Infective endocarditis prevention: Is it time to review NICE guidance?

Martin H Thornhill[1], Bernard D Prendergast[2], Mark J Dayer[3], Larry M Baddour[3]

Job Titles and Workplaces

[1]Professor of Translational Research in Dentistry, Unit of Oral & Maxillofacial Medicine, Surgery and Pathology, School of Clinical Dentistry, University of Sheffield, Sheffield, UK. [2]Professor of Interventional Cardiology and Valvular Heart Disease, Guy's and St Thomas' Hospital, London and Chair of Cardiology at Cleveland Clinic, London, UK. [3] Honorary Associate Professor, University of Plymouth, Faculty of Health and Cardiologist, Somerset NHS Foundation Trust, Somerset, UK. [4]Professor, Division of Public Health, Infectious Diseases, and Occupational Health, Departments of Medicine and Cardiovascular Medicine, Mayo Clinic College of Medicine, Rochester, Minnesota, USA.

Corresponding author

Professor Martin Thornhill,
Unit of Oral & Maxillofacial Medicine, Surgery and Pathology,
School of Clinical Dentistry,
University of Sheffield,
Sheffield, S10 2TA,
United Kingdom
Email: M.Thornhill@Sheffield.ac.uk
Tel: 0751 555 2925

Field Code Changed

Conflicts of Interests

MHT reports grant support from the National Institutes for Health (USA), Delta Dental of Michigan Research and Data Institute's Research Committee, and Renaissance Health Service Corporation (USA). BDP reports @@@. MJD reports payment for expert testimony from Bevan Brittan, honoraria for presentations and support for attending meetings from Biotronik. LMB reports consulting for Boston Scientific and Roivant Sciences and royalty payments from UpToDate, Inc.

Deleted: and Delta Dental of Michigan Research and Data Institute's Research Committee

Deleted: ,

Funding Statement

The authors received no specific funding for this work.

Keywords

Infective endocarditis
Antibiotic prophylaxis
Invasive dental procedures

Abbreviations

ADR = Adverse drug reaction
AHA = American Heart Association
AP = Antibiotic prophylaxis
BSAC = British Society for Antimicrobial Chemotherapy
ESC = European Society of Cardiology
IDPs = Invasive dental procedures
IE = Infective endocarditis
NICE = National Institute for Health and Clinical Excellence
OR = Odds ratio
OVGS = Oral viridans group streptococci
RCT = Randomised controlled trial
SDCEP = Scottish Dental Clinical Effectiveness Programme
UK = United Kingdom
US = United States of America

Take Home Messages

1. New data supports the hypothesis that there is an association between invasive dental procedures and the subsequent development of infective endocarditis (IE) for patients at high IE risk.
2. New data also demonstrates that antibiotic prophylaxis (AP) reduces IE incidence following invasive dental procedures in those at high IE risk.
3. New data also shows that poor oral hygiene is an important risk factor for oral streptococcal IE in all those at increased IE risk, i.e., those at moderate- as well as high-risk.
4. Most guidelines used to recommend AP for a range of invasive medical (as well as dental) procedures. However, these recommendations lapsed due to a need for more evidence associating these procedures with subsequent IE. Recent national data from Sweden and England has demonstrated a significant association between certain medical procedures previously recommended for AP cover and subsequent IE development. This new evidence may warrant a re-examination of the need for AP cover of these procedures.

Deleted: high-IE-risk

Deleted: high-IE-risk

Deleted: IE-risk

Deleted: lack of

Background

Infective endocarditis (IE) is a devastating infection of the heart valves with high in-hospital and 1-year mortality.[1,2] Valve replacement is often required, and inpatient stays can be prolonged. IE incidence is increasing in the UK [3-5] and across Europe.[6] Multiple factors are likely behind this increase. These include an ageing population, rising rates of medical intervention (hence increasing numbers of individuals at high IE risk) and possibly a reduction in the provision of antibiotic prophylaxis (AP) cover of invasive dental procedures (IDPs).

Links between the mouth and IE stretch back a century. In 1923, Lewis and Grant were the first to suggest that IE might result from the bacteraemia caused by IDPs.[7] In 1935, Okell and Elliott noted that most patients had detectable oral viridans group streptococci (OVGS) in their bloodstream following a dental extraction and directly linked this to the aetiology of IE.[8] They also noted that bacteraemia was most likely to occur in those with poor oral hygiene.

In 1955, the American Heart Association (AHA) produced the first guidelines recommending that individuals at increased IE risk should be given AP before IDPs to reduce their risk of IE.[9] There were further iterations of the AHA guidelines, with refinements and expansion in those recommended to receive AP and which "at risk" procedures should be considered for AP, culminating in the 1997 AHA guidelines.[10] These recommended AP before specific dental, respiratory, gastrointestinal and genitourinary tract procedures in those at moderate risk and high risk (Table 1).

Similar guidelines were developed in the UK, Europe and the rest of the world. The British Society of Antimicrobial Chemotherapy (BSAC) produced its first recommendation in 1982.[11] The European Society of Cardiology (ESC) produced its first consensus document in 1995.[12] These paralleled the AHA guideline recommendations. In 2004, the ESC, the British Cardiac Society and the Royal College of Physicians of London came together to produce a comprehensive set of guidelines. This also recommended AP for patients with a wide variety of cardiac conditions for various procedures.[13]

But there were concerns about the lack of evidence for AP efficacy in preventing IE, particularly for non-dental procedures. There were also concerns about the risk of adverse reactions to AP antibiotics and the development of antimicrobial resistance from any unnecessary antibiotic use. As a consequence, in 2006, BSAC recommended the use of AP before IDPs in the UK should be restricted to those at highest-IE-risk and cease for those at moderate risk (Table 1).[14] This represented a ~90% reduction in the number of individuals for whom AP was recommended.[15] This recommendation met with a strong reaction and was condemned by several cardiology professional bodies.[16,17] As a consequence, the issue was referred to the National Institute for Health and Clinical Excellence (NICE) for review. While this was happening, in 2007, the AHA recommended AP be restricted to those at highest-IE-risk undergoing dental procedures only,[18] and the ESC made almost identical recommendations in 2009.[19] There was considerable surprise, therefore, when NICE went further and effectively banned the use of AP to prevent IE for all patients.[20] The AHA[21] and ESC[19] considered the same body of evidence as NICE but, in the absence of RCT data, put more reliance on the results of observational, bacteraemia and animal studies and concluded that

Deleted: Worryingly,

Deleted: high-IE-risk

Deleted: .

Deleted: IE-risk

Deleted: a range of different

Deleted: moderate-risk

Deleted:

AP should continue to be recommended before IDPs but only for those at highest-IE-risk, until further data was available.

The NICE guidance resulted in an 88% fall in AP prescribing and a concomitant increase in IE incidence.[3] Following the publication of this data, NICE undertook a review of its guidance. Although a temporal association between the fall in AP prescribing and the increase in IE incidence was observed, this was not proof of causation. Furthermore, NICE required new RCT evidence to change guidance. Consequently, in 2015, NICE reiterated its guidance that "*antibiotic prophylaxis against infective endocarditis is not recommended for people undergoing dental procedures*".[22] In 2015, the ESC reviewed exactly the same evidence as NICE, but again came to the conclusion that AP should continue to be recommended before IDPs for patients at high IE risk.[23]

In 2016 however, following pressure from patients and politicians, and changes in the law on consent,[24] NICE changed the wording of their guidance without any review or consultation. They added the word 'routinely', so the guidance became "*antibiotic prophylaxis against infective endocarditis is not routinely recommended for people undergoing dental procedures*".[20]

This change caused enormous confusion for patients, their physicians and dentists. Although NICE defines patients that may be at increased IE risk, they do not distinguish between those who are at high-risk (for whom other guidelines recommend AP) and those at moderate- or lower risk (for whom other guidelines do not recommend AP). Hence they provide no indication of who should be considered for routine management (and not be prescribed AP) and who should be considered non-routine (for whom AP might be considered). There was no mention of which dental procedures should be considered for AP cover, and for those patients for whom AP might be a consideration, no information was provided about what AP protocol should be used. Unlike guidelines from elsewhere in the world, and particularly those from the AHA and ESC, the NICE guidelines are, therefore, confusing and provide no clinically useful guidance or advice for dentists, cardiologist or their patients. Consequently, some UK hospitals and cardiology centres e.g., the Adult Congenital Heart Centre at the Royal Brompton Hospital,[25] took matters into their own hands and adopted the ESC guidance instead.

The lack of clear guidance from NICE and the differing views of cardiologists has massively increased the confusion for dentists. To try and address this, the Scottish Dental Clinical Effectiveness Programme (SDCEP) produced advice (endorsed by NICE) on how to implement the NICE guidelines. It advises, "The vast majority of patients at increased risk of IE will not be prescribed antibiotic prophylaxis. However, for a very small number of patients, it may be prudent to consider antibiotic prophylaxis (non-routine management) in consultation with the patient and their cardiologist or cardiac surgeon".[26] The SDCEP list of patients for whom AP should be considered is the same as those high-IE-risk patients recommended for AP by the ESC and AHA. Dentists are advised to consult with the patient's cardiologist or cardiac surgeon to determine if they should be considered for AP before IDPs. In patients for whom cardiologists recommend consideration of AP, SDCEP advises dentists that they must "discuss the potential benefits and risks of prophylaxis for invasive dental procedures with the patient to allow them to make an informed decision about whether prophylaxis is right for them."

Deleted: .
Deleted: guideance
Deleted: IE-incidence
Deleted: IE-incidence
Deleted: ,
Deleted: high-IE-risk
Deleted: IE-risk
Deleted: er

Unfortunately, the data to inform such discussions has been lacking and is not provided by NICE or SDCEP. In the absence of clear clinically relevant guidance from NICE, the SDCEP advice remains confusing and lacks the precision and clarity of the ESC and AHA guidance.

When the NICE guidelines were introduced in March 2008, the medico-legal position relating to AP was clear. AP was no longer recommended. This meant that practitioners could be at risk if they prescribed AP and an adverse drug reaction (ADR) occurred. Indeed, dentists were informed they would be in breach of their NHS contracts if they did not follow NICE guidance and dental defence unions threatened to withdraw cover for adverse events following the use of AP. The situation facing dentists since the 2016 wording change to the NICE guidance is now very confusing. In light of the 2016 re-wording, the change in the law on consent,[27] the SDCEP implementation advice, and the current AHA and ESC recommendations, it is now essential that patients at high IE risk are told about the potential risks and benefits of AP prior to embarking on any IDPs. Not doing so potentially opens the practitioner up to legal challenge if they develop an ADR or develop IE.

In 2021, the AHA again reviewed its guidance, taking account of the NICE guideline position, but found no reason to change its advice that those at highest-IE-risk should receive AP before undergoing IDPs.[28] The ESC has also recently reviewed its guidance and the outcome is expected shortly, but it is not anticipated that the recommendation that those at high risk should receive AP before IDPs will change. Fifteen years after NICE recommended against the use of AP to prevent IE, therefore, it remains isolated in maintaining this view.

Since NICE last reviewed its guidance in 2015, much new evidence has emerged. Also, NICE has changed its methodology in two important respects; (i) NICE has acknowledged that a rigid reliance on RCT evidence may not be appropriate in all situations, particularly where RCT evidence is unavailable or unrealistic;[29,30] (ii) NICE has acknowledged that, in the interests of fairness, its decisions cannot be based on cost-effectiveness alone.[29,30] Given this, it may be time for NICE to take the opportunity to review its guidance again.

New evidence since the last NICE guideline review

(i) Evidence on the risk of adverse reactions to AP antibiotics

Very soon after the completion of the 2015 NICE guideline review, new UK evidence was published that quantified the risk of an ADR following AP with a single 3g oral dose of amoxicillin or 600mg dose of clindamycin.[31] It showed that the risk of ADR was substantially lower than the estimates used by NICE. For amoxicillin, no fatal ADRs were reported after more than 3 million amoxicillin AP prescriptions, and only 22.6 non-fatal ADRs/million prescriptions. Another UK study also found no recorded ADR deaths following the use of a single 3g oral dose of amoxicillin for AP.[32] The ADR rate due to clindamycin-associated *Clostridioides difficile* infections, however, was significantly worse (13 fatal and 149 non-fatal reactions/million prescriptions). Consequently, the AHA now recommends against the use of clindamycin AP for those allergic to penicillin (recommending cephalexin, clarithromycin, azithromycin or doxycycline instead).[28] NICE's evaluation used estimates from a 2005 health economic analysis[33] and their own 2008 health economic analysis,[34] that relied on fatal ADR data from 1968[35] and 1984[36] with an estimate of 20 fatal ADR/million prescriptions. The non-

Deleted: withdrew
Deleted: confused
Deleted: the
Deleted: high-IE-risk
Deleted: to do
Deleted: their
Deleted: no-reason
Deleted: it's
Deleted: ,
Deleted: it's
Deleted: high-risk
Deleted: it's
Deleted: dged
Deleted: zero
Deleted: detected
Deleted: clindamycin associated
Deleted: ially

fatal ADR rate for amoxicillin used by NICE was 20,000/million prescriptions obtained from a 1997 estimate.[33,37] However, all these studies used estimates for the risk of ADR following all doses, routes of administration and types of penicillin used for treating infections. Not surprisingly these estimates were much higher than for a single oral dose of amoxicillin prescribed for AP purposes. As a consequence, NICE concluded "antibiotic prophylaxis against IE for dental procedures may lead to a greater number of deaths through fatal anaphylaxis than a strategy of no antibiotic prophylaxis, and is not cost effective."[34] This conclusion, however, is not supported by the more recent data looking at the incidence of ADRs following the use of antibiotic regimens recommended for AP purposes only. In contrast, for their estimate of the ADR risk from clindamycin, NICE used Mazur's estimate of zero for the probability of fatal anaphylaxis following clindamycin.[33,38] However, this data only looked at anaphylaxis and took no account of the far more important and well-known clindamycin ADR risk of *Clostridioides difficile* infection.

Deleted: s

Deleted:

Deleted: r

(ii) Evidence on AP cost-effectiveness

In 2016, a new health economic analysis was published using UK data, including data on ADR directly related to the prescribing of AP.[39] It found that only a marginal reduction in annual IE rates (1.44 cases in high-risk and 33 cases in all at-risk patients) would be required for AP to be considered cost-effective at £20,000 per quality-adjusted life-year (the figure used by NICE to determine cost-effectiveness). It calculated that annual cost savings of £5.5 to £8.2 million and health gains >2,600 quality-adjusted life-years could be achieved from reinstating AP in England. Pre-publication data from the ADR and health economic studies were made available to NICE before their 2015 review, but were not taken into consideration, as they had not yet been published in a peer-reviewed journal.

Deleted: quality adjusted

(iii) Evidence on the association between IDPs and the subsequent occurrence of IE

In the period since the 2015 NICE guideline review there have been 8 studies that investigated the association between IDPs and IE, two each from Taiwan, France, the UK and the US. The Taiwanese studies were case-crossover[40,41] and self-controlled case series designs.[41] The first study of 739 patients with IE found no significant association between IDPs and IE occurring in the following 3 months.[40] It should be noted, however, that Taiwan follows the AHA guidelines recommending AP for individuals at high IE risk. AP prescribing data was not available, so a small sample size and AP masking of any association could have contributed to this outcome. The second case-crossover study found that 277 cases and 249 controls received IDPs in the 4 weeks before IE development (OR=1.12, 95%CI 0.94-1.34).[41] In the self-controlled case series study, however, 407 cases of IE developed in the 4 weeks after IDPs and the age-adjusted incidence rate-ratio (1.14, 95%CI 1.02-1.26) suggested a significant association between IDPs and IE. When longer exposure periods, e.g., 8 or 12 weeks, were used, this association was lost. Again, the sample size was not large and the recommendation for dentists to prescribe AP for high-risk patients may have served to reduce any association.

Deleted: guidline

Deleted: .

Deleted: T

Deleted:

Deleted: high-IE-risk

In 2017 a French study compared the incidence of IDPs in the 3 months before IE-development in 73 patients with OVGS-IE and 192 controls with IE caused by other bacterial species.[42] Cases were significantly more likely to have had IDPs in the 3 months before developing IE (OR 3.31, 95%CI 1.18-9.29). Again, this study is not large and the ESC guidelines

in France recommend AP for those at high IE risk. The authors also speculated that the 3-month exposure window they used between IDPs and IE might be too long and could have reduced the likelihood of detecting any association. A second and much larger French study in 2017 included both a cohort and a case-crossover study. It looked specifically at high-risk patients with prosthetic heart valves. There were 138,876 patients in the cohort study and no significant increase in the incidence of OVGS-IE was identified in the 3 months after IDPs. In contrast, the case-crossover study of 648 prosthetic heart valve patients who developed OVGS-IE identified a significant association between IDPs and IE development over the following 3 months (OR=1.66, 95%CI 1.05-2.63, p=0.03).[43] The authors concluded that IDPs may contribute to the development of IE in adults with prosthetic heart valves.

Because AP is not recommended in the UK, any association between IDPs and IE should be maximally exposed. A nationwide case-crossover study was therefore attempted to evaluate this. Unfortunately, limitations in the collection of dental procedure data by general dental practitioners in the period leading up to a patient being admitted to hospital or dying, made the data unreliable and the study impossible.[44] However, the same issue did not apply to the recording of IDPs performed in a hospital outpatient setting and a significant association was found between dental extractions or surgical tooth removal performed in hospitals in England and the subsequent development of IE (OR=2.14, 95%CI 1.22-3.76, p<0.05).[45]

Most studies have suffered from not being able to distinguish when a dental procedure performed in a specific individual was covered by AP or not. Two recent US studies, however, identified when procedures were, or were not, covered by AP and quantified the occurrence of IE following IDPs with and without AP cover using both cohort and case-crossover methodologies.[46,47] The first study included patients with employer-provided medical, dental and prescription benefits cover or employer-provided Medicare-supplemental cover.[46] Time-course studies showed that IE was most likely to occur within 4 weeks of IDPs. In the case-crossover study of 3,774 patients who developed IE, there was a significant association between IE and IDPs in the preceding 4 weeks for patients at high IE risk (OR=2.00, 95%CI 1.59-2.52, p=0.002). This relationship was strongest for dental extractions (OR=11.08, 95%CI 7.34-16.74, p<0.0001) and oral surgery procedures (OR 50.77, 95%CI 20.79-123.98, p<0.0001). The cohort study of 7,951,972 individuals also found the odds of developing IE were significantly increased following extractions (OR=9.22, 95%CI 5.54-15.88, p<0.0001) and oral surgical procedures (OR=20.18, 95%CI 11.22-36.74) in those at high-IE-risk.[46]

To eliminate the possibility that these associations were limited to patients with employer-provided health cover, these studies were repeated in patients with basic Medicaid medical, dental and prescription benefits cover.[47] The case-crossover study of 2,647 Medicaid IE-cases confirmed an association between IDPs and IE development within 30 days for those at high IE risk, particularly following extractions (OR=3.74, 95%CI 2.65-5.27, p<0.005) and oral surgery (OR=10.66, 95%CI 5.18-21.92, p<0.0001). The cohort study of 1.68 million Medicaid patients also identified an increased incidence of IE within 30 days of IDPs in those at high IE risk, particularly following extractions (OR=14.17, 95%CI 5.40-52.11, p<0.0001) and oral surgery procedures (OR=29.98, 95%CI 9.62-119.34).[47] There were also significant health disparities between those with employer-provided health cover and those on Medicaid, with a sixfold higher IE-incidence following IDPs in high-IE-risk Medicaid patients likely due to differences in general and dental health, access to care and AP use.[47]

Deleted: high-IE-risk

Deleted: ,

Deleted: ,

Deleted:

Deleted: high-IE-risk

Deleted: possibility

Deleted: employer provided

Deleted: IE-development

Deleted: high-IE-risk

Deleted: high-IE-risk

Deleted: employer provided

(iv) Evidence for AP efficacy

Because they quantified IE incidence following IDPs covered and not covered by AP, the two US studies were able to investigate the effect of AP on IE incidence. In patients with employer-provided medical/dental cover, AP was associated with a significant reduction in IE-incidence following IDPs in those at high IE risk (OR=0.38, 95%CI 0.22-0.62, p=0.002), particularly following extractions (OR=0.13, 95%CI 0.03-0.34, p<0.0001) or oral surgery procedures (OR=0.09, 95%CI 0.01-0.35, p=0.002) (Figure 1(a)).[46] In Medicaid patients AP also significantly reduced the IE-incidence within 4 weeks of IDPs for patients at high IE risk (OR=0.20, 95%CI 0.06-0.53, p<0.0001), particularly following extractions (OR=0.29, 95%CI 0.08-0.77, p<0.01) (Figure 1(b)).[47] The number of IDPs, extractions, or oral surgery procedures that needed AP cover to prevent one IE case (i.e., number needed to prevent) was, respectively, 1536, 125 and 45 for those with employer-provided medical/dental cover and 244, 143 and 71 for Medicaid patients (Figure 1).[47]

These studies suggest that AP is effective in reducing the IE risk following IDPs for patients at high-IE-risk and are supportive of the ESC and AHA recommendations that patients at high-IE-risk should receive AP before IDPs. Whilst still not providing RCT level evidence these large observational studies come close and may provide the new evidence needed for NICE to review its recommendations. These studies also provide data on the risk of IE following IDPs and the potential benefit provided by AP for those at high IE risk that can be used by clinicians to inform the type of discussions with patients advised by SDCEP[48] and NICE.[22]

@@@Could Stop Here (3,054 words, 1 Table, 1 Figure and 49 refs)@@@

(v) Evidence of the importance of good oral hygiene

The debate over OVGS-IE has tended to divide into two camps. Those who attribute cases to daily activities, e.g., toothbrushing, flossing and mastication, and those who attribute them to IDPs. Contributing to the stance taken by NICE in 2008 was the view that such cases were largely the result of the multiple bacteraemias caused by daily activities. However, there is no data on the relative risk from IDPs versus daily activities. A recent systematic review showed that bacteraemia followed both, although occurred with the highest frequency following dental extractions (62-66%) and other IDPs and lower frequency following toothbrushing (8-26% flossing and chewing (16%).[49] The size of bacteraemia resulting from any intervention is also likely to be important in determining the risk of developing IE, but very few studies have examined this. However, magnitude is also likely to influence the duration of bacteraemia and most studies that have examined this have found a longer duration of bacteraemia following IDPs than daily activities.[49] Overall, IDPs are likely to result in a larger bacteraemia than daily activities, while bacteraemias associated with daily activities occur with much greater frequency. No studies have yet addressed which is more likely to result in IE. It is important, therefore, to acknowledge that both mechanisms have the potential to cause IE, and prevention strategies should focus on both. If AP is effective in reducing IE following IDPs, it has an important role in preventing the iatrogenic IE that may result from IDPs but would be impractical for preventing the threat posed by daily activities.

Deleted: IE-incidence

Deleted: employer provided

Deleted: high-IE-risk

Deleted: high-IE-risk

Deleted: employer provided

Deleted: risk, and

Deleted: *on*

Deleted: to over whether cases

Deleted: IDPs, but

The threat of OVGS-IE from daily activities and IDPs is, however, likely to be higher in those with poor oral hygiene. The frequency and duration of bacteraemia following toothbrushing has been shown to be significantly greater in those with poor oral hygiene,[50] and the need for IDPs is also higher in those with poor oral hygiene. Maintenance of good oral hygiene is likely, therefore, to play an important role in reducing the likelihood of IE from both daily activities and IDPs. Indeed, a recent case-control study demonstrated that individuals at moderate IE risk, were significantly more likely to develop IE if they had markers of poor oral hygiene. The authors concluded that "those at risk for IE can reduce potential sources of IE-related bacteraemia by maintaining optimal oral health through regular professional dental care and oral hygiene procedures".[51] It is notable that the advantages of good oral hygiene are important not just for those at high IE risk (where the benefits of AP appear to be focussed) but for all those at increased IE risk (moderate- and high-risk). The benefits of improved oral hygiene may also explain why dental scaling, a relatively invasive procedure used to improve oral hygiene, does not seem to pose the same level of risk as other types of IDPs, e.g., extractions and oral surgery procedures, that are often the result of poor oral hygiene.

Although most guidelines make some mention of improving or maintaining oral hygiene as a component of IE-prevention, its importance should be emphasised for all those at increased IE risk at the same time as recommending AP cover of IDPs for those at highest risk.

@@@Could Stop Here (3,589 words, 1 Table, 1 Figure and 52 refs)@@@

(vi) Evidence on the association between other invasive procedures and IE development

Before 2007, AP was recommended for several invasive medical as well as dental procedures. Most guideline committees stopped advising AP cover of these medical procedures because of a lack of evidence linking these procedures to subsequent IE. A study of Swedish national data in 2018, however, found evidence that associated several medical procedures (previously recommended for AP cover) with a significantly increased risk of IE.[52] These included cardiovascular procedures, skin and wound management procedures, transfusion, bone marrow aspiration, endoscopy, and bronchoscopy. A recent study of English national data also identified an association between specific medical procedures and subsequent IE.[53] As expected, dental extractions and cardiac implantable electronic device implantation were significantly associated with IE development. However, there were also significant associations with other procedures, including upper and lower gastrointestinal endoscopy, bronchoscopy, transfusions and bone marrow biopsy. These associations were all strongest for those at high IE risk.[45] Interestingly, the association between some invasive medical procedures and IE was of a similar order to that between dental extractions and IE (Figure 2).

@@@Could Stop Here (3,768 words, 1 Table, 2 Figures and 54 refs)@@@

Deleted: case control
Deleted: -
Deleted: -
Deleted: ,
Deleted: -
Deleted: increased-IE-risk
Commented [MD1]: This is a really powerful section and should be left in.
Deleted: -
Deleted: -
Deleted: ing
Deleted: ;
Deleted: ;
Deleted: ;
Deleted: puncture
Deleted: ;
Deleted: ies
Deleted: -
Deleted: high-IE-risk

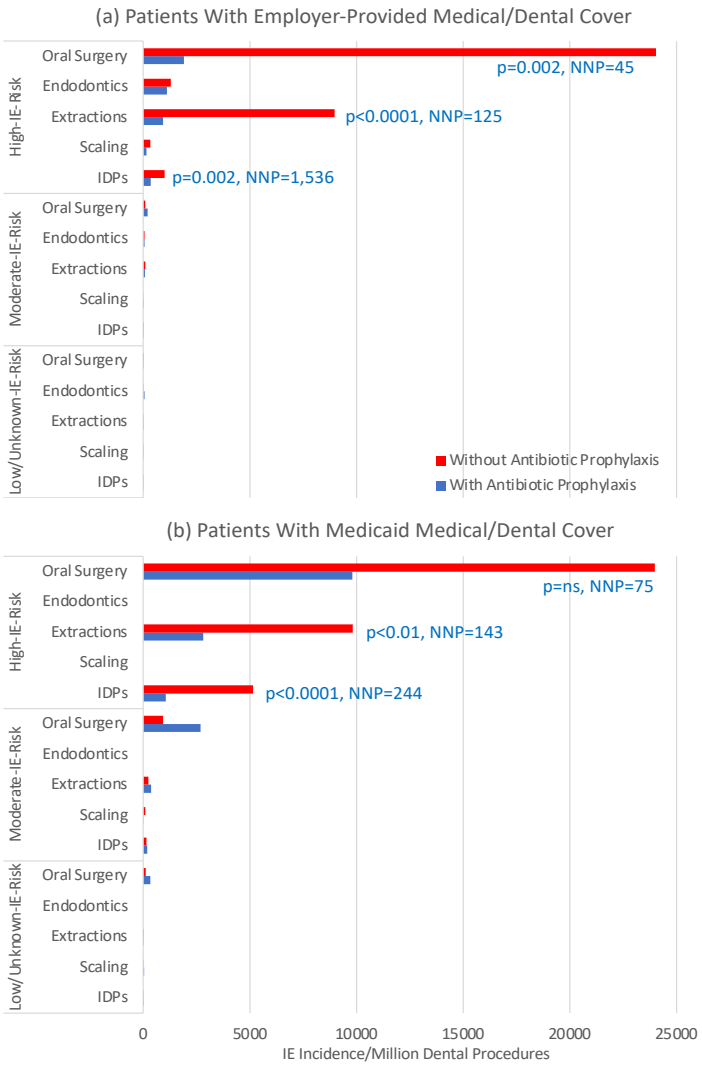
Table 1. Cardiac conditions used to classify individuals as being at high, moderate or low IE risk.

High-IE-Risk
Previous history of Infective endocarditis
Presence of prosthetic cardiac valve (including transcatheter valves)
Prosthetic material used for valve repair (including annuloplasty and percutaneous valve procedures using prosthetic material)
Unrepaired cyanotic congenital heart disease
Congenital heart disease in which palliative shunts or conduits were used
Completely repaired congenital heart defect with prosthetic material or device, whether placed by surgery or by transcatheter during the first 6 months after the procedure only.
Moderate-IE-Risk
Rheumatic heart disease
Non-rheumatic valve disease (including mitral valve prolapse)
Congenital valve anomalies (including aortic stenosis)
Hypertrophic cardiomyopathy
Low/Unknown-IE-risk
Patients not known to have any of the above high- or moderate-risk conditions

Notes: Based on the AHA[10,21,28] and ESC[19,23,54] guideline definitions of those at high, moderate- or low IE risk.

Deleted: -
Deleted: -
Deleted: -
Deleted: -risk
Deleted: H
Deleted: -
Deleted: M
Deleted: -
Deleted: -

Figure 1. Infective endocarditis (IE) Incidence in individuals at high, moderate or low risk of IE following Invasive Dental Procedures (IDPs), who have undergone IDPs of different types, with or without antibiotic prophylaxis cover. Study data from two different populations (a) patients with employer-provided medical/dental cover[46] and (b) patients with Medicaid medical/dental cover.[47]

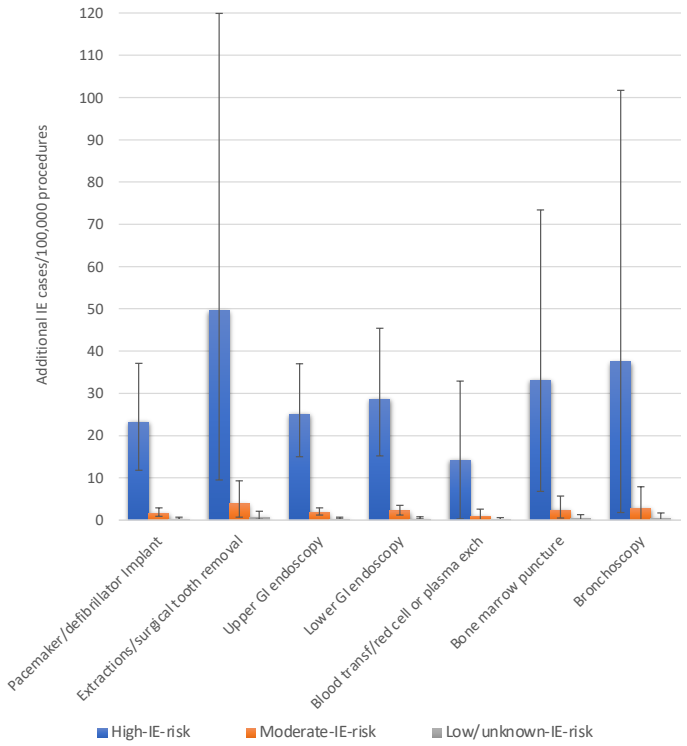


P-values compare IE incidence when procedure covered by AP v not covered, p=ns where no p-value shown. NNP= number needed to prevent i.e., the number of dental procedures that need to be covered by AP to prevent one case of IE. IE risk status based on ESC and AHA guidelines (see Table 1).

Deleted: -
Deleted: -
Deleted: -
Deleted: employer provided
Deleted:
Deleted: p value
Deleted: -

Figure 2. The attributable risk of IE following different invasive procedures according to IE risk status.

Deleted: -



Exch = exchange, GI = gastrointestinal, implant = implantation, transf = transfusion. IE risk status based on ESC and AHA guidelines (see Table 1).

Deleted: -

References

1. Ostergaard L, Voldstedlund M, Bruun NE, et al. Temporal Changes, Patient Characteristics, and Mortality, According to Microbiological Cause of Infective Endocarditis: A Nationwide Study. *J Am Heart Assoc* 2022; **11**(16): e025801.
2. Jensen AD, Ostergaard L, Petersen JK, et al. Temporal trends of mortality in patients with infective endocarditis: A nationwide study. *Eur Heart J Qual Care Clin Outcomes* 2022.
3. Dayer MJ, Jones S, Prendergast B, Baddour LM, Lockhart PB, Thornhill MH. Incidence of infective endocarditis in England, 2000-13: a secular trend, interrupted time-series analysis. *Lancet* 2015; **385**(9974): 1219-28.
4. Quan TP, Muller-Pebody B, Fawcett N, et al. Investigation of the impact of the NICE guidelines regarding antibiotic prophylaxis during invasive dental procedures on the incidence of infective endocarditis in England: an electronic health records study. *BMC Med* 2020; **18**(1): 84.
5. Thornhill MH, Dayer MJ, Nicholl J, Prendergast BD, Lockhart PB, Baddour LM. An alarming rise in incidence of infective endocarditis in England since 2009: why? *Lancet* 2020; **395**(10233): 1325-7.
6. Talha KM, Baddour LM, Thornhill MH, et al. Escalating incidence of infective endocarditis in Europe in the 21st century. *Open Heart* 2021; **8**(2).
7. Lewis T, Grant RT. Observations relating to subacute infective endocarditis. *Heart* 1923; (10): 21-99.
8. Okell CC, Elliott SD. Bacteraemia and oral sepsis with special reference to the aetiology of subacute endocarditis. *Lancet* 1935; **226**(5851): 869-72.
9. Jones TD, Baumgartner L, Bellows MT, et al. Committee on Prevention of Rheumatic Fever and Bacterial Endocarditis, American Heart Association. Prevention of rheumatic fever and bacterial endocarditis through control of streptococcal infections. . *Circulation* 1955; **11**: 317-20.
10. Dajani AS, Taubert KA, Wilson W, et al. Prevention of bacterial endocarditis. Recommendations by the American Heart Association. *JAMA* 1997; **277**(22): 1794-801.
11. The antibiotic prophylaxis of infective endocarditis. Report of a working party of the British Society for Antimicrobial Chemotherapy. *Lancet* 1982; **2**(8311): 1323-6.
12. Leport C, Horstkotte D, Burckhardt D. Antibiotic prophylaxis for infective endocarditis from an international group of experts towards a European consensus. Group of Experts of the International Society for Chemotherapy. *Eur Heart J* 1995; **16 Suppl B**: 126-31.
13. Horstkotte D, Follath F, Gutschik E, et al. Guidelines on prevention, diagnosis and treatment of infective endocarditis executive summary; the task force on infective endocarditis of the European society of cardiology. *Eur Heart J* 2004; **25**(3): 267-76.
14. Gould FK, Elliott TS, Foweraker J, et al. Guidelines for the prevention of endocarditis: report of the Working Party of the British Society for Antimicrobial Chemotherapy. *J Antimicrob Chemother* 2006; **57**(6): 1035-42.
15. Thornhill MH, Gibson TB, Cutler E, et al. Antibiotic Prophylaxis and Incidence of Endocarditis Before and After the 2007 AHA Recommendations. *J Am Coll Cardiol* 2018; **72**(20): 2443-54.
16. Gibbs JL, Cowie M, Brooks N. Defying explanation. *British dental journal* 2006; **201**(4): 188; author reply

17. Ramsdale DR, Morrison L, Palmer MD, Fabri B. Lethal consequences. *British dental journal* 2006; **201**(4): 187; author reply 8.
18. Wilson W, Taubert KA, Gewitz M, et al. Prevention of infective endocarditis: guidelines from the American Heart Association: a guideline from the American Heart Association Rheumatic Fever, Endocarditis, and Kawasaki Disease Committee, Council on Cardiovascular Disease in the Young, and the Council on Clinical Cardiology, Council on Cardiovascular Surgery and Anesthesia, and the Quality of Care and Outcomes Research Interdisciplinary Working Group. *Circulation* 2007; **116**(15): 1736-54.
19. Habib G, Hoen B, Tornos P, et al. Guidelines on the prevention, diagnosis, and treatment of infective endocarditis (new version 2009): the Task Force on the Prevention, Diagnosis, and Treatment of Infective Endocarditis of the European Society of Cardiology (ESC). Endorsed by the European Society of Clinical Microbiology and Infectious Diseases (ESCMID) and the International Society of Chemotherapy (ISC) for Infection and Cancer. *Eur Heart J* 2009; **30**(19): 2369-413.
20. National Institute for Health and Clinical Excellence: Prophylaxis Against Infective Endocarditis: Antimicrobial Prophylaxis Against Infective Endocarditis in Adults and Children Undergoing Interventional Procedures. CG64. Published: 17 March 2008 Last updated: 08 July 2016. London; 2008.
21. Wilson W, Taubert KA, Gewitz M, et al. Prevention of infective endocarditis: guidelines from the American Heart Association: a guideline from the American Heart Association Rheumatic Fever, Endocarditis, and Kawasaki Disease Committee, Council on Cardiovascular Disease in the Young, and the Council on Clinical Cardiology, Council on Cardiovascular Surgery and Anesthesia, and the Quality of Care and Outcomes Research Interdisciplinary Working Group. *Circulation* 2007; **116**(15): 1736-54.
22. National Institute for Health and Care Excellence (NICE). Prophylaxis against infective endocarditis. 2015. http://www.nice.org.uk/guidance/cg64/chapter/Recommendations (accessed 19-06-2015 2015).
23. Habib G, Lancellotti P, Antunes MJ, et al. 2015 ESC Guidelines for the management of infective endocarditis: The Task Force for the Management of Infective Endocarditis of the European Society of Cardiology (ESC)Endorsed by: European Association for Cardio-Thoracic Surgery (EACTS), the European Association of Nuclear Medicine (EANM). *Eur Heart J* 2015; **36**(44): 3075-128.
24. Montgomery v Lanarkshire Health Board (Scotland). UKSC 11; 2015.
25. Tutarel O, Alonso-Gonzalez R, Montanaro C, et al. Infective endocarditis in adults with congenital heart disease remains a lethal disease. *Heart* 2018; **104**(2): 161-5.
26. Antibiotic Prophylaxis Against Infective Endocarditis. Implementation Advice. Scottish Dental Clinical Effectiveness Programme. 2018.
27. Montgomery (Appellant) v Lanarkshire Health Board (Respondent) (Scotland). 2015. https://www.supremecourt.uk/cases/uksc-2013-0136.html (accessed 18/10/2022).
28. Wilson WR, Gewitz M, Lockhart PB, et al. Prevention of Viridans Group Streptococcal Infective Endocarditis: A Scientific Statement From the American Heart Association. *Circulation* 2021; **143**(20): e963-e78.
29. Charlton V, Lomas J, Mitchell P. NICE's new methods: putting innovation first, but at what cost? *BMJ* 2022; **379**: e071974.
30. NICE. NICE health technology evaluations: the manual. 2022. https://www.nice.org.uk/process/pmg36 (accessed 8th June 2023 2023).

Field Code Changed

Field Code Changed

Field Code Changed

31. Thornhill MH, Dayer MJ, Prendergast B, Baddour LM, Jones S, Lockhart PB. Incidence and nature of adverse reactions to antibiotics used as endocarditis prophylaxis. *J Antimicrob Chemother* 2015; **70**(8): 2382-8.
32. Lee P, Shanson D. Results of a UK survey of fatal anaphylaxis after oral amoxicillin. *J Antimicrob Chemother* 2007; **60**(5): 1172-3.
33. Agha Z, Lofgren RP, VanRuiswyk JV. Is antibiotic prophylaxis for bacterial endocarditis cost-effective? *Medical decision making : an international journal of the Society for Medical Decision Making* 2005; **25**(3): 308-20.
34. National Institute for Health and Care Excellence (NICE). Prophylaxis against infective endocarditis. Clinical Guideline [CG64]. 2008. http://www.nice.org.uk/guidance/cg64 (accessed March 2008.
35. Idsoe O, Guthe T, Willcox RR, de Weck AL. Nature and extent of penicillin side-reactions, with particular reference to fatalities from anaphylactic shock. *Bull World Health Organ* 1968; **38**(2): 159-88.
36. Ahlstedt S. Penicillin allergy--can the incidence be reduced? *Allergy* 1984; **39**(3): 151-64.
37. deShazo RD, Kemp SF. Allergic reactions to drugs and biologic agents. *JAMA* 1997; **278**(22): 1895-906.
38. Mazur N, Greenberger PA, Regalado J. Clindamycin hypersensitivity appears to be rare. *Annals of allergy, asthma & immunology : official publication of the American College of Allergy, Asthma, & Immunology* 1999; **82**(5): 443-5.
39. Franklin M, Wailoo A, Dayer M, et al. The cost-effectiveness of antibiotic prophylaxis for patients at risk of infective endocarditis *Circulation* 2016; **134**: 1568-78.
40. Chen PC, Tung YC, Wu PW, et al. Dental Procedures and the Risk of Infective Endocarditis. *Medicine (Baltimore)* 2015; **94**(43): e1826.
41. Chen TT, Yeh YC, Chien KL, Lai MS, Tu YK. Risk of Infective Endocarditis After Invasive Dental Treatments: Case-Only Study. *Circulation* 2018; **138**(4): 356-63.
42. Duval X, Millot S, Chirouze C, et al. Oral Streptococcal Endocarditis, Oral Hygiene Habits, and Recent Dental Procedures: A Case-Control Study. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America* 2017; **64**(12): 1678-85.
43. Tubiana S, Blotiere PO, Hoen B, et al. Dental procedures, antibiotic prophylaxis, and endocarditis among people with prosthetic heart valves: nationwide population based cohort and a case crossover study. *BMJ* 2017; **358**: j3776.
44. Thornhill MH, Crum A, Rex S, et al. Infective endocarditis following invasive dental procedures: IDEA case crossover study. *Health Technology Assessment* 2022; **26**(28): 1-86.
45. Thornhill MH, Crum A, Campbell R, et al. Temporal association between invasive procedures and infective endocarditis. *Heart* 2023; **109**(3): 223-31.
46. Thornhill MH, Gibson TB, Yoon F, et al. Antibiotic Prophylaxis Against Infective Endocarditis Before Invasive Dental Procedures. *J Am Coll Cardiol* 2022; **80**(11): 1029-41.
47. Thornhill MH, Gibson TB, Yoon F, et al. Endocarditis, invasive dental procedures, and antibiotic prophylaxis efficacy in US Medicaid patients. *Oral diseases* 2023.
48. Scottish Dental Clinical Clinical Effectiveness Programme. Antibiotic Prophylaxis Against Infective Endocarditis: Implementation Advice for National Institute for Health and Care Excellence (NICE) Clinical Guideline 64 Prophylaxis Against Infective Endocarditis. 2018. http://www.sdcep.org.uk/published-guidance/antibiotic-prophylaxis/ (accessed 31-08-2018 2018).

Field Code Changed

Field Code Changed

49. Martins CC, Lockhart PB, Firmino RT, et al. Bacteremia following different oral procedures: Systematic review and meta-analysis. *Oral diseases* 2023.
50. Lockhart PB, Brennan MT, Thornhill M, et al. Poor oral hygiene as a risk factor for infective endocarditis-related bacteremia. *J Am Dent Assoc* 2009; **140**(10): 1238-44.
51. Lockhart PB, Chu V, Zhao J, et al. Oral hygiene and infective endocarditis: A case control study. *Oral Surg Oral Med Oral Pathol And Oral Radiol* 2023.
52. Janszky I, Gemes K, Ahnve S, Asgeirsson H, Moller J. Invasive Procedures Associated With the Development of Infective Endocarditis. *J Am Coll Cardiol* 2018; **71**(24): 2744-52.
53. Thornhill MH, Crum A, Campbell R, et al. Temporal association between invasive procedures and infective endocarditis. *Heart* 2022.
54. Horstkotte D, Follath F, Gutschik E, et al. Guidelines on prevention, diagnosis and treatment of infective endocarditis executive summary; the task force on infective endocarditis of the European society of cardiology. *Eur Heart J* 2004; **25**(3): 267-76.