

Infective Endocarditis and Antibiotic Prophylaxis: A Systematic Review of Efficacy and Safety of the AHA Guidelines

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Abstract: This study examined the efficacy, safety and cost-effectiveness of administering antibiotic prophylaxis prior to endodontic procedure in an effort to clarify the 2007 IE prevention guidelines. Methods A non-parametric, meta-analysis of studies reporting antibiotic efficacy was executed. Antibiotic safety analysis was reported as IE cases prevented compared with antibiotic-associated deaths per 10 million patients receiving prophylaxis. Cost-effective analysis was reported in Quality Adjusted Life Years (QALY). No data exists demonstrating that a decreased frequency of bacteremias confers an IE prevention benefit. The pooled adjusted Odds Ratio (OR) for the development of IE with antibiotic prophylaxis among the four case-control studies was highly heterogeneous and statistically non-significant (0.48 [95% CI (0.2-1.16) p-value = 0.10]). Chemoprophylaxis utilizing amoxicillin or ampicillin presents a higher risk of fatal adverse drug reactions (20 cases per 1 million patients treated) than cephalosporin, macrolide and clindamycin regimens (0.5-5.7 cases per 10 million patients treated). IE chemoprophylaxis to moderate-risk patients costs, on average \$96,174 per QALY saved, exceeding the cost-effectiveness threshold. Oral chemoprophylactic therapy to high-risk patients is a cost-effective practice with an average cost of \$29,290 per QALY. The AHA, 2007 IE prevention guidelines appropriately reflect the efficacy, safety and cost-effective evidence for IE prophylaxis. Antibiotic administration to moderate and high-risk patients prior to endodontic procedure provides minimal to no protective efficacy. The administration of oral chemoprophylaxis prior to endodontic procedure only to patients with a high-risk of adverse outcomes subsequent to the acquisition of IE is a beneficial, safe and cost-effective practice.

Key words: Infective endocarditis antibiotic prophylaxis, prevention guidelines, patients, drug reaction, regimens, deaths

INTRODUCTION

Infective Endocarditis (IE) is an uncommon condition with an incidence rate of 3.95 cases per 100,000 person-years yet has an overall high mortality rate of 20-26% (Mylonakis and Calderwood, 2001). Despite the implementation of antibiotics into prophylactic practice during the 1940's and recent advances in the medical and surgical management of IE, the overall incidence and outcomes of IE remain unchanged (Mylonakis and Calderwood, 2001; Weinstein and Brusch, 1996; Di-Filippo *et al.*, 2006).

Since, the 1920's, endodontic procedures have been associated with a high incidence of bacteremia therefore, dental procedures were implicated as an independent risk factor for the development of bacterial endocarditis (Bender *et al.*, 1960; Rabinovich *et al.*, 1965). IE prevention practices advocated for the administration of

pre-endodontic procedural antibiotics to reduce the risks associated with endodontic-induced bacteremias. In 1955, the American Heart Association (AHA) published the first of ten subsequent IE prevention guidelines. The 2007, AHA IE prevention guidelines underwent changes intended to clarify patient eligibility criteria for receiving IE prophylaxis (Wilson *et al.*, 2007).

Significant changes in AHA 2007 IE prevention guidelines (Wilson *et al.*, 2007):

- Bacteremia resulting from daily activities is more likely to cause IE than bacteremia associated with a dental procedure
- Even if antibiotic prophylaxis is 100% effective only a small number of cases of IE might be prevented
- Antibiotic prophylaxis is no longer recommended based solely on an increased lifetime risk of acquisition of IE

- Antibiotic prophylaxis prior to dental procedures that involve manipulation of gingival tissues or periapical region of teeth or perforation of oral mucosa is recommended only to patients with underlying cardiac conditions associated with the highest risk of adverse outcome from IE
- Patients with underlying cardiac conditions associated with the highest risk of adverse outcome from IE are recommended to receive antibiotic prophylaxis prior to procedures on respiratory tract or infected skin, skin structures or musculoskeletal tissue
- Endocarditis prophylaxis with the administration of pre-procedural antibiotics is not recommended for GU or GI tract procedures, tattooing, ear or body piercing, vaginal delivery and hysterectomy

Major changes include the consideration that frequent exposures to bacteremias associated with daily activities are considered more likely to induce IE than endodontic-procedural induced bacteremias. Optimal oral hygiene is emphasized as an important practice for IE prevention. A patient's lifetime acquisition risk of IE is no longer a consideration for initiating prophylactic antibiotic therapy. The AHA now recommends the administration of single-dose prophylactic antibiotics prior to endodontic procedure only to patients with cardiac conditions associated with the highest risk of adverse outcomes following the acquisition of bacterial endocarditis (Wilson *et al.*, 2007).

Cardiac conditions associated with the highest risk of adverse outcome from endocarditis for which prophylaxis with dental procedures is recommended (Wilson *et al.*, 2007):

- Prosthetic cardiac valve
- Previous IE

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 1st 6 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

The new practice patterns associated with the 2007 AHA guidelines have raised concerns among dentists, physicians and patients. In concordance with the new recommendations, healthcare providers withhold prophylactic therapy to a substantial number of patients who previously received pre-procedural antibiotic prophylaxis. Healthcare providers who practice according to the new IE prevention guidelines are frequently met with inquiry and objection from both colleague and patients.

In this systematic review, researchers report the results of a comprehensive literature review and meta-analysis assessing the evidence for providing pre-endodontic procedural antibiotic prophylaxis as an IE prevention practice according to the 2007, AHA IE prevention guidelines. Evidence addressing the efficacy and safety of antibiotic administration prior to endodontic procedure for IE prophylaxis were of particular interest.

MATERIALS AND METHODS

Literature review and abstraction: A comprehensive search of the literature was performed. The search strategy was developed on MEDLINE PubMed, Cochrane Controlled Trials Register (CENTRAL), OLDMEDLINE (Ovid, 1966 to June 2002), EMBASE (Ovid, 1980 to June 2002) and International Pharmaceutical Abstracts (IPA) for relevant studies published in English with no publication date limits. The medical subject headings and text words used were infective endocarditis, antibiotic, antibiotic prophylaxis, chemoprophylaxis, bacteremia, endodontic procedures, dentistry, safety and quality adjusted life years and efficacy. No limits on combinations of inclusion terms were used. References of reviewed articles were also searched for relevant studies.

One reviewer independently conducted the literature search and abstraction of relevant articles. The inclusion criteria included randomized controlled trials, cohort studies, case-control studies and cross-sectional studies in humans, animals and *in vitro* models. Data and quality information were abstracted onto a custom data collection form. Abstracted characteristics of studies included author, year, study design, country of origin, duration, details of antibiotic intervention, types of dental procedure, underlying cardiac condition, matched population variables and population IE-risk factors. Outcomes data collected were number of deaths, new cases of endocarditis, cases of IE prevented, population randomization, Quality-Adjusted Life Year (QALY) per intervention and cost-effectiveness comparison per intervention.

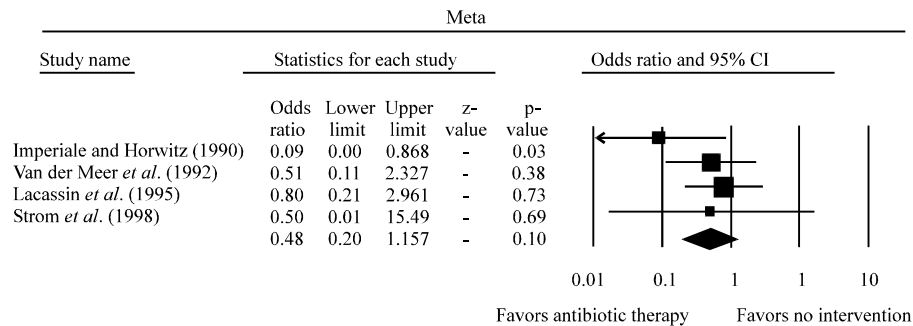


Fig. 1: Forest plot of antibiotic efficacy as reported by case-control studies

Statistical analysis: Clinical studies which analyzed the protective efficacy of administering pre-endodontic antibiotics for IE prevention were assessed for conceptual and statistical heterogeneity.

Heterogeneity between trial results was tested using a standard χ^2 -test and considered significant where $p < 0.1$. FAST*PRO Software was used to calculate the protective efficacy of antibiotic prophylaxis with associated confidence intervals based on the reported findings for each study (Fig. 1). A forest plot (Fig. 1) and Chi-square analysis were completed to assess for conceptual and statistical heterogeneity, respectively.

RESULTS

State of the evidence: No randomized controlled trials assessing whether the administration of antibiotics to at risk patients prior to bacteremia-inducing endodontic procedures confers a protective benefit against the development of IE have been completed. Previous AHA recommendations were extrapolated from *in vitro* susceptibility data of pathogens inducing endocarditis, prophylactic studies in experimental animal models, pharmacokinetic studies and observational analyses of endocarditis in humans (Girard *et al.*, 1993; Rouse *et al.*, 1997).

Numerous pre-clinical studies, expert reviews and editorials have questioned the appropriateness of previous AHA IE prevention recommendations (Bashore *et al.*, 2006; Seymour *et al.*, 2000; Agha *et al.*, 2005). The dogma that high-risk dental procedures produce a bacteremia of significant magnitude to induce IE has been questioned. Four case-control studies and one extrapolated population report calculated the IE acquisition risk in subjects receiving and not receiving antibiotic prophylaxis prior to endodontic procedure (Imperiale and Horwitz, 1990; Van der Meer *et al.*, 1992; Lacassin *et al.*, 1995; Strom *et al.*, 1998; Duval *et al.*,

2006). Recent data have questioned the safety of antibiotic administration to such large populations (Agha *et al.*, 2005).

Pathophysiology: The pathophysiology of new onset IE remains un-elucidated. There is a prerequisite for the existence of a bacteremia of significant intensity. One currently accepted theory suggests that conditions associated with mechanical destruction of the endocardium exposes the subendothelium thus, promoting local activation of the clotting cascade. Microbial pathogens (*Streptococcus viridans* representing 50% of the reported cases) associated with transient bacteremias from dental procedures, routine daily activities and otherwise bind to and activate inflammatory cytokines on the coagulum resulting in progressive enlargement of an infected vegetation (Heimdahl *et al.*, 1990). A second theory describes other bacteria, most notably *Staphylococcus aureus* which express surface fibronectin. Fibronectin facilitates bacterial adherence to the locally inflamed endothelium. The interaction of bacteria and inflammation initiates the milieu of a progressive vegetation (Prendergast, 2006). Subsequent local extension and tissue damage results in septic emboli disseminating to the brain, spleen, kidney and peripheral vasculature contributing to the sequelae of IE first described by Osler.

Endodontic procedures, bacteremia and infective endocarditis risk: About 80-90% of high-risk endodontic procedures induce a transient bacteremia in humans (Roberts *et al.*, 1992; Lee *et al.*, 2000). However, only 4-7.5% of all bacterial endocarditis cases are related to endodontic associated bacteremia (Gendron *et al.*, 2000). Following dental intervention, the absolute risk for developing IE is estimated at 1 case per 14 million dental procedures with the IE acquisition risk for high-risk patients with underlying cardiac conditions following dental intervention being substantially higher (Pallasch, 2003). IE acquisition risk estimates following an

endodontic induced bacteremia in patients with congenital heart disease are 1 per 475,000; rheumatic heart disease, 1 per 142,000; prosthetic heart valve, 1 per 114,000 and previous IE, 1 per 95,000 dental procedures (Pallasch, 2003).

The correlation of bacteremia frequency and duration on the acquisition risk of IE has not been assessed. However, considering the average American undergoes 2 dental visits per year (which may or may not include endodontic procedure), the frequency of exposure to an endodontic induced bacteremia is minimal. Transient bacteremia associated with endodontic procedure are of relative short duration. Blood cultures in humans remain positive for only 30-60 min immediately following endodontic procedure. The importance of bacterial inoculum magnitude has been demonstrated by experimental catheter-induced valvular insult in rabbit models. These studies established that inocula of 1×10^8 (100 million) colony forming units (cfu) mL^{-1} or greater are required to consistently induce experimental endocarditis (Carrion and Freedman, 1970; Bahn *et al.*, 1978; Cremieux *et al.*, 1993). Recent human quantitative blood culture data support the implication that endodontic associated bacteremia inocula are of insufficient magnitude to induce endocarditis. Bacteremia intensities immediately following invasive human dental procedures peaked at 1.5-5.9 cfu mL^{-1} and quickly precipitated over the proceeding minutes to hours. In retrospect, these are relatively low inocula; 5-6 orders of magnitude lower than the experimental model inocula intensities suggested were necessary to induce endocarditis.

Ironically, in their 1942 paper advocating antibiotic prophylaxis, Northrop and Crowley (1943), discovered that only 20% of confirmed cases of IE were associated with an endodontic procedure in the preceding 3 months. Evidence which suggested that new onset IE may not be attributed to endodontic procedure. Recent reports have confirmed low rates of previous dental intervention in association with new onset IE. In all, five reports have demonstrated that 0-17% of patients diagnosed with IE had undergone a dental procedure 30-180 days prior to diagnosis (Imperiale and Horwitz, 1990; Van der Meer *et al.*, 1992; Lacassin *et al.*, 1995; Strom *et al.*, 1998; Duval *et al.*, 2006). The most recent case-control study of 104 patients with known, high-risk structural heart disease discovered that patients who developed IE were actually less likely to have experienced an endodontic procedure within the 180 days prior to diagnosis than did control patients who did not develop IE (OR 0.2 [95% CI 0.04-0.7]) (Strom *et al.*, 1998). Risk for new onset IE and experiencing an endodontic procedure in the preceding 90 days was not demonstrated (OR 1.2 [95% CI 0.7-2.1]).

A follow-up analysis confirmed these early results concluding that IE was not associated with endodontic or other previously defined high-risk procedures. Among high-risk patients with underlying structural heart disease, kidney disease (OR 16.9 [95% CI 1.5-193.0]), diabetes (OR 2.7 [95% CI 1.4-5.2]) and skin flora infection (OR 3.5 [95% CI 0.7-17.0]) were associated with a greater risk for the development of bacterial endocarditis (Strom *et al.*, 2000). The role endodontic procedure induced bacteremia has on inducing IE remains inconclusive. Investigators have therefore assessed the IE acquisition risk associated with other known causes of transient bacteremias.

Daily activities such as chewing and oral hygiene practices result in bacteremias more frequently, of longer duration and of greater magnitude in comparison to high-risk endodontic procedures (Table 1) (Seymour *et al.*, 2000; Roberts, 1999). However, the duration and magnitude of bacterial inocula associated with routine activities are still remarkably low and may not be a risk factor for the induction of bacterial endocarditis (Seymour *et al.*, 2000; Roberts, 1999). Evidence supports an emphasis on optimizing oral hygiene to decrease the frequency of bacteremias associated with routine daily activities (Conner *et al.*, 1967). Although, no data exists demonstrating that a decreased frequency of bacteremias confers an IE prevention benefit.

These findings have led the AHA to conclude that the cumulative background bacteremia associated with chewing, daily dental hygiene practices, kidney disease, diabetes and skin colonization present a greater risk of significant bacteremia than any single invasive dental procedure (Wilson *et al.*, 2007). The AHA no longer advocates the lifelong prophylactic administration of antibiotics to at-risk patients to prevent IE from routine

Table 1: Prevalence of bacteremia arising after various types of dental procedures and oral activity (Seymour *et al.*, 2000)

Procedure prevalence of bacteremia	Values (%)
Extractions	
Single	51
Multiple	68-100
Periodontal surgery	
Flap procedure	36-88
Gingivectomy	83
Scaling and root planing	8-80
Periodontal prophylaxis	0-40
Endodontics	
Intracanal instrumentation	0-31
Extracanal instrumentation	0-54
Endodontic surgery	
Flap reflection	83
Periapical curettage	33
Toothbrushing	0-26
Dental flossing	20-58
Interproximal cleaning with toothpicks	20-40
Irrigation devices	7-50
Chewing	17-51

daily activities. Optimal oral hygiene is advocated as it may reduce bacteremia frequency associated with daily activities with minimal to no associated risks.

Prophylactic antibiotic efficacy: The efficacy of antibiotic regimens for IE prophylaxis has never been assessed under the scrutiny of a randomized controlled trial. Evidence supporting pre-endodontic chemoprophylaxis efficacy is extrapolated from data demonstrating reductions in bacteremia magnitudes immediately following the administration of antibiotics (Lockhart, 1996; Lockhart *et al.*, 2004). Additionally, recent *in vitro* studies suggested that the anti-inflammatory properties of antibiotics reduce bacterial adherence to compromised endocardial tissue and therefore confer an efficacy benefit (Frieling *et al.*, 1997). Whether antibiotic prophylaxis is effective for the prevention of endocarditis in patients prior to invasive endodontic procedure remains equivocal. The Cochrane Collaboration assessed whether prophylactic administration of penicillin to moderate to high-risk patients prior to endodontic intervention conferred a mortality, serious illness or endocarditis incidence benefit (Oliver *et al.*, 2004). Their extensive search and exclusion criteria resulted in three case-control studies analyzing patients undergoing any AHA defined moderate to high-risk oral-dental procedure. Encompassing 350 patients, the 3 case-control trials were published prior to 1997 and reported a range of 46-91% decreased incidence of new IE cases among patients receiving pre-endodontic procedural antibiotic therapy versus the control populations' who did not receive pre-procedural antibiotics (Table 2) (Imperiale and Horwitz, 1990; Van der Meer *et al.*, 1992; Lacassin *et al.*, 1995; Strom *et al.*, 1998). The pooled, adjusted odds ratio across all studies for the development of IE among patients receiving prophylaxis was non-significant (0.56 [95% CI (0.15-2.15)]). The Cochrane Collaboration concluded; it is unclear whether antibiotic prophylaxis is effective and there is a lack of evidence to support published guidelines using penicillin as chemoprophylaxis for IE.

The systematic literature review identified 4 case control studies assessing antibiotic efficacy for IE prevention. In addition to the previously mentioned 3 case control studies reviewed by The Cochrane Collaboration, the review identified an additional case control study subsequently published in 1998. In a comparison analysis of 29 high-risk patients with known structural heart disease who developed IE within 180 days of experiencing an endodontic procedure with matched, high-risk control patients who did not develop endocarditis, Strom *et al.* (1998) discovered the

administration pre-endodontic procedural antibiotics did not provide a protective benefit against the development of IE (OR 0.5 [CI .01-9.6]). Case patients were proportionally more likely to have received AHA guideline appropriate antibiotic prophylaxis than were the risk-equivalent, control patients (Table 2).

The protective efficacy of pre-endodontic antibiotic prophylaxis for IE prevention was calculated for each of the 4 case reports (Fig. 1). Interpretation of the results demonstrated a considerable variation in study outcomes. Imperiale and Horwitz (1990) reported a statistically significant protective effect whereas the remaining studies failed to demonstrate such an effect. Confirmation of statistical heterogeneity was completed first conceptually with a forest plot (Fig. 1) and then with chi-square test analysis (Chi-square 8.005 for 3 df, $p = 0.0459$). Large degrees of heterogeneity precluded the completion of a statistically meaningful meta-analysis of the protective effect of antibiotic prophylaxis across all 4 studies.

The most recent report investigating the efficacy of prophylactic antibiotics to high-risk IE patients prior to endodontic procedure was published in 2006 (Table 2) (Duval *et al.*, 2006). Utilizing a 2805-patient database of patients who developed IE within 3 months of experiencing endodontic intervention, Duval and colleagues estimated the efficacy of providing chemoprophylaxis to all high-risk patients who underwent an endodontic procedure in the preceding 30 days (estimated at 2.7 million). Providing chemoprophylaxis to all 2.7 million high-risk patients predicted a 70% lower incidence of new onset IE thus preventing 80 new cases of IE. The researchers concluded that the risk of adverse drug reactions must be weighed against the high, number needed to treat associated with practicing large population chemoprophylaxis.

Safety concerns with antibiotic prophylaxis: Adverse reactions associated with the administration of beta-lactam antibiotics are common. Ranging in severity from pruritus to fatal anaphylactic shock, the frequency of all adverse reactions from the administration of penicillin to the general population is 0.7-10% (Idsoe *et al.*, 1968). The incidence of fatal anaphylaxis among patients receiving single-dose penicillin, ampicillin or amoxicillin therapy is approximately 20 cases per 1 million patients treated (Idsoe *et al.*, 1968; The International Collaborative Study of Severe Anaphylaxis, 2003). Single-dose, cephalosporin-associated fatal anaphylaxis risk is estimated at 0.5-5.7 cases per 10 million patients treated (Kelkar and James, 2001). Macrolide and clindamycin single-dose fatal anaphylaxis risk is estimated at 0-5 cases per 1 million patients treated (Mazur *et al.*, 1999). With the highest

Table 2: Characteristics of 5 studies addressing antibiotic prophylaxis for at-risk patients

Source	Imperiale and Horwitz (1990) United States	Van der Meer <i>et al.</i> (1992) Netherlands	Lacassin <i>et al.</i> (1995) France	Strom <i>et al.</i> (1998) United States	Duval <i>et al.</i> (2006) France
Study objective	To determine whether pre-dental procedural antibiotic prophylaxis reduces the risk of infective endocarditis in persons with high-risk cardiac lesions	To assess the protective effect of antibiotic prophylaxis in subjects with native-valve and cardiovascular anomalies	To assess the relative risk of infective endocarditis associated with invasive procedures and the protective efficacy of antibiotic prophylaxis	To quantitate the risk for developing endocarditis in patients with underlying, at-risk cardiac conditions following invasive dental procedure	To estimate the risk of developing dental-procedural induced infective endocarditis in at-risk patients or received and did not receive antibiotic prophylaxis
Demographics and Pt characteristics	8 cases (native valve IE) and 24 controls. (without IE) Pts were matched for age and high-risk cardiac lesion All experienced a dental procedure within 12 weeks of review	48 cases (native valve IE) and 200 controls (without IE) Pts were matched for age, sex and cardiac condition All experienced a dental procedure 180 days prior to follow up interview	37 cases (prosthetic or native valve IE) and 33 controls (without IE) Pts were matched for age, sex and cardiac condition All experienced a dental procedure 3 months prior to follow up interview	29 cases (prosthetic or native valve IE) and 12 controls (without IE) Pts were matched for age, sex, cardiac condition and geographic location All experienced a dental procedure 3 months prior to follow up interview	2805 patient population who experienced a dental procedure in previous 30 days. Data reviewed to confirm the development of IE and administration of prophylactic antibiotic. Data was then extrapolated to estimate risk of developing IE and the protective efficacy of providing chemoprophylaxis to all high risk patients over 12 month period
Results	1/8 case pts (13%) received antibiotics. 15/24 control pts (63%) received antibiotics. Matched Odds Ratio: 0.09 (CI upper limit of 0.93) (p = 0.025) Protective Efficacy 91%	8/48 case pts (16%) received antibiotics. 26/200 control pts (13%) received antibiotics. Stratified Odds Ratio: 0.51 (0.11-2.29). Protective Efficacy 49%	Any causative organism: 6/37 case pts (23%) received antibiotics. 6/33 control pts (27%) received antibiotics. Matched and Adjusted Odds Ratio: 0.2 (0-0.8) Protective Efficacy 20% Viridans Strep and Negative blood cultures 3/18 case pts (16%) received antibiotics 6/22 control pts (27%) received antibiotics Matched and Adjusted Odds ratio: 0.46 (0-0.9) Protective Efficacy 46%	24/29 case pts (83%) received antibiotics 3/12 control pts (25%) received antibiotics Unadjusted Odds Ratio: 0.5 (.01-9.6) Protective Efficacy 50% Unadjusted Odds Ratio: 0.3 (.01-4.2) without abtc prophylaxis	Risk of developing IE per 2.7 million at risk patients not receiving prophylaxis: 1/46,000. Risk of developing IE with Antibiotic administration: 1/149,000 70% protective efficacy. Estimated number of IE cases prevented per 2.7 million treated: 39-41
Study limitations	Excluded pts who died from IE. Administration of antibiotics was confirmed by patient recall when dental records were not available. Low IE incidence rate	Low IE incidence rate, large variation in predisposing cardiac condition severity. Results did not reach statistical significance	Low IE incidence rate, large variation in predisposing cardiac condition severity and inability to rule out confounding IE risk factors. Total number of dental procedures in the case group was greater than control group	Low IE incidence rate and inability to rule out confounding IE risk factors	Estimated risk extrapolated from geographically limited population of 2805 patients
Authors conclusions	Results suggest a IE protective benefit for pre-endodontic procedural chemoprophylaxis to patients of high-risk. The adverse risks and benefits of antibiotic prophylaxis need precisely defined	In a developed affluent and medically well organized country, complete compliance with endocarditis prophylaxis might prevent about 5 cases of IE per year	The efficacy benefit from antibiotic prophylaxis may reduce IE incidence by 5-10% or prevent 60-120 new cases of IE per year	Even at 100% effectiveness, prophylaxis would reduce IE incidence by 2.0 cases per 1,000,000 person-years Dental procedures are not a risk factor for endocarditis even in high-risk patients	A very low number of IE cases would be prevented with a large population antibiotic prophylactic practice. The risk of fatal reactions to antibiotics, limits the use of prophylaxis to populations with the highest risk

associated mortality rate of all the recommended antibiotic regimens, the risk of anaphylaxis with the initiation of beta-lactam IE prophylactic therapy must be considered (Lin, 1992).

The importance of risk-benefit analysis prior to initiation of IE chemoprophylaxis with beta-lactam therapy was highlighted in a pivotal paper by Bor. Patients with mitral valve prolapse who according to the then current

AHA guidelines appropriately received IE chemoprophylaxis with penicillin were five times more likely to die from an antibiotic induced anaphylactic reaction than from the sequelae of IE (Bor and Himmelstein, 1984). Recommendations for IE prophylaxis with antibiotics to patients with mitral valve prolapse prior to endodontic procedure was rescinded in the proceeding AHA IE prevention guidelines.

Subsequent studies have addressed the risk to benefit ratio of practicing IE chemoprophylaxis with beta-lactam antibiotics to a broader patient population. The annual risk of mortality associated with the development of endodontic-induced IE is estimated at 26 deaths per 100 million (Bor and Himmelstein, 1984). Whereas the risk of mortality associated with the single-dose administration of beta-lactam antibiotics for IE prophylaxis is estimated at 1-3 anaphylactic deaths per 1 million patients treated (Wilson *et al.*, 2007). The mortality risk associated with single-dose antibiotic therapy has never been assessed under the scrutiny of a prospective trial (Helbling *et al.*, 2004).

The 2007 AHA IE prevention guidelines recommend amoxicillin as first-line, IE prevention chemoprophylactic therapy for high-risk patients without a documented type-I hypersensitivity to beta-lactam antibiotics. Amoxicillin provides adequate coverage against oral pathogens commonly implicated in post-dental endocarditis at a fraction of the cost for alternative regimens with comparable *in vitro* efficacy (Dajani *et al.*, 1990). Amoxicillin and ampicillin are as previously stated, associated with a higher risk of fatal anaphylactic reactions than alternative cephalosporin, macrolide and clindamycin regimens. According to the AHA, single dose administration of a beta-lactam antibiotic for IE prophylactic therapy is a safe practice as it has never resulted in a reportable case of fatal anaphylaxis.

DISCUSSION

Infective endocarditis is associated with a high risk of morbidity and mortality. The primary prevention of IE is therefore justified. The presumed correlation of endodontic induced bacteremia and new onset IE made pre-procedural antibiotic prophylaxis a reasonable practice for the preceding 60 years. However, there is a paucity of evidence in support of providing chemoprophylaxis for effective IE prevention. Bacterial inocula subsequent to endodontic procedures are infrequently experienced of short duration and of low magnitude. The temporal relationship of endodontic procedure and new onset IE is often prolonged. These findings fail to suggest a causality relationship between

endodontic procedures and new onset bacterial endocarditis. No data demonstrates that a decrease in frequency, magnitude or duration of bacteremias from the administration of antibiotics confers an IE prevention benefit. In addition, providing antibiotics for prophylactic practice has associated adverse risks.

Chewing, dental hygiene practices, kidney disease, diabetes and skin colonization present a greater risk of significant bacteremia and greater cumulative IE acquisition risk than any single invasive dental procedure. Frequency of bacteremias associated with daily activities in at risk patients are reduced with optimal oral hygiene with minimal to no associated adverse risks. The AHA recommends reducing the incidence of bacteremia with the optimization of oral hygiene in at-risk patients and does not recommend indiscriminant pre-procedural chemoprophylaxis as a safe, IE prevention practice.

The pre-procedural, estimated IE acquisition risk in at-risk patients with underlying cardiac conditions is significantly greater than for negligible-risk patients (Dajani *et al.*, 1997).

Cardiac conditions associated with increased IE acquisition risk (Dajani *et al.*, 1990):

- Prosthetic and mechanical cardiac valves
- Previous bacterial endocarditis
- Complex cyanotic congenital heart disease (single ventricle states, transposition of the great arteries, tetralogy of Fallot)
- Surgically constructed systemic pulmonary shunts or conduits
- Acquired valvular dysfunction (rheumatic heart disease)
- Hypertrophic cardiomyopathy
- Mitral valve prolapse with valvular regurgitation and/or thickened leaflets

Morbidity and mortality rates associated with high-IE acquisition risk patients are variable and must be considered prior to the initiation of pre-endodontic procedure chemoprophylaxis. Although, patients with mitral valve prolapse have a high-IE acquisition risk, the risk of adverse outcomes including death and morbidity is low. As demonstrated by Bor and Himmelstein (1984) providing antibiotics to this cohort of patients resulted in an excess of treatment associated adverse events compared to the number of adverse outcomes prevented. Other conditions with similar, high-IE acquisition risk and low-adverse outcomes risk following IE acquisition exist. Health care providers must perform a risk-benefit analysis for each individual patient prior to initiation of antibiotic prophylaxis. The 2007 AHA, IE prevention guidelines no

longer advocate the administration of pre-endodontic chemoprophylaxis to patients based on their lifetime IE acquisition risk as the risks from providing such therapy may outweigh the benefit. Withholding antibiotic prophylaxis in these circumstances seems a reasonable practice.

No randomized, placebo-controlled trials assessing the protective efficacy of single-dose of antibiotic prophylaxis prior to endodontic procedure for IE prevention have been completed. Case-control studies have reported conflicting results on the protective efficacy conferred from providing pre-procedural antibiotic prophylaxis to at-risk patients. A pooled meta-analysis of the protective benefit from chemoprophylaxis from these case-control studies was not completed as there is a high degree of statistically heterogeneity between the case-control results. Obtaining studies of complete clinical homogeneity was limited by the few published reports addressing IE prevention practices. Potential characteristic differences across reviewed studies include severity differences in predisposing cardiac conditions, inability to rule out confounding IE risk factors and utilization of different antibiotic regimens. Statistical heterogeneity was also attributable to differences in study design and the low incidence of IE (Table 2). The AHA acknowledges that even if chemoprophylaxis conferred 100% efficacy, few cases of IE would be prevented as the incidence of endodontic induced IE is so low. Therefore, the goal of prophylactic therapy is to identify patients who would derive the greatest benefit from IE prevention. The AHA now recommends the administration of pre-endodontic procedural prophylactic antibiotics to patients with the highest risk of adverse outcomes subsequent to the development of IE.

The AHA continues to recommend oral amoxicillin as a safe, first-line IE prevention practice for patients without a documented hypersensitivity to beta-lactam antibiotics who are at a high-risk of adverse outcomes from developing IE. Acknowledging an estimated 10-20 fold greater risk of single-dose fatal anaphylaxis with amoxicillin compared to single dose cephalosporin, macrolide and clindamycin regimens, the AHA believes prophylaxis with amoxicillin is a safe practice as there have been no reports of fatal anaphylaxis from a single-dose of pre-dental IE prophylaxis oral amoxicillin. Health care providers must weigh the IE acquisition risk, risk of IE associated adverse outcomes and efficacy benefit from prophylactic antibiotics with the risk of adverse drug reactions for individual patients prior to the administration of antibiotics for IE prevention.

Given the paucity of efficacy data, large estimates of number-needed to treat and adverse risks associated with IE prophylactic practices, the administration of prophylactic antibiotics is a public health policy issue.

CONCLUSION

This study shows that evidence for chemoprophylaxis efficacy remains equivocal and necessitates further investigation. Only a well designed and adequately powered randomized controlled trial will provide definitive guidance for the utilization of antibiotic prophylaxis for IE prevention. The current data supports the judicious assessment of a patient's risk for adverse outcomes subsequent to the acquisition of IE with the potential adverse outcomes associated with pre-endodontic antibiotic prophylaxis. The 2007, AHA IE prevention guidelines advocating chemoprophylaxis for patients with a high-risk of adverse outcomes subsequent to the acquisition of IE appropriately reflects the current data on the efficacy and of antibiotic prophylaxis.

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