litigation), it is wise to clearly indicate that you realized that this was an unusual situation by simply noting in writing in the chart that 'in my best clinical judgment' this was the course I chose, listing the reasons why and any authoritative sources you may have consulted. This can be a significant deterrent to those who feel qualified to criticize your treatment even though they do not have all the facts and were never there.

Orthopedic prosthetic joints

In the early 1980s, a number of speculative reports emerged that oral microorganisms were isolated from infections of prosthetic joints and were then extrapolated to the conclusion that dental treatment procedures were responsible for such infections; all without any data and no attention to the well-known association of daily living activity-caused bacteremias with endocarditis. Thus began a 20-year struggle to prove the veracity of these claims culminating with the 1997 Advisory Statement of the American Dental Association/American Academy of Orthopaedic Surgeons that: 'Presently, no scientific evidence supports the position that antibiotic prophylaxis to prevent hematogenous infections is required prior to dental treatment in patients with total joint prostheses' (10). Additionally, the Advisory Statement counsels that: 'There is limited evidence that some immunocompromised patients with total joint replacements may be at higher risk for hematogenous infections.'

Currently, there is not a single case report of a genetically identical microorganism isolated both from the oral cavity and the infected prosthetic joint and associated with dental treatment. This is required to prove that a dental treatment-induced bacteremia can cause a prosthetic joint infection. This association exists for *S. sanguis* as the identical bacterium has been isolated from the oral cavity and an infected prosthesis, but only in four individuals with massive ongoing oral sepsis (55).

The Advisory Statement has commonly been misinterpreted to mean that certain immunocompromised individuals (rheumatoid arthritis, systemic lupus erythematosus and other immunosuppressed states) and those with type I diabetes, hemophilia, malnourishment, previous prosthetic joint infections and within 2 years of joint placement *must* receive antibiotic prophylaxis when the guidelines state that antibiotic prophylaxis *should be considered*, but is never mandatory. Also, the Advisory Statement borrows from the 1997 AHA recommendations for endocarditis advising that only dental procedures associated with significant bleeding should be considered for prophylaxis (10).

Breast and penile implants

There are no data to support the contention that dental treatment procedures are a cause of breast and penile implant infections. The risk of late (after 7 months) breast implant infections is 1/10 000 (56), and most surveyed urologists do not suggest antibiotic prophylaxis before dental treatment for patients with penile prostheses (57). If the physician requests antibiotic prophylaxis for such patients, the dentist can advise that no scientific data support such a practice, that the harm from the antibiotic is likely greater than any risk from infection (particularly with penicillin) and that if the physician is convinced of the advisability of prophylaxis, then he/she should do the prescribing.

Immunocompromised patients

Dental patients with a suppressed granulocyte count ($\leq$500–1000) may be at risk of bacteremic or oral infections, although there are no controlled clinical studies to support this contention (58). In patients with blood or bone marrow transplants, the risk for VGS infections is greatest in the preparatory phase 30 days prior to hospitalization and is likely to be proportional to the degree of oral mucositis present (59). Dental patients with HIV/AIDS are at no greater risk for postoperative infection complications than patients without these disorders and should not receive any surgical antibiotic prophylaxis (12). The risk for BE in HIV/AIDS patients who are not nor ever have been IVDA is the same as the general population with no greater mortality rate if IE should occur (60). If such a patient has been or is an IVDA, then there is a 20–40% risk of cardiac valve pathology.

Diabetes

Antibiotic prophylaxis is not indicated for well-controlled non-ketonic diabetic dental patients to prevent postoperative complications and no data support antibiotic prophylaxis for uncontrolled diabetics requiring emergency dental treatment (61). Only 2% of surveyed infectious disease specialists would recommend antibiotic prophylaxis in poorly controlled diabetics (62).

Splenectomy

Individuals without spleens experience a small, but lifelong risk of infection particularly from encapsulated microorganisms (*S. pneumoniae*, *H. influenzae* and *Neisseria meningitidis*), none of which are oral

microorganisms (12). In a study of 5902 cases of postsplenectomy infection, only 0.8% were caused by VGS (63). There are no data to support the use of antibiotic prophylaxis for asplenic patients to prevent postoperative dental infection.

Hemodialysis

Virtually all infections in patients with indwelling catheters are caused by staphylococci (64). It has been suggested that dental patients on hemodialysis receive antibiotic prophylaxis prior to dental treatment (65), but there are no clinical studies to support this recommendation and the AHA has recently advised against prophylaxis in such patients (64).

Non-valvular cardiovascular devices

Because of very little data, numerous opinions have surfaced regarding the advisability of antibiotic prophylaxis prior to dental treatment in patients with non-valvular cardiovascular devices such as pacemakers, implantable cardioverter defibrillators, coronary and peripheral artery stents, prosthetic vascular grafts and Dacron carotid patches. Except for pacemakers, the infection rate of these devices is very low and virtually always due to staphylococci, indicating contamination from the skin during or after placement (64). Pacemakers have an infection rate of 0.13–19.9%, most of which are of the pacemaker pocket and caused by skin microbes (staphylococci and *Corynebacterium*) (64). The infection rate of peripheral vascular stents (femoral, renal) is less than 1/10 000 and only five cases of coronary artery stent infections have been reported: three from *S. aureus* and two from *P. aeruginosa* (64).

The AHA has recently reviewed the evidence for non-valvular cardiovascular device infections and has concluded that: (1) there is no current convincing evidence that microorganisms associated with dental procedures cause infection of these devices at any time after placement, (2) these infections are mostly caused by staphylococci, Gram-negative bacteria or other microorganisms in association with implantation of the devices or resulting from wound or other active infections, (3) accordingly, antibiotic prophylaxis is not recommended after device placement for patients who undergo dental procedures and (4) severely immunocompromised patients may have a risk of infection, but being immunocompromised is not an independent risk factor of these infections (64).

Summary

In the pantheon of medically abused drugs, antibiotic prophylaxis is likely second only to antibiotics employed for upper respiratory viral infections. Guidelines for the use of antibiotic prophylaxis have been available for over 30 years, but rarely consulted. Much of antibiotic prophylaxis has followed the path of 'drugs of fear' employed to 'prevent' malpractice allegations, thereby allowing attorneys to dictate medical treatment for which they bear no responsibility.

Dentistry has been responsible for such abuse primarily by prescribing antibiotics after dental treatment ostensibly to 'prevent' untoward postoperative dental sequelae, but often in an attempt to deter criticism if a postoperative infection should occur, as 'analgesics' or simply to feel more like a 'doctor'. The fact that there is no substantial evidence to support this practice has not been a significant deterrent in many cases. How much this practice in dentistry along with the abuse by our medical colleagues has contributed to the global epidemic on microbial antibiotic resistance can only at this point be a matter of conjecture, but is likely substantial.

Antibiotic prophylaxis prior to dental treatment in medically compromised patients to prevent BE remains reasonable and prudent, even though evidence for its efficacy is currently lacking. The difficulties associated with this concept of antibiotic prophylaxis will likely be addressed in the near future by experts with conclusions drawn and then established in the literature after considerable peer review. It is not for the individual practitioner to make these judgments. Antibiotic prophylaxis wisely employed may possibly be of benefit in carefully selected clinical situations, but its past history is one of ignorance, indifference to the rules and substantial abuse.

Disclaimer

The opinions and conclusions contained herein are those of the author and not necessarily of the American Heart Association.

Added in proof

The ADA/AAOS 1997 guidelines for antibiotic prophylaxis in dental patients with total joint replacements has been updated in 2003 (*J Amer Dent Assn* 2003: **134**(7): 895–899) and remains essentially the same with an added patient information form. As with the 1997 statement, the 2003 advisory does not mandate antibiotic prophylaxis for any artificial joint patients but allows for the dentist's clinical judgement regarding prophylaxis for certain patients possibly at greater risk for hematogenous bacteremias particularly within the first two years of placement.

References

1. Levy SB. *The Antibiotic Paradox*, 2nd edn. Cambridge, MA: Plenum Publishing, 2002.
2. Pallasch TJ. Antibiotic resistance. *Dent Clin N Am* (in press).
3. Kaye D. Prophylaxis for infective endocarditis: an update. *Ann Int Med* 1986: **104**: 419–423.
4. van der Meer JTM, Thompson J, Valkenburg HA, Michel MF. Epidemiology of bacterial endocarditis in the Netherlands. II. Antecedent procedures and use of prophylaxis. *Arch Int Med* 1992: **152**: 1869–1873.
5. van der Meer JTM, Thompson J, Valkenburg HA, Michel MF. Epidemiology of bacterial endocarditis in the Netherlands. I. Patient characteristics. *Arch Int Med* 1992: **152**: 1863–1868.
6. Durack DT. Prevention of infective endocarditis. *N Engl J Med* 1995: **322**: 38–44.
7. Pallasch TJ. Antibiotic prophylaxis: problems in paradise. *Dent Clin N Am* (in press).
8. Pallasch TJ, Wahl MJ. Focal infection: new age of ancient history. *Endod Topics* 2003: **4**(1): 32–45.
9. Dajani AS et al. Prevention of bacterial endocarditis: recommendations of the American Heart Association. *J Am Med Assoc* 1997: **277**: 1794–1801.
10. Advisory Statement Antibiotic prophylaxis for dental patients with total joint replacements. *J Am Dent Assoc* 1997: **128**: 1004–1008.
11. Stone HH, Haney BB, Kolb LD, Geheber CE, Hooper CA. Prophylactic and preventive antibiotic therapy: timing, duration and economics. *Ann Surg* 1979: **189**: 691–699.
12. Pallasch TJ, Slots J. Antibiotic prophylaxis for the medically compromised patient. *Periodontology 2000* 1996: **10**: 107–138.
13. Burke JF. Preventing bacterial infection by coordinating antibiotic and host activity: a time-dependent relationship. *South Med J* 1977: **70** (Suppl. 2). 24–26.
14. Stone HH. Basic principles in the use of prophylactic antibiotics. *J Antimicrob Chemother* 1984: **14** (Suppl. B). 33–37.
15. Paluzzi RG. Antibiotic prophylaxis for surgery. *Med Clin N Am* 1993: **77**: 427–441.
16. Antimicrobial prophylaxis for surgery. *Med Lett Drugs Therap* 1993: **35**: 91–94.
17. Neu HC. Prophylaxis—has it at last come of age? *J Antimicrob Chemother* 1979: **5**: 331–333.
18. Pallasch TJ. Pharmacokinetic principles of antimicrobial chemotherapy. *Periodontology 2000* 1996: **10**: 5–11.
19. Antibiotic prophylaxis in surgery. *Med Lett Drugs Ther* 1993: **35**: 91–94.
20. Waddell TK, Rotstein OD. Committee on Antimicrobial Agents, Canadian Infectious Disease Society: antimicrobial prophylaxis in surgery. *Can Med Assoc J* 1994: **151**: 925–931.
21. Hall G, Hedstrom A, Heimdahl SA, Nord CE. Prophylactic administration of penicillins for endocarditis does not reduce the incidence of postextraction bacteremias. *Clin Infect Dis* 1993: **17**: 188–194.
22. Hall G, Heimdahl A, Nord CE. Effect of prophylactic administration of cefaclor on transient bacteremia after dental extraction. *Eur J Clin Microbiol Infect Dis* 1996: **15**: 646–649.
23. Hall G, Nord CE, Heimdahl A. Elimination of bacteremia after dental extraction: comparison of erythromycin and clindamycin for prophylaxis of infective endocarditis. *J Antimicrob Chemother* 1996: **17**: 783–785.
24. Moreillon P, Francioli P, Overholser D, Meylan P, Glauser MP. Mechanisms of successful amoxicillin prophylaxis of experimental endocarditis due to *Streptococcus intermedius*. *J Infect Dis* 1986: **154**: 801–807.
25. Pallasch TJ. A critical appraisal of antibiotic prophylaxis. *Int Dent J* 1989: **39**: 183–196.
26. Tzukert AA, Leviner E, Benoliel R, Katz J. Analysis of the American Heart Association's recommendations for the prevention of infective endocarditis. *Oral Surg Oral Med Oral Pathol* 1986: **62**: 276–279.
27. Guntheroth WG. How important are dental procedures as a cause of infective endocarditis? *Am J Cardiol* 1984: **54**: 797–801.
28. Roberts RG. Dentists are innocent! ''Everyday'' bacteremia is the real culprit: a review and assessment of the evidence that dental surgical procedures are a principal cause of bacterial endocarditis in children. *Pediatr Cardiol* 1999: **20**: 317–325.
29. Nishi JI, Yoshinaga M, Nomura Y. Prevalence of penicillin-resistant viridans streptococci in the oral flora of Japanese children at risk for endocarditis. *Circulation* 1999: **99**: 1274–1275.
30. Jones RN, Wilson WR. Epidemiology, laboratory detection and therapy of penicillin-resistant streptococcal infections. *Diagn Microbiol Infect Dis* 1998: **319**: 453–459.
31. Doern GV, Ferraro MJ, Brueggeman AB, Ruolf KL. Emergence of high rates of antimicrobial resistance among viridans group streptococci in the United States. *Antimicrob Agents Chemother* 1996: **40**: 891–894.
32. Kuriyama T, Karasawa T, Nakagawa K, Saiki Y, Yamamoto E, Nakamura S. Bacteriologic features and

antimicrobial susceptibility in isolates from orofacial odontogenic infections. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2000: **90**: 600–608.
33. Pallasch TJ. Antibiotic prophylaxis: the clinical significance of its recent evolution. *Calif Dent Assoc J* 1997: **25**: 619–631.
34. Pallasch TJ. Antibiotic prophylaxis. In: Yagiela J, Dowd FJ, Neidle EA, eds. *Pharmacology and Therapeutics for Dentistry*, 5th edn. St Louis, MO: Harcourt Health Sciences (in press).
35. Glick M. Intravenous drug users: a consideration for infective endocarditis in dentistry? (editorial). *Oral Surg Oral Med Oral Path Oral Radiol Endod* 1995: **80**: 125.
36. Kaye D. Prophylaxis for infective endocarditis: an update. *Ann Int Med* 1986: **104**: 419–423.
37. Lytra V. Bactec v. lysis filtration for detection of bacteremias in children. 1–79. MSc Report, Eastman Dental Clinic, University of London.
38. Hockett RN, Loesche WJ, Soderman TM. Bacteremia in asymptomatic human subjects. *Arch Oral Biol* 1977: **22**: 91–98.
39. Steckelberg JM, Wilson WR. Risk factors for infective endocarditis. *Infect Dis Clin N Am* 1993: **7**: 9–19.
40. Tornos P et al. Clinical outcome and long-term prognosis of late prosthetic valve endocarditis: a 20-year experience. *Clin Infect Dis* 1997: **24**: 381–386.
41. Freed LA et al. Prevalence and clinical outcome of mitral-valve prolapse. *N Engl J Med* 1999: **341**: 1–7.
42. Devereux RB et al. Prevalence and correlates of mitral valve prolapse in a population-based sample of American Indians: the Strong Heart Study. *Am J Med* 2001: **111**: 679–685.
43. Singh RG et al. Severe mitral valve regurgitation due to mitral valve prolapse: risk factors for development, progression, and need for mitral valve surgery. *Am J Cardiol* 2000: **85**: 193–198.
44. Pellerin D, Brecker S, Veyrat C. Degenerative mitral valve disease with emphasis on mitral valve prolapse. *Heart* 2002: **88** (S IV): iv20–iv28.
45. Stouffer GA, Sheahan RG, Lenihan DJ, Jacobs W, Chamon A, Stouffer GA. Mitral valve prolapse: a review of the literature. *Am J Med Sci* 2001: **321**: 401–410.
46. Pallasch TJ. Current status of fenfluramine/dexfenfluramine-induced cardiac valvulopathy. *Calif Dent Assoc J* 1999: **27**: 400–404.
47. Gardin JM et al. Clinical and echocardiographic follow-up of patients previously treated with dexfenfluramine or phentermine/fenfluramine. *J Am Med Assoc* 2001: **286**: 2011–2014.
48. Gardin JM, Schumacher D, Constantine G, Davis KD, Leung C, Reid CL. Valvular abnormalities and cardiovascular status following exposure to dexfenfluramine or phentermine/fenfluramine. *J Am Med Assoc* 2000: **283**: 1703–1709.
49. Jollis JG, Landolfo CK, Kisslo J, Constantine GD, Davis KD, Ryan T. Fenfluramine and phentermine and cardiovascular findings: effect of treatment duration on prevalence of valve abnormalities. *Circulation* 2000: **101**: 2071–2077.
50. Mangione S, Nieman LZ. Cardiac auscultatory skills of internal medicine and family practice trainees: a comparison of diagnostic proficiency. *J Am Med Assoc* 1997: **278**: 717–722.
51. Pelech AN. The cardiac murmur: when to refer? *Pediatr Clin N Am* 1998: **45**: 107–122.
52. Guntheroth WG. Initial evaluation of the child for heart disease. *Pediatr Clin N Am* 1978: **25**: 657–675.
53. Cheitlin MD et al. ACC/AHA Guidelines for the Clinical Application of Echocardiography. *Circulation* 1997: **95**: 1686–1744.
54. Pallasch TJ, Gage TW, Taubert KA. The 1997 prevention of bacterial endocarditis recommendations by the American Heart Association: questions and answers. *Calif Dent Assoc J* 1999: **27**: 393–399.
55. Bartzokas CA, Johnson R, Jane M, Martin MV, Pearce PK, Saw Y. Relation between mouth and haematogenous infection in total joint replacements. *Br Med J* 1994: **309**: 506–508.
56. Brand KG. Infection of mammary prostheses: a survey and the question of prevention. *Ann Plast Surg* 1993: **30**: 289–295.
57. Little JW, Rhodus NL. The need for antibiotic prophylaxis of patients with penile implants during invasive dental procedures: a national survey of urologists. *J Urol* 1992: **148**: 1801–1804.
58. Emmanouilides C, Glaspy J. Opportunistic infections in oncologic patients. *Hematol/Oncol Clin N Am* 1996: **10**: 841–860.
59. Van Burik JAH, Weisdorf DJ. Infections in recipients of blood and bone marrow transplants. *Hematol/Oncol Clin N Am* 1999: **13**: 1065–1069.
60. Ribera E et al. Influence of human immunodeficiency virus 1 infection and degree of immunosuppression in the clinical characteristics and outcome of infective endocarditis in intravenous drug users. *Arch Int Med* 1998: **158**: 2043–2050.
61. Alexander RE. Routine prophylactic antibiotic use in diabetic dental patients. *Calif Dent Assoc J* 1999: **27**: 611–618.
62. Lockhart PB, Brennan MT, Fox PC, Norton HJ, Jernigan DB, Strausbaugh LJ. Decision-making on the use of antimicrobial prophylaxis for dental procedures: a survey of infectious disease consultants and review. *Clin Infect Dis* 2002: **34**: 1621–1626.
63. Holdsworth RJ, Irving AD, Cuschieri A. Postsplenectomy sepsis and its mortality rate: actual versus perceived risks. *Br J Surg* 1991: **78**: 1031–1035.
64. Baddour LM et al. Nonvalvular cardiovascular device-related infections. *Circulation* 2003 (in press).
65. DeRossi SS, Glick M. Dental considerations for the patient with renal disease receiving hemodialysis. *J Am Dent Assoc* 1996: **127**: 211–219.