Prophylaxis of infective endocarditis: current tendencies, continuing controversies

Xavier Duval, Catherine Leport

Infective endocarditis is a severe disease with high mortality, and results most often from the combination of bacteraemia (sometimes provoked) and a predisposing cardiac condition. Prophylaxis for infective endocarditis has been recommended by different countries on the basis of the supposed pathophysiology of the disease, although no randomised clinical trial has confirmed its efficacy. We review the data presented over the past few decades, challenge the principles underlying prophylaxis recommendations, and analyse the arguments that explain the general tendency in very recent years to decrease prophylaxis indications. Such arguments include the probable important role of everyday-life bacteraemia in the occurrence of infective endocarditis, the estimated huge number of prophylaxis doses to be given to avoid a single case of infective endocarditis, and the lack of scientific evidence to identify those procedures that should lead to prophylaxis. Recommendations for prophylaxis are now essentially focused on patients with high-risk predisposing cardiac conditions before dental procedures.

Introduction

Infective endocarditis is a rare but severe disease, with 100% mortality in the pre-antibiotic era. Its incidence seems to have been stable over the past few decades and has a range of 25–50 cases per million inhabitants per year. The epidemiology of infective endocarditis is complex to assess because diagnosis is difficult and referral bias has a large impact on the clinical characteristics of the population studied in different clinical settings. However, the profile of patients presenting with infective endocarditis seems to have changed during the past few decades, with an increased proportion of elderly patients, a decrease in patients with rheumatic heart disease, and a decrease in infective endocarditis caused by oral streptococci, although this latter point is the subject of controversy. Valve surgery for infective endocarditis is done in about one patient in two, with a perioperative mortality that remains high. Overall, in-hospital mortality is around 20%. Since 1954, prophylaxis of infective endocarditis has been recommended by different countries based on the supposed pathophysiology of the disease. Over time, various arguments have arisen to support a trend towards a reduction in prophylaxis and how this should be achieved in practice. The aim of our Review is to summarise recent data that support such a reduction, and to outline the current general principles of infective endocarditis prophylaxis. This Review will concentrate mainly on infective endocarditis prophylaxis for dental procedures, the most widely studied situation in which antibiotic prophylaxis is used.

Data supporting the current prophylaxis recommendations

The link between dental hygiene and infective endocarditis was made in 1909 by Horder,* who observed that, “infection is grafted upon a previously sclerosed endocardium...the source of infecting agent, in most of the cases, is the mouth”. In 1935, Okell and Elliott† reported the occurrence of bacteraemia after tooth extraction in 84 (61%) of 138 patients. Infective endocarditis is a condition that lends itself well to strategies that aim to prevent the development of bacteria on the endocardium of patients with a previously identified predisposing cardiac condition (PCC; panel). A preventive strategy targeting such patients is based not only on the screening and treatment of potential points of entry, but also on antibiotic prophylaxis given before invasive procedures that could potentially induce bacteraemia. Although its efficacy has not been shown in human beings, antibiotic prophylaxis of infective endocarditis has been recommended since 1954 for patients with PCC.† The recommendations for prophylaxis are based in part on the results of animal studies that showed the effectiveness of antibiotics in preventing the development of infective endocarditis after experimental inoculation of bacteria,* and in part on

<table>
<thead>
<tr>
<th>Panel: PCCs according to the risk of developing infective endocarditis (consensual classification)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>High risk</strong></td>
</tr>
<tr>
<td>Previous infective endocarditis</td>
</tr>
<tr>
<td>Mechanical or biological prosthetic valves</td>
</tr>
<tr>
<td>Surgically constructed systemic or pulmonary shunt or conduit</td>
</tr>
<tr>
<td>Complex cyanotic congenital heart disease (single ventricle states, transposition of the great arteries, tetralogy of Fallot)</td>
</tr>
<tr>
<td>Cardiac transplantation recipients who develop cardiac valvulopathy*</td>
</tr>
<tr>
<td><strong>Moderate risk</strong></td>
</tr>
<tr>
<td>Most other congenital cardiac malformations (except isolated secundum atrial septal defect)</td>
</tr>
<tr>
<td>Acquired valvular dysfunction†</td>
</tr>
<tr>
<td>Hypertrophic cardiomyopathy</td>
</tr>
<tr>
<td>Mitral-valve prolapse with valvar regurgitation and/or thickened leaflets</td>
</tr>
</tbody>
</table>

*In the 2007 American Heart Association recommendations. †With echocardiographic documentation of substantial leaflet pathology and regurgitation.
common practice. However, a Cochrane review concluded that there was little evidence to support the published guidelines. A randomised controlled trial should be implemented to assess the effectiveness of prophylaxis for infective endocarditis; however, the number of patients necessary to enrol (more than 6000 patients per group), has thus far discouraged any attempt. Furthermore, use of a testing strategy that runs counter to current guidelines would raise ethical and legal issues.

In the context of habitual application of weakly supported guidelines, several issues have been raised over the past decade that challenge the principles underlying prophylaxis recommendations and that explain the general tendency observed in very recent years to reduce prophylaxis indications. Transient repeated bacteraemia from everyday life activities (eg, tooth brushing, chewing, etc) might pose a greater risk for infective endocarditis than intermittent bacteraemia after occasional procedures. A theoretical study of cumulative bacteraemia over 1 year postulated that everyday bacteraemia is 6 million times greater than bacteraemia that caused the condition was induced by the dental procedure and the development of infective endocarditis, or was the result of a daily activity. Therefore, under the hypothesis of cumulative bacteraemia, the number of cases of infective endocarditis preventable through antibiotic prophylaxis given for occasional invasive procedure is probably very low.

The prevalence of PCCs for which prophylaxis is generally recommended is much higher than previously believed. Previously unknown PCCs detected with systematic echocardiography have been estimated to exist in 2·5% (95% CI 2·2–2·7) of the US general population. This prevalence reaches 13·3% (95% CI 11·7–15·0) in individuals aged over 75 years. Prevalence of previously known PCCs has been estimated to be 1·8% in the US general population and 3·3% in the 25–84-year-old French population. An estimate of at-risk dental procedures is 2·1 per patient per year in patients with PCC. Given that the proportion of patients who are treated in accordance with the prophylaxis recommendations is low (~40%), a very large number of dental procedures are probably done each year on at-risk patients without any prophylaxis (so-called unprotected procedures).

The risk of developing infective endocarditis in patients with PCC after an unprotected at-risk dental procedure seems to be extremely low. A French study estimated that one in 10700 adults with prosthetic valves and one in 54 300 adults with native-valve PCC developed infective endocarditis as a result of such a procedure. The risks reported in the USA are even lower (one in 114 000 adults with prosthetic valves, and one in 142 000 adults with rheumatic heart disease). Thus, a huge number of prophylaxis doses would be necessary to prevent a very small number of infective endocarditis cases.

This very low risk probably explains why case-control studies did not identify a clear relation between the onset of infective endocarditis and preceding at-risk dental procedures. Van der Meer and colleagues 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. They concluded that dental or other procedures probably caused only a small number of infective endocarditis cases and that prophylaxis would prevent only a small number of cases, even if it were 100% effective. The same investigators also did a 2-year case-control study. Because five of eight infective endocarditis cases occurred despite prophylaxis, they concluded that prophylaxis was not effective.

Strom and colleagues assessed dental prophylaxis and cardiac risk factors in a case-control study. Controls without infective endocarditis were more likely to have undergone a dental procedure than were patients with infective endocarditis (adjusted odds ratio [OR] 0·2 [95% CI 0·04–0·7] over 3 months; p=0·03). They concluded that dental procedures were not a risk factor, even in patients with PCCs, and that only a few cases of infective endocarditis could be prevented with prophylaxis, even if it were 100% effective.

In another case-control study, Lacassin and co-workers found that the mean number of procedures was significantly higher in cases than in controls (2·0 vs 1·5, p=0·05). In their multivariate analysis, the only procedure associated with a risk for infective endocarditis caused by Streptococcus viridans was tooth scaling (OR 5·25; p=0·025).
In a study by Imperiale and Horwitz,\textsuperscript{25} cases were eight patients with high-risk lesions whose first episode of native-valve infective endocarditis occurred within 12 weeks of a dental procedure. For each case, three controls were chosen from patients who underwent echocardiographic assessment, and who were matched for the specific high-risk lesion and age. Antibiotic prophylaxis was used in only one (13%) of the eight cases compared with 15 (63%) of 24 controls (OR 0.09; p=0.025).\textsuperscript{25}

The estimation of the benefit of prophylaxis must be weighed against the adverse effects of prophylaxis and the prognosis of the disease. 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.\textsuperscript{26–29} Furthermore, the widespread use of antibiotic therapy promotes the emergence of resistant microorganisms most likely to cause infective endocarditis, such as \textit{S viridans} 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 \textit{Staphylococcus aureus}.\textsuperscript{1} From this mortality and the risk of developing infective endocarditis (one in 54,300 unprotected oral procedures) for patients with native-valve PCC, the risk of death after an unprotected procedure in such patients can be estimated at one in 54,300 patients. Thus, it might be that prophylaxis with β-lactams could induce more deaths than the infection itself would in patients with native-valve PCC.

Several studies have estimated the cost-effectiveness of antibiotic prophylaxis and have found conflicting results.\textsuperscript{5,10–12} Agha and colleagues\textsuperscript{10} estimated that clarithromycin prophylaxis was cost effective in patients with moderate or high risk for infective endocarditis, whereas amoxicillin and ampicillin prophylaxis resulted in a loss of lives because of the occurrence of severe adverse drug reactions.

As the effectiveness of preventive antibiotic treatment remains to be proven, recommendations originating from different countries diverge according to the patient population to whom preventive antibiotic should be administered.\textsuperscript{5,10–12} Additionally, differences in the medicolegal context between different countries also influence recommendations and the way in which they are followed. 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.\textsuperscript{9} Recommendations for prophylaxis require the identification of the highest risk situations: those cardiac conditions at high risk for infective endocarditis, and those procedures most likely to induce bacteraemia and infective endocarditis.

**Identification of cardiac conditions at risk for occurrence or mortality from endocarditis**

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.\textsuperscript{18} This risk can also be estimated by monitoring cohorts of cardiac patients and calculating the incidence of infective endocarditis cases, thus determining the lifetime risk of acquisition of infective endocarditis associated with a specific PCC.\textsuperscript{5–42} Choice of the threshold above which risk for infective endocarditis can be considered too high is subjective. Therefore, any attempt at classification has only informational value. According to this risk gradation, patients with a history of infective endocarditis, a mechanical or a biological prosthetic valve, or a surgically constructed systemic or pulmonary shunt or conduit, are the patients with the highest incidence of infective endocarditis and are therefore considered at highest risk of developing infective endocarditis during their lifetime. This risk gradation is consensual.\textsuperscript{5,11–15}

The prognosis of infective endocarditis occurring in a given case of PCC must also be taken into account in the choice of PCC to be covered. Patients with infective endocarditis on prosthetic valves and those with a previous history of infective endocarditis are generally at higher risk of death than others. Other characteristics of patients’ general health background have also been associated with in-hospital death during infective endocarditis: older age, diabetes mellitus (mainly insulin-dependent diabetes mellitus), immunodeficiency, dialysis, and hepatic insufficiency.\textsuperscript{15–16} In most

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Proportion of positive blood cultures</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mastication</td>
<td>17–51%</td>
<td>47–51</td>
</tr>
<tr>
<td>Toothbrushing or irrigation</td>
<td>0–50%</td>
<td>47–51</td>
</tr>
<tr>
<td>Flossing</td>
<td>20–60%</td>
<td>47–51</td>
</tr>
<tr>
<td>Dental examination</td>
<td>17%</td>
<td>47–51</td>
</tr>
<tr>
<td>Dental polishing</td>
<td>24%</td>
<td>47S1–S3</td>
</tr>
<tr>
<td>Intraligamentary local anaesthetic injection</td>
<td>97%</td>
<td>47S1–S3</td>
</tr>
<tr>
<td>Matrix band placement</td>
<td>32%</td>
<td>47S1–S3</td>
</tr>
<tr>
<td>Rubber dam placement</td>
<td>30%</td>
<td>47S1–S3</td>
</tr>
<tr>
<td>Slow drill</td>
<td>12%</td>
<td>47S1–S3</td>
</tr>
<tr>
<td>Fast drill</td>
<td>4%</td>
<td>47S1–S3</td>
</tr>
<tr>
<td>Single dental extraction</td>
<td>18–54%</td>
<td>54–61</td>
</tr>
<tr>
<td>Multiple dental extraction</td>
<td>10–85%</td>
<td>54–61</td>
</tr>
<tr>
<td>Scaling</td>
<td>17–70%</td>
<td>60</td>
</tr>
<tr>
<td>Periodontal surgery</td>
<td>32–88%</td>
<td>60</td>
</tr>
<tr>
<td>Endodontic instrumentation</td>
<td>20–42%</td>
<td>60S62</td>
</tr>
<tr>
<td>Post-operative suture removal</td>
<td>5%</td>
<td>63</td>
</tr>
<tr>
<td>Endodontic treatment</td>
<td>42%</td>
<td>62,63</td>
</tr>
</tbody>
</table>

Table 1: Proportion of positive blood samples reported after various oral procedures
recommendations, these considerations have led to the identification of patients at moderate and high risk of infective endocarditis (panel). According to these classifications, infective endocarditis prophylaxis involves both groups or is limited to the patients at highest risk. To date, only the 2002 French recommendations take into consideration the patient’s health background in modulating the indication of prophylaxis.13

**Identification of at-risk procedures**

The identification of at-risk procedures for infective endocarditis include the consideration of different characteristics: (1) the number of identified infective-endocarditis-inducing pathogens (inoculum) colonising the area that could enter the bloodstream in case of an invasive procedure; (2) the amount of the bleeding induced by the procedure; (3) the proportion of bacteria-positive blood cultures after a given procedure (table 1); (4) the magnitude of bacteraemia after the procedure; (5) the duration of the bacteraemia; and (6) the number of reported cases of infective endocarditis after a given procedure. However, there is wide variation in reported frequencies of these characteristics after procedures. For example, bacteraemia is noted in 10–95% of patients after tooth extraction, which probably indicates the heterogeneity of these procedures, of the host, and of the experimental methods used (table 1).34–39 Because of the disparity of these data, it is difficult to clearly establish criteria for defining risk factors. A better knowledge of the factors that predispose a patient to infective endocarditis is necessary. Given the existence of everyday-life cumulative bacteraemia, and despite the high prevalence of PCC in the general population, the incidence of infective endocarditis is astonishingly low. Genetic host susceptibility that promotes attachment of microorganisms to the valvular endothelium probably exists; its identification could allow better focusing of prophylactic measures on the patients at highest risk.

Meanwhile, the proportion of patients with bacteraemia 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, bacteraemia does not respond to the prerequisite of a pertinent (appropriate) surrogate measure. There is no evidence-based method to decide which procedure should require prophylaxis because no data show that either the incidence, the magnitude, or the duration of bacteraemia after a procedure increase the risk of infective endocarditis. Thus, any attempt to identify the procedures that need prophylaxis is artificial. However, this identification method has resulted in a detailed and complex list of procedures for which prophylaxis is and is not recommended.

**Recent guidelines that suggest reduction in use of prophylaxis**

Table 2 and table 3 summarise and compare the current and previous recommendations for the prophylaxis of infective endocarditis. French guidelines that challenge the accepted practice were published in 2002,33,79 and...
proposed that prophylaxis should be restricted to “cases that have the highest ratio of individual benefit to individual and collective risk” (figure 2). Prophylaxis is suggested for many invasive dental, respiratory, gastrointestinal, and genitourinary procedures in the high-risk PCC group, but is optional in the moderate risk group (panel). The decision to use prophylaxis became based on the subsequent risks “from” infective endocarditis, by taking patients’ background characteristics into consideration, rather than on the direct risk “of” infective endocarditis from the procedure itself. Importantly, post-hoc prophylaxis may be administered in the event of unanticipated procedural complexity. Furthermore, limiting the number of patients with PCCs who are candidates for prophylaxis could improve overall adherence to prophylaxis among the most critical patients.

In the 2006 British Society for Antimicrobial Chemotherapy (BSAC) guidelines, prophylaxis is suggested for “all dental procedures involving dento-gingival manipulation or endodontics” only for those patients with previous infective endocarditis, a cardiac valve replacement, or a prosthetic systemic or pulmonary shunt or conduit. Prophylaxis is extended to all at-risk cardiac patients for extra-oral procedures. The guidelines include a detailed list of gastrointestinal, genitourinary, gynaecological, and respiratory procedures for which prophylaxis is recommended, on the basis of anecdotal associations and the risk of bacteraemia. This recommendation and those previously proposed (and diametrically opposed) by the UK and the European cardiology societies have led to vigorous exchanges between infectious diseases specialists, cardiologists, and dentists.

The most recent guidelines were established by the American Heart Association (AHA) in 2007: these new recommendations represent a radical change from the previous ones: antibiotic prophylaxis is no longer recommended before a dental procedure, except for patients with the highest risk of adverse outcome resulting from infective endocarditis (panel), and who are due to undergo “any dental procedure that involves manipulation of the oral mucosa”. Prophylaxis is thus abandoned in patients at moderate cardiac risk of infective endocarditis, such as those with a history of aortic regurgitation or mitral regurgitation who undergo a dental procedure (as in the BSAC recommendations), but also in all cardiac at-risk patients before extra-oral procedures (eg, colonoscopy), irrespective of their PCCs.

**General preventive measures**

Because of the limits of the data that support the current guidelines and the uncertainties of the effectiveness of antibiotic prophylaxis, early recognition and treatment of the source of infective endocarditis is essential. All at-risk patients should be educated to seek medical advice in case of fever or other symptoms, and for their physician to understand the importance of assessing blood cultures before any antibiotic administration. The patient should then remain under medical supervision until a diagnosis of infective endocarditis is excluded. Furthermore, patients and physicians should be informed that all localised infections, whatever the site, particularly those caused by *Staphylococcus* and *Streptococcus* spp, represent a potential portal of entry for infective endocarditis in at-risk cardiac patients and should be treated accordingly. Health practitioners should be instructed to limit catheters in both frequency and duration in at-risk cardiac patients. To improve the identification of at-risk patients and to increase the proportion of those following the
prophylactic recommendations, the use of infective endocarditis preventive cards have been proposed in several countries. Because of the frequency of everyday bacteraemia and its postulated primary role in infective endocarditis, the main preventive strategy is to limit spontaneous bacteraemia (through chewing, brushing) by reducing the global oral burden of bacteremia via improved oral hygiene. This strategy requires regular systematic dental check-ups of at least twice a year in high-risk patients.

The benefits and risks of silver-coated prosthetic valves, which were developed to decrease the rate of infection, were assessed in a clinical trial (AVERT study) because of the high risk of infective endocarditis in patients with prosthetic valves. This trial was prematurely suspended because of the occurrence of major paravalvular leakage in patients receiving silver-coated valves.

**Antibiotic choice and route of administration**

Antibiotics should act on the primary bacteremia responsible for infective endocarditis: oral streptococci for dental procedures, and enterococci and group D streptococci for digestive or urinary-tract procedures. The main antibiotics to have proved effective in experimental models are amoxicillin, vancomycin, teicoplanin, clindamycin, synergistins, azithromycin, and clarithromycin. When antibiotic prophylaxis is recommended before dental and upper respiratory procedures, amoxicillin is used in most countries, at doses varying from 2 g to 3 g (table 2 and table 4). For patients allergic to β-lactams, clindamycin or a glycopeptide are substituted; azithromycin or clarithromycin are recommended in some guidelines. For dental procedures, antibiotic prophylaxis is generally administered as a single dose in the hour before the procedure. Streptococci or enterococci originating from the digestive and urinary tract are less susceptible to antibiotics, and therefore the use of an ampicillin–gentamicin or glycopeptide–aminoglycoside synergistic combination is preferable.

The possible association between gastrointestinal and genitourinary procedures and infective endocarditis has not been studied as extensively as has the possible association with dental procedures. The determination of those requiring antibiotic prophylaxis is currently based on the risk of a procedure causing a bacteraemia and whether such a procedure has been anecdotally linked to cases of infective endocarditis. Current guidelines determine the procedure for which prophylaxis is or is not recommended based on assessment of the risks. For general intravenous prophylaxis just before the procedure or at induction of anaesthesia, 1–2 g amoxicillin or ampicillin plus 1·5 mg/kg gentamicin is recommended, with an additional 1 g amoxicillin or ampicillin given orally 6 h later in some guidelines (ie, France). Patients who are allergic to penicillin are recommended to receive 400 mg teicoplanin or 1 g vancomycin (at more than 60 min), plus 1·5 mg/kg gentamicin. However, prophylaxis is no longer recommended before extra-dental procedures in the 2007 AHA guidelines.

In patients who are due to undergo cardiac surgery, a careful preoperative dental assessment is recommended and dental treatment given before surgery whenever possible. Preoperative antibiotic prophylaxis is recommended and should be effective against microorganisms responsible for early post-operative infective endocarditis (ie, *S aureus* and coagulase-negative staphylococci). The choice of antibiotic should be determined based on the susceptibility of these microorganisms to antimicrobials in the institution where surgery is done.

**Conclusions**

To date, there is no evidence for the efficacy and the lack of adverse effects of prophylactic strategies for infective endocarditis. The current tendency is to limit prophylaxis to the procedures and populations with the highest risks. This process culminated with the 2007 AHA guidelines that limit infective endocarditis prophylaxis to the highest risk cardiac patients who are due to undergo dental procedures. Energy should be focused on the population with the highest risk to improve the adherence rate to prophylaxis recommendations. In all patients, oral and general hygiene should be reinforced, and regular preventive dental check-ups done. In case of fever, infective endocarditis should be excluded before prescribing antimicrobials. Patients should be educated about this point, and the reasons leading to the modification of the infective endocarditis prophylactic strategy explained. The strategy of targeting indications might be improved by a better analysis of factors associated with an increased risk of death from infective endocarditis or an increased risk of infective endocarditis from certain medico-surgical conditions, including staphylococcus bacteraemia. Epidemiological surveys must be done to monitor the potential consequences of guideline modifications on the profile of infective endocarditis epidemiology (ie, incidence and type of microorganisms).

**Conflicts of interest**

We declare that we have no conflicts of interest.
Review


83 Ramsdale DR, Palmer ND. Antimicrobial prophylaxis for endocarditis: emotion or science? Heart 2007; 93: 753.

