PREVENTION OF INFECTIVE ENDOCARDITIS --

GUIDELINES FROM THE AMERICAN HEART ASSOCIATION

A Guideline from the American Heart Association Rheumatic Fever, Endocarditis and Kawasaki Disease Committee, Council on Cardiovascular Disease in the Young, and the Council on Clinical Cardiology, Council on Cardiovascular Surgery and Anesthesia, and the Quality of Care and Outcomes Research Interdisciplinary Working Group

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The Council on Scientific Affairs of the American Dental Association has approved the paper as it relates to dentistry. These guidelines have been endorsed by the Infectious Diseases Society of America and by the Pediatric Infectious Diseases Society.

ABSTRACT

Background: The purpose of this statement is to update the recommendations by the American Heart Association (AHA) for the prevention of infective endocarditis, which were last published in 1997.

Methods and Results: A writing group appointed by the AHA for their expertise in prevention and treatment of infective endocarditis with liaison members representing the American Dental Association, the Infectious Diseases Society of America, and the American Academy of Pediatrics. The writing group reviewed input from national and international experts on infective endocarditis. The recommendations in this document reflect analyses of relevant literature regarding procedure-related bacteremia and infective endocarditis, in vitro susceptibility data of the most common microorganisms which cause infective endocarditis, results of prophylactic studies in animal models of experimental endocarditis, and retrospective and prospective studies of prevention of infective endocarditis. MEDLINE database searches from 1950-2006

were done for English language papers using the following search terms: endocarditis, infective endocarditis, prophylaxis, prevention, antibiotic, antimicrobial, pathogens, organisms, dental, gastrointestinal, genitourinary, streptococcus, enterococcus, staphylococcus, respiratory, dental surgery, pathogenesis, vaccine, immunization, and bacteremia. The reference lists of the identified papers were also searched. We also searched the AHA online library. The American College of Cardiology/American Heart Association classification of recommendations and levels of evidence for practice guidelines were used. The paper
was subsequently reviewed by outside experts not affiliated with the writing group and by the AHA Science Advisory and Coordinating Committee.

Conclusions: The major changes in the updated recommendations include the following: 1) The Committee concluded that only an extremely small number of cases of infective endocarditis might be prevented by antibiotic prophylaxis for dental procedures even if such prophylactic therapy were 100% effective. 2) Infective endocarditis prophylaxis for dental procedures should be recommended only for patients with underlying cardiac conditions associated with the highest risk of adverse outcome from infective endocarditis. 3) For patients with these underlying cardiac conditions, prophylaxis is recommended for all dental procedures that involve manipulation of gingival tissue or the periapical region of teeth or perforation of the oral mucosa. 4) Prophylaxis is not recommended based solely on an increased lifetime risk of acquisition of infective endocarditis. 5) Administration of antibiotics solely to prevent endocarditis is not recommended for patients who undergo a genitourinary of gastrointestinal tract procedure. * These changes are intended to define more clearly when infective endocarditis prophylaxis is or is not recommended and to provide more uniform and consistent global recommendations.

(*Note: Throughout this JADA document intended for dentistry, the reader will see references to GI, GU and respiratory tract procedures, surgical procedures which involve infected skin, skin

structures or musculoskeletal tissue, and some types of cardiac surgery. Reference to these conditions has been retained in the narrative of this version of the AHA antibiotic prophylaxis recommendations directed to dentistry because of the historical context of their inclusion by the American Heart Association. However, the sections of the original AHA Infective Endocarditis Recommendations that go into detail on these these conditions have been removed from the current document. Interested readers should consult the full AHA Recommendations.

Key Words: AHA Scientific Statements; cardiovascular disease; endocarditis; prevention; antibiotic prophylaxis

Infective endocarditis (IE) is an uncommon but life threatening infection. Despite advances in diagnosis, antimicrobial therapy, surgical techniques, and management of complications, patients with IE still have substantial morbidity and mortality. Since the last AHA publication on prevention of IE in 1997,[1] many authorities, societies, and the conclusions of published studies have questioned the efficacy of antimicrobial prophylaxis to prevent IE in patients who undergo a dental, gastrointestinal (GI) or genitourinary (GU) tract procedure and have suggested that the AHA guidelines should be revised.[2-5] Members of the Rheumatic Fever, Endocarditis, and Kawasaki Disease Committee of the AHA Cardiovascular Disease in the Young ("the Committee") Council, and a national and international group of experts on IE extensively reviewed data published on the prevention of IE. The Committee is especially grateful to a group of international experts on IE who provided content review and input on this document (see Acknowledgments). The revised guidelines for IE prophylaxis are the subject of this report.

The writing group was charged with the task of performing an assessment of the evidence and giving a classification of recommendations and a level of evidence (LOE) to each recommendation. The American College of Cardiology/American Heart Association classification system was used as follows.

Classification of Recommendations:

Class I: Conditions for which there is evidence and/or general agreement that a given procedure or treatment is beneficial, useful, and effective.
Class II: Conditions for which there is conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of a procedure or treatment.
Class IIa: Weight of evidence/opinion is in favor of usefulness/efficacy.
Class IIb: Usefulness/efficacy is less well established by evidence/opinion.
Class III: Conditions for which there is evidence and/or general agreement that a procedure/treatment is not useful/effective and in some cases may be harmful.

Level of Evidence:

- **Level of Evidence A:** Data derived from multiple randomized clinical trials or meta-analyses.
- **Level of Evidence B**: Data derived from a single randomized trial, or nonrandomized studies.

- **Level of Evidence C**: Only consensus opinion of experts, case studies, or standard-of-care.

History of American Heart Association Statements on Prevention of Infective Endocarditis

The AHA has made recommendations for the prevention of IE for more than 50 years. In 1955, the first AHA document was published in *Circulation*.[6] Table 1 shows a summary of the documents published from 1955-1997.[1, 6-13] The 1960 document called attention to the possible emergence of penicillin-resistant oral microflora as a result of prolonged therapy for prevention of IE, and pediatric patients were included for the first time.[8] Chloramphenicol was recommended for patients allergic to penicillin. In 1965, the Committee published for the first time a document devoted solely to the prophylaxis of IE, and recognized the importance of enterococci following GI or GU tract procedures (Ref 9). The revised recommendations published in 1972 were endorsed for the first time by the American Dental Association (ADA) and emphasized the importance of maintenance of good oral hygiene.[10] This version introduced a recommendation for ampicillin in patients undergoing a GI or GU tract procedure. The 1977 revisions categorized both patients and procedures into high- and low-risk groups.[11] This resulted in complex tables with many footnotes. The duration of post-procedure therapy was reduced from two days to two doses. The 1984 recommendations attempted to simplify prophylactic regimens by providing clear lists of procedures for which prophylaxis was and was not recommended and reduced post procedure prophylaxis for dental, GI and GU tract procedures to only one oral or parenteral dose.[12] In 1990, a more complete list of cardiac conditions and dental or surgical procedures for which prophylaxis was and was not recommended was provided.[13] These previous recommendations recognized the potential medicolegal risks associated with IE prophylaxis and suggested that the recommendations were intended to serve as a guideline, not as established standard of care. The most recent AHA document on IE prophylaxis was published in 1997.[1] The 1997 document stratified cardiac

conditions into high, moderate, and low (negligible) risk categories with prophylaxis not recommended for the low risk group.[1] An even more detailed list of dental, respiratory, GI and GU tract procedures for which prophylaxis was and was not recommended was provided. The 1997 document was notable for its acknowledgment that most cases of IE are not attributable to an invasive procedure but rather are the result of randomly occurring bacteremias from routine daily activities and for acknowledging possible IE prophylaxis failures.

Rationale for Revising the 1997 Document:

It is clear from the above chronology that the AHA guidelines for IE prophylaxis have been in a process of evolution over 50 years. The rationale for prophylaxis was based largely upon expert opinion and what seemed to be a rational and prudent attempt to prevent a life threatening infection. On the basis of the American College of Cardiology (ACC) and AHA Task Force on rPactice Guidelines' evidence based grading system for ranking recommendations, the recommendations in the AHA documents published during the last 50 years would be class IIb, LOE C. Accordingly, the basis for recommendations for IE prophylaxis was not well established and the quality of evidence was limited to a few case controlled studies or was based upon expert opinion, clinical experience, and descriptive studies which utilized surrogate measures of risk.

Over the years, other international societies have published recommendations and guidelines for the prevention of IE.[14, 15] Recently, the British Society for Antimicrobial Chemotherapy issued new IE prophylaxis recommendations.[15] This group now recommends prophylaxis before dental procedures only for patients who have a history of previous IE or who have had cardiac valve replacement or surgically constructed pulmonary shunts or conduits.

Fundamental underlying principles which drove the formulation of the AHA guidelines and the 9 previous AHA documents were that 1) IE is an uncommon but life threatening disease and prevention is preferable to treatment of established infection; 2) certain underlying cardiac

conditions predispose to IE; 3) bacteremia with organisms known to cause IE occurs commonly in association with invasive dental, GI or GU tract procedures; 4) antimicrobial prophylaxis was proven to be effective for prevention of experimental IE in animals; and 5) antimicrobial prophylaxis was thought to be effective in humans for prevention of IE associated with dental, GI or GU tract l procedures. The Committee believes that of these 5 underlying principles the first 4 are valid and have not changed during the past 30 years. Numerous publications have questioned the validity of the fifth principle and suggested revision of the guidelines, primarily for reasons as shown in Table 2**.**

Another reason that led the Committee to revise the 1997 document was that over the past 50 years the AHA guidelines on prevention of IE became overly complicated, making it difficult for patients and healthcare providers to interpret or remember specific details, and contained ambiguities and some inconsistencies in the recommendations. The decision to substantially revise the 1997 document was not taken lightly. The present revised document was not based upon the results of a single study but rather upon the collective body of evidence published in numerous studies over the past 2 decades. The Committee sought to construct the present recommendations such that they would be in the best interest of patients and providers; reasonable and prudent., and wodl represent the conclusions of published studies and the collective wisdom of many experts on IE and relevant national and international societies.

Potential Consequences of Substantive Changes in Recommendations:

Substantive changes in recommendations could (1) violate longstanding expectations and practice patterns; (2)make fewer patients eligible for IE prophylaxis; (3) reduce malpractice claims related to IE prophylaxis; and (4) Stimulate prospective studies on IE prophylaxis. The Committee and others[16] recognize that substantive changes in IE prophylaxis guidelines may violate longstanding expectations and practice patterns by patients and healthcare providers.

The Committee recognizes that these new recommendations may cause concern among patients who have previously taken antibiotic prophylaxis to prevent IE prior to dental or other procedures and are now advised that such prophylaxis is unnecessary. Table 2 includes the main talking points that may be helpful for clinicians in re-educating their patients regarding these changes. To recommend such changes demands due diligence and critical analysis. For 50 years, since the publication of the first AHA guidelines on the prevention of IE,[6] patients and healthcare providers assumed that antibiotics administered in association with a bacteremia producing procedure effectively prevented IE in patients with underlying cardiac risk factors. Patients were educated about bacteremia producing procedures and risk factors for IE, and they expected to receive antibiotic prophylaxis; healthcare providers, especially dentists, were expected to administer them. Patients with underlying cardiac conditions that have a lifetime risk of acquisition of IE, such as mitral valve prolapse, had a sense of reassurance and comfort that antibiotics administered in association with a dental procedure was effective and usually safe to prevent IE. Healthcare providers, especially dentists, felt a sense of obligation and professional and legal responsibility to protect their patients from IE that might result from a procedure. On the basis of recommendations in this revised document, substantially fewer patients will be recommended for IE prophylaxis.

Cases of IE either temporally or remotely associated with an invasive procedure, especially a dental procedure, have frequently been the basis for malpractice claims against healthcare providers. Unlike many other infections for which there is conclusive evidence for the efficacy of preventive therapy, the prevention of IE is not a precise science. Because previously published AHA guidelines for the prevention of IE contained ambiguities and inconsistencies and were often based on minimal published data or expert opinion, they were subject to conflicting interpretations among patients, healthcare providers, and the legal system about patient eligibility for prophylaxis and whether or not there was strict adherence by healthcare providers to AHA recommendations for prophylaxis. This document is intended to

identify which, if any, patients may possibly benefit from IE prophylaxis and to define, to the extent possible, which dental procedures should have prophylaxis in this select group of patients. Accordingly, the Committee hopes that this document will result in greater clarity for patients, healthcare providers and consulting professionals.

The Committee believes that recommendations for IE prophylaxis must be evidence based. A placebo controlled, multicenter, randomized, double blinded study to evaluate the efficacy of IE prophylaxis in patients who undergo a dental, GI or GU tract procedure has not been done. Such a study would require a large number of patients per treatment group and standardization of the specific invasive procedures and the patient populations. This type of study would be necessary to answer definitively long standing unresolved questions regarding the efficacy of IE prophylaxis. The Committee hopes that this revised document will stimulate additional studies on the prevention of IE. Future published data will be reviewed carefully by the AHA, Committee on Rheumatoid Fever, Endocarditis and Kawasaki Disease , and other societies, and further revisions to the current document will be based upon relevant studies.

Pathogenesis of IE

The development of IE is the net result of the complex interaction between the bloodstream pathogen with matrix molecules and platelets at sites of endocardial cell damage. In addition, many of the clinical manifestations of IE emanate from the host's immune response to the infecting microorganism. The following sequence of events is thought to result in IE: formation of nonbacterial thrombotic endocarditis (NBTE) on the surface of a cardiac valve or elsewhere that endothelial damage occurs, bacteremia, adherence of the bacteria in the bloodstream to NBTE, and proliferation of bacteria within a vegetation.

Formation of NBTE

Turbulent blood flow produced by certain types of congenital or acquired heart disease, such as flow from a high to low pressure chamber or across a narrowed orifice, traumatizes the

endothelium. This creates a predisposition for deposition of platelets and fibrin on the surface of the endothelium, which results in NBTE. Invasion of the bloodstream with a microbial species that has the pathogenic potential to colonize this site can then result in IE.

Transient Bacteremia

Mucosal surfaces are populated by a dense endogenous microflora. Trauma to a mucosal surface, particularly the gingival crevice around teeth, oropharynx, gastrointestinal tract, urethra or vagina, c releases many different microbial species transiently into the blood stream. Transient bacteremia caused by viridans group streptococci and other oral microflora occurs commonly in association with dental extractions or other dental procedures or with routine daily activities. Although controversial, the frequency and intensity of the resulting bacteremias are believed to be related to the nature and magnitude of the tissue trauma, the density of the microbial flora, and the degree of inflammation or infection at the site of trauma. The microbial species entering the circulation depends upon the unique endogenous microflora that colonizes the particular traumatized site.

Bacterial Adherence:

The ability of various microbial species to adhere to specific sites determines the anatomic localization of infection caused by these microorganisms. Mediators of bacterial adherence serve as virulence factors in the pathogenesis of IE. Numerous bacterial surface components present in streptococci, staphylococci, and enterococci have been shown in animal models of experimental endocarditis to function as critical adhesins. Some viridans group streptococci contain a fimA protein which is an lipoprotein receptor antigen I (LraI)) that serves as a major adhesin to the fibrin platelet matrix of NBTE.[17] Staphylococcal adhesins function in at least two ways. In one, microbial surface components recognizing adhesive matrix molecules facilitate the attachment of staphylococci to human extracellular matrix proteins and to medical devices which become coated with matrix proteins after implantation. In the other, bacterial extracellular

structures contribute to the formation of biofilm which forms on the surface of implanted medical devices. In both cases, staphylococcal adhesins are important virulence factors.

Both FimA and staphylococcal adhesins are immunogenic in experimental infections. Vaccines prepared against FimA and staphylococcal adhesins provide some protective effect in experimental endocarditis caused by viridans group streptococci and staphylococci.[18, 19] The results of these experimental studies are highly intriguing because the development of an effective vaccine for use in humans to prevent viridans group streptococcal or staphylococcal IE would be of major importance.

Proliferation of Bacteria within a Vegetation

Microorganisms adherent to the vegetation stimulate further deposition of fibrin and platelets on their surface. Within this secluded focus, the buried microorganisms multiply as rapidly as do bacteria in broth cultures to reach maximal microbial densities of 10^{8} to ^{1011} colony forming units per gram of vegetation within a short time on the left side of the heart, apparently uninhibited by host defenses in left-sided lesions. Right-sided vegetations have lower bacterial densities, which may be the consequence of host defense mechanisms active at this site, such as polymorphonuclear activity or platelet-derived antibacterial proteins. More than 90% of the microorganisms in mature left- or right-sided valvular vegetations are metabolically inactive, rather than in an active growth phase, and are therefore less responsive to the bactericidal effects of antibiotics.[20]

Rationale for or Against Prophylaxis of Infective Endocarditis

Historical Background

Viridans group streptococci are part of the normal skin, oral, respiratory and GI tract flora, and they cause at least 50% of cases of community-acquired native valve IE not associated with intravenous drug use.[21] More than a century ago, the oral cavity was recognized as a potential source of the bacteremia that caused viridans group streptococcal IE. In 1885, Osler noted an

association between bacteremia from surgery and IE.[22] Okell and Elliott in 1935 reported that 11% of patients with poor oral hygiene had positive blood cultures with viridans group streptococci, and that 61% of patients had viridans group streptococcal bacteremia with dental extraction.[23]

As a result of these early and subsequent studies, during the past 50 years the AHA guidelines recommended antimicrobial prophylaxis to prevent IE in patients with underlying cardiac conditions who underwent bacteremia-producing procedures based on the following factors: (1) bacteremia causes endocarditis; (2) viridans group streptococci are part of the normal oral flora and enterococci are part of the normal GI, GU tract flora ;(3) these microorganisms were usually susceptible to antibiotics recommended for prophylaxis; (4) antibiotic prophylaxis prevents viridans group streptococcal or enterococcal experimental endocarditis in animals; (5) a large number of poorly documented case reports which implicated a dental procedure as a cause of IE; (6) in some cases, there was a temporal relationship between a dental procedure and the onset of symptoms of IE; 7) an awareness of bacteremia caused by viridans group streptococci associated with a dental procedure exists; (8) the risk of significant adverse reactions to an antibiotic is low in an individual patient; (9) morbidity and mortality of IE are high. Most of these factors remain valid, but collectively they do not compensate for the lack of published data that demonstrate a benefit from prophylaxis.

Bacteremia Producing Dental Procedures

The large majority of published studies have focused on dental procedures as a cause of IE and the use of prophylactic antibiotics to prevent IE in patients at risk. Few data exist on the risk of or prevention of IE associated with a GI or GU tract procedure. Accordingly, the Committee undertook a critical analysis of published data in the context of the historical rationale for recommending antibiotic prophylaxis for IE prior to a dental procedure. The following factors were considered: (1) frequency, nature, magnitude, and duration of bacteremia associated with

dental procedures; (2) impact of dental disease, oral hygiene, and type of dental procedure on bacteremia; (3) impact of antibiotic prophylaxis on bacteremia from a dental procedure; (4) the exposure over time of frequently occurring bacteremia from routine daily activities compared with bacteremia from various dental procedures.

Frequency, Nature, Magnitude, and Duration of Bacteremia Associated with a Dental Procedure

Transient bacteremia is common with manipulation of the teeth and periodontal tissues, and there is a wide variation in reported frequencies of bacteremia in patients resulting from dental procedures: tooth extraction (10-100%), periodontal surgery (36-88%), scaling and root planing (8-80%), teeth cleaning (up to 40%), rubber dam matrix/wedge placement (9-32%), and endodontic procedures (up to 20%).[24-30] Transient bacteremia also occurs frequently during routine daily activities unrelated to a dental procedure: tooth brushing and flossing (20-68%), use of wooden toothpicks (20-40%), use of water irrigation devices (7-50%), and chewing food (7-51%). [26-29, 31-36] Considering that the average person living in the United States has less than 2 dental visits per year, the frequency of bacteremia from routine daily activities is far greater.

There has been a disproportionate focus on the frequency of bacteremia associated with dental procedures rather than the species of bacteria recovered from blood cultures. Studies suggest that more than 700 species of bacteria, including aerobic, and anaerobic Gram-positive and Gram-negative microorganisms, may be identified in the human mouth, particularly on the teeth and in the gingival crevices. [24, 37-40] Approximately 30% of the flora of the gingival crevice is streptococci, predominantly of the viridans group. Of the more than 100 oral bacterial species recovered from blood cultures following dental procedures, the most prevalent of these are viridans group streptococci, the most common microbiologic cause of community acquired native valve IE in nonintravenous drug users.[21] In healthy mouths, a thin surface of mucosal epithelium separates potentially pathogenic bacteria from entering the bloodstream and lymphatic system. Anaerobic microorganisms are commonly responsible for periodontal

disease and frequently enter the bloodstream but rarely cause IE with fewer than 120 cases reported.[41] Viridans group streptococci are antagonistic to periodontal pathogens and predominate in a clean, healthy mouth.[42]

Few published studies exist on the magnitude of bacteremia after a dental procedure or from routine daily activities, and most of the published data used older, often unreliable microbiologic methodology. There are no published data that demonstrate that a greater magnitude of bacteremia, compared with a lower magnitude, is more likely to cause IE in humans. The magnitude of bacteremia resulting from a dental procedure is relatively low (less than 10^4 colony forming units of bacteria per mL), similar to that resulting from routine daily activities, and is less than that used to cause experimental IE in animals (10^6-10^8 colony forming units of bacteria per mL).[20, 43, 44] Although the infective dose required to cause IE in humans is unknown, the number of microorganisms in blood after a dental procedure or associated with daily activities is low. Cases of IE caused by oral bacteria probably result from the exposures to low inocula of bacteria in the bloodstream resulting from routine daily activities and not from a dental procedure. Additionally, the vast majority of patients with IE have not had a dental procedure within 2 weeks prior to the onset of symptoms of IE.[2-4]

The role of duration of bacteremia on the risk of acquisition of IE is uncertain.[45, 46] Early studies reported that sequential blood cultures were positive for up to ten minutes after tooth extraction and that the number of positive blood cultures dropped sharply after 10 to 30 minutes.[24, 45-51] More recent studies support these data but report a small percentage of positive blood cultures from 30-60 minutes after tooth extraction.[43, 52, 53] Intuitively, it seems logical to assume that the longer the duration of bacteremia the greater the risk of IE, but no published studies support this assumption. Given the preponderance of published data, there may not be a clinically significant difference in the frequency, nature, magnitude, and duration of bacteremia associated with a dental procedure compared with that resulting from routine daily activities. Accordingly, it is inconsistent to recommend prophylaxis of IE for dental procedures but not for

these same patients during routine daily activities. Such a recommendation for prophylaxis for routine daily activities would be impractical and unwarranted.

Impact of Dental Disease, Oral Hygiene, and Type of Dental Procedure on Bacteremia

It is assumed that a relationship exists between poor oral hygiene, the extent of dental and periodontal disease, the type of dental procedure, and the frequency, nature, magnitude, and duration of bacteremia, but the presumed relationship is controversial.[23, 29, 30, 38, 45, 54-61] Nevertheless, available evidence supports an emphasis on maintaining good oral hygiene and eradicating dental disease to decrease the frequency of bacteremia from routine daily activities.[45, 56-58, 62, 63] In patients with poor oral hygiene, the frequency of positive blood cultures just prior to dental extraction may be similar to that following extraction. [62, 63]

More than 80 years ago, it was suggested that poor oral hygiene and dental disease were more important as a cause of IE than were dental procedures.[64] Most studies since that time have focused instead on the risks of bacteremia associated with dental procedures. For example, tooth extraction is thought to be the dental procedure most likely to cause bacteremia, with an incidence ranging from 10-100%.[23, 24, 27, 29, 45, 48, 52, 54, 57, 65-67] However, numerous other dental procedures have been reported to be associated with risks of bacteremia that are similar to that resulting from tooth extraction.[27, 28, 47, 51, 54, 56, 58, 68-71] A precise determination of the relative risk of bacteremia resulting from a specific dental procedure in patients with or without dental disease is probably not possible.[27, 72, 73]

Bleeding often occurs during a dental procedure in patients with or without periodontal disease. Previous AHA guidelines recommended antibiotic prophylaxis for dental procedures in which bleeding was anticipated but not for procedures for which bleeding was not anticipated.[1] However, no data show that visible bleeding during a dental procedure is a reliable predictor for bacteremia.[62] These ambiguities in the previous AHA guidelines led to further uncertainties among healthcare providers about which dental procedures should be covered by prophylaxis.

These factors complicated recommendations in previous AHA guidelines on prevention of IE which suggested antibiotic prophylaxis for some dental procedures but not for others. The collective published data suggest that the vast majority of dental office visits result in some degree of bacteremia;however, there is no evidence-based method to decide which procedures should require prophylaxis because no data show that the incidence, magnitude, or duration of bacteremia from any dental procedure increase the risk of IE. Accordingly, it is not clear which dental procedures are more or less likely to cause a transient bacteremia or result in a greater magnitude of bacteremia than which results from routine daily activities such as chewing food, tooth brushing, or flossing.

In patients with underlying cardiac conditions, lifelong antibiotic therapy is not recommended to prevent IE which might result from bacteremias associated with routine daily activities.[5] In patients with dental disease, the focus on the frequency of bacteremia associated with a specific dental procedure and the AHA guidelines for prevention of IE have resulted in an over-emphasis on antibiotic prophylaxis and an under-emphasis on maintenance of good oral hygiene and access to routine dental care, which are likely more important in reducing the lifetime risk of IE than is the administration of antibiotic prophylaxis for a dental procedure. However, there are no observational or controlled studies to support this contention.

Impact of Antibiotic Therapy on Bacteremia from a Dental Procedure

The ability of antibiotic therapy to prevent or reduce the frequency, magnitude, or duration of bacteremia associated with a dental procedure is controversial.[24, 74] Some studies reported that antibiotics administered prior to a dental procedure reduced the frequency, nature, and/or duration of bacteremia[53, 75, 76] while others did not.[24, 66, 77, 78] Recent studies suggest that amoxicillin therapy has a statistically significant impact on reducing the incidence, nature, and duration of bacteremia from dental procedures, but it does not eliminate bacteremia.[52, 53, 76] However, no data show that such a reduction as a result of amoxicillin therapy reduces the risk

of or prevents IE. Hall[78] reported that neither penicillin V nor amoxicillin therapy was effective in reducing the frequency of bacteremia compared with untreated control subjects. In patients who underwent a dental extraction, penicillin or ampicillin therapy compared with placebo diminished the percentage of viridans group streptococci and anaerobes in culture, but there was no significant difference in the percentage of patients with positive cultures 10 minutes after tooth extraction.[24, 66] In a separate study, Hall[77] reported that cefaclor-treated patients did not have a reduction of post-procedure bacteremia compared with untreated control subjects. Contradictory published results from 2 studies showed reduction of post-procedure bacteremia by erythromycin in one[75] but lack of efficacy for erythromycin or clindamycin in another.[78] Finally, results are contradictory regarding the efficacy of the use of topical antiseptics in reducing the frequency of bacteremia associated with dental procedures, but the preponderance of evidence suggests that there is no clear benefit. One study reported that chlorhexidine and povidone iodine mouth rinse were effective,[79] while others showed no statistically significant benefit.[52, 80] Topical antiseptic rinses do not penetrate beyond 3 mm into the periodontal pocket and, therefore, do not reach areas of ulcerated tissue where bacteria most often gain entrance to the circulation. On the basis of these data, it is unlikely that topical antiseptics are effective to significantly reduce the frequency, magnitude, and duration of bacteremia associated with a dental procedure.

Cumulative Risk Over Time of Physiologic Bacteremias from Routine Daily Activities Compared with the Bacteremia from a Dental Procedure

Guntheroth[81] estimated a cumulative exposure of 5370 minutes of bacteremia over a one month period in dentulous patients resulting from random bacteremia from chewing food, and from oral hygiene measures, such as tooth brushing and flossing, and compared that with a duration of bacteremia lasting 6 to 30 minutes associated with a single tooth extraction. Roberts[62] estimated that tooth brushing 2 times daily for one year had a 154,000 times greater

risk of exposure to bacteremia than that resulting from a single tooth extraction. The cumulative exposure during one year to bacteremia from routine, daily activities may be as high as 5.6 million times greater than that resulting from a single tooth extraction, the dental procedure reported to be most likely to cause a bacteremia.[62]

Data exist for the duration of bacteremia from a single tooth extraction, and it is possible to estimate the annual cumulative exposure from dental procedures for the average individual. However, calculations for the incidence, nature, and duration of bacteremia from routine daily activities are at best rough estimates, and it is, therefore, not possible to compare precisely the cumulative monthly or annual duration of exposure for bacteremia from dental procedures compared with routine daily activities. Nevertheless, even if the estimates of bacteremia from routine daily activities are off by a factor of 1000, it is likely that the frequency and cumulative duration of exposure to bacteremia from routine daily events over one year are much higher than those resulting from dental procedures.

Results of Clinical Studies of IE Prophylaxis for Dental Procedures

There are no prospective randomized placebo controlled studies on the efficacy of antibiotic prophylaxis to prevent IE in patients who undergo a dental procedure. Data from published retrospective or prospective case controlled studies are limited by the following factors: (1) the low incidence of IE which requires a large number of patients per cohort for statistical significance; (2) the wide variation in the types and severity of underlying cardiac conditions, which would require a large number of patients with specific matched controls for each cardiac condition; and (3) the large variety of invasive dental procedures and dental disease states which would be difficult to standardize for control groups. These and other limitations complicate the interpretation of the results of published studies of the efficacy of IE prophylaxis in patients who undergo dental procedures.

Although some retrospective studies suggested that there was a benefit from prophylaxis, these studies were small in size and reported insufficient clinical data. Furthermore, in a number of cases, the incubation period between the dental procedure and the onset of symptoms of IE was prolonged.[80, 82-84]

van der Meer and colleagues[85] published a study of dental procedures in the Netherlands and the efficacy of antibiotic prophylaxis to prevent IE in patients with native or prosthetic cardiac valves. They concluded that dental or other procedures probably caused only a small fraction of cases of IE and that prophylaxis would prevent only a small number of cases even if it were 100% effective.These same authors[86] performed a 2-year case control study. Among patients for whom prophylaxis was recommended, 5 of 20 cases of IE occurred despite receiving antibiotic prophylaxis. The authors concluded that prophylaxis was not effective. In a separate study,[87] these authors reported that there was poor awareness of recommendations for prophylaxis among both patients and healthcare providers.

Strom and colleagues[2] evaluated dental prophylaxis and cardiac risk factors in a multicenter case control study. These authors reported that mitral valve prolapse (MVP), congenital heart disease (CHD), rheumatic heart disease (RHD), and previous cardiac valve surgery were risk factors for the development of IE. In this study, controls without IE were more likely to have undergone a dental procedure than were cases of IE (P=0.03). The authors concluded that dental treatment was not a risk factor for IE even in patients with valvular heart disease and that few cases of IE could be prevented with prophylaxis even if it were 100% effective.

The studies are in agreement with a recently published French study of the estimated risk of IE in adults with predisposing cardiac conditions who underwent dental procedures with or without antibiotic prophylaxis.[88] These authors concluded that a “huge number of prophylaxis doses would be necessary to prevent a very low number of IE cases.”

Absolute Risk of IE Resulting from a Dental Procedure

No published data that determine accurately the absolute risk of IE resulting from a dental procedure. One study reported that 10-20% of patients with IE caused by oral flora underwent a preceding dental procedure (within 30 or 180 days of onset).[85] The evidence linking bacteremia associated with a dental procedure with IE is largely circumstantial, and the number of cases related to a dental procedure is overestimated for a number of reasons. For 60 years noted opinion leaders in medicine suggested a link between bacteremia-causing dental procedures and IE,[23] and for 50 years the AHA published regularly updated guidelines that emphasized the association between dental procedures and IE and recommended antibiotic prophylaxis.[1] Additionally, bacteremia-producing dental procedures are common; it is estimated that at least 50% of the population in the U.S. visits a dentist at least once a year. Further, there are numerous poorly documented case reports that implicate dental procedures associated with the development of IE, but these reports did not prove a direct causal relationship. Even in the event of a close temporal relationship between a dental procedure and IE, it is not possible to determine with certainty whether the bacteremia that caused IE originated from a dental procedure or from a randomly occurring bacteremia as a result of routine daily activities during the same time period. Many case reports and reviews have included cases with a remote preceding dental procedure often 3 to 6 months before the diagnosis of IE. Studies suggest that the time frame between bacteremia and the onset of symptoms of IE is usually 7 to 14 days for viridans group streptococci or enterococci. Reportedly 78% of such cases of IE occur within 7 days of bacteremia and 85% within 14 days.[89] Although the upper time limit is not known, it is likely that many cases of IE with incubation periods longer than 2 weeks after a dental procedure were incorrectly attributed to the procedure. These and other factors have led to a heightened awareness among patients and healthcare providers of the possible association with dental procedures and IE, which likely has led to substantial over reporting of cases attributable to dental procedures.

Although the absolute risk for IE from a dental procedure is impossible to measure precisely, the best available estimates are as follows: If dental treatment causes 1% of all cases of viridans group streptococcal IE annually in the United States, the overall risk in the general population is estimated to be as low as 1 case of IE per 14 million dental procedures.[41, 90, 91] The estimated absolute risk rates for IE from a dental procedure in patients with underlying cardiac conditions are: MVP 1 per 1.1 million procedures; CHD 1 per 475,000; RHD 1 per 142,000; presence of a prosthetic cardiac valve 1 per 114,000; and previous IE 1 per 95,000 dental procedures.[41, 91] Although these calculations of risk are estimates, it is likely that the number of cases of IE that results from a dental procedure is exceedingly small. Therefore, the number of cases that could be prevented by antibiotic prophylaxis, even if 100% effective, is similarly small. One would not expect antibiotic prophylaxis to be near 100% effective, however, due to the nature of the organisms and choice of antibiotics.

Risk of Adverse Reactions and Cost-Effectiveness of Prophylactic Therapy

Nonfatal adverse reactions, such as rash, diarrhea, and gastrointestinal upset, occur commonly with use of the antimicrobials; however, only single dose therapy is recommended for dental prophylaxis, and these common adverse reactions are usually not severe and are self-limited. Fatal anaphylactic reactions were estimated to occur in 15-25 individuals per 1 million patients who receive a dose of penicillin.[92, 93] Among patients with a prior penicillin use, 36% of fatalities from anaphylaxis occurred in those with a known allergy to penicillin, compared with 64% of fatalities among those with no history of penicillin allergy.[94] These calculations are at best rough estimates, and may overestimate, the true risk of death caused by fatal anaphylaxis from administration of a penicillin. They are based upon retrospective reviews or surveys of patients or on healthcare providers recall of events. A prospective study is necessary to accurately determine the risk of fatal anaphylaxis resulting from administration of a penicillin.

For 50 years, the AHA has recommended a penicillin as the preferred choice for dental prophylaxis for IE. During these 50 years, the Committee is unaware of any cases reported to the AHA of fatal anaphylaxis resulting from the administration of a penicillin recommended in the AHA guidelines for IE prophylaxis. The Committee believes that a single dose of amoxicillin or ampicillin is safe and is the preferred prophylactic agent for individuals who do not have a history of type I hypersensitivity reaction to a penicillin, such as anaphylaxis, urticaria, or angioedema. Fatal anaphylaxis from a cephalosporin is estimated to be less common than from penicillin and is estimated to be approximately 1 case per 1 million patients.[95] Fatal reactions to a single dose of a macrolide or clindamycin are extremely rare.[96, 97] There has been only one case report of documented *Clostridium difficile* colitis following a single dose of prophylactic clindamycin.[98]

Summary

Although it has long been assumed that dental procedures may cause IE in patients with underlying cardiac risk factors and that antibiotic prophylaxis is effective, scientific proof is lacking to support these assumptions. The collective published evidence suggests that of the total number of cases of IE that occur annually, it is likely that an exceedingly small number of these cases are caused by bacteremia-producing dental procedures. Accordingly, only an extremely small number of cases of IE might be prevented by antibiotic prophylaxis even if it were 100% effective. The vast majority of cases of IE caused by oral microflora most likely result from random bacteremias caused by routine daily activities, such as chewing food, tooth brushing, flossing, use of toothpicks, use of water irrigation devices, and other activities. The presence of dental disease may increase the risk of bacteremia associated with these routine activities. There should be a shift in emphasis away from a focus on a dental procedure and antibiotic prophylaxis towards a greater emphasis on improved access to dental care and oral

health in patients with underlying cardiac conditions associated with the highest risk of adverse outcome from IE and those conditions that predispose to the acquisition of IE.

Cardiac Conditions and Endocarditis

Previous AHA guidelines categorized underlying cardiac conditions associated with the risk of IE as those with high risk, moderate risk, and negligible risk and recommended prophylaxis for patients in the high and moderate risk categories.[1] For the present guidelines on prevention of IE, the Committee considered three distinct issues: (1) What underlying cardiac conditions over a lifetime have the highest predisposition to the acquisition of endocarditis? (2) What underlying cardiac conditions are associated with the highest risk of adverse outcome from endocarditis? (3) Should recommendations for IE prophylaxis be based upon either or both of these 2 conditions?

Underlying Conditions Over a Lifetime That Have the Highest Predisposition to the Acquisition of Endocarditis

In Olmsted County, Minnesota, the incidence of IE in adults ranged from 5 to 7 cases per 100,000 person years.[99] This incidence has remained stable during the past four decades and is similar to that reported in other studies.[100-103] Previously, RHD was the most common underlying condition predisposing to endocarditis, and RHD is still common in developing countries.[99] In developed countries, the frequency of RHD has declined, and MVP is now the most common underlying condition in patients with endocarditis.[104]

Few published data quantitate the lifetime risk of acquisition of IE associated with a specific underlying cardiac condition. Steckelberg et al[90] reported the lifetime risk of acquisition of IE which ranged from 5 per100,000 patient years in the general population with no known cardiac conditions to 2160 per100,000 patient years in patients who underwent replacement of an infected prosthetic cardiac valve. In this study,[90] the risk of IE per 100,000 patient years was

4.6 in patients with MVP without an audible cardiac murmur and was 52 in patients with MVP with an audible murmur of mitral regurgitation. Per 100,000 patient years, the lifetime risk (380 to 440) for RHD was similar to that (308 to 383) for patients with a mechanical or bioprosthetic cardiac valve. The highest lifetime risk per 100,000 patient years were as follows: cardiac valve replacement surgery for native valve IE,630; previous IE,740; and prosthetic valve replacement done in patients with PVE,2160. In a separate study, the risk of IE per 100,000 patient years was 271 in patients with congenital aortic stenosis and was 145 in patients with ventricular septal defect.[105] In that same study, the risk of IE before closure of ventricular septal defect was more than twice that after closure. Although these data provide useful ranges of risk in large populations, it is difficult to utilize them to define accurately the lifetime risk of acquisition of IE in an individual patient with a specific underlying cardiac risk factor. This difficulty is based in part upon the fact that each individual cardiac condition, such as RHD or MVP, represents a broad spectrum of pathology from minimal to severe, and the risk of IE would likely be influenced by the severity of valvular disease.

CHD is another underlying condition with multiple different cardiac abnormalities that range from relatively minor to severe complex cyanotic heart disease. During the past 25 years, there has been an increasing use of various different intracardiac valvular prostheses and intravascular shunts, grafts, and other devices for repair of valvular heart disease and CHD. The diversity and nature of these prostheses and procedures likely present different levels of risk for acquisition of IE. These factors complicate an accurate assessment of the true lifetime risk of acquisition of IE in patients with a specific underlying cardiac condition.

On the basis of data from Steckelberg and Wilson[90] and others,[2] it is clear that the underlying conditions discussed above represent a lifetime increased risk of acquisition of IE compared with individuals with no known underlying cardiac condition. Accordingly, when utilizing previous AHA guidelines in the decision to recommend IE prophylaxis for a patient scheduled to undergo a dental, GI or GU tract procedure, healthcare providers were required to

base their decision on population-based studies of risk of acquisition of IE that may or may not be relevant to their specific patient. Further, practitioners had to weigh the potential efficacy of IE prophylaxis in a patient who may neither need nor benefit from such therapy against the risk of adverse reaction to the antibiotic prescribed. Finally, healthcare providers had to consider the potential medicolegal risk of not prescribing IE prophylaxis. For dental procedures, there is a growing body of evidence that suggests that IE prophylaxis may prevent only an exceedingly small number of cases of IE as discussed in detail above.

Cardiac Conditions Associated with the Highest Risk of Adverse Outcome from Endocarditis

Endocarditis, irrespective of the underlying cardiac condition, is a serious, life threatening disease that was always fatal in the pre-antibiotic era. Advances in antimicrobial therapy, early recognition and management of complications of IE, and improved surgical technology have reduced the morbidity and mortality of IE. Numerous co-morbid factors, such as older age, diabetes mellitus, immunosuppressive conditions or therapy, and dialysis, may complicate IE. Each of these co-morbid conditions independently increases the risk of adverse outcome from IE, and they often occur in combination, which further increases morbidity and mortality. Additionally, there may be long-term consequences of IE. Over time, the cardiac valve damaged by IE may undergo progressive functional deterioration that may result in the need for cardiac valve replacement.

In native valve viridans group streptococcal or enterococcal IE, the spectrum of disease may range from a relatively benign infection to severe valvular dysfunction, dehiscence, congestive heart failure, multiple embolic events, and death; however, the underlying conditions shown in Table 3 virtually always have an increased risk of adverse outcome. For example, patients with viridans group streptococcal prosthetic valve endocarditis (PVE) have a mortality of approximately 20% or greater[106-109]; whereas, the mortality from patients with viridans group

streptococcal native valve IE is 5% or less.[108, 110-116] Similarly, the mortality of enterococcal PVE is higher than that of native valve enterococcal IE.[107, 108, 114, 117] Moreover, patients with PVE are more likely than those with native valve endocarditis to develop heart failure, the need for cardiac valve replacement surgery, perivalvular extension of infection, and other complications.

Patients with relapsing or recurrent IE are at greater risk of congestive heart failure, increased need for cardiac valve replacement surgery, and have a higher mortality than do patients with a first episode of native valve IE.[118-124] Additionally, patients with multiple episodes of native or prosthetic valve IE are at greater risk of additional episodes of endocarditis, each of which is associated with the risk of more serious complications.[90]

Published series regarding endocarditis in patients with CHD are underpowered to determine the extent to which a specific form of CHD is an independent risk factor for morbidity and mortality. Nevertheless, most retrospective case series suggest that patients with complex cyanotic heart disease and those who have postoperative palliative shunts, conduits, or other prostheses have a high lifetime risk of acquiring IE, and these same groups appear at highest risk for morbidity and mortality among all patients with CHD.[125-129] In addition, multiple series and reviews reported that the presence of prosthetic material[130, 131] and complex cyanotic heart disease in patients of very young age (newborns and infants under 2 years of age)[132, 133] are 2 factors associated with the worst prognoses from IE. Some types of CHD may be repaired completely without residual cardiac defects. In Table 3, the Committee recommends prophylaxis for dental procedures for these patients during the first six months after the procedure. In these patients, endothelialization of prosthetic material or devices occurs within 6months after the procedure.[134] The Committee does not recommend prophylaxis for dental procedures more than 6 months after the procedure provided that there is no residual defect from the repair. In most instances, treatment of patients who have infected prosthetic materials requires surgical removal in addition to medical therapy with associated high morbidity and mortality rates.

Should IE Prophylaxis be Recommended for Patients with the Highest Risk of Acquisition of IE or for Patients with the Highest risk of Adverse Outcome from IE?

In a major departure from previous AHA guidelines, the Committee no longer recommends IE prophylaxis based solely on an increased lifetime risk of acquisition of IE. It is noteworthy that patients with the conditions listed in Table 3 with a prosthetic cardiac valve, those with a previous episode of IE, and some patients with CHD are also among those patients with the highest lifetime risk of acquisition of endocarditis. No published data demonstrate convincingly that the administration of prophylactic antibiotics prevents IE associated with bacteremia from an invasive procedure. We cannot exclude the possibility that there may be an exceedingly small number of cases of IE that could be prevented by prophylactic antibiotics in patients who undergo an invasive procedure. However, if prophylaxis is effective, such therapy should be restricted to those patients with the highest risk of adverse outcome from IE who would derive the greatest benefit from prevention of IE. In patients with underlying cardiac conditions associated with the highest risk of adverse outcome from IE (Table 3), IE prophylaxis for dental procedures may be reasonable, even though we acknowledge that the effectiveness is unknown **(Class IIb, LOE B)**.

Compared with previous AHA guidelines, under these revised guidelines, many fewer patients would be candidates to receive IE prophylaxis. We believe these revised guidelines are in the best interest of the patients and healthcare providers and are based on the best available published data and expert opinion. Additionally, the change in emphasis to recommend prophylaxis for only those patients with the highest risk of adverse outcome should reduce the uncertainties among patients and providers about who should receive prophylaxis. MVP is the most common underlying condition that predisposes to acquisition of IE in the Western world; however, the absolute incidence of endocarditis is extremely low for the entire population with MVP, and it is not usually associated with the grave outcome associated with

the conditions identified in Table 3. Thus, IE prophylaxis is no longer recommended in this group of individuals.

Finally, the administration of prophylactic antibiotics is not risk free as discussed above. Additionally, the widespread use of antibiotic therapy promotes the emergence of resistant microorganisms most likely to cause endocarditis, such as viridans group streptococci and enterococci. The frequency of multidrug-resistant viridans group streptococci and enterococci has increased dramatically during the past 2 decades. This increased resistance has reduced the efficacy and number of antibiotics available for the treatment of IE.

Regimens Recommended

General Principles

An antibiotic for prophylaxis should be administered in a single dose before the procedure. If the dosage of antibiotic is *inadvertently* not administered before the procedure, the dosage may be administered up to 2 hours after the procedure. However, administration of the dosage after the procedure should be considered only when the patient did not receive the pre-procedural dose. Some patients who are scheduled for an invasive procedure may have a coincidental endocarditis. The presence of fever or other manifestations of systemic infection should alert the provider to the possibility of IE. In these circumstances, it is important to obtain blood cultures and other relevant tests before administration of antibiotics intended to prevent IE. Failure to do so may result in delay in diagnosis or treatment of a concomitant case of IE.

Regimens for Dental Procedures

Previous AHA guidelines on prophylaxis listed a substantial number of dental procedures and events for which antibiotic prophylaxis was recommended and those procedures for which prophylaxis was not recommended. On the basis of a critical review of the published data, it is clear that transient viridans group streptococcal bacteremia may result from any dental

procedure that involves manipulation of the gingival or periapical region of teeth or perforation of the oral mucosa. It cannot be assumed that manipulation of a healthy appearing mouth or a minimally invasive dental procedure reduces the likelihood of a bacteremia. Therefore, antibiotic prophylaxis is recommended for patients with conditions listed in Table 3 who undergo any dental procedure that involves the gingival tissues or periapical region of a tooth and for those procedures that perforate the oral mucosa (Table 4). Although IE prophylaxis may be reasonable for these patients, its effectiveness is unknown **(Class IIb, LOE C)**. This includes procedures such as biopsies, suture removal, and placement of orthodontic bands, but does not include routine anesthetic injections through noninfected tissue, taking dental radiographs, placement of removable prosthodontic or orthodontic appliances, placement of orthodontic brackets, or adjustment of orthodontic appliances. Finally, there are other events that are not dental procedures and for which prophylaxis is not recommended, such as shedding of deciduous teeth and trauma to the lips and oral mucosa.

In this limited patient population, prophylactic antimicrobial therapy should be directed against viridans group streptococci. During the past 2 decades, there has been a significant increase in the percentage of strains of viridans group streptococci resistant to antibiotics recommended in previous AHA guidelines for the prevention of IE. Prabhu et al[135] studied susceptibility patterns of viridans group streptococci recovered from patients with IE diagnosed during a period from 1971 to1986 and compared these susceptibilities with those of viridans group streptococci from patients with IE diagnosed from 1994 to 2002. In this study, none of the strains of viridans group streptococci were penicillin resistant in the early time period compared with 13% of strains that were intermediate or fully penicillin resistant during the later time period. In this study macrolide resistance increased from 11% to 26% and clindamycin resistance from 0 to 4%.

Among 352 blood culture isolates of viridans group streptococci, resistance rates were 13% for penicillin, 15% for amoxicillin, 17% for ceftriaxone, 38% for erythromycin, and 96% for

cephalexin.[136] The rank order of decreasing level of activity of cephalosporins in this study was cefpodoxime equal to ceftriaxone, greater than cefprozil, equal to cefuroxime, and cephalexin was the least active. In other studies, resistance of viridans group streptococci to penicillin ranged from 17% to 50%[137-142] and resistance to ceftriaxone from 22% to 42%.[131, 140] Ceftriaxone was 2 to 4 times more active in vitro than was cefazolin (131).[140] Similarly high rates of resistance were reported for macrolides, ranging from 22% to 58%[137, 141, 143, 144]; resistance to clindamycin ranged from 13% to 27% (128,129,131).[137, 138, 140]

Most of the strains of viridans group streptococci in the above cited studies were recovered from patients with serious underlying illnesses, including malignancies and febrile neutropenia. These patients are at increased risk of infection and colonization by multiply drug-resistant microorganisms, including viridans group streptococci. Accordingly, these strains may not be representative of susceptibility patterns of viridans group streptococci recovered from presumably normal individuals who undergo a dental procedure. Diekema[137] reported that 32% of strains of viridans group streptococci were resistant to penicillin in patients without cancer. King et al[144] reported erythromycin resistance in 41% of streptococci recovered from throat cultures in otherwise healthy individuals who presented with mild respiratory tract infections. In this study, after treatment with either azithromycin or clindamycin, the percentage of resistant streptococci increased to 82% and 71%, respectively. Accordingly, the resistance rates of viridans group streptococci are similarly high in otherwise healthy individuals or in patients with serious underlying diseases.

The impact of viridans group streptococcal resistance on antibiotic prevention of IE is unknown. If resistance in vitro is predictive of lack of clinical efficacy, the high resistance rates of viridans group streptococci provide additional support for the assertion that prophylactic therapy for a dental procedure is of little, if any, value. It is impractical to recommend prophylaxis with only those antibiotics, such as vancomycin or a fluoroquinolone that are highly active in vitro against viridans group streptococci. There is no evidence that such therapy is

effective for prophylaxis of IE, and their use might result in the development of resistance of viridans group streptococci and other microorganisms to these and other antibiotics.

In Table 5, amoxicillin is the preferred choice for oral therapy because it is well absorbed in the gastrointestinal tract and provides high and sustained serum concentrations. For individuals who are allergic to penicillins or amoxicillin, the use of cephalexin or another first generation oral cephalosporin, clindamycin, azithromycin or clarithromycin is recommended. Even though cephalexin was less active against viridans group streptococci than other first generation oral cephalosporins in one study,[136] cephalexin is included in Table 5. No data show superiority of 1 oral cephalosporin over another for prevention of IE, and generic cephalexin is widely available and is relatively inexpensive. Because of possible cross reactions, a cephalosporin should not be administered to patients with a history of anaphylaxis, angioedema, or urticaria following treatment with any form of penicillin, including ampicillin or amoxicillin. Patients who are unable to tolerate an oral antibiotic may be treated with ampicillin, ceftriaxone, or cefazolin administered intramuscularly or intravenously. For ampicillin allergic patients who are unable to tolerate an oral agent, therapy is recommended with parenteral cefazolin, ceftriaxone or clindamycin.

Specific Situations and Circumstances

Patients Already Receiving Antibiotics

If a patient is already receiving chronic antibiotic therapy with an antibiotic that is also recommended for IE prophylaxis for a dental procedure, it is prudent to select an antibiotic from a different class rather than to increase the dosage of the current antibiotic. For example, antibiotic regimens used to prevent the recurrence of acute rheumatic fever are administered in dosages lower than those recommended for the prevention of IE. Individuals who take an oral penicillin for secondary prevention of rheumatic fever or for other purposes are likely to have viridans group streptococci in their oral cavity that are relatively resistant to penicillin or

amoxicillin. In such cases, the provider should select either clindamycin, azithromycin, or clarithromycin for IE prophylaxis for a dental procedure but only for patients shown in Table 3. Because of possible cross resistance of viridans group streptococci with cephalosporins, this class of antibiotics should be avoided. If possible, it would be preferable to delay a dental procedure until at least 10 days after completion of the antibiotic therapy. This may allow time for the usual oral flora to be re-established.

Patients receiving parenteral antibiotic therapy for IE may require dental procedures during antimicrobial therapy, particularly if subsequent cardiac valve replacement surgery is anticipated. In these cases, the parenteral antibiotic therapy for IE should be continued and the timing of the dosage adjusted to be administered 30 to 60 minutes prior to the dental procedure. This parenteral antimicrobial therapy is administered in such high doses that the high concentration would overcome any possible low level resistance developed among mouth flora (unlike the concentration that would occur following oral administration).

Patients Who Receive Anticoagulants

Intramuscular injections for IE prophylaxis should be avoided in patients who are receiving anticoagulant therapy **(Class I, LOE A)**. In these circumstances, orally administered regimens should be given whenever possible. Intravenously administered antibiotics should be used for patients who are unable to tolerate or absorb oral medications.

Patients Who Undergo Cardiac Surgery

A careful dental evaluation is recommended so that required dental treatment may be completed whenever possible before cardiac valve surgery or replacement or repair of CHD. Such measures may decrease the incidence of late prosthetic valve endocarditis caused by viridans group streptococci.

Other Considerations

There is no evidence that coronary artery bypass graft surgery is associated with a long-term risk for infection. Therefore, antibiotic prophylaxis for dental procedures is not needed for individuals who have undergone this surgery. Antibiotic prophylaxis for dental procedures is not recommended for patients with coronary artery stents **(Class III, LOE C)**. The treatment and prevention of infection for these and other endovascular grafts and prosthetic devices are addressed in a separate AHA publication.[145] There are insufficient data to support specific recommendations for patients who have undergone heart transplantation. Such patients are at risk of acquired valvular dysfunction, especially during episodes of rejection. Endocarditis that occurs in a heart transplant patient is associated with a high risk of adverse outcome (Table 3).[146] Accordingly, the use of IE prophylaxis for dental procedures in cardiac transplant recipients who develop cardiac valvulopathy may be reasonable but the usefulness is not well established **(Class IIb, LOE C)** (Table 4). The use of prophylactic antibiotics to prevent infection of joint prostheses during potentially bacteremia inducing procedures is not within the scope of this document.

Future Considerations

Prospective placebo-controlled double blinded studies of antibiotic prophylaxis of IE in patients who undergo a bacteremia producing procedure would be necessary to evaluate accurately the efficacy of IE prophylaxis. Additional prospective case control studies are needed. The AHA has made substantial revisions to previously published guidelines on IE prophylaxis. Based on our current recommendations, we anticipate that significantly fewer patients will receive IE prophylaxis for a dental procedure. Studies are necessary to monitor the effects, if any, of these recommended changes in IE prophylaxis. The incidence of IE could change or stay the same. Because the incidence of IE is low, small changes in incidence may take years to detect. Accordingly, we urge that such studies be designed and instituted promptly so that any change in incidence may be detected sooner rather than later. Subsequent revisions of the AHA

guidelines on the prevention of IE will be based upon the results of these studies and other published data.

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Table 1: Summary of 9 Iterations of AHA Recommended Antibiotic Regimens from 1955 to 1997 for Dental/Respiratory Tract Procedures*

Year	Primary Regimens for Dental Procedures
1955[6]	aqueous penicillin 600,000 U IM and procaine penicillin in oil containing 2% aluminum monostearate 600,000 U IM administered 30 minutes before the operative procedure.
1957[7]	For two days prior to surgery, penicillin 200,000 to 250,000 U by mouth 4 times per day. On day of surgery, penicillin 200,000 to 250,000 U by mouth 4 times per day and aqueous penicillin 600,000 U with procaine penicillin 600,000 U IM 30 to 60 minutes before surgery. For two days after, 200,000 to 250,000 U by mouth 4 times per day.
1960[8]	Step I – prophylaxis 2 days before surgery with procaine penicillin 600,000 U IM on each day. Step II – day of surgery: procaine penicillin 600,000 U IM supplemented by crystalline penicillin 600,000 U IM 1 hour before surgical procedure. Step III – for 2days after surgery: procaine penicillin 600,000 U IM each day.
1965[9]	Day of procedure: Procaine penicillin 600,000 U, supplemented by crystalline penicillin 600,000 U MI 1 to 2 hours before the procedure. For t2 days after procedure: procaine penicillin 600,000 U IM each day.
1972[10]	Procaine penicillin G 600,000 U mixed with crystalline penicillin G 200,000 U IM 1 hour prior to procedure and once daily for the 2days after the procedure.
1977[11]	Aqueous crystalline penicillin G 1,000,000 U IM mixed with procaine penicillin G 600,000 U IM. Give 30 minutes to 1 hour before procedure and then give penicillin V 500 mg orally every 2 hours for 2 doses.
1984[12]	Penicillin V 2 grams orally 1 hour before; then 1 gram 6 hours after initial dose.
1990[13]	Amoxicillin 3 grams orally 1 hour before procedure; then 1.5 grams 6hours after initial dose.
1997[1]	Amoxicillin 2 grams orally 1 hour before procedure.

IM indicates intramuscularly

*These regimens were for adults and represented the initial regimen listed in each version of the recommendations. In some versions, more than 1 regimen was included.

Table 2: Primary Reasons for Revision of the IE Prophylaxis Guidelines

- IE is much more likely to result from frequent exposure to random bacteremias associated with daily activities than from bacteremia caused by a dental, GI tract or GU tract procedure.

- Prophylaxis may prevent an exceedingly small numberof cases of IE, if any, in individuals who undergo a dental, GI tract, or GU tract procedure.

- The risk of antibiotic-associated adverse events exceeds the benefit, if any, from prophylactic antibiotic therapy.

- Maintenance of optimal oral health and hygiene may reduce the incidence of bacteremia from daily activities and is more important than prophylactic antibiotics for a dental procedure to reduce the risk of IE.

Table 3: Cardiac Conditions Associated with the Highest Risk of Adverse Outcome from Endocarditis for Which Prophylaxis with Dental Procedures Is Recommended

- Prosthetic cardiac valve
- Previous infective endocarditis
- Congenital heart disease (CHD)*
    - Unrepaired cyanotic CHD, including palliative shunts and conduits
    - Completely repaired congenital heart defect with prosthetic material or device, whether placed by surgery or by catheter intervention, during the first six months after the procedure**
    - Repaired CHD with residual defects at the site or adjacent to the site of a prosthetic patch or prosthetic device (which inhibit endothelialization)
- Cardiac transplantation recipients who develop cardiac valvulopathy

* Except for the conditions listed above, antibiotic prophylaxis is no longer recommended for any other form of CHD

**Prophylaxis is recommended because endothelialization of prosthetic material occurs within 6 months after the procedure

Table 4: Dental Procedures for which Endocarditis Prophylaxis is Recommended for Patients in Table 3

All dental procedures that involve manipulation of gingival tissue or the periapical region of teeth or perforation of the oral mucosa *

*The following procedures and events do not need prophylaxis: routine anesthetic injections through noninfected tissue, taking dental radiographs, placement of removable prosthodontic or orthodontic appliances, adjustment of orthodontic appliances, placement of orthodontic brackets, shedding of deciduous teeth and bleeding from trauma to the lips or oral mucosa.

Table 5: Regimens for a Dental Procedure

Situation	Agent	Regimen – Single Dose 30-60 minutes before procedure	
		Adults	Children
Oral	Amoxicillin	2 gm	50 mg/kg
Unable to take oral medication	Ampicillin OR Cefazolin or ceftriaxone	2 g IM or IV* 1 g IM or IV	50 mg/kg IM or IV 50 mg/kg IM or IV
Allergic to penicillins or ampicillin Oral	Cephalexin**† OR Clindamycin OR Azithromycin or clarithromycin	2 g 600 mg 500 mg	50 m/kg 20 mg/kg 15 mg/kg
Allergic to penicillins or ampicillin and unable to take oral medication	Cefazolin or ceftriaxone† OR Clindamycin	1 g IM or IV 600 mg IM or IV	50 mg/kg IM or IV 20 mg/kg IM or IV

*IM – intramuscular; IV – intravenous.
**or other first or second generation oral cephalosporin in equivalent adult or pediatric dosage.
†Cephalosporins should not be used in an individual with a history of anaphylaxis, angioedema, or urticaria with penicillins or ampicillin

Table 6: Summary of Major Changes In Updated Document

- We concluded that bacteremia resulting from daily activities is much more likely to cause IE than bacteremia associated with a dental procedure.
- We concluded that only an extremely small number of cases of IE might be prevented by antibiotic prophylaxis even if prophylaxis is 100% effective.
- Antibiotic prophylaxis is not recommended based solely on an increased lifetime risk of acquisition of IE.
- Limit recommendations for IE prophylaxis only to those conditions listed in Table 3.
- Antibiotic prophylaxis is no longer recommended for any other form of CHD, except for the conditions listed in Table 3.
- Antibiotic prophylaxis is recommended for all dental procedures that involve manipulation of gingival tissues or periapical region of teeth or perforation of oral mucosa only for patients with underlying cardiac conditions associated with the highest risk of adverse outcome from IE (Table 3).
- Antibiotic prophylaxis is recommended for procedures on respiratory tract or infected shin, skin structures or musculoskeletal tissue only for patients with underlying cardiac conditions associated with the highest risk of adverse outcome from IE (Table 3).
- Antibiotic prophylaxis solely to prevent IE is not recommended for GI OU GU tract procedures.
- The writing group reaffirms the procedures noted in the 1997 prophylaxis guidelines for which endocarditis prophylaxis is not recommended, and extends this to other common procedures including ear piercing and body piercing, tattooing, and vaginal delivery and hysterectomy.

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Prevention of Infective Endocarditis

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Matthew Levison	Drexel University College of Medicine	None	None	None	None	Merck*	None
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Jane Newburger	Boston Children's Heart Foundation	None	None	None	None	None	None

Thomas Pallasch	University of Southern California	None	None	None	None	Consultation & expert witness testimony on patient records w/ endocarditis	None
Anne Rowley	Children's Memorial Hospital, Chicago	None	None	None	None	None	None
Stanford Shulman	Children's Memorial Hospital, Chicago	None	None	None	None	None	None
Brian Strom	University of Pennsylvania School of Medicine	Pfizer*	Merck*, Novartis*, Wyeth*, Pfizer*	None	None	Abbott*, GlaxoSmith Kline*, Eli Lilly*, Pfizer*, Sanofi Pasteur*, Johnson and Johnson*, Schering AG*, Tap Pharma*, Wyeth*	None
Masato Takahashi	University of Southern California	Bristol-Myers Squibb Medical Imaging*	None	None	None	None	None
Lloyd Tani	University of Utah School of Medicine	None	None	None	None	None	None
Kathryn Taubert	American Heart Association	None	None	None	None	None	None

*Modest
+ Significant

This table represents the relationships of writing group members that may be perceived as actual or reasonably perceived conflicts of interest as reported on the Disclosure Questionnaire which all members of the writing group are required to complete and submit. A relationship is considered to be "Significant" if (a) the person receives $10,000 or more during any 12 month period, or 5% or more of the person's gross income; or (b) the person owns 5% or more of the voting stock or share of the entity, or owns $10,000 or more of the fair market value of the entity. A relationship is considered to be "Modest" if it is less than "Significant" under the preceding definition.