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Antibiotic Prophylaxis of Infective Endocarditis: A Scoping Review

Salem Saleh Mohammed Al-Zuria (1) *, Mohammed Hamad Ali Al-Saqoor (2), Muhammad Hussein Masoud Al Mansour (3), Salem Mohammed Alkulayb (4), Fiasal Hadi Hasan Alyami (5), Sarran Mahdi Hasan Alyami (2), Mohammed Salem Mana Alharid (5), Salem Mohammed Mahdi Alsagoor (6), Nasser Saleh Husain Al Hateelah (7)

(1) Nurse, Technical Institute for Health Training, Ministry of Health, Saudi Arabia.
(2) Pharmacy Technician, Ministry of Health, Saudi Arabia.
(3) Hospital Management, Ministry of Health, Saudi Arabia.
(4) Radiological Technology, Khobash Hospital, Najran, Saudi Arabia.
(5) Medical Device Technician, Ministry of Health, Saudi Arabia.
(6) Dental Technology, Ministry of Health, Saudi Arabia.
(7) Nurse, Ministry of Health, Saudi Arabia.

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Corresponding author

Abstract

Introduction: Infective endocarditis is a rare fatal infection, affecting around 5-10 people per 100,000 per annum. Consequently, this is a disease that is important to prevent using antibiotic prophylaxis. However, the rationale for antibiotic prophylaxis to help prevent IE is itself surrounded in controversy, as there is no definitive evidence for its efficacy.

Methods: An electronic search was conducted in the Medline, Embase, and Cochrane Central Register of Controlled Trials. Search terms used included subject headings and title/abstract keywords for bacterial endocarditis, antibiotics and prophylaxis. We also searched the reference lists of all included articles. The primary outcome of interest was the incidence of IE, incidence of (any) bacteremia, or for time-trend studies, population-adjusted incidence of IE. Where total incidence of bacteremia was not reported, the time point at which the highest incidence of bacteremia was observed in the placebo group was used for comparison.

Results: The electronic search identified 830 articles, after removal of case reports, editorials, animal studies and duplicates. After screening of the title and/or abstract of these, 27 articles were deemed eligible for full-text assessment. In total, 16 studies were considered suitable for inclusion. All identified trials used bacteremia as a surrogate endpoint for IE. We identified 10 studies assessing the effect of changing national and international guidelines concerning the use of AP on the population incidence of IE. These included nine studies of relative AP restriction (from the USA and Europe) and one study examining the effect of total AP restriction (from the UK).

Conclusions: The adequacy of the antibiotic prophylaxis regimen currently recommended for the prevention of infective endocarditis in periodontitis patients should be discussed. The population at risk of infection are no longer young people with

known rheumatic valvular heart disease and are now elderly people with no apparent valve disease. Thus, an extensive systematic review is needed to summarize all the evidence on this question and to assess whether the current restrictions in the use of AP are justified.

Keywords: Infective Carditis, Antibiotic, Prophylaxis, Bacteremia, Prevention.

Introduction

Infective endocarditis (IE) is an infection of the endothelium of the heart. Conversely, prior administration of antibiotic therapy is the singular most prevalent reason for culture negative endocarditis and results in untargeted antimicrobial therapy, diagnostic uncertainty and frequently longer and more toxic treatment regimens. Infective endocarditis is a rare but severe disease, with 100% mortality in the pre-antibiotic area. A threshold of 4 mm for a vegetation has been shown to be associated with clinically silent neurological emboli, while 10 mm is taken as a taken as a threshold in the European guidelines for early intervention in the setting of one established systemic embolic event while on appropriate antibiotic therapy. In patients with a microorganism that is highly responsive to antibiotic therapy who demonstrate an uncomplicated clinical course following treatment, consideration is given to outpatient parenteral antibiotic therapy (OPAT). Inpatient treatment is usually advised for the first 2 weeks when the complication rates are the highest [1].

Infective endocarditis is a rare infection, affecting around 5-10 people per 100,000 per annum [2]. Consequently, this is a disease that is important to prevent, and for many years antibiotic prophylaxis prior to invasive, particularly dental, procedures has been normal practice across the world. In 1941, the first recorded use of antibiotic prophylaxis (AP) took place [2]. antibiotic prophylaxis was initially based upon the assumption that giving antibiotics to individuals susceptible to IE, prior to a procedure known to release bacteria into the bloodstream, would reduce the risk of developing IE subsequently. David Durack and colleagues published the first animal model studies demonstrating that infective endocarditis might be prevented with prophylactic antibiotics in the early 1970s [2]. The impact of antibiotic prophylaxis prior to dental or other medical procedures on the development of bacteremia in humans has been extensively studied. In recent times data collected at a national level has become available for analysis and has enabled researchers to assess the impact of guideline changes on the rates of infective endocarditis [3]. A French study estimated that one in 10,700 adults with prosthetic valves and one in 54,300 adults with native-valve PCC developed infective endocarditis as a result of such a procedure. Van der Meer and colleagues 17 published a prospective study exploring the possibility of a causal relation between dental procedures and infective endocarditis, and assessed the efficacy of antibiotic prophylaxis to prevent infection in patients with native or prosthetic cardiac valves [4]. Strom and colleagues 18 assessed dental prophylaxis and cardiac risk factors in a case-control study. antibiotic prophylaxis is not risk free. β-lactam exposes patients to the risk of anaphylactic reaction (15-40 per 100,000 uses), which is potentially fatal in 1-3 per 100,000 uses [5].

Furthermore, the widespread use of antibiotic therapy promotes the emergence of resistant microorganisms most likely to cause infective endocarditis, such as S. viridians and enterococci. However, the extent to which a single dose of antibiotic prophylaxis could be implicated in the selection of resistant microorganisms is unknown. infective endocarditis caused by oral microorganisms (ie, streptococci) has the best prognosis, with a mortality of 10% in the French epidemiological survey on infective endocarditis, compared with 35% for Staphylococcus aureus [6]. Several studies have estimated the cost-effectiveness of antibiotic prophylaxis and have found conflicting results. Given the high mortality of infective endocarditis, fear of medicolegal consequences has been shown to lead practitioners in some countries to overuse prophylaxis compared with the use

recommended in current guidelines. The risk of occurrence of infective endocarditis in any given case of PCC is most often very indirectly estimated by comparing the frequency of different cardiac diseases in patients with infective endocarditis to its estimated frequency in the overall population. recommendations, these considerations have led to the identification of patients at moderate and high risk of infective endocarditis (panel). Meanwhile, the proportion of patients with bacteremia after an at-risk procedure has been used as a surrogate measure of the risk of infective endocarditis to identify procedures requiring antibiotic prophylaxis. However, this identification method has resulted in a detailed and complex list of procedures for which prophylaxis is and is not recommended. The prophylactic recommendations, the use of infective endocarditis preventive cards have been proposed in several countries. Because of the frequency of everyday bacteremia and its postulated primary role in infective endocarditis, the main preventive strategy is to limit spontaneous bacteremia (through chewing, brushing) by reducing the global oral burden of bacteremia via improved oral hygiene [7].

The recent publication of new Australian guidelines 1 for antibiotic prophylaxis for the prevention of infective endocarditis (IE) represents a major revision of previously accepted protocols. antibiotic prophylaxis for patients with congenital or acquired cardiac conditions who were considered to be at risk of IE, and who required dental treatment, was introduced by the American Heart Association (AHA) in 1955, not long after penicillin became widely available. The rationale for recommending antibiotic prophylaxis was that dental treatment was known to cause a spread of oral bacteria into the circulation (bacteremia), and these bacteria (especially viridians group streptococci) had the potential to colonize damaged heart valves and result in what was then known as bacterial endocarditis, either acute, sub-acute or chronic. For half a century, between 1955 and 2006, the alterations to antibiotic guidelines in various countries related mainly to antibiotic choice and route of administration. The first guidelines to recommend a major departure from the traditional belief that all patients at risk of IE required antibiotic prophylaxis prior to dental or other invasive procedures were produced by a working party of the British Society for Antimicrobial Chemotherapy in 2006 [8]. In 2007, the American Heart Association released new guidelines for antibiotic prophylaxis [9]. The European Society of Cardiology updated its 2004 guidelines for the prevention of IE in 2009. In the UK, we reviewed "Yellow Card" data to determine the rate of adverse events from the use of amoxicillin and clindamycin as antibiotic prophylaxis. "Yellow Cards" are completed by health care professionals when adverse drug reactions are recorded, particularly after the introduction of a medication or if there has been a severe side effect. The impact of AP on antibiotic resistance has not been formally assessed, and is an important consideration. However, antibiotic resistance is believed to be encouraged when repeated courses of antibiotics at inadequate doses are given and is minimized by infrequent doses of antibiotics at high doses e as is the case for AP [10]. Even with the introduction of molecular detection methods, infective endocarditis (IE) continues to be difficult to diagnose and is associated with a high rate of mortality (21-35%). Although there have been many developments with respect to antibiotic therapy in the treatment of the disease, its incidence is continuing to rise, affecting 3.3 cases per 100 000 population per year in the UK, with similar figures for the USA and 1.4-4.0 cases per 100 000 population per year in Europe as a whole [11]. Although localized infective episodes are relatively common, cases of IE as a result of body piercing are rare in the general population, but are of more concern to those individuals with an underlying cardiac condition, which may predispose them to IE.

To date, there have been relatively few reports published involving piercing and IE; however, of those reports published, there has been a dramatic rise in the last decade. Antibiotic prophylaxis is recommended by several national guidelines for the prevention of IE, 16-18 however there have been no guidelines to date that have specifically described the need for antibiotic prophylaxis associated with body piercing procedures for susceptible individuals. The rationale for antibiotic prophylaxis to help prevent IE is itself surrounded in controversy, as there is no definitive evidence for its efficacy [12]. This Review will concentrate mainly on infective endocarditis

prophylaxis with the most widely situations in which antibiotic prophylaxis are used.

Methods

An electronic search was conducted in the Medline, Embase, and Cochrane Central Register of Controlled Trials. Search terms used included subject headings and title/abstract keywords for bacterial endocarditis, antibiotics and prophylaxis. We also searched the reference lists of all included articles. The following categories of study were excluded: studies conducted prior to 1970, studies of AP in patients undergoing cardiac surgery or implantation of cardiac electronic devices, topical therapies and comparative antibiotic trials with no placebo/control arm.

We extracted data on the study design: for case–control studies, we extracted baseline characteristics on the cases and the controls; for time-trend studies, we extracted study population characteristics, the study time period, relevant guideline changes and effects on incidence of IE per 100,000 population. The primary outcome of interest was the incidence of IE, incidence of (any) bacteremia, or for time-trend studies, population- adjusted incidence of IE. Where total incidence of bacteremia was not reported, the time point at which the highest incidence of bacteremia was observed in the placebo group was used for comparison.

Results and discussion

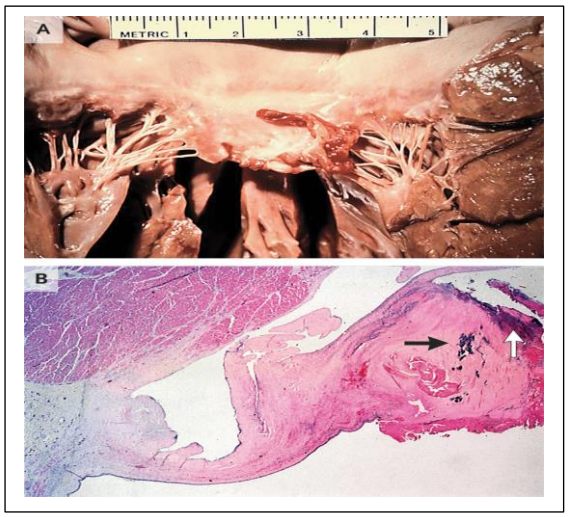
The electronic search identified 830 articles, after removal of case reports, editorials, animal studies and duplicates. After screening of the title and/or abstract of these, 27 articles were deemed eligible for full-text assessment. In total, 16 studies were considered suitable for inclusion. All identified trials used bacteremia as a surrogate endpoint for IE. We identified 10 studies assessing the effect of changing national and international guidelines concerning the use of AP on the population incidence of IE. These included nine studies of relative AP restriction (from the USA and Europe) and one study examining the effect of total AP restriction (from the UK) . Changes in the guidelines between 2007 and 2009 by the ESC, ACC/AHA and NICE greatly reduced the use of AP. Annual incidence was reported in two studies and obtained from the authors for two studies. Studies reported the incidence of IE per 100,000 population before and after changes in ACC/AHA and NICE guidelines. While only one study identified a significant rise in the incidence trend of IE, it is important to note that this change was observed in the only population with total AP restriction. Studies showed that bacteremia occurred after tooth extractions, especially in patients who had periodontal disease or who underwent multiple extractions. Uncomplicated vaginal delivery causes bacteremia in less than 5% [13]. In a retrospective survey of 533 patients with valvular prostheses who underwent 677 dental or surgical procedures, 6 cases of endocarditis occurred in 229 patients who received no antibiotic prophylaxis, as compared with none in 304 patients who did (P=0.04). In the first, only 1 of 8 case patients (13 percent) had received antibiotic prophylaxis, as compared with 15 of 24 control patients (63 percent) with comparable predisposing heart disorders (P=0.025); these results indicated a protective efficacy of 91 percent for prophylaxis [13].

Only eight cases were examined, and misclassification of a single case would have reversed the authors' conclusion that prophylaxis was effective. Two cases were culture-negative, and in two cases there was an interval of 10 to 12 weeks between the dental procedure and the diagnosis of endocarditis; both these factors make misclassification likely [14]. In a second case-control study of 438 patients, representing nearly all identifiable patients with infective endocarditis in the Netherlands during a two-year period, prophylaxis was not protective. When this analysis was limited to the 13 percent of patients in whom endocarditis occurred within 30 days after a procedure, there was a protective effect, but the most optimistic calculations indicated only 49 percent efficacy. Many cases of apparent failure of antibiotic prophylaxis against endocarditis have been reported. In the largest series (52 cases), two thirds of the causative bacteria were sensitive to the antibiotics that had been given prophylactically [15]. Failures were not due primarily to antibiotic resistance, as a similar conclusion was reached by decision analysis in a study of the cost-benefit ratio of penicillin prophylaxis against endocarditis in patients with mitral-valve prolapse; the

use of parenteral penicillin to prevent endocarditis could result in a net loss of life due to deaths from anaphylaxis, especially in young patients. A survey of dentists in the United Kingdom revealed that most were well aware of the concept of prevention and believed that it had been proved efficacious [16]. Subsequent surveys have revealed a common theme; health care providers are familiar with the concept of prophylaxis against endocarditis, are aware of published recommendations, and believe them to be authoritative. Seventy percent of Dutch patients recalled receiving advice about prophylaxis against endocarditis, but only 22 percent reported actually taking antibiotics before a dental or surgical procedure for which prophylaxis against endocarditis is recommended. In another study, prophylaxis was given four times more often to young than to elderly patients, even though the American Heart Association's recommendations make no such distinction. For patients with pacemakers and automatic internal cardioverter-defibrillators, surgeons were twice as likely to recommend prophylaxis against endocarditis as cardiologists, and physicians in the United States recommended prophylaxis more often than physicians from other countries [17].

The British guidelines reduced the number of cardiac conditions requiring antibiotic prophylaxis to only those individuals with previous IE, those who had undergone cardiac valve replacement surgery, or those who had surgically constructed systemic or pulmonary shunts or conduits. Patients with mitral valve prolapse or rheumatic heart disease were no longer recommended to receive antibiotic cover [2]. In 2007, the AHA introduced new guidelines which were significantly different from previous AHA recommendations. Like the British guidelines, the new American guidelines significantly reduced the categories of cardiac conditions which required antibiotic prophylaxis for dental or other mucosal invasive procedures. The AHA guidelines concluded that the death rate for native valve IE caused by viridians group streptococci was 5% or less, whilst it was approximately 20% for viridians streptococcal prosthetic valve endocarditis. As such, there was a professional and medico-legal responsibility on behalf of dentists to protect their patients from IE. In their discussion of the reasons for revising the IE guidelines, the AHA acknowledged that the new recommendations "could violate long-standing expectations and practice patterns" but they also suggested that the new recommendations could reduce malpractice claims related to IE prophylaxis. The reason for the major departure from previous guidelines was the impact of evidence-based medicine on current health care practice. Both the American 2 and UK 3 guidelines were closely evaluated and interpreted in the Australian context. The UK guidelines 3 were carefully considered but it was decided that the abolition of antibiotic prophylaxis for all patients at risk of IE could not be supported at this time. Therefore, it was the consensus of the expert group that antibiotic prophylaxis is necessary in this particular group. Consideration was given to deleting the moderate risk group of dental procedures [18].

The rationale for prophylaxis against endocarditis with antibiotics is as follows: endocarditis usually follows bacteremia; certain health care procedures cause bacteremia with organisms that can cause endocarditis; these bacteria are usually sensitive to antibiotics; therefore, antibiotics should be given to patients with predisposing heart disease before procedures that may cause bacteremia [19]. On the basis of this logical and intuitively appealing formulation, prophylaxis against endocarditis has become routine in most developed countries, even though no prospective study has proved that it is effective. Incidentally, these studies detected occasional spontaneous bacteremia in normal subjects, indicating that the prolific oral flora often enters the bloodstream. These frequent, transient episodes of bacteremia usually cause no symptoms because the inoculum is small and the virulence of the organisms is low, but they probably represent a far greater cumulative risk of endocarditis in patients with predisposing heart disease than do occasional dental procedures [20]. The relative frequency of endocarditis associated with these procedures follows the same order. The introduction of catheters or other instruments into the normal urinary tract can induce bacteremia; the proportion of patients in whom it develops is higher if urinary tract infection is present [21]. The rate of bacteremia associated with defecation, rectal examination, is actually negligible.



There were insufficient data to calculate the incidence of bacteremia after the removal of tympanostomy tubes or cesarean section. of cases and has seldom been associated with endocarditis. Procedure-related bacteremia are short-lived. The frequency of positive blood cultures is highest seconds after a tooth extraction, and most episodes of bacteremia associated with dental procedures last less than 10 minutes. Colonization of the endocardium must occur immediately when endocarditis results from a procedure-associated bacteremia [22]. This assumption is consistent with the short interval between the procedure and the onset of symptoms when endocarditis follows a procedure. In most patients in whom incubation periods are longer, the suspected procedure was probably not the cause of the endocarditis. These retrospective case reports are subject to recall bias and exposure-suspicion bias, however, so the upper limit of the incubation period is not known with any certainty. The choice of a strategy for prevention must take into account the incidence of the disease in question. Known cardiac disorders identify candidates for prophylaxis, but the selection of a cost-effective preventive strategy requires a consideration of the risk that each poses for the development of endocarditis [23]. Although precise figures are lacking, the ranking of risk can be based on the frequency with which each pre-existing cardiac disorder occurs in large series of patients with endocarditis as compared with the general population.

Conclusions

Based on this, the adequacy of the antibiotic prophylaxis regimen currently recommended for the prevention of infective endocarditis in periodontitis patients should be discussed. The population at risk of infection are no longer young people with known rheumatic valvular heart disease and are now elderly people with no apparent valve disease. In addition, effective prevention measures to decrease the rate of bacteremia after dental treatment should be analyzed. However, preprocedural rinsing had no significant effect on the bacteremia rate compared to no rinsing. Thus, an extensive systematic review is needed to summarize all the evidence on this question and to assess whether the current restrictions in the use of AP are justified.

Conflict of interests

The authors declared no conflict of interests.

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