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This issue of Mayo Clinic Proceedings contains an important report by De Simone et. al. that investigates the impact of the 2007 American Heart Association (AHA) guidelines on the prescribing of antibiotic prophylaxis (AP) by dentists to protect patients at risk of infective endocarditis (IE) from developing the disease following invasive dental procedures.[1] Infective endocarditis affects the endocardial lining of the heart, particularly the valve leaflets, and has a yearly incidence of 3-10 per 100,000 in most parts of the world.[2] It is characterized by the development of infected heart valve vegetations, and prognosis is poor, with 15-20% mortality during the initial hospital admission, increasing to approximately 30% by the end of the first year.[2] The concept that bacteria released into the circulation during invasive dental procedures might cause IE was first suggested by Lewis and Grant in 1923,[3] and in 1935 Okell and Elliott[4] discovered that following dental extractions 61% of patients had a positive blood culture for oral viridans group Streptococci. The latter group also found that oral viridans group Streptococci could be isolated from the damaged heart tissue of 40-45% of IE cases they examined.[3]

In 1955, soon after antibiotics became widely available, the AHA produced the first guidelines recommending the use of AP to prevent IE in those considered at risk of the disease and who were undergoing invasive procedures (including dental procedures). Over time, AP recommendations have become simpler and more focussed. Prior to 2007, AHA guidelines recommended AP for those undergoing invasive dental procedures who were considered at high-risk or moderate-risk of developing IE, but in 2007 the AHA recommended that it should be given only to those at high-risk.[5] In 2009, the European Society of Cardiology (which sets guidance for most of Europe),[6] and most other guideline committees around the world, followed suit. The exception was the United Kingdom, where the quasi-governmental National Institute for Health and Care Excellence (NICE)

recommended the complete cessation of AP in 2008.[7] This decision was based on the lack of randomized placebo controlled trial (RCT) evidence to support the efficacy of AP and their assessment of the lack of cost-effectiveness of AP.

The best evidence for AP efficacy would come from a RCT. Unfortunately, a RCT has never been performed and it is unlikely one will be performed in the foreseeable future. AP is a prevention strategy, and IE is comparatively rare. This means that hundreds of patients at risk of endocarditis would need to receive AP to prevent one case, and many thousands of individuals at risk of endocarditis would need to be randomized to placebo or prophylaxis to have sufficient statistical power to detect an effect.[8] This means that the size, cost, and complexity of a RCT would be enormous. A further barrier is the ethical concern about randomizing individuals at risk of endocarditis to placebo.

An alternative is to use observational studies to see if changes in AP guidelines have altered the incidence of IE, and several studies have done this. DeSimone et al refer to the observational study by Dayer et al.[9] This study used administrative data for the whole of England to study the effect of the 2008 NICE guidelines on the prescribing of AP and the incidence of IE in England. It found an 89% decrease in AP prescribing and a significant increase in the incidence of IE. As observational data, however, the Dayer et al research did not prove a cause-and-effect relationship between these changes and the 2008 NICE guidance, and therefore did not meet the criteria set by NICE to change its guidance. Nonetheless, following further debate, as well as the publication of data showing the low incidence of adverse drug reactions with AP[10] and the cost-effectiveness of AP,[11] NICE amended its guidance in 2016 to make clear that in individual cases antibiotic prophylaxis may be appropriate.[12]

The Dayer et al study also showed the very large population needed to achieve the statistical power to identify a significant increase in the incidence of IE associated with changes in AP prescribing.[9] In the Dayer et al study, NICE guidance changed from recommending AP for moderate- and high-risk individuals to recommending no AP. The population needed to power a study looking at a change from recommending AP for those at moderate- and high-risk of IE to recommending it just for those at high-risk would be even larger than the number needed to power the Dayer et al study. Unfortunately, several of the studies that claimed to demonstrate no change in the incidence of IE following AHA or European Society of Cardiology guideline changes were underpowered to detect a change.[13] This means we cannot be sure if there really was no change in IE incidence or if the lack of change was caused by the study having insufficient power to detect it. It is important therefore to ensure such studies are adequately powered.

Recently, several studies have, like the Dayer et al study, used large administrative data sets to increase the population size being studied when looking at the effect of the AHA or European Society of Cardiology guideline changes, and some have claimed to demonstrate a significant increase in IE.[14-17] Again however, it is impossible to prove a cause-and-effect relationship with observational studies like this. In addition, studies to date, (with the exception of the Dayer et al study) have lacked data to demonstrate the size and timing of any associated change in AP prescribing. Accompanying AP prescribing data is essential for any study that intends to claim that a guideline change had no effect on IE incidence. No change in incidence could simply be the result of no change in AP prescribing. Prescribing data are also essential for the power calculations needed to demonstrate that a study has the statistical power to detect a change. Even when AP prescribing data are available, failure of patient compliance in taking AP could confound attempts to prove AP efficacy.

The DeSimone et al study is the first from North America to show that the 2007 AHA guideline change did indeed result in a highly significant reduction in AP prescribing by dentists, and this is an important first. Indeed, the size and timing of the change was closely similar to that observed in England.[9] If the small number of dentists studied reflects the response of dentists nationwide, this suggests a high level of compliance with the AHA guideline change.

DeSimone et al also identified some concerns, however. Although there was the expected fall in AP prescribing for those at moderate-risk of IE, they also identified a significant reduction in AP prescribing for those at high-risk. Specifically, the proportion of high-risk individuals who should have received AP decreased from 96.9% before 2007 to 81.3% (P=0.02) after, suggesting that a significant proportion of those who should have received AP did not. The fall was even larger, from 98% to 80.2% (P=0.03), for dental cleaning visits. This is worrying since a whole mouth dental cleaning (a.k.a. scaling) is one of the most bacteremia-inducing dental procedures, particularly in those with poor oral hygiene.

On the other hand, a reduction in AP prescribing for non-indicated dental procedures from 7.1% to 0% AUTHOR: PLEASE SEND US A REFERENCE CITATION FOR THE ORIGINS OF THESE DATA, AND WE'LL ADD IT TO THE MANUSCRIPT, DURING THE FORMULATION OF PROOFS suggests that the description of those dental procedures that should be covered by AP are much clearer in the 2007 AHA guidelines than before.

The decrease in AP prescribing to those at high-risk of IE since the 2007 guidelines and the continued prescribing of AP to 8.6% of individuals at moderate risk of IE (noted in the DeSimone et al study) mirrors similar findings in a study of Canadian dentists and hygienists[18] and suggests some difficulty on the part of dentists in distinguishing high-risk from moderate-risk patients. This is perhaps not surprising since the categorization of patients

is based on cardiological diagnoses and procedures that, whilst familiar to cardiologists, are not familiar to many dentists. In particular, congenital and native valve conditions and more complex cardiac repair procedures can be difficult for a non-cardiologist to categorize, and the dentist is frequently reliant on the patient's understanding of his condition, which is often poor, to categorize it.

As concluded by DeSimone et al, continued medical education of dentists and other clinicians is needed to better ensure compliance with national guidelines. But simplification of risk stratification and the terminology used to describe it would also help. Perhaps most important, however, would be better communication between cardiologists and dentists. Cardiologists are best placed to identify the risk status of their patient and the need for AP, while the dentist is best placed to identify when a risk prone dental procedure needs to be performed and, therefore, when AP is needed. Clear and direct communication between cardiologist and dentist is therefore essential. Patients also need to be fully informed of their risk status and the potential benefits and disadvantages of AP, so that they can participate in the decision making. Again this is perhaps a discussion best undertaken by the cardiologist, but it is clearly very important that the dentist is kept fully informed.

In conclusion, DeSimone et al have published an interesting study that reports for the first time the high level of compliance by dentists with the most recent AHA guidelines on AP prescribing. This is critical information that needs to be validated on a larger scale. Such additional data are needed to support large administrative data studies on the incidence of IE, if we are to understand the real impact of the 2007 AHA guideline changes. Importantly, the DeSimone et al study also helps us to identify deficiencies in guideline compliance, as well as possible ways to improve clinical practice.

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