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PRACTICE

UNCERTAINTIES

Do patients at risk of infective endocarditis need antibiotics before dental procedures?

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Infective endocarditis is a life threatening disease with 30% one year mortality[1] that affects 3-10 per 100 000 population per year—the average general practitioner will see one case every 20 years.[2] Infective endocarditis occurs when bacteria enter the bloodstream through the mouth, gut, or skin, and replicate within the heart to form a "vegetation," which is usually adherent to one of the valves (fig 1⇓, fig 2⇓). Specific patient subgroups are at increased risk of infective endocarditis as a result of damaged cardiac endothelium, abnormal blood flow, intracardiac prosthetic material, immunosuppression, or recurrent bacteraemia (box 1).[3 4]

Streptococci which colonise the mouth are the causative organism in 20%-40% of patients with infective endocarditis,[5 6] and poor oral hygiene is a known risk factor.[7] Invasive dental procedures that disrupt gingival integrity allow oral bacteria to access the circulation, which can lead to infective endocarditis in at-risk patients. Strategies that prevent bacteraemia or bacterial adherence might be expected to reduce the risk of infective endocarditis.

Oral antibiotic prophylaxis has been used for more than 50 years as a preventative strategy in at-risk patients undergoing invasive dental procedures.[8] The efficacy of antibiotic prophylaxis has been confirmed in animal models,[9] however the clinical evidence base is weak and its use has been challenged in the last decade. Nonetheless, guidelines from the European Society of Cardiology and the American Heart Association/American College of Cardiology committees continue to advocate antibiotic prophylaxis for those at highest risk.[10 11] Controversially, in 2008 the UK National Institute for Health and Care Excellence (NICE) advised complete cessation of antibiotic prophylaxis to prevent infective endocarditis.[12] In this article, we outline the evidence for and against antibiotic prophylaxis, the controversy surrounding its use, and ongoing research in the field. We provide a framework for clinical practice in the context of uncertainty.

What is the evidence of uncertainty?

Do invasive dental procedures cause infective endocarditis?

Invasive dental procedures cause bacteraemia, which is a necessary precursor to infective endocarditis,[13] but it is unclear if dental interventions cause infective endocarditis. In a prospective Dutch cohort of 427 cases of infective endocarditis, only 31 (11%) had undergone an invasive procedure (medical or dental) within the preceding 30 days.[14] In a French case control study of 171 infective endocarditis cases and matched controls, there was no substantial difference in the number of dental procedures in the preceding three months (odds ratio 1.2, 95% confidence interval 0.7 to 2.1).[15] In a similar case control study of 273 cases and matched controls, an invasive dental procedure was undertaken during the three months before infective endocarditis diagnosis in 36 cases (13.2%) and 27 controls (9.9%) (odds ratio 1.6, 95% confidence interval 0.8 to 3.4), suggesting no statistically significant risk associated with dental intervention.[4] More recently, a retrospective analysis of 739 patients in Taiwan found no increased likelihood of exposure to dental procedures in the three month period before infective endocarditis hospitalisation, compared with a control period when infective endocarditis did not develop.[16] These studies suggest that invasive dentistry is not the trigger for most cases of infective endocarditis, however the studies were conducted in populations already using antibiotic prophylaxis, which might mask an association. All studies were underpowered to address the question.[4-15]

If invasive dental procedures are not the main trigger, an alternative explanation is that community acquired infective endocarditis might arise from low level bacteraemia occurring

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What you need to know

- Patients with prosthetic heart valves, previous infective endocarditis, and some types of congenital heart disease are at highest risk of infective endocarditis
- Invasive dental procedures cause bacteraemia, which can be complicated by infective endocarditis in those at increased risk of the disease
- Antibiotic prophylaxis reduces the incidence of bacteraemia, but high level studies confirming that this reduces the incidence of infective endocarditis are lacking
- Warn high risk patients undergoing high risk dental interventions of the risk of infective endocarditis. Offer these patients antibiotic prophylaxis, and discuss with them the risks and benefits of this option
- Where patients are at moderate risk, encourage preventative measures, such as maintaining good oral hygiene and infection control, and discourage tattooing or piercing

Box 1: Risk factors for infective endocarditis

Cardiac

- Prosthetic heart valve*
- Previous infective endocarditis*
- Congenital heart disease* †
- Rheumatic heart disease
- Degenerative valve disease
- Cardiac transplant with valvulopathy
- Implantable electronic cardiac device (pacemaker or defibrillator)
- Hypertrophic cardiomyopathy

Non-cardiac

- Haemodialysis
- Diabetes mellitus
- Injected drug use
- Indwelling venous catheters
- Immunosuppression
- Poor oral hygiene

*at highest risk
†see specific subgroups in ⇓

as bacteria translocate across the relatively permeable oral mucosa in the course of everyday activities, such as chewing, flossing, or tooth brushing (especially in those with poor oral hygiene or periodontal disease).[17] The cumulative burden of this "everyday" bacteraemia is several orders of magnitude greater than rare episodes of "surgical" bacteraemia that result from dental procedures. This could explain why many cases of infective endocarditis arise in the absence of a preceding dental intervention.[18]

In the context of this uncertainty, a French population based cohort study published in this edition of the *The BMJ* is timely.[19] Among 138 876 adults with prosthetic heart valves, there was no statistically significant increase in the risk of oral streptococcal infective endocarditis in the three month period after an invasive dental procedure (risk ratio 1.25, 95% confidence interval 0.82 to 1.82, P=0.26) compared with controls exposed to non-invasive dental procedures. Findings were similar in the large subset of 21 471 patients undergoing procedures without antibiotic prophylaxis (49.9% of all invasive dental procedures; risk ratio 1.57, 95% confidence interval 0.90 to 2.53, P=0.08). Over median follow-up of 1.7 years, there were 267 cases—an incidence of oral streptococcal infective endocarditis of 93.7 per 100 000 person-years and overall rate of oral streptococcal infective endocarditis of 1.4 cases per 10 000 invasive dental procedures.

However, these findings were not replicated in a case crossover analysis in the same study, in which each of the cases served as their own control. The analysis compared the frequency of invasive dental procedures in the three months before a diagnosis of infective endocarditis with earlier control periods. Exposure to invasive dental procedures was substantially more frequent during case than control periods (5.1% *v* 3.2%, odds ratio 1.66, 95% confidence interval 1.05 to 2.63, P=0.03).

This description of a large, representative, population at risk of infective endocarditis is a valuable addition to the evidence base. The apparently discordant findings between analyses might be explained by unrecognised differences between the overall cohort and infective endocarditis cases: for example, oral hygiene and dental status were unknown on account of the limitations of coding. The case crossover analysis is likely to better control for individual patient risk factors and suggests that invasive dental procedures are associated with oral streptococcal infective endocarditis in some patients. Importantly, however, both analyses support the concept that most cases of infective endocarditis arise independently of invasive dental procedures.

If invasive dental procedures cause infective endocarditis in some patients, does antibiotic prophylaxis reduce the risk?

Antibiotic prophylaxis has been shown to reduce bacteraemia in multiple studies: a recent meta-analysis of 21 trials of antibiotic prophylaxis in patients undergoing dental intervention showed a substantial reduction in the incidence of post procedural bacteraemia (risk ratio 0.53, 95% confidence interval 0.49 to 0.57, P<0.01).[20] It is not clear, however, whether reduction in the incidence of bacteraemia translates into reduction in the incidence of infective endocarditis.

No randomised controlled trial of antibiotic prophylaxis for prevention of infective endocarditis has ever been conducted. The evidence base evaluating antibiotic prophylaxis is therefore derived from observational data. Meta-analysis of three case-control studies[15-22] showed no statistically significant association between cases and failure to use antibiotic prophylaxis (odds ratio 0.59, 95% confidence interval 0.27 to 1.30, P=0.14).[20] However, these studies were underpowered to address this question and were at high risk of intrinsic bias, so the overall level of evidence is weak.[20] Many of the patients within these studies were not high risk and would not be eligible for antibiotic prophylaxis according to current guidelines. The study published in this issue found that the crude incidence of infective endocarditis in the three months after an invasive dental procedure was lower in patients taking antibiotic prophylaxis (78.1 [95% confidence interval 1.6 to 154.6] *v* 149.5 [95% confidence interval 56.8 to 242.2] per 100 000 person years). These rates were not statistically significantly different, however, possibly because of the small number of cases in each group.[19] In a moderate size retrospective cohort study, a protective effect of antibiotic prophylaxis was identified in high risk patients with a prosthetic heart valve undergoing invasive procedures (a proportion of which were dental).[23] Similarly, a population based cohort study found a protective effect of antibiotic prophylaxis in individuals with cardiac conditions, using extrapolated estimates of the incidence of infective endocarditis after protected or unprotected dental procedures.[24]

An alternative observational approach has been to examine changes in the incidence of infective endocarditis after guideline amendments to restrict the use of antibiotic prophylaxis. In 2008, NICE recommended the cessation of antibiotic prophylaxis in the UK for all patients. Subsequent follow-up showed an 88% reduction in the use of antibiotic prophylaxis and an increase in the incidence of infective endocarditis above the projected historical trend (corresponding to an additional 35 cases in England per month).[2] This study, however, lacked microbiological data to confirm that this change was secondary to an increase in oral streptococci infective endocarditis. Similar studies in Europe and the USA have shown varying results, but in the context of continued antibiotic prophylaxis in high risk patients (table 1⇓). In July 2016, NICE updated its guidance to indicate that antibiotic prophylaxis is not recommended "routinely" and that "this amendment should make clear that in individual cases antibiotic prophylaxis may be appropriate."[36]

What are the risks and benefits of antibiotic prophylaxis?

There are legitimate concerns that the risks and low cost-effectiveness of antibiotic prophylaxis might outweigh the benefits.[37] Widespread use of antibiotic prophylaxis might contribute to antibiotic resistance, although this has not been linked specifically to single dose antibiotic prophylaxis, and the risk of anaphylaxis might exceed the protective effect of antibiotic prophylaxis. However, recent analysis of UK adverse event reporting identified only two adverse events per year and no deaths from antibiotic prophylaxis with single dose amoxicillin, and clindamycin antibiotic prophylaxis (used in penicillin allergic patients) resulted in twice as many adverse events and one death every three years.[38] Risk benefit analysis suggests that reinstatement of antibiotic prophylaxis for those at moderate or high risk of infective endocarditis would be associated with beneficial clinical effects overall.[39] Moreover, such a change would lead to cost savings of £5.5-£8.2 million and health gains of >2600 quality adjusted life years in England per annum.[40]

Is ongoing research likely to provide relevant evidence?

Infective endocarditis rarely arises after a dental intervention, so conducting a randomised controlled trial is challenging. It is unclear whether even an international multicentre trial would be able to recruit sufficient numbers of patients in a pragmatic timescale. In the last decade, national funding agencies in both the USA and UK have balked at the projected cost. Since the standard of care recommended by the European Society of Cardiology and American Heart Association/American College of Cardiology guidelines is that patients at highest risk of infective endocarditis should receive antibiotic prophylaxis, it is unclear whether a placebo controlled, "no antibiotic prophylaxis" trial would receive international ethical approval.

In this context, the priority is to further clarify the link between infective endocarditis and invasive dental procedures. To do this, we are conducting an observational study, the IDEA Study, to link NHS Digital hospital admissions data to the NHS Business Services Authority Dental Database and to determine whether the frequency of invasive dental procedures is higher in the three months before the diagnosis of infective endocarditis, compared with earlier three month "control" periods (https://www.journalslibrary.nihr.ac.uk/programmes/hta/155732/#/). This study will be highly powered to assess the link between invasive dentistry and infective endocarditis: in the proposed period of study between April 2009 and March 2015, there are data for 10 593 infective endocarditis admissions and 90.6 million invasive dental procedures. The study will be conducted in the English population, for whom antibiotic prophylaxis was not recommended during this period, thereby fully exposing any potential link between invasive dental procedures and infective endocarditis and the case crossover design will reduce any effect from residual confounders. Refuting a link between dental interventions and infective endocarditis would logically support a move away from antibiotic prophylaxis as a preventative strategy. Conversely, confirmation of the link would provide further justification for a randomised trial.

What should we do in light of the uncertainty?

The first step is to risk stratify the patient (fig 3⇓). Consistent with European Society of Cardiology and American Heart Association/American College of Cardiology guidelines, we advocate that antibiotic prophylaxis is only considered for high risk patients: those with prosthetic valves, previous infective endocarditis, or certain types of congenital heart disease. We also suggest dental risk stratification: high risk procedures are those in which there is manipulation of the gingival or periapical region of the teeth (fig 3⇓).

If both the patient and dental procedure are high risk, it is reasonable to offer the option of antibiotic prophylaxis. When offering antibiotic prophylaxis,

- outline what is known about the potential risks and benefits
- explain that the evidence base is weak
- reassure the patient that the overall risk of infective endocarditis after a dental intervention is extremely low (even in those at high risk).

For patients who choose antibiotic prophylaxis, we advise single dose amoxicillin 3 g given orally 60 minutes before the procedure, or clindamycin 600 mg in those who are allergic to penicillin.[41]

Educate patients at risk (including those with native valve disease or a bicuspid aortic valve, who are at moderate risk) of the importance of disease prevention. Advise patients on

- good oral hygiene with at least yearly dental review
- infection control including disinfection of cutaneous wounds, curative antibiotics for any focus of bacterial infection
- discourage tattooing or piercing
- the symptoms of infective endocarditis for patients at risk[42] (see supplementary file: Patient information leaflet on infective endocarditis).

Early diagnosis of infective endocarditis can be life saving but it requires a high index of suspicion among dentists, general practitioners, and hospital doctors.

Conflicts of interest BP does expert medicolegal work that sometimes involves discussions regarding the relationship to dental procedures and the need for antibiotic prophylaxis. BP has received payment for lectures on TAVI valves and has advised AstraZeneca on pharmaceuticals not related to endocarditis or valve disease. BP has an unrestricted educational grant to attend conferences from Edward Lifesciences. MD has advised St Jude Medical on new heart failure products and devices and his department has received funding from Novartis for studies on heart failure and myocardial infarction. MD also has had a relationship with Pfizer-Bristol Myers Squibb, Boehringer-Ingelheim and Biotronik not related to this article. MD has received educational support from Bayer to attend conferences.

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Recommendations for further research

A properly powered randomised controlled trial of antibiotic prophylaxis in dental procedures would resolve the current controversy over its efficacy in reducing the risk of developing infective endocarditis.

A registry of all infective endocarditis cases and associated microbiology would also greatly further our knowledge.

The IDEA study mentioned above will hopefully determine if there really is a link between invasive dental procedures and infective endocarditis.

Since the majority of endocarditis cases caused by oral bacteria appear to result from daily activities and poor oral hygiene rather than invasive dental procedures, we also need further research to elucidate the link between poor oral hygiene, periodontal disease, and infective endocarditis and to identify other methods, besides antibiotic prophylaxis, that could prevent infective endocarditis.

How patients were involved in this article

We are very grateful for comments and suggested changes to this article from two individuals whose spouses died of infective endocarditis, which developed after dental intervention.

Through the charity Heart Valve Voice (https://www.heartvalvevoice.com/) we approached patients at risk of infective endocarditis, who suggested that overall awareness of infective endocarditis is poor. Individual patients have found a lack of consensus regarding antibiotic prophylaxis and are consequently seeking unfiltered internet advice.

Search strategy

The search strategy for our systematic review addressing the efficacy of antibiotic prophylaxis before invasive dental procedures has been published in full at http://heart.bmj.com/content/early/2017/02/17/heartjnl-2015-309102.long.[20]

In summary, using subject headings or title/abstract keywords for bacterial endocarditis, antibiotics, and prophylaxis, we searched Medline, Medline In-Process (OvidSP), Embase (OvidSP), Cochrane Central Register of Controlled Trials (Cochrane Library, Wiley), Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effects (Cochrane Library, Wiley), Science Citation Index Expanded and Conference Proceedings Citation Index—Science (Web of Science Core Collection), Clinicaltrials.gov, and the WHO International Clinical Trials Registry Platform from inception up to 25 February 2016.

Education into practice

- How do you identify patients at high and moderate risk of infective endocarditis? How could you make this process more robust?
- Has this article given you new ideas about how to discuss antibiotic prophylaxis for invasive dental procedures with patients at risk of infective endocarditis?
- Do you routinely give all high risk patients an infective endocarditis patient leaflet like that in the supplementary file attached to this article?
- Are you aware of the cardinal symptoms of infective endocarditis? Do you make sure that your high risk patients are aware of how to spot these symptoms and what to do if they occur?

Table

Table 1| Time trend studies examining effect of antibiotic prophylaxis guideline change on the incidence of infective endocarditis (IE)

First author, year	PMID	Paper/abstract	Region, country	Population	Diagnosis	Study period	Guideline change. Level of antibiotic prophylaxis restriction	Increased incidence after-guideline change	Increase in rate of change of incidence after guideline	Guideline time point identified by change point analysis?
Bates 2016[25]	27418041	Paper	USA	Children ≤18 identified from Paediatric Health Information System Database (29 hospitals)	All cases: acute and subacute bacterial IE	2003-2014	AHA/ACC April 2007. Relative restriction	No	No	NA
Bikdeli 2013[26]	23994421	Paper	USA	Adults ≥65	All cases: principal or secondary discharge dx of IE	1999-2010	AHA/ACC April 2007. Relative restriction	No	NA	NA
Dayer 2015[2] **& Thornhill 2011**[27*]	25467569	Paper	UK	All	All cases: primary dx acute or subacute IE	January 1, 2000-March 31, 2013	NICE March 2008. Total restriction	Yes	Yes	Yes
DeSimone 2015[28] **& De Simone 2012**[29*]	26141329	Paper	Olmsted County, Minnesota, USA	Adults ≥18	VGS IE	January 1 1999-December 31 2013	AHA/ACC April 2007. Relative restriction	No	NA	NA
Duval 2012[30]	22624837	Paper	Greater Paris, Lorraine, and Rhône-Alpes regions of France	Adults ≥20	All cases of IE and subgroups by causative organism	Survey years 1991, 1999, 2008	French guideline restrictions 2002. Relative restriction	No	NA	NA
Keller 2016[31]	27816113	Paper	Germany	All patients hospitalised with acute or subacute IE	IE caused by Streptococcus and Staphylococcus (reported separately)	2005-2014	ESC October 2009. Relative restriction	Yes	Yes	No
Mackie 2016[32]	26868840	Paper	Canada (except Quebec and the Northern Territories)	All patients hospitalised with acute or subacute IE as main diagnosis	All hospitalisations with primary dx of IE	April 2002-March 2013	AHA/ACC April 2007. Relative restriction	Total IE increase, decrease in VGS	Yes	No
Pant 2015[33]	25975469	Paper	USA	Patients in Nationwide Inpatient Sample with ICD codes for IE	All cases of IE and subgroups by causative organism	2000-2011	AHA/ACC April 2007. Relative restriction	Yes	Yes	Not performed
Salam 2014[34]	NA	Abstract	Qatar	All patients hospitalised with IE in State of Qatar	All cases	2002-2012	AHA/ACC April 2007. Relative restriction	No	NA	NA

Table 1 (continued)

First author, year	PMID	Paper/abstract	Region, country	Population	Diagnosis	Study period	Guideline change. Level of antibiotic prophylaxis restriction	Increased incidence after-guideline change	Increase in rate of change of incidence after guideline	Guideline time point identified by change point analysis?
van den Brink 2016[35]	Pending	Paper	Netherlands	All patients identified from the national healthcare insurance database	All cases of IE	2005-2011	ESC October 2009. Relative restriction	Yes, substantial increase in VGS	Yes	NA

*Earlier publications from same research group using same methodology. Study with longer follow-up used for analysis

AHA/ACC: American Heart Association/American College of Cardiology

ESC: European Society of Cardiology

VGS: Viridans group streptococci

ICD: International Classification of Diseases

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Figures

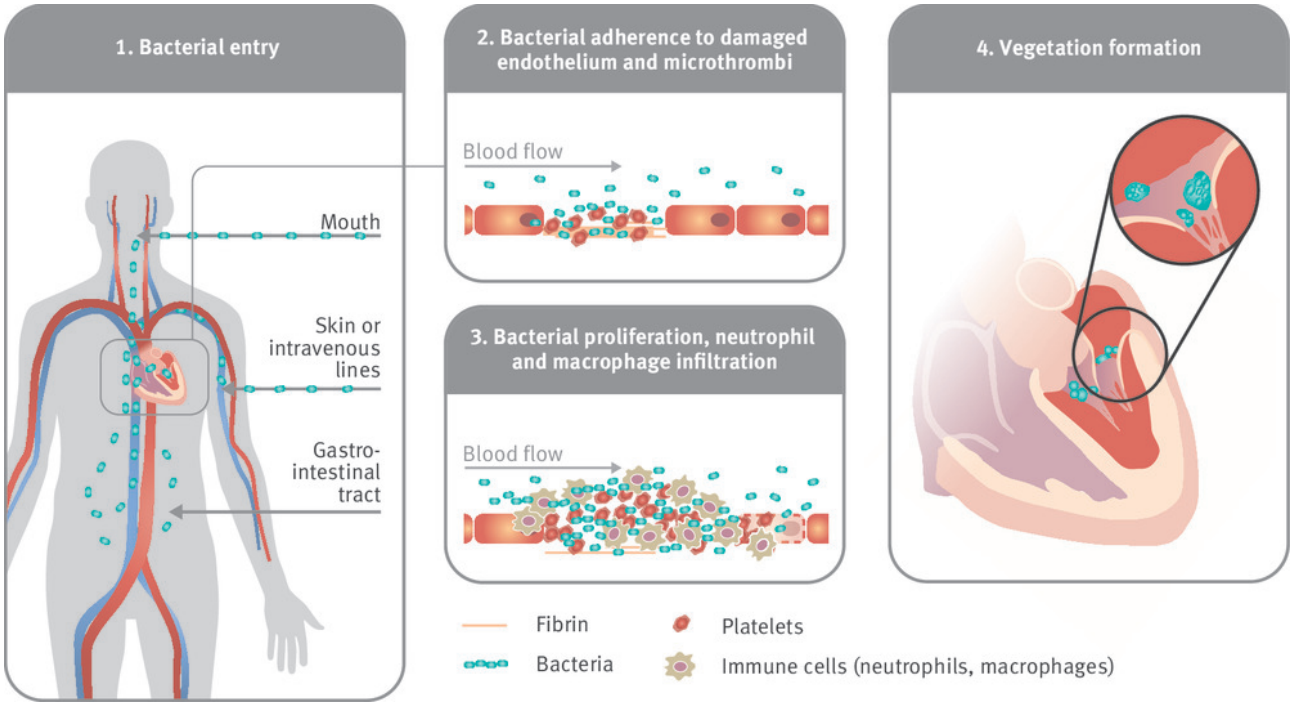

Fig 1 Pathogenesis of infective endocarditis

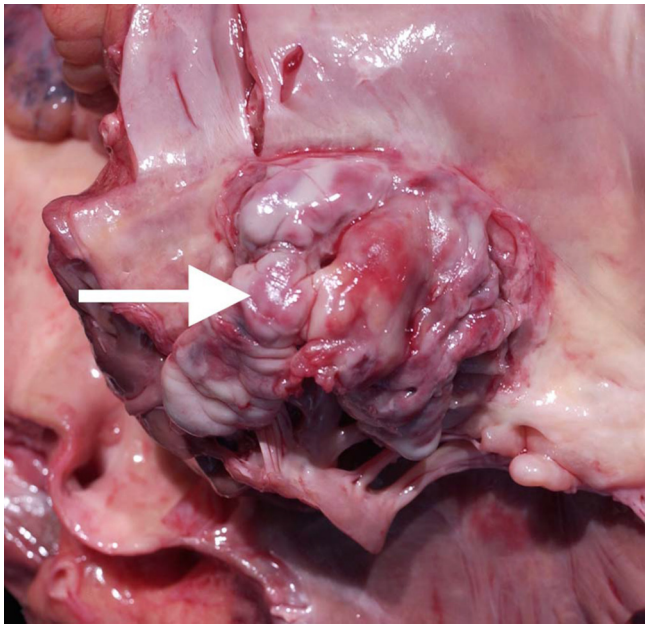

Fig 2 Infective endocarditis. Vegetation can be seen on the mitral valve (arrow)

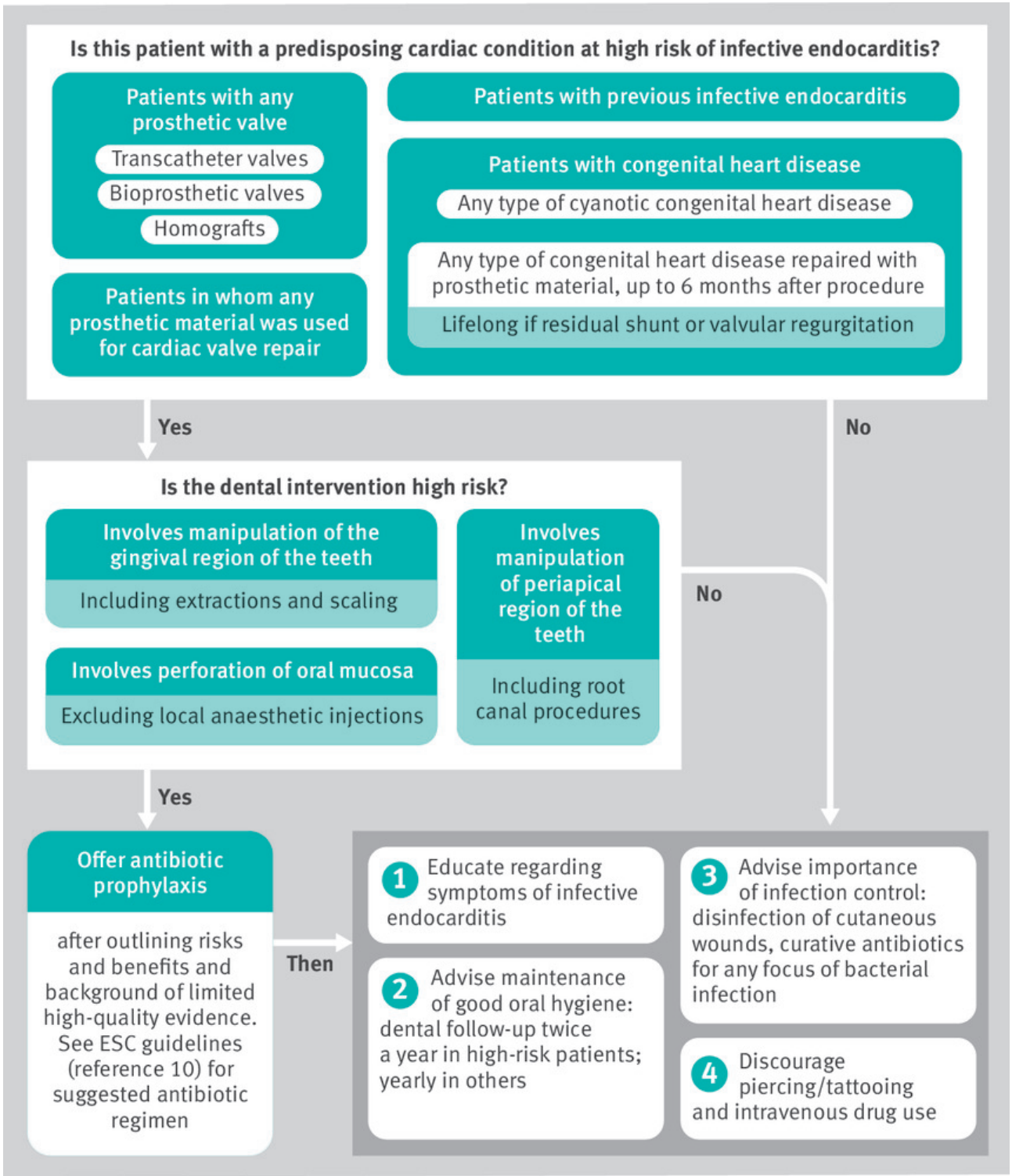

Fig 3 Identifying patients at risk of infective endocarditis who might benefit from antibiotic prophylaxis and other preventative measures