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Abstract: Infective endocarditis (IE) is a rare condition which is associated with considerable morbidity and mortality. Almost 100 years ago, the links between endocarditis and procedures, particularly dental procedures, were postulated. Over 50 years ago the first guidelines recommending antibiotic prophylaxis (AP), with the aim of preventing IE developing after procedures, were proposed. However, there has only ever been circumstantial evidence in humans that AP prevents IE. The rarity of IE has made a randomised controlled clinical trial impractical to date. This article outlines the history of AP and reviews the evidence base for the use of AP to prevent IE.

Is Antibiotic Prophylaxis to Prevent Infective Endocarditis Worthwhile?

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Conflicts of Interest

Neither Dr Mark Dayer or Professor Martin Thornhill have any relevant conflicts of interest to declare.

Abstract

Infective endocarditis (IE) is a rare condition which is associated with considerable morbidity and mortality. Almost 100 years ago, the links between endocarditis and procedures, particularly dental procedures, were postulated. Over 50 years ago the first guidelines recommending antibiotic prophylaxis (AP), with the aim of preventing IE developing after procedures, were proposed. However, there has only ever been circumstantial evidence in humans that AP prevents IE. The rarity of IE has made a randomised controlled clinical trial impractical to date. This article outlines the history of AP and reviews the evidence base for the use of AP to prevent IE.

Infective Endocarditis

Infective endocarditis is a rare infection, affecting around 5-10 people per 100,000 per annum.[1-3] It has a high morbidity, typically requiring prolonged courses of antibiotics and often valve replacement surgery. Mortality is also high, not only in hospital, but also in the first year after discharge. Consequently, this is a disease that is important to prevent, and for many years antibiotic prophylaxis prior to invasive, particularly dental, procedures has been normal practice across the world.

In Japan, a recent survey of 513 cases has described the epidemiology of the disease between 2007 and 2009.[4] The most common age of presentation was 61-80 years. 62% were men. 11% died. 69% of cases had known underlying heart disease; 36% of cases were related to native valve disease. Periodontitis / tooth decay was noted in 25%, and dental treatment was identified as a predisposing factor in 16% of cases, although the timing of intervention was not given. Approximately 1/3rd had AP, but it was unclear in another 1/3rd whether AP was used or not. Oral viridans group Streptococci (OVGS) were identified as the causative organism in 26% of cases. This is a relatively high percentage compared with other contemporary studies,[5, 6] and is a more "classical" picture of IE.[7]

This article will set out the history behind the development of AP as a potential preventative measure, and the evidence behind it. It will become clear that the evidence is not robust, and that practice reflects a consensus opinion, rather than strong evidence.

The Origins of Antibiotic Prophylaxis

In 1923 Lewis and Grant first suggested that infective endocarditis (IE) might be caused by bacteria released into the circulation during a dental procedure.[8] In 1935, Okell and Elliot confirmed that this was the case, isolating *Streptococcus viridans* in blood cultures in 84/138 (61%) of individuals.[9] Shortly after this, in 1941, the first recorded use of antibiotic prophylaxis (AP) took place.[10] In 1955 the American Heart Association (AHA) issued the first guidelines, stating that “It is good medical and dental practice to protect patients with rheumatic or congenital heart disease by prophylactic measures”.[11]

But, whereas many guidelines in other aspects of cardiology are clearly “evidence based”, guidelines for AP to prevent IE have largely been based on consensus. In 1962, Hook and Kaye stated “There is no proof that prophylaxis with antibiotics is effective … However, the use of prophylactic antibiotics appears to be a reasonable approach to the problem and the consensus of opinion strongly supports the use of antibiotics in this situation”.[12]

Since the original AHA guidelines, there have been many revisions and, furthermore, guidelines have been developed around the world to suit local populations. There is now considerable variation between countries as to what is recommended.

In Japan, patients considered to be at high risk, such as those with previous IE or a prosthetic valve, as well as patients at moderate risk, such as acquired valve disease or hypertrophic cardiomyopathy, are currently recommended to have AP.[13] In Europe and America, patients considered to be at high risk only are recommended to have AP prior to dental procedures.[14, 15] At the opposite extreme to Japan, UK guidelines recommend against AP.[16] This situation reflects the uncertainty as to whether AP is effective or not.

The Evidence for Antibiotic Prophylaxis

Antibiotic prophylaxis was initially based upon the assumption that giving antibiotics to individuals susceptible to IE, prior to a procedure known to release bacteria into the bloodstream, would reduce the risk of developing IE subsequently.

A number of different types of experiment have been performed to try to ascertain the efficacy of AP:

1. Animal studies.
2. The impact of antibiotics prior to dental, or other, procedures on bacteraemias in humans.
3. Case control and cohort studies.
4. Studies using administrative databases before and after changes to guidelines.
5. Studies using administrative databases to determine the impact of prophylaxis prior to procedures in at-risk individuals.

Animal Studies

David Durack and colleagues published the first animal model studies demonstrating that infective endocarditis might be prevented with prophylactic antibiotics in the early 1970s. In 1973, Durack and Petersdorf described an animal model of endocarditis. In this model, a polyethylene catheter was passed into the right side of the heart via the jugular vein, or the left side via the carotid artery and secured in place. After 1-3 days 10^8 colony-forming units of *Streptococcus viridans* was given intravenously. It was reported that this procedure produced endocarditis in every animal. To determine the efficacy of antibiotic prophylaxis, antibiotics were given orally, intramuscularly or intravenously, depending on the antibiotic. Procaine penicillin was successful in preventing Streptococcal endocarditis.[17] Other groups soon replicated the results. However, there has never been, to our knowledge, a systematic review of these studies.

The animal studies are often dismissed as being unrealistic models, both because of the presence of the indwelling catheter and the very large number of bacteria used to produce the bacteraemia. However, as medical knowledge progresses in a Bayesian fashion, the fact that these studies have been positive means that studies purporting to show an effect in humans are more likely to be true than would be the case If AP had not been shown to work in animal models; therefore, these results should not be overlooked.

The Impact of Antibiotic Prophylaxis Prior to Dental or Other Procedures on Bacteraemias in Humans

The impact of antibiotic prophylaxis prior to dental or other procedures on the development of bacteraemias in humans has been extensively studied. However, the effects of antibiotics are controversial, with some studies reporting a positive effect, and others not. More recent studies, carefully performed, have demonstrated that amoxicillin can reduce the frequency of bacteraemias, but that it is not 100% effective.[18, 19] Importantly, a number of more recent studies have suggested that clindamycin may not be particularly effective.[19, 20]

What has also become clear is that everyday activities, such as tooth-brushing, dental flossing and chewing,[18, 21-23] can also release bacteria into the bloodstream, although the frequency of bacteraemia is less than after a dental extraction and the duration less, suggesting that the magnitude of bacteraemia is also less. The frequency and magnitude of bacteraemia caused by daily activities is also likely to be influenced by the state of oral hygiene and presence of periodontal disease. Indeed, individuals with markers of poor oral hygiene are 4-8 times more likely to develop a bacteraemia with organisms that can cause IE following tooth brushing than those with better standards of oral hygiene.[24]

It has therefore been cogently argued that as dental interventions are relatively rare, whereas tooth brushing is common, it is illogical to give antibiotic prophylaxis, as there is no sense in preventing bacteraemia once or perhaps twice a year, when it is happening on a daily basis in between times. It is hard to argue with this stance, however, there are no studies which have reliably quantified the magnitude of bacteraemias after extractions in comparison with tooth-brushing or other similar activities, and it is unknown as to whether or not there is a threshold below which the number of bacteria present are unable to cause endocarditis. Furthermore, the argument does not exclude the possibility that AP may prevent some cases of IE.

Case Control and Cohort Studies

Case control and cohort studies have been undertaken in an effort to understand whether dental procedures can cause IE and also whether AP might be effective.

Horstkotte in 1986 compared 229 patients with prosthetic heart valves in whom 287 procedures were performed and who had AP, with 304 patients with prosthetic heart valves in whom 390 similar interventions were performed and who did not have AP.[25] In the first group no patient developed IE. In the second group, 6 developed IE within 14 days. This study has been cited frequently as evidence that AP works. However, due to the limited information contained within the study, more recent reviews have discounted it.[26]

Imperiale and Horowitz published a very small case control study in 1990.[27] They enrolled 8 patients with “high-risk” lesions who had IE for the first time on a native valve within 12 weeks of a dental procedure. They were matched with 3 patients who had also undergone a dental procedure and who had a similar valve lesion and age. AP was used by 1/8 patients and by 15/24 controls. They concluded that AP offered protection from IE. It is hard to draw conclusions from such a small study.

Van Der Meer et al. published two linked studies from the Netherlands in 1992. The first was an observational study of 427 cases with late prosthetic or native valve infective endocarditis.[28] 275 were eligible for AP with previously known valve disease or a prosthetic valve. Only 31 had undergone any invasive procedure within the previous 30 days. 8 of these had had AP. This study suggested that medical and dental procedures were responsible for only a small proportion of cases of IE and also that AP is inconsistently applied in the real world. The second study was a case-control study that examined the efficacy of antibiotic prophylaxis to prevent IE in patients with native valve disease.[29] 48 patients who developed IE within 180 days of a medical or dental procedure requiring AP were compared with 200 age-matched controls who had a relevant procedure but did not develop IE. Most patients and controls had undergone a dental procedure. AP was given to 8/48 cases and 26/200 controls. It was estimated that AP, when given to patients who had not had IE before, reduced the risk of developing IE within 30 days by 49%. However, it was noted, in the discussion, that 9/10 patients who developed IE did not develop IE as a consequence of a procedure, meaning that AP would only prevent a minority of cases.

Lacassin et al compared 171 cases of IE with 171 controls matched for age, sex and underlying heart condition.[30] They found no increased risk of IE for dental procedures as a whole, although scaling and root canal treatment came close to reaching conventional levels of significance. 48 subjects with known heart disease underwent a dental procedure (26 cases and 22 controls). 6 cases and 6 controls received AP. For *Streptococcus viridans* and those with negative blood cultures 3/18 cases received AP whereas 6/22 controls did. Although there was some evidence of protection therefore, this did not reach statistical significance.

Strom et al. published a case-control study in 1998. Patients with community acquired IE not associated with intravenous drug use were compared with healthy controls matched for age, sex and neighbourhood of residence. It was concluded that dental procedures were no more frequent in patients with IE than controls and that AP would be unlikely to prevent many cases, even if 100% effective.[31]

Taken together, these studies do not exclude the possibility that AP is effective, but the numbers are small, and precise definitions of cases, procedures and risk factors limited. What is clear is that AP will only prevent a small proportion of IE cases.

Studies Using Administrative Databases Before and After Changes to Guidelines

In recent times data collected at a national level has become available for analysis and has enabled researchers to assess the impact of guideline changes on the rates of infective endocarditis. We have recently reviewed this literature,[32] and further studies have been published since. The data is complex to interpret and conflicting in its conclusions.

It is first instructive to review the guideline changes that have been studied.

In 2007, the American Heart Association released new guidelines for antibiotic prophylaxis.[33] The previous iteration in 1997[34] had recommended antibiotic prophylaxis for patients at high risk, including those with prosthetic valves, previous bacterial endocarditis, complex cyanotic congenital heart disease and surgical shunts used to correct complex congenital heart disease. They also recommended antibiotic prophylaxis for patients deemed to be at moderate risk of developing endocarditis. These included patients with congenital heart disease, acquired valvular heart disease and hypertrophic cardiomyopathy. The 2007 guidance restricted antibiotic prophylaxis to those at high risk of developing or suffering an adverse outcome from IE. They also modified the criteria slightly, with more detail regarding congenital heart disease, and including patients who had undergone cardiac transplantation and had evidence of valve disease in the high-risk cohort.

The impact of this guideline change has been examined in both the United States and also Canada. Bikdeli et al. looked at Medicare beneficiaries in the United States.[35] Medicare patients are those aged greater than or equal to 65 years only. A total of 52,145 patients were hospitalised with a principal diagnosis of IE during the study period. They noted that the rates of infective endocarditis were falling, and that the fall appeared to accelerate after the guideline change.

Pant et al. used the Nationwide Inpatient Sample database.[36] This is a representative sample of all patients looked after in the US, and comprises about 20% of the population. In this study, the rates of infective endocarditis were rising, but there was no acceleration in the rate of rise after the guideline change. However, they reported that the incidence of endocarditis caused by all Streptococci (not just OVGS) did accelerate after the guideline change.

De Simone et al. also looked at the Nationwide Inpatient Sample, but they used different codes to Pant to identify patients more likely to have OVGS.[37] In contrast to the previous study, they found that the rates of infective endocarditis likely to be due to OVGS were falling after the guideline change.

Mackie et al. looked at the changes in Canada, except for patients in Quebec and the Northern Territories.[38] They noted a gradual rise in the of cases of infective endocarditis. The rate of rise did not change after the new guidelines were introduced. However, there was a trend that endocarditis cases likely to be due to OVGS were rising following the guideline change, whereas before there was a clear decline in the number of cases.[39]

Most recently, Toyoda et al. published one of the most detailed studies looking at the impact of the 2007 guidelines in the US.[6] They looked at trends in California and New York only. They noted no change in the number of cases of OVGS endocarditis, and a slight fall in the total number of cases of endocarditis since the guideline change.

A slightly different study by DeSimone looked at antibiotic prescribing in Olmstead county before and after the guideline change.[40] One of the criticisms that has been levelled at the studies above is that no assessment of antibiotic prescribing was made, and therefore the impact of the guideline change on clinical practice was unclear. This study demonstrated that the percentage of patients at moderate risk given AP fell dramatically and significantly after the introduction of the guidelines, from 64.6% to 8.6%. However, it cannot be assumed that these results can be generalised across the United States.

The European Society of Cardiology updated its 2004 guidelines[41] for the prevention of IE in 2009.[42] They adopted a similar approach to the Americans, moving from advising that patients at moderate or high risk should have AP, to just recommending it for patients at high risk.

Van den Brink et al. looked at the incidence of IE in the Netherlands before and after the ESC guideline change in 2009 using their National Healthcare Insurance Database.[43] There was a steady growth in the number of cases of IE over the time period, with no change in the rate of rise after 2009. However, as a sub-analysis, they also performed an in-depth review of all patients admitted with IE in 3 district general hospitals. They noted that there was a significant increase in the proportion of cases due to Streptococci after 2009 when compared with the time period before, from 31.1% to 53.2% (p=0.0031).

Keller et al. used Nationwide Inpatient Statistics to look at the change in IE incidence in Germany between 2005 and 2014.[3] These cover about 25% of the patients in Germany. In contrast to the van den Brink study, they demonstrated a significant rate of rise in the number of cases of IE after 2009. When they looked in more detail at cases due to Streptococci, however, there was no change in the rate of rise.

In March 2008 the National Institute for Health and Care Excellence published their recommendations regarding the use of AP in England.[44] To everyone's surprise they recommended that AP should no longer be used, citing the lack of strong evidence for its efficacy, and expressing concerns about potential side effects from the use of AP, the potential development of antibiotic resistance, and the cost. The UK went from prescribing AP widely to patients at moderate and high risk of IE to not using AP at all.[45]

Our group have investigated the impact of this change, publishing articles in the BMJ in 2011[46] and the Lancet in 2015 using Hospital Episode Statistics.[2] We have demonstrated that since the introduction of the NICE guidelines there has been a dramatic fall in antibiotic prescribing, from an average of 10,900 prescriptions per month before the guidelines were introduced, to 2,236 prescriptions per month (p<0.0001). We also showed that, starting in March 2008, the number of cases of infective endocarditis increased significantly above the projected historical trend, by 0.11 cases per 10 million people per month (95% CI 0.05-0.16, p<0.0001). To date, this is the only study to have looked at the impact of stopping AP for those at high-risk of IE as well as those at moderate-risk. It is also the only study to have looked at the effect of guideline change on AP prescribing as well as incidence of IE.

How to understand the variation in the conclusions of these studies? The first thing to appreciate is that the coding used between the various studies to identify cases of endocarditis is different (Table 1). Furthermore, only one study – the recent study published by Toyoda et al.[6] – published data on the sensitivity and specificity of the coding used in identifying cases of IE. Even this study did not confirm that coding has not changed over time. It is reasonable to hypothesise that coding has improved over time. Coding is used to determine funding in a number of countries and finance is becoming ever more important.

It is also important to realise that there are no ICD-9 or 10 codes that identify OVGS specifically. Again, codes used to identify cases of Streptococcal, and particularly OVGS endocarditis vary markedly between studies, making comparison difficult (Table 2).

Finally, these studies are observational and cannot explain the changes observed. Over the time periods studied there have been many changes, other than to guidelines for AP. Some of these, such as a growing and ageing society, better diagnostic techniques and the increasing use of new medical technologies such as percutaneous prosthetic valve insertion, may naturally tend to increase rates of endocarditis. Other changes, such as a focus on practices to reduce healthcare associated infection, most notably espoused by such organisations as the Institute for Healthcare Improvement, may tend to reduce rates.

In conclusion, despite earlier hopes, taken together, these studies have not answered the question as to whether antibiotic prophylaxis is effective.

Studies Using Administrative Databases to Determine the Impact of Prophylaxis Prior to Procedures in At-Risk Individuals

It is clear from some of the cohort studies that AP is given inconsistently, i.e. not all patients recommended for AP by guidelines are given AP in real life. By combining prescribing data, dental procedure data, and hospital record data it should be possible to observe whether AP is effective or not. It does require quite sophisticated administrative systems, and often requires particular permissions to allow the synthesis of data across databases to avoid transgressing data protection regulations.

The first of these such studies, and we are aware of at least one other which is in progress, has recently been accepted for publication. Tubiana et al.[47] identified 138,076 individuals with a prosthetic valve in France, and followed them for a total of 285,034 person-years. 69,303 individuals underwent 103,463 dental procedures which had an indication for AP. However, AP was given in only 50.5% of these cases. A total 267 patients developed IE likely to have been caused by OVGS during the follow-up period. Of these, a total of 4 patients developed IE within 3 months of an invasive dental procedure after receiving AP, whereas 10 who did not receive AP developed IE within 3 months of the procedure. This difference approached, but did not reach significance (p=0.08).

This study is important. It again suggests that AP may be effective, but importantly confirms that, firstly AP is given inconsistently in the real world, and also that even if AP is effective it is unlikely to prevent large numbers of cases of IE. It is imperative that this study is replicated in other countries where such data is available.

What are the risks and costs of AP?

In order to determine if AP should be recommended, it is not enough to simply assess whether or not AP can prevent cases of IE. It is also important to understand the potential adverse effects of giving AP.

In the UK, we reviewed “Yellow Card” data to determine the rate of adverse events from the use of amoxicillin and clindamycin as antibiotic prophylaxis.[48] “Yellow Cards” are completed by health care professionals when adverse drug reactions are recorded, particularly after the introduction of a medication or if there has been a severe side effect. Over a 34-year period, there were no fatal reactions recorded with a single 3g oral dose of Amoxicillin and we could find no other reports of a fatal reaction in the world-wide literature either. For clindamycin given as a single 600mg dose orally, however, we identified 13 fatal reactions per million prescriptions. Most were due to Clostridium Difficile infection. If you believe that AP is effective, then it is easy to recommend amoxicillin as AP, as the risks of a fatal complication are extremely low. However, if a patient requires Clindamycin, then the decision to give AP is a little more nuanced, and is likely to require a more careful discussion with the patient.

Combining data from the Lancet paper with the Yellow Card data enabled us to determine the cost-effectiveness of AP.[49] We demonstrated that for patients at high-risk, AP would only have to prevent 3 cases every 2 years to be cost effective.

The impact of AP on antibiotic resistance has not been formally assessed, and is an important consideration. As a community, we have a duty to minimise the prescription of antibiotics wherever possible. However, antibiotic resistance is believed to be encouraged when repeated courses of antibiotics at inadequate doses are given and is minimised by infrequent doses of antibiotics at high doses – as is the case for AP.[50]

Conclusions

It remains unclear as to whether AP is effective. It is a subject which divides clinicians. A quote by Stuart Chase, an American economist, is apt: “For those who believe, no proof is necessary. For those who don’t believe, no proof is possible.”

There are no adequately powered randomised controlled clinical trials (RCTs) to help inform decision making in this field, and due to the rarity of the disease, there may never be. Therefore, a different approach is required, as elegantly discussed by Thomas Freiden in an article in the New England Journal of Medicine.[51]

What is required is a synthesis of the evidence that does exist, followed by an honest balancing of the risks and benefits. We believe that when the evidence is taken as a whole it is impossible to exclude the possibility that AP does have an impact, albeit small. Furthermore, AP, particularly amoxicillin appears safe. Because IE is a devastating illness, very few cases have to be prevented to make it cost effective. There are clearly concerns about the promotion of antibiotic resistance and the overall costs of healthcare, but AP is cheap and the recommended dosing regimens are likely to minimise the development of antibiotic resistance.

The concept of marginal gains has become important in many fields in recent years, particular in sports such as cycling. It seems likely that a similar strategy is required to reduce the burden of IE and to improve outcomes. We believe, when all of the evidence is considered, that AP is just one such “marginal gain” in the ongoing battle against IE, and that the benefits outweigh the risks, particularly for the use of AP in those at high-risk of IE, and possibly for those at moderate-risk, although we accept that definitive evidence is lacking.

References

1. Hoen B and Duval X. Clinical practice. Infective endocarditis. N Engl J Med. 2013;368:1425-33.
2. Dayer MJ, Jones S, Prendergast B, Baddour LM, Lockhart PB and Thornhill MH. Incidence of infective endocarditis in england, 2000-13: A secular trend, interrupted time-series analysis. Lancet. 2015;385:1219-28.
3. Keller K, von Bardeleben RS, Ostad MA, Hobohm L, Munzel T, Konstantinides S and Lankeit M. Temporal trends in the prevalence of infective endocarditis in germany between 2005 and 2014. Am J Cardiol. 2017;119:317-22.
4. Nakatani S, Mitsutake K, Ohara T, Kokubo Y, Yamamoto H, Hanai S and Investigators C. Recent picture of infective endocarditis in japan--lessons from cardiac disease registration (cadre-ie). Circ J. 2013;77:1558-64.
5. Slipczuk L, Codolosa JN, Davila CD, Romero-Corral A, Yun J, Pressman GS and Figueredo VM. Infective endocarditis epidemiology over five decades: A systematic review. PLoS One. 2013;8:e82665.
6. Toyoda N, Chikwe J, Itagaki S, Gelijns AC, Adams DH and Egorova NN. Trends in infective endocarditis in california and new york state, 1998-2013. JAMA. 2017;317:1652-60.
7. Iwakura K. Current profile of infective endocarditis in japan. Circ J. 2013;77:1411-3.
8. Lewis T and Grant R. Observations relating to subacute infective endocarditis. Heart. 1923;10:21-77.
9. Okell CC and Elliott SD. Bacteraemia and oral sepsis: With special reference to the aetiology of subacute endocarditis. Lancet. 1935;226:869-72.
10. Thomas CB, France R and Reichsman F. Prophylactic use of sulfanilamide. JAMA. 1941;116:551-60.
11. Jones TD, Baumgartner L, Bellows MT, Breese BB, Kuttner AG, McCarty M and Rammelkamp CH. Prevention of rheumatic fever and bacterial endocarditis through control of streptococcal infections. Circulation. 1955;11:317-20.
12. Hook EW and Kaye D. Prophylaxis of bacterial endocarditis. J Chronic Dis. 1962;15:635-46.
13. Guidelines on the prevention and treatment of infective endocarditis. JCS. 2008.
14. Wilson W, Taubert KA, Gewitz M, Lockhart PB, Baddour LM, Levison M, Bolger A, Cabell CH, Takahashi M, Baltimore RS, Newburger JW, Strom BL, Tani LY, Gerber M, Bonow RO, Pallasch T, Shulman ST, Rowley AH, Burns JC, Ferrieri P, Gardner T, Goff D, Durack DT and American Heart A. 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. J Am Dent Assoc. 2008;139 Suppl:3S-24S.
15. Habib G, Lancellotti P, Antunes MJ, Bongiorni MG, Casalta JP, Del Zotti F, Dulgheru R, El Khoury G, Erba PA, Iung B, Miro JM, Mulder BJ, Plonska-Gosciniak E, Price S, Roos-Hesselink J, Snygg-Martin U, Thuny F, Tornos Mas P, Vilacosta I, Zamorano JL, Document R, Erol C, Nihoyannopoulos P, Aboyans V, Agewall S, Athanassopoulos G, Aytekin S, Benzer W, Bueno H, Broekhuizen L, Carerj S, Cosyns B, De Backer J, De Bonis M, Dimopoulos K, Donal E, Drexel H, Flachskampf FA, Hall R, Halvorsen S, Hoen B, Kirchhof P, Lainscak M, Leite-Moreira AF, Lip GY, Mestres CA, Piepoli MF, Punjabi PP, Rapezzi C, Rosenhek R, Siebens K, Tamargo J

and Walker DM. 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;36:3075-128.

16. Prophylaxis against infective endocardits. National institute for health and care excellence. 2008.

17. Durack DT and Petersdorf RG. Chemotherapy of experimental streptococcal endocarditis. I. Comparison of commonly recommended prophylactic regimens. J Clin Invest. 1973;52:592-8.

18. Lockhart PB, Brennan MT, Sasser HC, Fox PC, Paster BJ and Bahrani-Mougeot FK. Bacteremia associated with toothbrushing and dental extraction. Circulation. 2008;117:3118-25.

19. Limeres Posse J, Alvarez Fernandez M, Fernandez Feijoo J, Medina Henriquez J, Lockhart PB, Chu VH and Diz Dios P. Intravenous amoxicillin/clavulanate for the prevention of bacteraemia following dental procedures: A randomized clinical trial. J Antimicrob Chemother. 2016;71:2022-30.

20. Diz Dios P, Tomas Carmona I, Limeres Posse J, Medina Henriquez J, Fernandez Feijoo J and Alvarez Fernandez M. Comparative efficacies of amoxicillin, clindamycin, and moxifloxacin in prevention of bacteremia following dental extractions. Antimicrob Agents Chemother. 2006;50:2996-3002.

21. Mougeot FK, Saunders SE, Brennan MT and Lockhart PB. Associations between bacteremia from oral sources and distant-site infections: Tooth brushing versus single tooth extraction. Oral Surg Oral Med Oral Pathol Oral Radiol. 2015;119:430-5.

22. Maharaj B, Coovadia Y and Vayej AC. An investigation of the frequency of bacteraemia following dental extraction, tooth brushing and chewing. Cardiovasc J Afr. 2012;23:340-4.

23. Tomas I, Diz P, Tobias A, Scully C and Donos N. Periodontal health status and bacteraemia from daily oral activities: Systematic review/meta-analysis. J Clin Periodontol. 2012;39:213-28.

24. Lockhart PB, Brennan MT, Thornhill M, Michalowicz BS, Noll J, Bahrani-Mougeot FK and Sasser HC. Poor oral hygiene as a risk factor for infective endocarditis-related bacteremia. J Am Dent Assoc. 2009;140:1238-44.

25. Horstkotte D, Friedrichs W, Pippert H, Bircks W and Loogen F. [benefits of endocarditis prevention in patients with prosthetic heart valves]. Z Kardiol. 1986;75:8-11.

26. Oliver R, Roberts GJ, Hooper L and Worthington HV. Antibiotics for the prophylaxis of bacterial endocarditis in dentistry. Cochrane Database Syst Rev. 2008, doi 10.1002/14651858.CD003813.pub3:CD003813.

27. Imperiale TF and Horwitz RI. Does prophylaxis prevent postdental infective endocarditis? A controlled evaluation of protective efficacy. Am J Med. 1990;88:131-6.

28. Van der Meer JT, Thompson J, Valkenburg HA and Michel MF. Epidemiology of bacterial endocarditis in the netherlands. Ii. Antecedent procedures and use of prophylaxis. Arch Intern Med. 1992;152:1869-73.

29. Van der Meer JT, Van Wijk W, Thompson J, Vandenbroucke JP, Valkenburg HA and Michel MF. Efficacy of antibiotic prophylaxis for prevention of native-valve endocarditis. Lancet. 1992;339:135-9.

30. Lacassin F, Hoen B, Leport C, Selton-Suty C, Delahaye F, Goulet V, Etienne J and Briancon S. Procedures associated with infective endocarditis in adults. A case control study. Eur Heart J. 1995;16:1968-74.
31. Strom BL, Abrutyn E, Berlin JA, Kinman JL, Feldman RS, Stolley PD, Levison ME, Korzeniowski OM and Kaye D. Dental and cardiac risk factors for infective endocarditis. A population-based, case-control study. Ann Intern Med. 1998;129:761-9.
32. Cahill TJ, Harrison JL, Jewell P, Onakpoya I, Chambers JB, Dayer M, Lockhart P, Roberts N, Shanson D, Thornhill M, Heneghan CJ and Prendergast BD. Antibiotic prophylaxis for infective endocarditis: A systematic review and meta-analysis. Heart. 2017;103:937-44.
33. Wilson W, Taubert KA, Gewitz M, Lockhart PB, Baddour LM, Levison M, Bolger A, Cabell CH, Takahashi M, Baltimore RS, Newburger JW, Strom BL, Tani LY, Gerber M, Bonow RO, Pallasch T, Shulman ST, Rowley AH, Burns JC, Ferrieri P, Gardner T, Goff D, Durack DT, American Heart Association Rheumatic Fever E, Kawasaki Disease Committee CoCDitY, Council on Clinical C, Council on Cardiovascular S, Anesthesia, Quality of C, Outcomes Research Interdisciplinary Working G and American Dental A. 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. J Am Dent Assoc. 2007;138:739-45, 47-60.
34. Dajani AS, Taubert KA, Wilson W, Bolger AF, Bayer A, Ferrieri P, Gewitz MH, Shulman ST, Nouri S, Newburger JW, Hutto C, Pallasch TJ, Gage TW, Levison ME, Peter G and Zuccaro G, Jr. Prevention of bacterial endocarditis: Recommendations by the american heart association. Clin Infect Dis. 1997;25:1448-58.
35. Bikdeli B, Wang Y, Kim N, Desai MM, Quagliarello V and Krumholz HM. Trends in hospitalization rates and outcomes of endocarditis among medicare beneficiaries. J Am Coll Cardiol. 2013;62:2217-26.
36. Pant S, Patel NJ, Deshmukh A, Golwala H, Patel N, Badheka A, Hirsch GA and Mehta JL. Trends in infective endocarditis incidence, microbiology, and valve replacement in the united states from 2000 to 2011. J Am Coll Cardiol. 2015;65:2070-6.
37. DeSimone DC, Tleyjeh IM, Correa de Sa DD, Anavekar NS, Lahr BD, Sohail MR, Steckelberg JM, Wilson WR, Baddour LM and Mayo Cardiovascular Infections Study G. Incidence of infective endocarditis due to viridans group streptococci before and after the 2007 american heart association's prevention guidelines: An extended evaluation of the olmsted county, minnesota, population and nationwide inpatient sample. Mayo Clin Proc. 2015;90:874-81.
38. Mackie AS, Liu W, Savu A, Marelli AJ and Kaul P. Infective endocarditis hospitalizations before and after the 2007 american heart association prophylaxis guidelines. Can J Cardiol. 2016;32:942-8.
39. Mackie AS, Liu W, Savu A, Marelli AJ and Kaul P. Reply to letter from thornhill et al.-infective endocarditis hospitalizations before and after the 2007 american heart association prophylaxis guidelines. Can J Cardiol. 2016;32:1578 e11.
40. DeSimone DC, El Rafei A, Challener DW, Carr AB, Kelly JA, Rocca WA, St Sauver JL, Bock-Goodner CM, Lahr BD, Steckelberg JM, Wilson WR and Baddour LM. Effect of the american heart association 2007 guidelines on the practice of dental prophylaxis for the prevention of infective endocarditis in olmsted county, minnesota. Mayo Clin Proc. 2017, doi 10.1016/j.mayocp.2017.03.013.

41. Horstkotte D, Follath F, Gutschik E, Lengyel M, Oto A, Pavie A, Soler-Soler J, Thiene G, von Graevenitz A, Priori SG, Garcia MA, Blanc JJ, Budaj A, Cowie M, Dean V, Deckers J, Fernandez Burgos E, Lekakis J, Lindahl B, Mazzotta G, Morais J, Oto A, Smiseth OA, Lekakis J, Vahanian A, Delahaye F, Parkhomenko A, Filipatos G, Aldershvile J, Vardas P, Task Force Members on Infective Endocarditis of the European Society of C, Guidelines ESCCfP and Document R. 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;25:267-76.
42. Habib G, Hoen B, Tornos P, Thuny F, Prendergast B, Vilacosta I, Moreillon P, de Jesus Antunes M, Thilen U, Lekakis J, Lengyel M, Muller L, Naber CK, Nihoyannopoulos P, Moritz A, Zamorano JL and Guidelines ESCCfP. 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;30:2369-413.
43. van den Brink FS, Swaans MJ, Hoogendijk MG, Alipour A, Kelder JC, Jaarsma W, Eefting FD, Groenmeijer B, Funke Kupper AJ and ten Berg JM. Increased incidence of infective endocarditis after the 2009 european society of cardiology guideline update: A nationwide study in the netherlands. European Heart Journal: Quality of Care and Clinical Outcomes. 2016;3:141-7.
44. Prophylaxis against infective endocarditis. Antimicrobial prophylaxis against infective endocarditis in adults and children undergoing interventional procedures. NICE Clinical Guideline 64. 2008.
45. Ramsdale DR, Turner-Stokes L, Advisory Group of the British Cardiac Society Clinical Practice C, Effectiveness RCPC and Evaluation U. Prophylaxis and treatment of infective endocarditis in adults: A concise guide. Clin Med. 2004;4:545-50.
46. Thornhill MH, Dayer MJ, Forde JM, Corey GR, Chu VH, Couper DJ and Lockhart PB. Impact of the nice guideline recommending cessation of antibiotic prophylaxis for prevention of infective endocarditis: Before and after study. BMJ. 2011;342:d2392.
47. Tubiana S, Blotiere P, Hoen B, Lesclous P, Millot S, Rudant J, Weill A, Coste J, Alla F, Duval X and Bichat C. Dental procedures, antibiotic prophylaxis and endocarditis among individuals with cardiac prosthetic valves: A nationwide population-based cohort and case-crossover study. BMJ. 2017;358:jXXXX.
48. Thornhill MH, Dayer MJ, Prendergast B, Baddour LM, Jones S and Lockhart PB. Incidence and nature of adverse reactions to antibiotics used as endocarditis prophylaxis. J Antimicrob Chemother. 2015;70:2382-8.
49. Franklin M, Wailoo A, Dayer MJ, Jones S, Prendergast B, Baddour LM, Lockhart PB and Thornhill MH. The cost-effectiveness of antibiotic prophylaxis for patients at risk of infective endocarditis. Circulation. 2016;134:1568-78.
50. Opatowski L, Mandel J, Varon E, Boelle PY, Temime L and Guillemot D. Antibiotic dose impact on resistance selection in the community: A mathematical model of beta-lactams and streptococcus pneumoniae dynamics. Antimicrob Agents Chemother. 2010;54:2330-7.
51. Frieden TR. Evidence for health decision making - beyond randomized, controlled trials. N Engl J Med. 2017;377:465-75.

Tables

Table 1

Codes used to identify cases of infective endocarditis

Studies	Year	P +/- S	ICD-9										ICD-10		
			421.0	421.1	421.9	424.9	112.81	036.42	098.84	115.04	115.14	115.94	I33.0	I33.9	I38
Bikdeli	2013	P+S	X	X	X	X									
Pant	2015	P+S	X	X	X										
DeSimone	2015	P	X												
Mackie	2016	P	X	X	X								X	X	
Toyoda	2017	P+S	X	X	X	X	X	X	X	X	X	X			
Dayer	2015	P											X		
Keller	2016	P+S											X		
Van den Brink	2016	N/A	ICD-9/10 codes not used; unique code in database												

P – Code searched for in primary position only; P+S – Codes searched for in any position

Table 2

Codes used to identify oral viridans group Streptococci (OVGS)

Studies	Year	ICD-9										ICD-10								
		0380	0382	0410	04100	04101	04102	04103	04104	04105	04109	B95.0	B95.1	B95.2	B95.3	B95.4	B95.5	A40.8	A40.9	A49.1
Bikdeli	2013	None																		
Pant	2015	X	X	X	X	X	X	X	X	X	X									
DeSimone	2015				X						X									
Mackie	2016	X			X						X					X	X	X	X	X
Toyoda*	2017				X						X									
Dayer	2015	None																		
Keller	2016											X	X	X	X	X	X			
Van den Brink	2016	Subset of patients from 3 general hospitals with IE had their case notes reviewed directly; no population sample																		

* Positive predictive value for OVGS: 84% (68-100%)