NICE National Institute for Health and Care Excellence

2024 exceptional surveillance of prophylaxis against infective endocarditis (NICE guideline CG64)

Surveillance report
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Surveillance proposal

We propose to update recommendation 1.1.3 in the NICE guideline on prophylaxis against infective endocarditis.

The update will focus on antibiotic prophylaxis against infective endocarditis for people at high risk undergoing dental procedures.

A review of published evidence since the last update to NICE guidelines in 2016, shows that while there is some new evidence, this remains inadequate to draw firm conclusions about the effectiveness of antibiotic prophylaxis (AP) before dental procedures for individuals at increased risk of infective endocarditis (IE). This scarcity of high-quality evidence is acknowledged in both the American Heart Association (AHA) and European Society of Cardiology (ESC) guidelines. Studies show that the proportion of IEs in high-risk patients that is attributable to invasive dental procedures (IDPs) is around 5%.

The Scottish Dental Clinical Effectiveness Programme (SDCEP) produced a resource to support the implementation of the recommendation in the NICE guideline in August 2018, providing further clarification on what 'routinely' refers to in recommendation 1.1.3, and this was endorsed by NICE. This resource provides information on a sub-group of people who are at increased risk of IE who require special consideration for antibiotic prophylaxis when undergoing invasive dental procedures, defining those invasive dental procedures for non-routine management, and advice for prescribing. This implementation support document is in line with the AHA and ESC guidelines with regard to patients for whom AP should be considered, but differs in the advice for which antibiotics to prescribe.

Based on limited new evidence identified and the availability of resources from SDCEP, it is proposed that an update of the evidence review on AP against IE will not add value to the topic area, but recommendation 1.1.3 should be updated to include, or better signpost, the information provided in the SDCEP implementation document.

Triggers for the exceptional review

In April 2024 a coroner asked NICE to consider taking action relating to its guidance on preventing infective endocarditis after highlighting inconsistencies with advice from other guideline recommendations to dentists. The coroner's report details the case of a 79-year-

old patient who developed IE after a dental extraction procedure and had not been prescribed AP.

The coroner highlighted 3 main concerns:

- NICE's lack of advice to dentists on how they should manage patients who are at increased risk of IE.
- The difference from advice given to dentists in Scotland (In Scotland, the SDCEP has produced NICE endorsed implementation guidance that advises dentists to give special consideration to whether higher risk patients, such as those with a prosthetic valve, need antibiotic prophylaxis).
- Conflicting advice from the European Society for Cardiology (ESC), the ESC guidelines were updated in 2023 and recommend antibiotic prophylaxis for high-risk individuals undergoing invasive dental procedures.

The purpose of this exceptional review is to address the raised concerns through the assessment of the evidence base for AP for preventing IE following invasive dental procedures, to assess NICE recommendations and that of the SDCEP implementation support against international guidelines and summarise relevant system intelligence.

Methods

The exceptional surveillance process consisted of:

- Considering the new evidence and intelligence that triggered the exceptional review.
- Considering the economic aspects of the changes in the clinical evidence.
- Considering the evidence used to develop the guideline in 2015.
- Examining related NICE guidance and quality standards.
- Examining the NICE event tracker for relevant ongoing and published events.
- Assessing the new evidence and topic expert feedback against current recommendations to determine whether or not to update sections of the guideline, or the whole guideline.

For further details about the process and the possible update decisions that are available,

see ensuring that published guidelines are current and accurate in developing NICE guidelines: the manual.

Other relevant guidelines

The AHA published a scientific statement on the prevention of infective endocarditis in May 2021. This was an update to the 2007 guidelines. In the statement the AHA suggest that:

'Antibiotic prophylaxis for a dental procedure that involves manipulation of gingival tissues, periapical region of teeth, or perforation of the oral mucosa is suggested only for patients with the highest risk of adverse outcome from VGS IE.'

The statement also acknowledges that:

'VGS IE is much more likely to develop as a result of transient VGS bacteraemia attributable to routine daily activities such as chewing food and toothbrushing than from a dental procedure.'

and,

'An exceedingly small number of cases of VGS IE could be prevented by AP for a dental procedure, even if prophylaxis is 100% effective.'

The AHA list the groups of patients with underlying conditions for which AP is suggested:

- Prosthetic cardiac valve or material (presence of cardiac prosthetic valve; transcatheter implantation of prosthetic valves; cardiac valve repair with devices, including annuloplasty, rings, or clips; left ventricular assist devices or implantable heart).
- Previous, relapse or recurrent IE.
- CHD (unrepaired cyanotic congenital CHD, including palliative shunts and conduits; completely repaired congenital heart defect with prosthetic device, whether placed by surgery or by transcatheter during the first 6 months after the procedure; repaired CHD with residual defects at the site of or adjacent to the site of a prosthetic patch or prosthetic device; surgical or transcatheter pulmonary artery valve or conduit

placement such as Melody valve and Contegra conduit).

- Cardiac transplant recipients who develop cardiac valvulopathy.

The ESC published updated guidelines for the management of endocarditis in 2023. The guideline revised and updated the risk categories for IE, clarifying the definition of the population at risk.

The ESC guidelines define at-risk dental procedures as including dental extractions, oral surgery procedures (including periodontal surgery, implant surgery, and oral biopsies), and dental procedures involving manipulation of the gingival or periapical region of the teeth (including scaling and root canal procedures).

The ESC recommends that the following patients with cardiovascular disease are prescribed AP:

- Patients with previous IE.
- Patients with surgically implanted prosthetic valves and with any material used for surgical cardiac repair.
- Patients with transcatheter implanted aortic and pulmonary valvular prostheses.
- Patients with untreated cyanotic CHD, and patients treated with surgery or transcatheter procedures with post-operative palliative shunts, conduits or other prostheses. After surgical repair, in the absence of residual defects or valve prostheses, AP is recommended only for the first 6 months after the procedure.
- Patients with ventricular assist devices.

Evidence considered when developing the guideline recommendations

The NICE guideline was first developed in March 2008. At the time it had been accepted clinical practice to use preventive (prophylactic) antibiotics before dental and some non-dental procedures in people who are considered to be at risk of IE. However, the effectiveness of this treatment in humans had never been properly investigated and clinical practice had been dictated by clinical guidelines based on expert opinion.

The evidence reviews for the guideline in 2008 found that:

- there is no consistent association between having an interventional procedure, dental or non-dental, and the development of IE
- regular toothbrushing almost certainly presents a greater risk of IE than a single dental procedure because of repetitive exposure to bacteraemia with oral flora
- the clinical effectiveness of antibiotic prophylaxis is not proven
- 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.

The guideline stated that antibiotic prophylaxis is not recommended for people undergoing dental procedures.

A UK study published in the BMJ in 2011 (Thornhill et al. 2011) looked at the impact of the NICE guideline and showed an 80% fall in antibiotic prescribing thereby indicating that the guideline had been effectively implemented. A longstanding increase in the incidence of IE was also noted but with no clear evidence of any additional increase following publication of the guideline. This increase in the incidence of IE was not well understood and there were a number of possible reasons for this. The publication of further research by the same research group, covering the period 2000 to 2013 (Dayer et al. 2015), suggested that the incidence of IE increased in both low and high-risk groups above the baseline trend, in contrast to the 2011 study, following the publication of NICE's guidance in 2008. Given the uncertainty of the association as suggested by the research, this triggered an update to assess all new evidence relevant to this guidance. The objective of this update was to assess new evidence since 2008 for all review questions covered by the original Scope, except the review question on the information needs of patients regarding the benefits and risks of antimicrobial prophylaxis for IE.

The guideline update in 2015 included a critique of the study by Dayer et al. commissioned by NICE. This found that multiple change-points seem possible rather than only one at the point of guideline introduction in 2008, and that taking all evidence into account the effect of the change in slope (of IE incidence) at guideline introduction is biased and the published estimates are likely too high. These findings are further supported by a study published in 2020 that investigated the temporal association between IE incidence and change in AP following change in guidance in 2008 in England (Quan et al. 2020). The study found no evidence associated specifically with the date of withdrawal of dental

antibiotic prophylaxis on the incidence of IE as opposed to any other arbitrary date within the period of study.

The update of the NICE guideline in 2015 included a review of the evidence on the effectiveness of AP in those at risk of developing IE when undergoing invasive dental procedures. Very low quality evidence from 2 case-control studies and 1 retrospective cohort study, all of which were included in the original guideline in 2008. Overall, the committee concluded that there was insufficient evidence to recommend prophylactic use of antibiotics in those at risk of IE undergoing interventional procedures. Three studies were included in the literature review of economic evaluations examining the cost effectiveness of antibiotic prophylaxis against infective endocarditis prior to dental procedures. A further economic analysis was presented to the committee that was an adaptation of the 2008 NICE model. The results of all models were highly sensitive to the risk of developing infective endocarditis following a procedure and the efficacy of antibiotic prophylaxis to reduce that risk. The committee noted that there was limited evidence to quantify either of these parameters.

New published evidence considered in this exceptional surveillance review

Previous surveillance review

A surveillance review was conducted in 2011.

Ongoing studies

No ongoing studies currently being tracked by NICE impact these recommendations.

Evidence availability (quality)

We have identified the following new relevant evidence since the publication of the guidelines in 2015:

All evidence reported in this section comes from observational studies, and these are subject to both bias and confounding, and are not the most appropriate design to assess the causal relationship between an intervention and an outcome as several characteristics

might differ or change over time between the different intervention groups. Meta-analysis of observational studies are challenging due to the high risk of both within-study and between-study biases.

A systematic review and meta-analysis from 2024 analysed the evidence on the association between AP and IE following invasive dental procedures (Sperotto et al. 2024). By meta-analysis, antibiotic prophylaxis was associated with a significantly lower risk of infective endocarditis after invasive dental procedures in individuals at high risk (pooled relative risk [RR], 0.41; 95% confidence interval [CI], 0.29 to 0.57; p for heterogeneity =0.51; I^2 =0%). Meta-analysis combined results from 4 studies, 2 cohort and 2 case-crossover (Thornhill et al. 2022 and 2024, detailed below).

A systematic review published in 2023 investigated the effect of AP before dental procedures on developing IE in high-risk patients (Birgada-Pijuan 2023). The review included 1 prospective cohort study that addressed the research question. The included study (Tubiana 2017) included adults with prosthetic heart valves who underwent invasive and non-invasive dental procedures. The study showed a small decrease in the risk of developing IE when high-risk patients received AP, although the results were not statistically significant, and the included study was deemed to be at high risk of bias using the Cochrane risk of bias tool for observational studies.

A Cochrane review published in 2022 investigated whether prophylactic antibiotic administration, compared to no antibiotic administration or placebo, before invasive dental procedures in people at risk or at high risk of bacterial endocarditis, influences mortality, serious illness or the incidence of endocarditis (Rutherford et al. 2022). The review included 1 study where 48 people who had contracted bacterial endocarditis over a specific 2-year period and had undergone a medical or dental procedure with an indication for prophylaxis within the past 180 days were matched to a similar group of people who had not contracted bacterial endocarditis. All study participants had undergone an invasive medical or dental procedure. The 2 groups were compared to establish whether those who had received preventive antibiotics (penicillin) were less likely to have developed endocarditis. The authors found no significant effect of penicillin prophylaxis on the incidence of endocarditis. No data on other outcomes were reported. The level of certainty in the evidence was very low.

A systematic review and meta-analysis of antibiotic prophylaxis for IE published in 2017 included 36 studies: 10 time-trend studies, 5 observational studies and 21 trials (Cahill et al. 2017). All trials identified used bacteraemia as a surrogate endpoint rather than IE.

Meta-analysis was conducted on 3 studies with available data concerning the numbers of cardiac patients exposed to dental procedures, use of AP, and infective endocarditis outcome. Overall, the odds ratio (OR) for use of AP in patients with infective endocarditis was 0.59 (95% CI 0.27 to 1.30, p=0.14, I^2=48%), suggesting no statistically significant difference in exposure to AP between cases (patients with infective endocarditis) and controls, and moderate heterogeneity in the meta-analysis. All included observational studies were found to be at high risk of bias.

Thornhill et al. 2024 conducted cohort and case crossover studies on USA Medicaid patients with linked medical, dental and prescription data. For those at high IE-risk, AP was associated with a significant reduction in IE-risk (OR 0.20, 95% CI 0.06 to 0.53, p<0.0001) compared to no AP, particularly following extractions (OR 0.29, 95% CI 0.08 to 0.77, p<0.01). Although AP before oral surgery was also associated with a reduction in IE-risk (OR 0.40, 95% CI 0.04 to 1.75), this did not reach significance. The NNP (for example, the number of IDPs that would need to be AP covered to prevent 1 IE case) in those at high IE-risk was 244, 143, and 71 for IDPs, extractions and oral surgical procedures, respectively. The case crossover study found that although AP before IDPs in individuals at high IE-risk was associated with reduced likelihood of IE, this association did not reach statistical significance (OR 0.499, 95% CI 0.167 to 1.492). IE cases in this study were not restricted to the 30% to 40% of IE cases caused by oral streptococci, and therefore authors were unable to comment on the bacteraemia associated with each case of IE.

Vahasarja et al. 2023 conducted a nest case-control and case crossover study in a cohort of Swedish individuals at high risk of IE. The frequency of invasive dental procedures (IDPs) during the 3 months before Viridians Group Streptococcal Infective Endocarditis was calculated and compared to controls. The study could not confirm that IDPs were more common among cases (4.6%) than controls (4.1%), OR 1.22 (95% CI 0.64 to 2.3), or during case (3.3%) than reference periods (3.8%), OR 0.89 (95% CI 0.68 to 1.17). Restricting the analysis to the period when cessation of antibiotic prophylaxis for the prevention of IE in Swedish dentistry was recommended, from the 1st of October 2012 to the 1st of January 2018, did not alter the results of the case-control study: OR 0.64 (95% CI 0.20 to 2.09), or the case crossover study: OR 0.58 (95% CI 0.15 to 2.19).

Thornhill et al. 2022 performed a case crossover analysis and cohort study of the association between invasive dental procedures (IDP) and IE, and AP efficacy in the USA, using data from subjects with employer-provided Commercial/Medicare-Supplemental coverage. The cohort study found that the odds of developing IE were higher following invasive dental procedures compared with non-IDP procedures in high–IE-risk patients (OR

1.17; 95% CI 0.74 to 1.94), but that this was not statistically significant. However, sub-analysis of IDPs demonstrated that the odds of IE were statistically increased following extractions (OR 9.22; 95% CI 5.54 to 15.88; p<0.0001) and other oral surgical procedures (OR 20.18; 95% CI 11.22 to 36.74; p<0.0001). In the case crossover study AP administration before IDPs in individuals at high IE risk was associated with significant reduction in the odds of developing IE within 30 days (OR 0.49; 95% CI 0.29 to 0.85; p<0.01). IE cases in this study were not restricted to the 30% to 40% of IE cases caused by oral streptococci, and therefore authors were unable to comment on the bacteraemia associated with each case of IE.

Tubiana et al. 2017 conducted a nationwide population-based cohort and case-crossover study using French national health insurance administrative data linked with the national hospital discharge database. The study included all adults with medical procedure codes for positioning or replacement of prosthetic heart valves between 2008 and 2014. The main outcome measure was oral streptococcal IE. The cohort included 138,876 patients, 69,303 of whom underwent at least 1 dental procedure. In the antibiotic prophylaxis dental procedures model, no statistically significant difference was observed for the rate of oral streptococcal infective endocarditis after an invasive dental procedure without antibiotic prophylaxis compared with the non-exposure period (fully adjusted relative rate 1.57, 0.90 to 2.53; p=0.08). The case crossover study included 648 cases of patients with a primary discharge diagnosis of IE, 33 of whom had undergone an invasive dental procedure in the 3 months prior to IE diagnosis. Overall, in the dental procedures model, exposure to invasive procedures was more common during case periods than during the matched control periods (5.1% versus 3.2%; OR 1.66, 95% CI 1.05 to 2.63; p=0.03).

Budget impact and economic considerations

The 2008 NICE model was updated by the University of Sheffield for the 2015 update (the APPIE model). The base case analysis found that antibiotic prophylaxis using amoxicillin prior to dental procedures was not cost effective. The base case analysis found that antibiotic prophylaxis using clindamycin prior to dental procedures resulted in higher costs and reduced health effects compared with no prophylaxis, mainly due to the risk of fatal anaphylaxis associated with clindamycin. The results of the study were highly sensitive to the risk of developing infective endocarditis following a dental procedure, the efficacy of antibiotic prophylaxis to reduce this risk, and the cost of amoxicillin and clindamycin. Variation of these key parameters resulted in incremental cost-effectiveness ratios for antibiotic prophylaxis compared with no prophylaxis ranging from highly cost effective to highly cost ineffective and dominated (more costly and a reduction in health benefits). The

study was directly applicable because it complied with the NICE reference case for economic evaluations. It had only minor methodological limitations due to the limited evidence on the risk of developing infective endocarditis following a dental procedure and the efficacy of amoxicillin and clindamycin to reduce that risk.

System impact

Eighteen topic experts were contacted (June 2024) to comment on whether the recommendations for antibiotic prophylaxis for people undergoing invasive dental procedures were still appropriate, and whether they were aware of any published evidence that could impact on the recommendations since the guideline was last updated in 2015. Responses were received from seven topic experts, 4 of whom were dentists, 2 cardiologists and 1 general practitioner.

Four of the seven topic experts thought that the recommendation was no longer appropriate: 1 thought that the addition of the word 'routinely' to the recommendation in 2015 was unhelpful and ambiguous. Another expert recommended that NICE recommendations should be brought in line with ESC guidance and specifically clarify who should and should not be prescribed AP. All who agreed that the recommendation was no longer appropriate discussed the continuing publication of research in this area and contradiction with current recommendations. Other feedback through an informal meeting with members of the SDCEP was that dentists needed clear advice on this topic area, particularly further clarification on who 'routinely' refers to in the NICE recommendation, and that dentists may not be aware of the cardiologist led guidelines (AHA/ESC). They suggested that the recommendations in the NICE guideline could make better use of the implementation document, which provides additional information on the high-risk sub-group applicable to whom 'routinely' refers to in the NICE recommendation, to bring it to the attention of dentists across the UK.

Population impact

It is estimated that there are approximately 400,000 people who are at high-risk of IE, with 261 a year contracting IE, and 78 deaths. About 30% to 40% of the cases are caused by bacteria from the mouth, either from poor dental hygiene or invasive dental procedures.

Health inequalities

No inequalities issues were identified during the surveillance process. Proposed update to the guideline recommendations should not introduce new inequalities.

Impact of new evidence and intelligence

While high quality research evidence remains scarce, there is some evidence with uncertainty that a small proportion of IE in patients at high risk may be attributable to invasive dental procedures. Current wording of 'routinely' in NICE recommendations have been found to be unhelpful, but inclusion of the advice provided in the SDCEP implementation document will help clarify those patients that require special consideration for antibiotic prophylaxis. Inclusion of a direct link to this implementation plan in updated NICE recommendations would help address uncertainties faced by patients and dentists.

Overall decision

We will update bullet 1 of recommendation 1.1.3 on antibiotic prophylaxis against infective endocarditis for people undergoing invasive dental procedures to include a link to the Scottish Dental Clinical Effectiveness Programme's implementation advice.

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