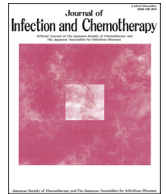




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## Review Article

## Is antibiotic prophylaxis to prevent infective endocarditis worthwhile?

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## ABSTRACT

Infective endocarditis (IE) is a rare condition which is associated with considerable morbidity and mortality. Almost 100 years ago, the links between endocarditis and procedures, particularly dental procedures, were postulated. Over 50 years ago the first guidelines recommending antibiotic prophylaxis (AP), with the aim of preventing IE developing after procedures, were proposed. However, there has only ever been circumstantial evidence in humans that AP prevents IE. The rarity of IE has made a randomised controlled clinical trial impractical to date. This article outlines the history of AP and reviews the evidence base for the use of AP to prevent IE.

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## 1. Infective endocarditis

Infective endocarditis is a rare infection, affecting around 5–10 people per 100,000 per annum [1–3]. It has a high morbidity, typically requiring prolonged courses of antibiotics and often valve replacement surgery. Mortality is also high, not only in hospital, but also in the first year after discharge. 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 Japan, a recent survey of 513 cases has described the epidemiology of the disease between 2007 and 2009 [4]. The most common age of presentation was 61–80 years. 62% were men. 11% died. 69% of cases had known underlying heart disease; 36% of cases were related to native valve disease. Periodontitis/tooth decay was noted in 25%, and dental treatment was identified as a predisposing factor in 16% of cases, although the timing of intervention was not given. Approximately 1/3rd had AP, but it was unclear in another 1/3rd whether AP was used or not. Oral viridans group Streptococci (OVGS) were identified as the causative

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organism in 26% of cases. This is a relatively high percentage compared with other contemporary studies [5,6], and is a more “classical” picture of IE [7].

This article will set out the history behind the development of AP as a potential preventative measure, and the evidence behind it. It will become clear that the evidence is not robust, and that practice reflects a consensus opinion, rather than strong evidence.

## 2. The origins of antibiotic prophylaxis

In 1923 Lewis and Grant first suggested that infective endocarditis (IE) might be caused by bacteria released into the circulation during a dental procedure [8]. In 1935, Okell and Elliot confirmed that this was the case, isolating *Streptococcus viridans* in blood cultures in 84/138 (61%) of individuals [9]. Shortly after this, in 1941, the first recorded use of antibiotic prophylaxis (AP) took place [10]. In 1955 the American Heart Association (AHA) issued the first guidelines, stating that “It is good medical and dental practice to protect patients with rheumatic or congenital heart disease by prophylactic measures” [11].

But, whereas many guidelines in other aspects of cardiology are clearly “evidence based”, guidelines for AP to prevent IE have largely been based on consensus. In 1962, Hook and Kaye stated “There is no proof that prophylaxis with antibiotics is effective ... However, the use of prophylactic antibiotics appears to be a reasonable approach to the problem and the consensus of opinion strongly supports the use of antibiotics in this situation” [12].

Since the original AHA guidelines, there have been many revisions and, furthermore, guidelines have been developed around the world to suit local populations. There is now considerable variation between countries as to what is recommended.

In Japan, patients considered to be at high risk, such as those with previous IE or a prosthetic valve, as well as patients at moderate risk, such as acquired valve disease or hypertrophic cardiomyopathy, are currently recommended to have AP [13]. In Europe and America, patients considered to be at high risk only are recommended to have AP prior to dental procedures [14,15]. At the opposite extreme to Japan, UK guidelines recommend against AP [16]. This situation reflects the uncertainty as to whether AP is effective or not.

## 3. The evidence for antibiotic prophylaxis

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.

A number of different types of experiment have been performed to try to ascertain the efficacy of AP:

1. Animal studies.
2. The impact of antibiotics prior to dental, or other, procedures on bacteraemias in humans.
3. Case control and cohort studies.
4. Studies using administrative databases before and after changes to guidelines.
5. Studies using administrative databases to determine the impact of prophylaxis prior to procedures in at-risk individuals.

### 3.1. Animal studies

David Durack and colleagues published the first animal model studies demonstrating that infective endocarditis might be prevented with prophylactic antibiotics in the early 1970s. In 1973, Durack and Petersdorf described an animal model of endocarditis.

In this model, a polyethylene catheter was passed into the right side of the heart via the jugular vein, or the left side via the carotid artery and secured in place. After 1–3 days  $10^8$  colony-forming units of *Streptococcus viridans* was given intravenously. It was reported that this procedure produced endocarditis in every animal. To determine the efficacy of antibiotic prophylaxis, antibiotics were given orally, intramuscularly or intravenously, depending on the antibiotic. Procaine penicillin was successful in preventing Streptococcal endocarditis [17]. Other groups soon replicated the results. However, there has never been, to our knowledge, a systematic review of these studies.

The animal studies are often dismissed as being unrealistic models, both because of the presence of the indwelling catheter and the very large number of bacteria used to produce the bacteraemia. However, as medical knowledge progresses in a Bayesian fashion, the fact that these studies have been positive means that studies purporting to show an effect in humans are more likely to be true than would be the case if AP had not been shown to work in animal models; therefore, these results should not be overlooked.

### 3.2. The impact of antibiotic prophylaxis prior to dental or other procedures on bacteraemias in humans

The impact of antibiotic prophylaxis prior to dental or other procedures on the development of bacteraemias in humans has been extensively studied. However, the effects of antibiotics are controversial, with some studies reporting a positive effect, and others not. More recent studies, carefully performed, have demonstrated that amoxicillin can reduce the frequency of bacteraemias, but that it is not 100% effective [18,19]. Importantly, a number of more recent studies have suggested that clindamycin may not be particularly effective [19,20].

What has also become clear is that everyday activities, such as tooth-brushing, dental flossing and chewing [18,21–23], can also release bacteria into the bloodstream, although the frequency of bacteraemia is less than after a dental extraction and the duration less, suggesting that the magnitude of bacteraemia is also less. The frequency and magnitude of bacteraemia caused by daily activities is also likely to be influenced by the state of oral hygiene and presence of periodontal disease. Indeed, individuals with markers of poor oral hygiene are 4–8 times more likely to develop a bacteraemia with organisms that can cause IE following tooth brushing than those with better standards of oral hygiene [24].

It has therefore been cogently argued that as dental interventions are relatively rare, whereas tooth brushing is common, it is illogical to give antibiotic prophylaxis, as there is no sense in preventing bacteraemia once or perhaps twice a year, when it is happening on a daily basis in between times. It is hard to argue with this stance, however, there are no studies which have reliably quantified the magnitude of bacteraemias after extractions in comparison with tooth-brushing or other similar activities, and it is unknown as to whether or not there is a threshold below which the number of bacteria present are unable to cause endocarditis. Furthermore, the argument does not exclude the possibility that AP may prevent some cases of IE.

### 3.3. Case control and cohort studies

Case control and cohort studies have been undertaken in an effort to understand whether dental procedures can cause IE and also whether AP might be effective.

Horstkotte in 1986 compared 229 patients with prosthetic heart valves in whom 287 procedures were performed and who had AP, with 304 patients with prosthetic heart valves in whom 390 similar interventions were performed and who did not have AP [25]. In the

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