ANTIBIOTIC PROPHYLAXIS FOR INFECTIVE ENDOCARDITIS: ETHICAL CARE IN THE ERA OF REVISED GUIDELINES

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Introduction

Beginning in 1955, the American Heart Association recommended antibiotic prophylaxis among patients with certain structural heart diseases to decrease the likelihood of infective endocarditis (IE) following dental procedures.[1] Over the ensuing 52 years, the American College of Cardiology/American Heart Association (ACC/AHA) guidelines were revised to address gastrointestinal and genitourinary procedures[2] and to modify the assessment of relative risks and specific regimens for prophylaxis.[3–6] Throughout the various revisions, prophylaxis was recommended for individuals who were at increased risk of developing IE based on best evidence and consensus opinion, albeit in the absence of randomized controlled trials.

In 2007, the AHA published a revised guideline statement dramatically restricting its recommendations for antibiotic prophylaxis against IE.[7] In 2008, these views were incorporated in an ACC/AHA guideline update on the management of patients with heart valve disease.[8] The revisions represent a dramatic shift in terms of the patients for whom antibiotic prophylaxis is recommended and the procedures for which it is recommended. What is striking about the new guidelines is that the change in recommendations was based not on new data, but on a change in philosophy despite the lack of new data.

To some degree, the arguments for and against antibiotic prophylaxis become those of philosophy, ethics, and the role of evidence-based medicine. This manuscript attempts to briefly examine those arguments and discuss why the revised guidelines may fail to respect the ethical principles of beneficence and patient autonomy.

Rationale for the Use of Antibiotic Prophylaxis

Dental procedures, bacteremia, and antibiotics. In 1935, Okell and colleagues published a seminal study that associated bacteremia with dental manipulation, documenting a dose-response relationship between the extent of observed bacteremia and the severity of underlying gingival disease and extent of dental manipulation.[9] In 1948, Hirsh documented a reduced frequency of bacteremia associated with dental extractions after pretreatment with oral penicillin.[10] With the documented association of bacteria as the causative agent of IE, these studies formed the logical groundwork for the use of oral antibiotic prophylaxis against bacteremia (and therefore against IE), complicating dental procedures.

Bacteremia is not unique to dental procedures and is recognized to occur after brushing as well as spontaneously; however, bacterial load is significantly greater after dental procedures. In one randomized trial, brushing was associated with a positive blood culture in 23% of cases, and the duration was transient. In contrast, bacteremia occurred in 60% of cases after dental extraction, and bacteremia was more prolonged.[11] In the same study, antibiotic prophylaxis before dental extraction decreased bacteremia to a rate similar to that observed after brushing.

Animal models of IE. Even among populations at risk, the incidence of IE is relatively low. As such, it is logistically difficult to perform randomized trials on IE prevention in patients. Animal models typically involve the mechanical creation of a sterile vegetation followed by inoculation with intravenous bacteria (of a species associated with IE, and at a dose associated with the minimum inoculum needed to produce IE).

Animal models of IE have led to 2 important observations. First, pretreatment with antibiotics prior to bacteremia results in a substantially lower incidence of IE. In one study performed in rats, the incidence of IE was 85–90% in control animals, but only 5–10% among animals pretreated with either erythromycin or clindamycin.[12] Second, antibiotic prophylaxis probably is effective in preventing IE through mechanisms other than a simple bactericidal effect and is likely related to interference of bacterial adherence. In another animal study, the use of amoxicillin or erythromycin resulted in a moderate decrease in the presence of bacteremia measured as colony-forming units, but reduced from about 80% to zero the incidence of IE.[13]

Animal studies can be criticized because the incidence of IE in control animals is much higher than that observed spontaneously in patients. However, they nonetheless create a controlled scenario for the study of IE prevention. Extrapolation of results to a patient population is based on the belief that prevention of IE occurs regardless of the rate of IE in controls.

Observational data in humans. Two observational studies have been published that address the role of antibiotic prophylaxis in preventing IE. The first, performed in the Netherlands, was a case-matched study of IE occurrence among patients at risk following a dental or medical procedure.[14] This study observed 438 cases of native valve IE over a 2-year interval; case controls comprised patients at risk who underwent similar procedures but did not develop IE. Approximately 1 in 6 patients in both groups received appropriate antibiotic prophylaxis. In this study, prophylaxis was associated with an estimated 49% protective efficacy in preventing IE.[14]

The second observational study was based on data from France.[15] In this study, a survey of 2,805 patients was used to estimate the number of patients with predisposing cardiac conditions that placed them at risk of IE, the annual number of dental procedures during which antibiotic prophylaxis should have been used, and the number of procedures during which antibiotics were or were not used. A 1-year epidemiological study conducted in an area comprising 16 million people was used to estimate the annual number of IE cases potentially due to an unprotected procedure. The risk of IE was about 1 in 46,000 procedures performed without prophylaxis and about 1 in 150,000 procedures performed with antibiotic prophylaxis, defining a 69% reduction of risk associated with antibiotic prophylaxis.[15]

Both studies have in common the finding that many cases of IE occur without apparent association with a preceding dental or medical procedure, and both suggest that antibiotic prophylaxis would be needed in a large number of procedures in order to prevent relatively few cases of IE. However, neither study suggested that antibiotic prophylaxis is ineffective in the prevention of at least some cases of IE.

Rationale Against the Use of Antibiotic Prophylaxis

The revised ACC/AHA guidelines. Current guidelines shift the recommendation for antibiotic prophylaxis from all patients with an increased lifetime risk of developing IE to only patients with an underlying cardiac condition that increases the risk of an adverse outcome from IE (therefore deriving the greatest benefit from preventing IE).[7,8] Antibiotic prophylaxis for dental procedures now is recommended only among patients with a prosthetic heart valve; previous IE; cyanotic congenital heart disease that is un-repaired, within 6 months of repair, or repaired but with residual defect at or near the location of prosthetic material; or in cardiac transplant recipients with cardiac valvulopathy. Antibiotic prophylaxis is no longer recommended for patients with native structural heart valve disease. There is no suggestion that patients with native heart valve disease are at any less risk of IE than are other patients; the guidelines simply state that the outcome of IE would be more problematic among the cited patient groups. Antibiotic prophylaxis is not recommended in conjunction with any gastrointestinal tract or genitourinary tract procedure.

Rationale. Citing rationale for the change in recommendations, current ACC/AHA guidelines stress the absence of randomized controlled trials in humans that support the efficacy of antibiotic prophylaxis in the prevention of IE.[7,8] Further, because many cases of IE are felt to result from frequent exposure to bacteremia associated with daily activities, prophylaxis before dental and medical procedures is felt to be of limited potential benefit. Specifically, the guidelines argue that even widespread use of effective antibiotic prophylaxis would prevent only a limited number of IE cases.

The revised guideline statements further cite potential risks associated with antibiotic prophylaxis. The

AHA document cites the risk of anaphylaxis,[7] and the ACC/AHA guideline update cites a more general risk of antibiotic-associated adverse effects.[8] Of note, however, the AHA guideline statement discloses that during the 50 years that the AHA had recommended a penicillin as the preferred prophylaxis to prevent IE, no case of fatal anaphylaxis has been reported in a patient receiving a penicillin administered for IE prophylaxis.[7]

The AHA statement explicitly notes that potential consequences of the revised recommendations include reduced malpractice claims related to IE prophylaxis and stimulation of prospective research on IE prophylaxis.[7] The latter outcome is echoed in the ACC/AHA guideline update, noting that fewer patients receiving IE prophylaxis will stimulate prospective studies on IE prevention.[8]

Evidence-Based Medicine

Data hierarchy. Paramount in the revised ACC/AHA recommendations is a reliance on evidence-based medicine,[16] which seeks to apply to medical decision-making the best evidence available from scientific methods. Inherent to evidence-based medicine is an intrinsic judgment of the quality of evidence; this leads to the creation of a hierarchy of study methods, the gold standard of which is taken to be the randomized controlled trial. However, the belief that the validity of evidence is a function of the underlying study design might be flawed.[17] In a general sense, extrapolation of conclusions from a randomized controlled trial requires that the patient being treated matches in all characteristics the subjects in the trial, including both known and unknown factors. These conditions might never be realistically satisfied. As such, the cost of randomized controlled trials is their narrowness of scope and lack of applicability to individual patients.

The ACC/AHA recommendations regarding IE prophylaxis raise another issue in the application of data hierarchy and evidence-based medicine. The revised guidelines interpret the absence of randomized controlled trials supporting the efficacy of prophylaxis as a priori evidence of absence of benefit. In this sense, the revised guidelines serve as an excellent example of the dangers of evidence-based medicine: an absence of proof (of efficacy) is confused for proof of absence (of efficacy).

An absence of randomized controlled trials. Practitioners in cardiology have become accustomed to making medical decisions using evidence-based medicine founded on results of randomized controlled trials. However, some aspects of cardiology do not readily lend themselves to randomized controlled trials due to limited patient numbers, low disease prevalence, therapies (including surgery) that are not easily randomized, and outcomes that are meaningfully measured only years or decades after intervention. These limitations affect most decisions among patients with heart valve disease.

Antibiotic prophylaxis for the prevention of IE has never been tested in a large randomized controlled trail. However, IE occurs only rarely even among patients at high risk, and existing data suggest that large numbers of patients would need to undergo prophylaxis for a large number of procedures in order to prevent relatively few cases of IE. It seems unlikely that an appropriately powered randomized trial testing the efficacy of antibiotic prophylaxis is feasible and would ever be performed.

Ethical Considerations

Guideline statements are written with the intent to provide guidance rather than dictate therapy. However, it seems reasonable to believe that, if followed, practice guidelines should be compatible with ethical care. The 6 values that commonly apply to medical ethics are autonomy, beneficence, nonmaleficence, justice, dignity, and truthfulness and honesty. Beneficence (that the practitioner should act in the best interest of the patient) and autonomy (that a patient has the right to choose or refuse their medical treatment) deserve consideration.

Beneficence. Existing data suggest that not all cases of IE can be prevented. However, it is beneficial to the individual patient to avoid even some cases of IE. If risks of prophylaxis are sufficiently low, failing to attempt to prevent the preventable in an individual patient (even if prevention in a population is incomplete) fails to respect the principle of beneficence. The AHA and ACC/AHA guideline statements are not unique in their apparent failure to make recommendations based on the best interests of the individual patient. The previously cited observational study from the Netherlands noted "… whereas a protective efficacy of about 50% may be worthwhile for the individual patient, the effect is negligible on the scale of the whole population."[14]

Further at issue is the recommendation of prophylaxis for patients at especially high risk of an adverse outcome from IE, but not for all patients at high risk of acquiring IE.[7,8] Many patients not included in the groups for whom prophylaxis is recommended also would experience an adverse outcome. Approximately 50% of patients with IE require surgery for heart valve repair or replacement,[18] and in-hospital mortality associated with IE is approximately 25% among patients ≥65

years of age and approximately 19% among patients <65 years of age).[19] Clearly, death or heart valve surgery is an adverse outcome from the perspective of the individual. That current guidelines consider one patient's adverse outcome more important than another's fails to respect the principle of beneficence and fails to honor the physician's responsibility to the individual patient.

Autonomy. When treatment options are available, a patient should be informed and allowed to choose. There may be inadequate data to conclude with certainty whether antibiotic prophylaxis reduces the risk of IE. However, it is paternalistic not to inform a patient of conflicting opinions and simply prescribe no antibiotic prophylaxis based on incomplete data.

Even more problematic are the arguments that discontinuation of prior recommendations for prophylaxis could stimulate prospective research on the topic and might result in fewer medical liability suits. If even part of the purpose of discontinuing recommendations for antibiotic prophylaxis is to prospectively observe the prevalence of IE after a change in the guidelines, patient autonomy (as well as truthfulness and honesty) dictates that the individual should be informed of that intent. Finally, not only is there is no precedent in medicine to write practice guidelines with the specific goal of avoiding malpractice claims when they are not followed, but respect for autonomy and truthfulness again dictate that individual patients should be made aware that recommended therapy is based (even in part) on this.

An Alternative to the Current Guidelines

There is an absence of data to definitively conclude to what degree antibiotic prophylaxis prevents IE and at what risk. However, prophylaxis has been the standard of care for more than 50 years, and there are data that support its use. In the absence of definitive data, analysis of risks and benefits appears appropriate.

Risk-benefit analysis. Rationale supporting the use of antibiotic prophylaxis before non-sterile procedures includes evidence that antibiotics blunt periprocedural bacteremia and prevent IE in animal models, and observational data suggests that antibiotic prophylaxis decreases the prevalence of IE in humans. IE is a devastating disease. Because of substantial associated morbidity and mortality, prevention appears superior to treatment. If antibiotic prophylaxis is associated with no risk, then any benefit might be enough to support its use.

Stated rationale against the use of antibiotic prophylaxis includes the absence of randomized trials that prove efficacy in humans; potential risk associated with prophylaxis; and limited potential benefit in that not all IE is caused by an antecedent procedure, and prophylaxis is not 100% effective.[7, 8] However, there may be no risk associated with antibiotic prophylaxis. Although resistant organisms clearly are produced by the overuse of antibiotics, isolated single-dose prophylaxis is not the source of the problem, and it seems disingenuous to suggest otherwise. Cost does not play a significant role. A 2-gram dose of amoxicillin typically used for dental prophylaxis costs less than $2.00. Finally, as noted above, no case of fatal anaphylaxis has been reported for a patient receiving a penicillin administered for IE prophylaxis during the 50 years that it was recommended by the AHA.[7]

Individualized decisions. The revised guidelines for antibiotic prophylaxis[7, 8] are not based on data and do not appear to satisfy requirements for ethical care. The concept of allowing patients to individually weigh risks and benefits appears sound, especially in a setting where there are no data that refute a time-honored standard of care.

I have personally adopted an approach of informed decision-making. For patients with organic heart valve disease, I briefly discuss the history of IE prophylaxis, the previous guideline recommendations, the new recommendations, the rationale for change, and the absence of definitive data to support or refute their use. Such a discussion typically takes only a few minutes. Informed patients seem capable of making rational decisions about their own care, and it is paternalistic to think — especially in a scenario in which definitive trials have not been performed — that patients should not be involved. When given a choice, a preponderance of patients opt to use antibiotic prophylaxis. Whether patients opt for or against IE prophylaxis, decisions are made with autonomy and in a spirit of beneficence. Unless or until more definitive trials are performed, the best practice guideline might be one of informed consent.

References

1. Jones TD, Baumgartner L, Bellows MT, Breese BB, Kuttner AG, McCarty M, Rammelkamp CH; Committee on Prevention of Rheumatic Fever and Bacterial Endocarditis, American Heart Association). Prevention of rheumatic fever and bacterial endocarditis through control of streptococcal infections. Circulation. 1955;11:317–320.
2. Rheumatic Fever Committee and the Committee on Congenital Cardiac Defects, American Heart Association. Prevention of bacterial endocarditis. Circulation. 1972;46:S3–6.
3. Kaplan EL, Anthony BF, Bisno A, Durack D, Houser H, Millard HD, Sanford J, Shulman ST, Stillerman M,

Taranta A, Wenger N; Committee on Rheumatic Fever and Bacterial Endocarditis, American Heart Association). Prevention of bacterial endocarditis. Circulation. 1977;56:139A–143A.

4. Shulman ST, Amren DP, Bisno AL, Dajani AS, Durack DT, Gerber MA, Kaplan EL, Millard HD, Sanders WE, Schwartz RH, Watanakunakorn C; Committee on Rheumatic Fever and Infective Endocarditis, American Heart Association). Prevention of bacterial endocarditis: a statement for health professionals by the Committee on Rheumatic Fever and Infective Endocarditis of the Council on Cardiovascular Disease in the Young. Circulation. 1984 Dec;70(6):1123A–1127A.
5. Dajani AS, Bisno AL, Chung KJ, Durack DT, Freed M, Gerber MA, Karchmer AW, Millard HD, Rahimtoola S, Shulman ST, Watanakunakorn C, Taubert KA. Prevention of bacterial endocarditis. Recommendations by the American Heart Association. JAMA. 1990 Dec;264(22):2919–22.
6. 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, Zuccaro G Jr. Prevention of bacterial endocarditis. Recommendations by the American Heart Association. JAMA. 1997 Jun;277(22):1794 –801.
7. 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. 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. Circulation. 2007 Oct 9;116(15):1736-54.
8. Nishimura RA, Carabello BA, Faxon DP, Freed MD, Lytle BW, O'Gara PT, O'Rourke RA, Shah PM. ACC/AHA 2008 Guideline update on valvular heart disease: focused update on infective endocarditis: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol. 2008 Aug 19;52(8):676-85.
9. Okell CC, Camb MB, Elliott SD. Bacteriaemia and oral sepsis with special reference to the etiology of subacute endocarditis. Lancet. 1935;2:869-72.
10. Hirsh HL, Vivino JJ, Merril A, Dowling HF. Effect of prophylactically administered penicillin on incidence of bacteremia following extraction of teeth: Results in patients with healed rheumatic and bacterial endocarditis. Arch Intern Med. 1948;81:868-78.
11. Lockhart PB, Brennan MT, Sasser HC, Fox PC, Paster BJ, Bahrani-Mougeot FK. Bacteremia associated with toothbrushing and dental extraction. Circulation. 2008 Jun 17;117(24):3118-25.
12. Glauser MP, Francioli P. Successful prophylaxis against experimental streptococcal endocarditis with bacterostatic antibiotics. J Infect Dis. 1982 Dec;146(6):806-10.
13. Malinverni R, Overholser CD, Bille J, Glauser MP. Antibiotic prophylaxis of experimental endocarditis after dental extractions. Circulation. 1988 Jan;77(1):182-7.
14. Van der Meer JT, Van Wijk W, Thompson J, Vandenbroucke JP, Valkenburg HA, Michel MF. Efficacy of antibiotic prophylaxis for prevention of native-valve endocarditis. Lancet. 1992 Jan 18;339(8786):135-9.
15. Duval X, Alla F, Hoen B, Danielou F, Larrieu S, Delahaye F, Leport C, Briançon S. Estimated risk of endocarditis in adults with predisposing cardiac conditions undergoing dental procedures with or without antibiotic prophylaxis. Clin Infect Dis. 2006 Jun 15;42(12):e102-7.
16. Evidence-Based Medicine Working Group. Evidence-based medicine. A new approach to teaching the practice of medicine. JAMA. 1992 Nov 4;268(17):2420-5.
17. Goldenberg MJ. Iconoclast or creed? Objectivism, pragmatism, and the hierarchy of evidence. Perspect Biol Med. 2009 Spring;52(2):168-87.
18. Prendergast BD, Tornos P. Surgery for infective endocarditis: who and when? Circulation. 2010 Mar 9;121(9):1141-52.
19. Durante-Mangoni E, Bradley S, Selton-Suty C, Tripodi MF, Barsic B, Bouza E, Cabell CH, Ramos AI, Fowler V Jr, Hoen B, Koneçny P, Moreno A, Murdoch D, Pappas P, Sexton DJ, Spelman D, Tattevin P, Miró JM, van der Meer JT, Utili R: International Collaboration on Endocarditis Prospective Cohort Study Group. Current features of infective endocarditis in elderly patients: results of the International Collaboration on Endocarditis Prospective Cohort Study. Arch Intern Med. 2008 Oct 27;168(19):2095-103.