Guidelines for the Prescription of Antibiotic Prophylaxis

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On March 7th, 2007, the American Heart Association Science Advisory and Coordinating Committee approved new guidelines for the prescription of antibiotic prophylaxis (AP). The AHA appointed a writing group, comprised of members of the Rheumatic Fever, Endocarditis, and Kawasaki Disease Committee of the AHA, the Council on Cardiovascular Disease in the Young, the Council on Clinical Cardiology, the Council on Cardiovascular Surgery and Anesthesia, and the Quality of Care and Outcomes Research Interdisciplinary Working Group. Liaison members from the ADA, the Infectious Diseases Society of America, and the American Academy of Pediatrics also contributed. Evidence, or lack thereof, was assessed using classifications of recommendation and levels of evidence from the American College of Cardiology and the AHA. Finally, the paper was revised by an outside group of international experts not affiliated with the AHA committee.

In 2017, a focused review added some specific points while continuing to reinforce the existing guidelines. In the last update of March 23rd, 2020, the ADA reiterated the same guidelines, which included updates for the prevention of PJI.

In May 2021, the AHA published a scientific statement following an extensive retrospective review to assess the impact of the latest 2007 evidence-based guidelines to prevent Viridans Group Streptococcal Infective Endocarditis (VGS IE).

It assessed the impact of the recent guidelines on practice in terms of incidence and mortality as well as the rationale used to develop and promote the recent guidelines.

It revealed that over 70% of dentists reported that some patients continued with the older guidelines, primarily because either their physician recommended it (57%) or because of patient preference (33%). Although there was a generally good awareness of the new guidelines, there was a general lack of compliance. Prescriptions for antibiotic prophylaxis were reduced by 52% for low or unknown risk patients, 64% for more moderate risk and, surprisingly, by 15-20% for high-risk cardiac conditions for which the prophylaxis was still recommended.

Changes have now been made to the regimen, but no changes were made regarding the indications for the use of antibiotic prophylaxis for the prevention of VGS IE, which is recommended only for the patients at highest risk of adverse outcome, instead of risk of occurrence.

Challenges occurred during the review of data and research obtained since 2007. Limitations included a lack of coding in the International Classification of Diseases for VSG IE and statistical flaws. Even though the data revealed an overall increase in IE occurrence, there was no evidence proving an increase in VGE IE. Even in the UK, where all antibiotic prophylaxis measures were dropped and a sharp rise occurred in IE cases, it was not possible to validly prove that these were caused by VGS. A suggestion that an increase was caused by VGS was made in the Netherlands, but the sample was too small to be statistically significant. A study from Canada showed that although there was an increase in IE in both high and moderate risk patients, there was a decline in VGS IE. In some countries, if IE increased, they were mediated by another class of bacteria such as Staphylococcus. The conclusion was that there is no high-quality data suggesting an increase in VGE IE since the new guidelines.

The AHA suggests optimization prevention with multiple approaches focused on dental health, risk stratification, avoidance of co-morbidities and contributory risks, and vigilance for infection.

Efforts need to be made to facilitate access to care for those patients who are at particularly higher risk. Patients need to be educated about the fact that there is no proven benefit from AP to prevent VSG IE following dental procedures and there are real risks in taking AP. That said, patients who have any risk factors should be advised to consult if they develop a fever.

Reiterated Principles

The committee concluded that:
• Only an extremely small number of IE cases might be prevented by antibiotic prophylaxis, even if this therapy were 100% effective.

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• Bacteremia resulting from daily activities is much more likely to cause IE than bacteremia associated with a dental procedure.

• IE prophylaxis for dental procedures should only be administered to patients with underlying cardiac conditions that have the highest risk of adverse outcome from IE, such as heart failure, aortic root abscess, need for valvular replacement, surgical revision in patients with congenital heart disease, recurrent VGS IE, or death.

• For those patients only, prophylaxis is recommended for all dental procedures that involve manipulation of the gingival tissue, the periapical region of the teeth, or the perforation of the oral mucosa.

• Prophylaxis is no longer recommended for the limited condition of an increased lifetime risk of acquiring IE.

• Antibiotics to prevent IE are no longer recommended for GU or GI procedures.

INFECTIVE ENDOCARDITIS

Abnormal development, multiple diseases, foreign bodies, and/or turbulent blood flow can give rise to disruptions in the endothelial lining of the heart. This facilitates the deposition of platelets and fibrin to produce non-bacterial thrombotic endocarditis (NBTE). Colonization of this lesion occurs once bacteria possessing the proper adherence capacity invade the bloodstream. These bacteria further stimulate the aggregation of platelets and fibrin, thus incorporating the bacteria in the lesion.

Bacteria most commonly implicated in IE are Viridans Group Streptococci (VGS), Staphylococci, and Enterococci. Other bacteria classified as HACEK (Haemophilus, Actinobacillus, Cardiobacterium, Eikenella, and Kingella) as well as occasional fungi have been implicated in past literature. Mediators of adherence for these bacteria serve as virulence factors in the development of IE. Adherence factors also interact with the matrix proteins deposited on implanted medical devices, effectively forming a biofilm on the devices. Location of adherence may affect the virulence depending also on host response.

PROSTHETIC JOINT INFECTIONS

In 2015, the ADA issued guidelines after a panel of experts conducted two systematic reviews in 2012 and 2014. The conclusion was that there was no association found between dental procedures and prosthetic joint infections. Therefore, prophylactic antibiotics are not recommended before dental procedures to prevent PJI.

Certain comorbidities warrant special consideration: a previous history of PJI, existing morbidity at the surgical site, existing spreading infections in other areas of the body, increased immunosuppression, whether induced by medications or not, congenital or acquired immunodeficiency, systemic immunosuppressive disorder (as in Rheumatoid Arthritis, Lupus Erythematosus), diabetes with poor glycemic control, or the possibility of osteonecrosis of the jaw following a surgery. A patient presenting with such comorbidities requires consultation with the treating physician.

In such cases, the ADA recommends not only discussing the case with the physician, but also it is most appropriate for the physician to issue the prescription.

BACTEREMIA AND DENTAL PROCEDURES

The reported frequencies of bacteremia following a dental procedure vary widely from 9-32% for rubber dam or wedge placement, to 10-100% for extractions. Daily activities have frequencies reported from 20-68% with brushing and flossing, and 7-51% with chewing food. There is no evidence-based study to confirm which procedures are more likely associated with a transient bacteremia or produce a bacteremia of greater magnitude, nor is there confirmation that the incidence, magnitude, or duration of bacteremia post-procedure leads to IE.

Yet, it is confirmed from several studies that the magnitude of the bacteremia following a dental procedure is similar to that following daily routine activities and less than that used to cause IE in both human studies and animal experiments. The infective dose required to cause IE in humans is not known, however. The assertion is made nonetheless that cases of IE caused by oral bacteria probably result from the exposures to low inocula of bacteria in the bloodstream resulting from daily activities and not from a dental procedure. This also takes into account that most individuals see their dentist on average twice a year and that most patients with IE had not had a dental procedure in more than 2 weeks.

The duration of the bacteremia in the studies is reported from anywhere between 10 minutes to over an hour. No study exists to demonstrate that a longer duration causes IE. No clinically significant difference in the frequency, nature, magnitude, and duration of bacteremia associated with a dental procedure compared with that resulting from routine daily activities was found.

The Need to Emphasize Good Dental Hygiene

Evidence, in fact, supports emphasizing good oral hygiene habits and maintaining good oral health to decrease the frequency of bacteremia from routine daily activities. The review concluded that the previous guidelines led to an overemphasis on antibiotic prophylaxis and an underemphasis on maintenance of good oral hygiene and access to routine dental care, which are likely more important in reducing the lifetime risk of IE than is the administration of antibiotic prophylaxis for a dental procedure.

The Risk from Dental Procedures

A precise determination of the relative risk of bacteremia following specific dental procedures is not possible. While it is thought that bleeding is a determining factor in developing IE, there is no data confirming that visible bleeding during a dental procedure is a reliable predictor for bacteremia and IE.

Studies have shown that amoxicillin was effective in reducing the incidence, nature, and duration of the bacteremia, but did not eliminate it altogether. Other studies show no statistical difference in frequency or magnitude 10 minutes post-procedure with penicillin or ampicillin. No data confirms whether amoxicillin could avoid IE.

The usual onset of IE is between 7 to 14 days with 78% of cases occurring within 7 days and 84% within 14 days. Extensive literature and case reviews have included information from Europe, as well as North America, with the following statistical assessment.

Estimated risks from a dental procedure are listed per underlying cardiac condition:

- Mitral valve prolapse (MVP) -1/1.1million procedures
- Congenital Heart Disease (CHD) -1/475,000 procedures
- Rheumatic Heart Disease RHD -1/142,000 procedures
- Prosthetic valve -1/114,000 procedures
- Previous IE -1/95,000 dental procedures

These risks are categorized as "exceedingly small" and given the fact that an antibiotic may not be 100% effective, prophylaxis may not prevent IE.

CARDIAC CONDITIONS AND ENDOCARDITIS

In native valve IE, the disease can progress from relatively benign infection to valvular dysfunction, congestive heart failure, embolic events, and death. In a patient with a prosthetic valve or with a previous episode of IE, there is an increased risk for needing valve replacement surgery. There is an increased likelihood of heart failure, heart block, or requirement for valvular replacement due to perivalvular extension, abscess, and other complications. Mortality is over 20% compared to less than 5% for those with native valve IE.

Advances in cardiac procedures warrant more specificity in prescribing AP and they are reflected in the table. This underlines the need to obtain specifics for any cardiac procedure the patient has undergone.

MVP has supplanted RHD as the most common underlying pathology in patients with IE in developed countries. Both conditions can present with various degrees of pathology thus affecting the risk of acquisition of IE. The same can be said for CHD, further complicated by the fact that treatments increasingly include various intracardiac valvular prostheses, intravascular shunts, grafts, and devices. Patients with CHD have the highest risk for morbidity and mortality. Prophylaxis is recommended during the first 6 months postoperatively, particularly in pediatric patients, to allow for endothelialization of the prosthetic material. No further prophylaxis is recommended provided there is no residual effect postoperatively.

While all these conditions are known to be associated with an increased lifetime risk of acquisition for IE, a growing body of evidence suggests that IE prophylaxis may prevent only a small number of cases of IE. Antibiotic prophylaxis is only recommended based solely on an increased high risk of severe morbidity or death should IE develop. MVP patients are no longer listed as recommended for prescription of antibiotic prophylaxis, no matter if they present with abnormal leaflets or regurgitation.

Comorbid factors such as immuno-suppressive pathologies and treatments, age, and diabetes, to name a few, may increase the risk of adverse outcome (i.e., morbidity and mortality rates) for IE. Surgical history of solid organ transplant, breast, and penile implants do not require prophylaxis.

In the case of a patient predisposed to infection for whatever reason, be it a severe autoimmune disease or a patient undergoing chemotherapy, especially with a central venous catheter, a consultation with the treating physician/oncologist is warranted.

REGIMEN

The regimen still calls for a single dose administration of an antibiotic before the procedure. Only if the dose is inadvertently not given prior to a procedure, may the dose be given up to 2 hours post-procedure. There is also a difference between the use of an antibiotic to treat an established infection versus the use of antibiotic for prophylaxis. Administered in a single dose, the antibiotic prophylaxis may be effective with various susceptibility.

A patient presenting with fever should have blood cultures drawn before any procedure to rule out the fact that the patient may have a coincidental endocarditis.

Please see the companion reference card to this article for a list of indications and non-indications for prophylaxis.

The guidelines address one recurring and fundamental issue: the rate at which multi-drug resistant VgS and Enterococci have developed in the past 30 years is alarming. This makes IE more difficult to treat. The CDC reports that bacterial resistance for clindamycin has gone from 0% to 30%, for penicillin from 0% to 51%, and for macrolides from 11% to 65%. Another study rated resistance to cephalexin at 96%. The rate of resistance for azithromycin and clarithromycin now surpasses that for penicillin. King reported that the percentage of resistance to erythromycin of Streptococci went from 41% to 82% after one course of azithromycin and 71% after clindamycin.

According to the CDC, more than 2.8 million antibiotic-resistant infections occur every year in the US, from which more than 35,000 people die. An increasing number die from the resulting microbial imbalance which leads to increases in Clostridioides Difficile, from which 12,800 patients died in 2017, and this number keeps climbing. This brought the total deaths to 48,000 in 2019.

Macrolides such as azithromycin are to be prescribed with caution for patients with known prolonged QTc interval on their ECG. They can precipitate a serious cardiac event. Doxycycline is a good alternative for those who cannot take Penicillin, Cephalosporin, or macrolides.

Of important note, up to 90% of patients who have been labeled as allergic to Penicillin have a negative skin test when performed by an allergist. It is important to take a thorough history of the type of reaction the patient has had in the past; a slight gastric upset is not an allergy, whereas an anaphylactic reaction is. The recommendation is that a patient get a skin test in case of uncertainty.

Research showed that the post-dosing rate of resistance to amoxicillin increased by an average of at least 10-31 %. The proportion of reduced susceptibility to amoxicillin increased on days 2 and 5 and persisted for 21-24 days. When given at weekly intervals, the number of resistant VGS increased substantially after the second and third doses and persisted

for 4 to 7 weeks. High risk patients requiring dental treatment in shorter intervals than at least 4 weeks should be given an alternate antibiotic.

Vancomycin and Fluoroquinolone are very active against VgS, but their use is to be avoided, lest we find ourselves without anything to treat IE.

Of interesting note, cephalexin has been maintained in the regimen "even though (it) was less active against VgS than other first generation oral cephalosporins in one study(...) No data show superiority on one cephalosporin over another for prevention of IE and generic cephalexin is widely available and is relatively inexpensive."

SPECIAL CONSIDERATIONS

A patient presently undergoing a short course of antibiotic should receive an antibiotic from a different class. Elective procedure should be delayed for at least 10 days.

However, a patient returning the next day can be treated with another same preoperative dose of the same antibiotic.

Conversely, if a patient is being treated with parenteral antibiotics, the same antibiotic should be continued with the dosage adjusted to be given 30-60 minutes before the dental procedure. It is asserted that in such high doses, "the concentration would overcome any possible low-level resistance developed among mouth flora."

Patients who receive anti-coagulo therapy should not receive intramuscular antibiotics.

Heart transplant patients are at higher risk for acquired valvular dysfunction, especially during episodes of rejection. Though no study confirms or negates the effectiveness of antibiotic prophylaxis coverage, it is prescribed for cardiac transplant patients only once they have developed valvulopathy.

LEGAL AND RISK MANAGEMENT PERSPECTIVE

Some doctors and patients still react to the revised guidelines with some insecurity and skepticism. The new guidelines have arisen not so much as a result of new studies proving the ineffectiveness of antibiotic prophylaxis, but rather because of lack of evidence of its effectiveness. With no proof one way or another, the question remains that if VGS is the predominant bacteria in the healthy, clean mouth, and if the level of the bacteremia post dental procedure may resemble that of routine activity, would a doctor not want to at least make sure that this healthy patient not risk acquiring IE?

Countering that argument is the real and present threat of rapidly increasing multi-drug resistant bacteria. In stating that the risk of taking the antibiotics outweighs the benefit derived (i.e., protection against IE) from taking them, the reference may not be so much about one individual's risk of adverse reaction (there are no known case of anaphylactic death from the administration of antibiotic prophylaxis for the prevention of IE with dental procedures), but rather the ensuing lack of effectiveness of an antibiotic if it were needed in a life-threatening event.

The doctor, in considering the wellbeing of their patient, may not feel swayed by what they perceive as a purely statistical or cost-effectiveness-based argument. While most doctors are sensitive to a patient's financial limitations, the decision on which antibiotic to use should be based more on the probability of maximum therapeutic benefit from the medication prescribed than on financial considerations.

The ADA supports the principle of doctors' independent professional judgment in the application of this or any other guideline. Current guidelines are usually cited in litigation. Derogation from guidelines, which can effectively be considered as standard of care in a court of law, must be supported with a rationale reflecting accurate knowledge and interest of the patient.

A situation may arise where the dentist and the physician disagree on the regimen or its application for a given patient. In such situations, discussion of the case with the treating physician is paramount. The physician may indeed be aware of medical factors that may complicate a patient's risk. Also, a patient may have not disclosed her or his full medical history because of a lack of understanding of its relevance to dental treatment, because the patient may have simply forgotten, or because the patient may be having difficulty accepting or facing a diagnosis. Documentation is crucial; calls and conversations must be noted in the patient record with time, date, and content. Ideally, confirmation in writing (e-mail and fax are acceptable) should be obtained. If confirmations are obtained verbally, they should follow a conversation between both doctors. If disagreement persists, the dentist assumes the decision and the responsibility of its consequences. The dentist must inform the patient of this disagreement and encourage the patient to discuss the issue with the physician.

The patient has the right to autonomous decision-making, and even though shared decision-making between patient and healthcare giver is important, the patient should not direct the course of treatment. Informed consent can protect a doctor from liability as long as the doctor is acting within the standard of care and has explained the risks and benefits of all options available. The dentist is never obligated to render treatment that they deem not to be in the patient's best interest, no matter how strongly the patient may feel about it.

Of note: signed refusals to follow the doctor's recommendations, such as not filling out a medical questionnaire, submitting to a dental examination, agreeing to a consultation, or taking prescribed antibiotics will not absolve a dentist from responsibility in case of an adverse event.

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