Antimicrobial prophylaxis for the prevention of infective endocarditis

National and international guidelines on antimicrobial prophylaxis to prevent infective endocarditis have provoked controversy and consternation among many doctors and patients. This article addresses the evidence that underlies these guidelines.

Most cases of infective endocarditis arise spontaneously or as a complication of infection or bacterial colonization elsewhere in the body; increasingly it is occurring in association with intravenous drug abuse or health care. The premise that endocarditis commonly results from bacteraemia caused by dental and invasive medical procedures, and that these cases can be prevented by prophylactic antibiotic therapy has, for more than 50 years, sustained the practice of antimicrobial therapy to cover a wide range of interventions in the mouth and the respiratory, gastrointestinal and urogenital tracts. As recently as 1993 a cost-effectiveness analysis was based on the assumption that 15% of all deaths from endocarditis resulted from tooth extractions, and that all could have been prevented by prophylactic penicillin (Gould and Buckingham, 1993).

This review addresses the evidence that underpins current guidelines on antimicrobial prophylaxis for the prevention of endocarditis in patients with predisposing cardiac conditions and focuses principally on the recommendations from the National Institute for Health and Clinical Excellence (NICE, 2008).

Guidelines

In recent years the evidence for antimicrobial prophylaxis for the prevention of endocarditis has been re-evaluated and recommendations for prophylactic therapy have been restricted to fewer interventions and focussed on patients considered to be at particularly high risk of developing endocarditis or of an adverse outcome in the event of their becoming infected. Thus a French guideline, published in 2002, recommended prophylaxis for all dental, respiratory, gastrointestinal and genitourinary procedures but only in patients with a heart valve replacement, a prosthetic systemic or pulmonary shunt, a history of infective endocarditis, or an associated condition that exposes them to high risk (Danchin et al, 2005).

This approach was substantially endorsed by a working group of the British Society for Antimicrobial Chemotherapy (Gould et al, 2006). The following year a guideline sponsored by the American Heart Association expanded the high risk category of predisposing cardiac conditions but restricted the recommendation for prophylaxis to specified interventions involving the teeth and respiratory tract; the 55-year-old mandate to cover interventions on the gastrointestinal and urogenital tracts was dropped (Wilson et al, 2007). More controversially, the 2008 NICE guideline proposed that the practice of prophylactic antimicrobial therapy should be abandoned except when suspected or definite infection exists at the site of intervention (NICE, 2008). The American Heart Association subsequently downgraded the recommendation for prophylaxis in high-risk patients from class I (mandatory) to class IIA (reasonable practice) (Nishimura et al, 2008).

Finally a new guideline from the European Society of Cardiology (Habib et al, 2009) affirmed a class IIA recommendation for prophylactic therapy for a high-risk category of patients (similar, although not identical, to that in the American Heart Association guideline), but only for dental procedures requiring manipulation of the gingival or peri-apical region of the teeth or perforation of the oral mucosa.

The evidence

While there is substantial agreement over the interpretation of the evidence, there is less consensus over how it should be translated into clinical practice. The starkest contrast lies between the NICE recommendation for routine prophylaxis to be abandoned and the British Society for Antimicrobial Chemotherapy, European and American guidelines that propose its continued use in selected patients. A strength of the NICE guideline is that it details how the search for evidence was conducted and the criteria applied to a research paper for it to be judged sufficiently free from bias as to be suitable for consideration by the guideline development group. The studies that contributed to the final recommendations are summarized in the report (NICE, 2008).

The evidence falls into the following categories:

1. Spontaneous and procedure-related bacteraemia
2. Suppression of procedure-related bacteraemia by prophylactic antibiotic therapy
3. The causal link between procedures and endocarditis
4. Prevention of endocarditis by prophylactic antibiotic therapy

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5. Cardiac conditions associated with an increased risk of developing endocarditis
6. Cardiac conditions associated with a relatively poorer outcome from infective endocarditis
7. The potential for prophylactic therapy to harm the patient and society.

Spontaneous and procedure-associated bacteraemia

Roberts (1999), in an extensive review, reported the occurrence of bacteraemia in 10–100% of patients with dental disease at various time points after virtually all types of procedure, but also in 10–86% before tooth extraction and, albeit less frequently and for a shorter duration, after tooth-brushing, flossing, the use of toothpicks and irrigation devices, and chewing. The intensity of the bacteraemia, measured in colony-forming units/ml, is similar in all these different circumstances indicating that repetitive exposure to bacteraemia must constitute a risk thousands, if not millions, of times greater over the course of a year than from a single dental procedure.

Bacteraemia of endocarditis-causing organisms has also been documented after, and occasionally before, virtually all diagnostic and therapeutic procedures on the gastrointestinal, respiratory and urogenital tracts, although less often than after dental treatment (NICE, 2008).

The case for prophylaxis derives partly from animal experiments in which endocarditis was induced by damaging the aortic valve endothelium and inoculating bacteria into the circulation. The applicability of these experiments to human endocarditis is questionable because the magnitude of bacteraemia required to induce infection (1×10^6 to 1×10^8/ml) is many orders of magnitude higher than the level (up to 1×10^2/ml) occurring in patients after a dental extraction (Roberts, 1999). Moreover, since no data exist on the intensity or duration of bacteraemia required to cause endocarditis in man, the designation of certain procedures to be covered with prophylactic therapy and others not is scientifically unsound.

Suppression of procedure-related bacteraemia by prophylactic antibiotic therapy

The suppression of post-procedural bacteraemia is an area of endocarditis research that is well populated with randomized trials in which antibiotic prophylaxis has been compared with placebo or control.

For dental procedures most, although not all, studies have demonstrated a reduction in the frequency and duration of bacteraemia with antibiotic therapy (NICE, 2008). For example, a double-blind placebo controlled trial by Lockhart et al (2008) reported bacteraemia of endocarditis-causing organisms after tooth-brushing, tooth extraction with amoxicillin prophylaxis and extraction with placebo. In the extraction-placebo group 58% of patients had positive blood cultures within 5 minutes of the procedure compared with 33% in the extraction-prophylaxis group. In the tooth-brushing group 19% had positive cultures.

Non-dental procedures have been studied less intensively but also with variable results. A systematic review of transurethral prostatectomy in men with uninfected urine reported that the frequency of bacteraemia was reduced from 4% in control or placebo-treated patients to 1% in those who received antibiotics (Qiang et al, 2005), whereas a meta-analysis of studies of endoscopic retrograde cholangiopancreatography found a non-significant reduction of bacteraemia between prophylaxis and placebo-treated or control patients (Harris et al, 1999).

The causal link between dental and non-dental procedures and development of endocarditis

The presumption, superficially supported by case reports and series, that procedure-related bacteraemia causes endocarditis is central to the argument for prophylaxis. The only reliable evidence, however, comes from the epidemiological and their linked case-control studies conducted in the Netherlands, France and the USA.

The Netherlands study (van der Meer et al, 1992b) provided some support for a causal association of dental procedures with endocarditis: among 427 cases of native valve infection with α haemolytic streptococci, endocarditis was associated with a known predisposing cardiac condition, natural dentition and recent dental procedures; with all three of these risk factors the odds ratio for endocarditis was 4.9 (95% confidence interval 2.8–8.7). Subsequent studies, from France and the USA, however, failed to confirm this association.

The French study (Lacassin et al, 1995) reported an adjusted odds ratio of 1.6 (95% confidence interval 1.01–2.53) for the risk of endocarditis related to any medical or surgical procedure, but no link between preceding dental, urological or gastrointestinal interventions (odds ratio 1.2; 95% confidence interval 0.7–2.1) except for an association with tooth scaling. Surgery (abdominal, gynaecological or soft tissue) was associated with an odds ratio of 4.7 (95% confidence interval 1.02–22) and multiple procedures were linked to increased risk, but multivariate analysis left only infectious episodes and skin wounds as significant risk factors.

The US case-control studies (Strom et al, 1998, 2000) reported no association of endocarditis with preceding non-dental or dental procedures, even among those infected with dental flora (odds ratio 0.8; 95% confidence interval 0.4–1.5). A link, on multivariate analysis, with barium enema was discounted as in many cases it had been carried out as part of the investigation of symptoms that were subsequently ascribed to the endocarditis. Among patients infected with skin flora, however, a significant association with skin infections was identified

(odds ratio 5.0; 95% confidence interval 1.3–27) and, when the analysis was confined to those infected with oral micro-organisms, edentulous patients had a lower risk of infection compared with those having natural dentition.

Based on estimates of the prevalence of individuals in the French population with a predisposing cardiac condition, the annual number of dental treatments, the use of prophylaxis and the incidence of endocarditis 'possibly related' to dentistry (infection with oral flora within a month), Duval et al (2006) estimated that 1 in 46 000 cases of native valve and 1 in 10 700 cases of prosthetic valve endocarditis might be caused by dental exposure.

This inconsistent evidence indicates that an exceedingly small number of cases, if any, of endocarditis might be caused by dentistry or non-dental procedures. It is plausible, if not probable, that many cases of endocarditis attributed to an intervention acquired their infection not from the procedure but from the condition for which it was undertaken. In others the temporal proximity of a procedure to the development of endocarditis may be coincidental because – as is apparent from the case-control studies – a high proportion of the at-risk population is likely to undergo some sort of medical intervention once or twice a year.

Prevention of infective endocarditis by prophylactic antibiotic therapy

In the context of the inconsistent evidence that procedures are a significant cause of endocarditis, it is inevitable that evidence for the efficacy of antimicrobial prophylaxis is equally inconclusive.

The Netherlands study (van der Meer et al, 1992a) reported similar rates of prophylactic therapy among cases and controls and, in the epidemiological study (van der Meer et al, 1992b), eight out of 48 patients with native valve endocarditis and nine of 16 with prosthetic valve infections had received prophylaxis with an antibiotic to which the infecting organism was sensitive. Likewise, the US case-control study reported a similar risk of endocarditis among patients with heart valve disease who had undergone recent dental treatment irrespective of the use of prophylaxis (Strom et al, 1998).

Partial efficacy was, however, suggested by the two French studies. In Lacassin et al's (1995) investigation 23% of cases and 27% of controls had received prophylaxis for a preceding intervention, suggesting a protective efficacy of about 20%. Duval et al (2006) estimated that prophylaxis reduced the risk for patients undergoing dental procedures from 1:46 000 to 1:54 300 for patients with native valve disease and from 1:10 700 to 1:149 000 for those with prosthetic valves but these estimates have wide confidence intervals.

These studies indicate that prophylactic therapy is frequently ineffective or, alternatively, that in many cases the procedures for which it was prescribed were not the cause of the subsequent endocarditis. Combining these conclusions with the infrequency with which procedures cause endocarditis, it is clear that a very large number of prophylactic treatments would be needed to prevent a single case, if any.

The relative risk of predisposing cardiac conditions to development of infective endocarditis

Traditionally, predisposing cardiac conditions have been stratified into low, intermediate and high risk categories. With the exception of prosthetic heart valves, however, for which the risk is several times greater than for native valve disease (Duval et al, 2006), determination of the relative risk of different predisposing cardiac conditions is not based on firm scientific evidence (Horstkotte et al, 2004). This is because the risk associated with specific conditions cannot be deduced from the number of patients with endocarditis unless the prevalence of the lesions is known and, among the cohort studies, the number of individual lesions is small and the estimates have wide confidence intervals. Accordingly in the NICE (2008) guideline underlying conditions are separated only into two categories:

1. Those subject to little or no greater risk than the general population:
   - Fully repaired ventricular septal defect
   - Fully repaired patent ductus arteriosus
   - Closure devices that are judged to be endothelialized
   - Isolated atrial septal defect.
2. Those associated with increased risk of developing infective endocarditis:
   - Acquired valvular disease with stenosis or regurgitation
   - Valve replacement
   - Other structural congenital heart disease, including surgically corrected or palliated structural conditions
   - Previous infective endocarditis
   - Hypertrophic cardiomyopathy.

Predisposing cardiac conditions associated with relatively poorer outcomes from infective endocarditis

Assessment of the relative risk of death or serious complications from endocarditis is also hindered by the small number of individual predisposing cardiac conditions in published series and by other factors: co-morbidities including chronic kidney disease and diabetes that may affect the outcome. Patients with prosthetic heart valves are, however, at greater risk of dying than those with acquired or congenital heart disease: in a report from the International Collaboration on Endocarditis the odds ratio for death with prosthetic valve endocarditis was 1.47 (95% confidence interval 1.13–1.90) (Murdoch et al, 2009) but it must be emphasized that the risk of an adverse outcome is high among all patients with endocarditis, irrespective of the underlying pathology.

The epidemiology is highly relevant to recommendations to offer prophylaxis to prosthetic, but not native, valve disease patients. In an earlier report by the International Collaboration on Endocarditis (Wang et al, 2007) in-hospital mortality was 22.8% among 556 patients with prosthetic valve endocarditis and 16.4% in 2114 with native valve endocarditis. However, more than a third of the prosthetic valve endocarditis cases were health-care-related, occurred mainly in the first year after valve replacement, and were caused predominantly by staphylococci; the mortality among these patients was 30.5%. Among the non-health-care-related prosthetic valve infections mortality was 18.1%. The NICE guideline group considered that even the overall 22.8% *vs* 16.4% mortality difference could not logically justify a recommendation for prophylaxis for one group of patients but not the other since both are at high risk, and it becomes even more illogical when the highest-risk prosthetic valve endocarditis cases, for whom prophylaxis would not have been a consideration, are removed from the equation.

Potential for harm from prophylactic therapy

Single-dose antibiotic therapy is generally well tolerated, but penicillin-based regimens are associated with a small risk of fatal anaphylaxis. Previous uneventful exposure does not exclude the possibility of this catastrophe. The American Heart Association guideline concluded that 'the risk of antibiotic-associated adverse effects exceeds the benefit (if any) from prophylactic antibiotic therapy' (Nishimura et al, 2008).

Abundant evidence testifies to the progressive development of bacterial resistance to antibiotics. While prescriptions for endocarditis prophylaxis cannot be held to be solely responsible, endocarditis-causing organisms are among those becoming resistant to commonly used antimicrobial agents (Prabhu et al, 2004).

Other considerations: the avoidance and treatment of sepsis

The guidelines acknowledge the potential of infection to cause endocarditis and the most important approach to prevention in susceptible patients: meticulous attention to the maintenance of good oral health, the avoidance of infections wherever possible (for example, by discouraging body piercing) and prompt investigation and treatment of skin and other infections, together with patient education. The NICE guideline recommends that an antibiotic active against potential endocarditis-causing micro-organisms should be prescribed to cover interventions at an infected site.

NICE *vs* the US and European guidelines

Despite agreement on the evidence, a chasm exists between the UK guideline and the European Society of Cardiology and American Heart Association recommendations. This chasm reflects the tension between the doctor as scientist and as physician: NICE, on the basis of a rigorous appraisal of the evidence, concluded that prophylactic therapy lacks scientific validity and should be abandoned. The European and American experts acknowledged the frailty of the scientific basis for their recommendations but left open the possibility that some patients might benefit and argued that, pending new evidence, the practice should continue. Thus, the American Heart Association stated:

> **'Prophylaxis may prevent an exceedingly small number of cases of infective endocarditis (if any) in individuals who undergo a dental, GI [gastrointestinal] tract or GU [genitourinary] procedure.' (Nishimura et al, 2008)**

and the European Society of Cardiology acknowledged that:

> **'even strict adherence to generally accepted recommendations for prophylaxis might have little impact on the total number of patients with IE [infective endocarditis] in the community.' (Habib et al, 2009)**

Endocarditis is not a notifiable disease in the UK and Hospital Episode Statistics are notoriously unreliable; it is, accordingly, impossible to use existing data sources to monitor the effects of the NICE recommendations. Ironically the new guidance makes it ethically possible to resolve the uncertainty with a randomized placebo-controlled trial (Prendergast et al, 2008). Until such a trial is conducted, however, the widely accepted interpretation of the available evidence points inexorably to the abandonment of the practice of routine prophylaxis, even for patients with prosthetic valves. **BJHM**

Conflict of interest: Dr N Brooks was a member of the development group for the National Institute for Health and Clinical Excellence (2008) clinical guideline Prophylaxis against infective endocarditis.

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KEY POINTS

The evidence

- Cumulative exposure to bacteraemia in everyday life greatly exceeds that from a single dental or other interventional procedure.
- Procedures rarely, if ever, cause endocarditis.
- Antimicrobial prophylaxis partially suppresses procedure-related bacteraemia but is at best only partially effective in preventing endocarditis.
- Endocarditis is associated with a high risk of severe complications irrespective of the predisposing cardiac condition. No basis exists for managing those perceived to be at higher risk differently from the others.
- Penicillin-based prophylaxis might cause more deaths from anaphylaxis than lives saved from preventing endocarditis.
- Widespread use of antibiotics leads to bacterial resistance.

Recommendations

- Patients with structural heart conditions should be categorized as being either at risk or not at risk compared with the general population.
- Antimicrobial prophylaxis should not be prescribed to prevent endocarditis before dental, non-dental or obstetric procedures unless infection is present or suspected at the site of intervention, in which case the patient should receive an antibiotic that is active against endocarditis-causing organisms.
- Episodes of infection in patients at risk of endocarditis should be investigated and treated promptly.
- Patients at risk of endocarditis should be educated on the importance of good oral health, the risks associated with medical and non-medical procedures and symptoms that may indicate infective endocarditis and when to seek expert help.

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