

# INPLASY PROTOCOL

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None declared.

## Antibiotic Prophylaxis before Invasive Dental Procedures for Patients at High-Risk of Infective Endocarditis

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**Review question / Objective:** The aim of the present systematic review and meta-analysis is to determine whether there is a genuine clinical need for Antibiotic Prophylaxis (AP) for the prevention of Infective Endocarditis (IE) in high-risk individuals (particularly those with demonstrable structural heart diseases or valve surgery) undergoing invasive dental procedures.

**Information sources:** PubMed, Science Direct, British Dental Journal and Cochrane Register of Controlled Trials. Search terms used included various combinations of the following subject headings and title or abstract keywords – prophylactic antibiotics, antibiotic prophylaxis, antimicrobial, dentist, extraction, implant, infective endocarditis, or bacterial endocarditis.

**INPLASY registration number:** This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 03 July 2022 and was last updated on 03 July 2022 (registration number INPLASY202270011).

### INTRODUCTION

**Review question / Objective:** The aim of the present systematic review and meta-analysis is to determine whether there is a genuine clinical need for Antibiotic Prophylaxis (AP) for the prevention of Infective Endocarditis (IE) in high-risk individuals (particularly those with demonstrable structural heart diseases or

valve surgery) undergoing invasive dental procedures.

**Condition being studied:** Infective endocarditis (IE) is a cardiac condition characterized by infection of the endocardial surface of the heart, which may involve the mural endocardium, one or more heart valves, or a septal defect. It is a low prevalent disease but with high

mortality and morbidity. The overall incidence of IE in the general population ranges between 1 and 5 per 100,000 person years. Its intracardiac complications include severe valvular insufficiency, which can result in intractable congestive heart failure (HF) and myocardial abscesses. The main etiologic agent of IE is bacteraemia although the presence of fungi and other pathogens in the bloodstream can also be causative. Normally, bacteria cannot adhere to the normal smooth endocardial lining unless it is damaged, which can occur in the presence of certain types of congenital and acquired structural heart diseases or valve surgery. The damage causes the release of substances including tissue factors and cytokines leading to the formation of a platelet-fibrin thrombus (also known as non-bacterial thrombotic endocarditis) to which bacteria in the bloodstream can adhere and colonize to cause IE<sup>1</sup>. Thus, individuals with damaged endocardium and high loads of bacteria in the blood are at the highest risk of developing IE.

#### Oral Bacteria and IE

The link between oral bacteria and IE has been known for decades and is a cause of concern for dentists, patients and cardiologists. The oral microbiota is highly diverse but non-uniformly spread throughout the oral cavity. The maximum concentration occurs in bacterial plaque estimated at 10<sup>11</sup> and 10<sup>12</sup> microorganisms per gram of wet weight although the high concentration may also occur at the back of the tongue, cheek and the palatal mucosa. More than 700 bacterial species have been isolated from the oral cavity but the usual candidates are 20 species, with streptococci of the viridans group (mostly streptococcus mutans and streptococcus sanguis) being the most abundant. In 90% of IE cases, streptococci are the causative agent.

Damage in the oral mucosa barrier exposes the internal body environment to a high concentration of bacteria found in the oral cavity leading to bacteraemia and IE, usually characterized by systemic symptoms of infection, embolic phenomenon or endocardial vegetation. An injury to the oral mucosa by invasive dental

procedures that causes bacteraemia has been termed as the antecedent to the classical form of IE. Of the listed invasive dental procedures, tooth extraction is the most studied cause of bacteraemia in about 88% to 96.2% of patients undergoing the procedure. However, in most clinical cases, the bacteraemia is transient, because the body's innate immunity clears the bacteria from the bloodstream within a few minutes, although in some patients it may last a few hours. Daily life activities such as eating, chewing gum, brushing teeth or using toothpicks can also induce low-level bacteraemia detectable by means of blood cultures in variable populations.

#### Antibiotic Prophylaxis

With the introduction of antibiotics into the general medical practice around the mid-1900s, many expert societies, the American Heart Association (AHA), European Society of Cardiology (ESC), National Institute for Health and Care Excellence (NICE), and French Consortium recommended antibiotic prophylaxis (AP) for certain cardiac conditions and dental procedures. The clinical aim was to neutralize the deleterious effect of transient bacteraemia. However, controversy about the usefulness of AP for the prevention of IE began to emerge in the 1990s. Inspiring the controversy was an editorial by Sackett et al. in 1996, which emphasised evidence-based medicine but was undermined by the lack of randomized large-scale clinical trials investigating the efficacy of AP for IE.

## METHODS

**Search strategy:** The following databases were searched from inception to until 4 August 2020 to identify studies investigating AP for the prevention of IE in patients undergoing invasive dental procedures: PubMed, Science Direct, British Dental Journal and Cochrane Register of Controlled Trials. Search terms used included various combinations of the following subject headings and title or abstract keywords – prophylactic antibiotics, antibiotic prophylaxis, antimicrobial, dentist, extraction, implant, infective endocarditis, or bacterial endocarditis. Reference lists of all the

included studies were also searched to identify additional articles. Studies were excluded if they were published prior to 1955, the year when the first recommendation for AP for the prevention of IE was made. Also excluded were studies of AP enrolling patients undergoing cardiac surgery or implantation of cardiac devices and comparative antibiotic trials without a placebo or control arm. Other studies excluded were animal studies, case reports and editorials. The outcome of interest was the incidence of IE or bacteraemia, defined as at least one positive culture of the blood drawn during, immediately after, and during follow-up, which can be minutes or hours post-surgery, depending on the study.

**Participant or population:** The methodological quality of each study was assessed using the Cochrane Handbook for Systematic Reviews of Interventions against four criteria – patient blinding, assessor blinding, allocation concealment and participant compliance with follow-up recommendations.

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**Comparator:** Two reviewers independently adjudicated the eligibility of studies, assessed the methodological quality and performed data extraction, and resolved any disagreement through consensus.

**Study designs to be included:** Data extracted included patient baseline characteristics on cases and controls, study period, dental procedures, AP used, and the effect on IE. The primary outcome of interest was the incidence of IE or bacteraemia for the control group and the treatment group.

**Eligibility criteria:** Data extracted included patient baseline characteristics on cases

and controls, study period, dental procedures, AP used, and the effect on IE. The primary outcome of interest was the incidence of IE or bacteraemia for the control group and the treatment group.

**Information sources:** PubMed, Science Direct, British Dental Journal and Cochrane Register of Controlled Trials. Search terms used included various combinations of the following subject headings and title or abstract keywords – prophylactic antibiotics, antibiotic prophylaxis, antimicrobial, dentist, extraction, implant, infective endocarditis, or bacterial endocarditis.

**Main outcome(s):** Clinical Implications  
With concerns on the validity of bacteraemia as a surrogate marker for IE, and the lack of high-quality evidence due to significant barriers to RCT, uncertainty in findings will likely persist. However, since dentists prescribe 1 in 10 antibiotic medications and are considered the top speciality prescriber of antibiotics, when faced with high-risk individuals, AP remains low-risk and inexpensive intervention for dentists that has demonstrable clinical benefits of reducing bacteraemia. Thus, the AHA, ESC, and French Consortium guidelines on the use of AP pre-dental procedures for at high-risk patients is a pragmatic and justified approach.

**Quality assessment / Risk of bias analysis:** Not Applicable.

**Strategy of data synthesis:** 2.3 Data Analysis - Frequency and percentage analysis were used to describe categorical data. Fixed effect model was used to analyse dichotomous data and generate forest plots using risk ratio (RR) as the summary measure. Heterogeneity was assessed using I<sup>2</sup> values, with 25%, 50% and 75% representing mild, moderate and substantial heterogeneity, respectively. Forest plots were compiled using RevMan version 5.3 (Cochrane UK). Table 2 provides the summary of characteristics of the included studies

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**Subgroup analysis:** Prevalence of Bacteraemia - The primary interest of the present meta-analysis was the efficacy of AP for IE in high-risk patients undergoing invasive dental procedures, However, the included studies evaluated the incidence of bacteraemia in which IE is its most prevalent and life-threatening sequelae. The incidence of bacteraemia was defined as at least one positive culture of blood drawn from the patient during the dental procedure and between 5 minutes to 6 hours post-procedure. However, most of the studies assessed bacteraemia during and immediately after dental surgery because of its transient nature (reduces with time as the innate immunity clears the bacteria from the blood) 1,4. Of the 2,410 patients included in the 17 studies, bacteraemia was detected in blood cultures in 664 patients (27.6%) consisting of 302 and 362 patients who received and did not receive prophylactic antibiotics, respectively.

**Sensitivity analysis:** Risk of Bacteraemia - Data were pooled using REVMAN 5.3 software. The overall results indicate that incidence of bacteraemia was significantly lower in antibiotic prophylactic (302 cases in 1,366 patients; 22.1%) versus no antibiotic prophylaxis (362 cases in 1,044 patients; 34.7%), risk ratio (RR: 0.51; 95% CI; 0.45 to 0.58). The RR describes the multiplication of risk of bacteraemia which occurs due to the use of AP before an invasive dental manipulation surgery. The risk ratio of 0.51 imply prophylactic antibiotic reduce the risk of bacteraemia in patients undergoing dental manipulation surgery by 49% ( $(100 \times (1 - RR)) \%$ ) based on the findings of the 2,588 included in the 19 studies under normal conditions. The risk reduction is statistically significant since the p-value ( $p=0.00001$ ) for the overall effect is lower than 0.05, which is the present study's threshold for statistical significance.

**Country(ies) involved:** India.

**Keywords:** Antibiotic prophylaxis [AP], bacterial endocarditis, Infective

endocarditis [IE], Invasive Dental Procedure.

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