Prophylaxis to Prevent Infective Endocarditis: To Use or Not to Use?

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ABSTRACT

The American Heart Association (AHA) published their revised guidelines in 2007 in which they markedly limited the recommendations for the use of antimicrobial prophylaxis for the prevention of infective endocarditis (IE), except for patients who are at highest risk of adverse outcomes. A recent focused update on valvular heart diseases changed the recommendation for antibiotic use for patients with many underlying heart conditions including mitral valve prolapse (MVP) which were considered as “low risk” heart defects. In this article, we argue that antibiotic prophylaxis should be considered until concrete clinical evidence is provided to dispute against the use of this strategy, especially for patients with MVP. This approach is cost efficient, and provides a chance to prevent a dreadful disease. We have also enlisted 2 clinical cases to support our argument. These are not uncommon clinical scenarios, and emphasize that IE can be fatal in spite of optimum treatment. Patients have the right to make the final decision, and they should be allowed to participate in choosing for or against this approach until adequate clinical evidence is available.

Introduction

One more set of practice guidelines on the antimicrobial prophylaxis of infective endocarditis (IE) has been published,¹ this time eliminating many valvular lesions from the list of conditions that used to require periprocedural antibiotic prophylaxis. Last year, the American Heart Association (AHA) published guidelines for the prevention of IE,² 10 years after their last publication on this critical issue.³ Many international committees and societies had published their own guidelines and statements on the prevention of IE in the interim.^{4–6} In all of these guidelines the paradigm shift has been on minimizing the use of antimicrobial prophylaxis for the prevention of IE in patients who undergo dental, respiratory, gastrointestinal, or genitourinary tract procedures. The first set of recommendations were published by the AHA in 1955, which emphasized the usefulness of this prophylaxis,⁷ and these guidelines have been religiously followed by physicians and dentists ever since. For the first time in the last 50 years, the AHA has challenged the clinical efficiency of antimicrobial prophylaxis to prevent IE, and has markedly limited its use.

Reports of IE were described in medical literature as early as in the 15th century. The role of bacteria in the pathogenesis of IE was proposed in the 18th century. Later on in the early 19th century, clinical observations led to the belief that invasive procedures including dental manipulation can increase the risk of IE.⁸ Although the guidelines for the prevention of IE have been with us for

quite some time, there have been no randomized controlled trials done to assess the efficacy of antibiotic prophylaxis due to several reasons.⁹ The guidelines were based on a few case control studies, clinical observations, and largely expert opinion. The rationale for recommending prophylaxis was to avoid a life threatening infection, where prevention would be preferable to treatment. The guidelines were recently changed due to lack of evidence to support this strategy. The evidence being used in the recent guidelines is based on the concept of cumulative bacteremia due to daily activities rather than bacteremia related to invasive procedures as a basis for most instances of IE.¹⁰

Other supporting evidence has also been used to limit the use of antibiotic prophylaxis including lack of effectiveness of such approach and risk of adverse reactions to antibiotics.² Again, results of retrospective clinical studies were taken into consideration while formulating these guidelines due to the lack of randomized trials. Furthermore, the focused update on valvular heart diseases and infective endocarditis prophylaxis eliminated recommendations for prophylaxis for many cardiac lesions including mitral valve prolapse (MVP).¹

The recent guidelines^{1,2} are very succinct and clear, and do not recommend antimicrobial prophylaxis for people without a prosthetic cardiac valve, complex congenital heart defects, postcardiac transplant valvular lesions, or history of IE. They evidently do not recommend prophylaxis for patients with MVP, which is one of the more common valvulopathies. Clearly, the recommendations are only

limited to the group of patients with the above-mentioned conditions prior to invasive dental procedures involving manipulation of gingival tissue, the periapical region of the teeth, or perforation of the oral mucosa.^{1,2}

There has been a scarcity of information or evidence for antimicrobial prophylaxis added to the literature since the previously published guidelines in 1997. A report from Cochrane Collaboration in 2004 was based on a pooled analysis of previously done studies¹¹ which was used to substantiate the current guidelines. Potential harm caused by antibiotics was also considered to be a major limiting factor for recommending antibiotics for prophylaxis. In summary, the guidelines were modified solely based on expert opinions and previously available evidence.

Dr. Weaver writes in his article,⁹ “lack of evidence is not necessarily equivalent to lack of benefit.” He has also raised a valid question: If prophylaxis is futile, why select high-risk patients for prophylaxis? One more question that remains unanswered is: If we markedly limit antibiotic prophylaxis for IE, would it be in favor of national and patient interest as far as risks, benefits, and cost efficiency is considered? We will use the following 2 cases from a series of similar cases that we encountered in the last 10 years to highlight this issue.

Case 1

A 61-year-old white male was admitted to the hospital with complaints of back pain of 1 week in duration. He underwent dental extraction 2 weeks prior to admission, and did not receive antimicrobial prophylaxis. Magnetic resonance imaging (MRI) imaging of the thoracic spine revealed features consistent with osteomyelitis of the thoracic-T7 vertebra. Biopsy of T7 was performed the

next day. The surgical specimen showed evidence of osteomyelitis and microbiology culture grew group B beta-hemolytic *Streptococcus*. He was started on intravenous (IV) vancomycin and ceftriaxone. On the third day of his hospital stay, he developed mild dyspnea with chest pain. Subsequently, a 2-dimensional echocardiogram was done which revealed normal left ventricular function with evidence of an echo density on the aortic valve without signs of aortic regurgitation (Figure 1). A transesophageal echocardiogram (TEE) was scheduled, but unfortunately the patient died on the same night due to cardiac arrest in spite of optimum resuscitative efforts. An autopsy was performed which demonstrated a very fragile aortic valve with vegetations involving the right anterior and posterior semilunar cusps. The right anterior semilunar cusp was perforated by the vegetation which was about 1.8 cm in size. Sections of the lung revealed pulmonary edema. So, the patient died due to cardiogenic shock resulting from the mechanical complication of aortic valve IE.

Case 2

A 64-year-old Asian Indian female with history of MVP was admitted to the hospital for evaluation of pyrexia. She also had dental work 2 weeks prior to developing fever, and did not receive antibiotic prophylaxis for that. She had a systolic murmur of mitral regurgitation on examination, of which she was aware previously. Subsequently, a TEE was performed which demonstrated an independently mobile pedunculated vegetation on the anterior leaflet of the mitral valve (Figure 2). Consequently, she was treated with 6 weeks of IV penicillin therapy and 2 weeks of IV gentamicin. Repeat TEE after 6 months showed clearance of the vegetations.

Figure 1. Case 1: Echodensity on the AV. Abbreviations: LA, left atrium; LVOT, left ventricular outflow tract.

Figure 2. Case 2: pedunculated vegetation on the anterior leaflet of mitral valve.

These are not uncommon clinical scenarios where both patients had some dental work prior to presentation (developing IE). The first patient did not have any predisposing heart conditions, but still developed IE and died of its complications. The second patient had a predisposing cardiac condition (MVP with murmur) which is not considered to be “high risk” as per recent AHA guidelines, and is fairly common in the general population.¹² There was a chance for the prevention of IE in both patients, especially in the second case with a documented history of MVP with systolic murmur; although, this is difficult to predict based on current evidence. In fact, it is impossible to envisage the response of antibiotic prophylaxis with the current levels of evidence. But, a missed opportunity due to lack of evidence resulted in a demise!

Risks, Benefits, and Financial Considerations

According to the 1997 guidelines,² 2 gm of amoxicillin was recommended prior to a dental procedure. At minimum, 2 million units of penicillin G is usually required 4 to 6 times a day for 4 weeks to treat proven IE cases due to *streptococci viridens*. According to Epocrates¹³ and the John Hopkins antibiotic guide,¹⁴ the average price for a single 2 gm dose of amoxicillin is about \$2, and the average price for a standard 4 weeks of therapy with penicillin G is about \$1484. If different new generation antibiotics are used to treat IE as a single agent or in combination, the cost aggrandizes, and may go up to hundreds of thousands of dollars. Obviously, this is excluding other health care costs including hospitalization, diagnostic investigations, cost for administration, and periodic follow-ups. The patient suffers significant psychosocial and physical morbidity even if medical complications of IE are not developed. Even if a single case of IE is prevented out of 742 patients that receive prophylaxis, cost-benefit analysis favors prevention over treatment. Although there is a lack of evidence to support use of antibiotics for the prophylaxis, it is unclear whether the possible harm outweighs any beneficial effect.¹¹

Cost of prevention is clearly negligible as compared to the treatment of IE, and possibly has financial benefits in the nation’s interest. Considering ambiguous evidence, patients should be given a chance to make decisions about their health.

Better designed prospective studies need to be done to guide us on this critical issue. Even if the prevention potential of antibiotics is negligible, this has conventionally been a standard of care for the last 50 years, and might have prevented this catastrophic illness on several occasions. We think that this traditional approach should be honored until well designed clinical trials are performed, especially for patients with underlying heart conditions. Mitral valve prolapse is very common, and has been consistently shown to be associated with IE^{15,16} with increased mortality and morbidity.¹⁷ Several studies have actually proved the cost effectiveness of antibiotic prophylaxis in patients with MVP.^{17,18}

At least 5 authoritative societies have published their guidelines for the prevention of IE in the last 5 years.^{2,4–6,19} There is marked discrepancy in the recommendations for prevention of IE from these societies (Table 1). For example, the European Society of Cardiology includes MVP with valve regurgitation in the high risk category of those who should receive antibiotic prophylaxis. High risk procedures differ among different societies as is apparent from the Table. In this global environment where such marked discrepancies are apparent from “authoritative groups,” it is little wonder that clinicians are confused and wonder which authoritative groups’ recommendations should be followed. Hence a more “traditional” approach is appropriate until these discrepant recommendations can be resolved. Physicians and dentists need to discuss the possible harm and benefits of antibiotic prophylaxis with their patients, and allow them to choose the option before depriving them of a chance for prophylaxis. We believe that, at least patients with valvulopathies and no clear evidence of antibiotic allergy should be offered the option of prophylaxis before any dental procedure to prevent this cataclysmic condition until sufficient evidence is generated to argue against this approach.

Conclusion

Infective endocarditis is a life threatening disease, and prevention is always better to avoid dreadful complications or death. There is insufficient evidence to guide us on the issue of antibiotic prophylaxis. Patients with valvulopathies are particularly at high risk of acquiring IE, which could be prevented with antibiotics. This approach is reasonably cost effective to prevent cumulative morbidity and higher health care costs. Ethically, patients should be allowed to choose for or against this approach after being informed of the current AHA recommendations until sufficient clinical evidence is available.

Table 1. Summary of Current Guidelines from Top International Societies

	Highest Risk Predisposing Cardiac Conditions	High Risk Procedures
AHA/ACC ² (2007–2008)	Prosthetic cardiac valve. Previous IE. CHD. <ul style="list-style-type: none"> ● Unrepaired cyanotic CHD, including palliative shunts and conduits. ● Completely repaired congenital heart defect with prosthetic material or device, during the first 6 mo after the procedure. ● Repaired CHD with residual defects at the site or adjacent to the site of a prosthetic patch or prosthetic device. Cardiac transplantation recipients who develop cardiac valvulopathy.	Dental procedures that involve manipulation of gingival tissue or the periapical region of teeth or perforation of the oral mucosa. Invasive procedures of the respiratory tract needing incision or biopsy.
Australian Guidelines for Prevention of Endocarditis ¹⁹ (2008)	Same as for AHA/ACC <i>plus</i> rheumatic heart disease in indigenous Australians only.	Most of the invasive dental, respiratory, genitourinary, and gastrointestinal procedures involving trauma to mucosa.
National Institute for Health and Clinical Excellence ⁶ (2008)	Acquired VHD with stenosis or regurgitation. Prosthetic valve. Structural CHD, including surgically corrected or palliated structural conditions, excluding isolated atrial septal defect, fully repaired ventricular septal defect, or fully repaired patent ductus arteriosus, and closure devices. Previous IE. Hypertrophic cardiomyopathy.	Gastrointestinal and genitourinary procedures at a site where there is suspected infection.
British Society of Antimicrobial Chemotherapy ³ (2006)	Previous IE. Cardiac-valve replacement. Prosthetic shunt or conduit.	All invasive dental, respiratory, gastrointestinal, and genitourinary procedures.
European Society of Cardiology ⁴ (2004)	Prosthetic heart valve. Complex cyanotic CHD with surgically corrected pulmonary or systemic conduits, and noncyanotic CHD except secundum type ASD. Mitral valve prolapsed with regurgitation or severe valve thickening. Previous IE. Acquired VHD. Hypertrophic cardiomyopathy.	Most of the invasive dental, respiratory, genitourinary, and gastrointestinal procedures involving trauma to mucosa, especially in the presence of an infection.

Abbreviations: ACC, American College of Cardiology; AHA, American Heart Association; ASD, atrial septal defect; CHD, congestive heart disease; IE, infective endocarditis; VHD, valvular heart disease.

References

1. Nishimura RA, Carabello BA, Faxon DP, et al. 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 endorsed by the Society of Cardiovascular Anesthesiologists, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons. *J Am Coll Cardiol.* 2008; 52(8):676–685.

2. Wilson W, Taubert KA, Gewitz M, et al; American Heart Association Rheumatic Fever, Endocarditis, and Kawasaki Disease Committee; American Heart Association Council on Cardiovascular Disease in the Young; American Heart Association Council on Clinical Cardiology; American Heart Association Council on Cardiovascular Surgery and Anesthesia; Quality of Care and Outcomes Research Interdisciplinary Working Group. 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; 116(15):1736–1754.
3. Dajani AS, Taubert KA, Wilson W, et al. Prevention of bacterial endocarditis: recommendations by the American Heart Association. *JAMA*. 1997;277:1794–1801.
4. Horstkotte D, Follath F, Gutschik E, et al; Task Force Members on Infective Endocarditis of the European Society of Cardiology; ESC Committee for Practice Guidelines (CPG); Document Reviewers. 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(3):267–276.
5. Gould FK, Elliott TS, Fowleraker J, et al; Working Party of the British Society for Antimicrobial Chemotherapy. Guidelines for the prevention of endocarditis: report of the Working Party of the British Society for Antimicrobial Chemotherapy. *J Antimicrob Chemother*. 2006;57(6):1035–1042.
6. Richey R, Wray D, Stokes T; Guideline Development Group. Prophylaxis against infective endocarditis: summary of NICE guidance. *BMJ*. 2008;336(7647):770–771.
7. Jones TD, Baumgartner L, Bellows MT, et al; 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.
8. Millar BC, Moore JE. Emerging issues in infective endocarditis. *Emerg Infect Dis*. 2004;10(6):1110–1116.
9. Weaver WD, Nishimura RA, Warnes CA. President's page: antimicrobial prophylaxis to prevent infective endocarditis: why did the recommendations change? *J Am Coll Cardiol*. 2008;52(6): 495–497.
10. Roberts GJ. Dentists are innocent! "Everyday" bacteremia is the real culprit: a review and assessment of the evidence that dental surgical procedures are a principal cause of bacterial endocarditis in children. *Pediatr Cardiol*. 1999;20:317–325.
11. Oliver R, Roberts GJ, Hooper L. Penicillins for the prophylaxis of bacterial endocarditis in: Dentistry. *Cochrane Database Syst Rev*. 2004;CD003813 <http://mrw.interscience.wiley.com/cochrane/clsysrev/articles/CD003813/frame.html>. Accessed January 1, 2009.
12. Grau JB, Pirelli L, Yu PJ, Galloway AC, Ostrer H. The genetics of mitral valve prolapse. *Clin Genet*. 2007;72(4):288–295.
13. Epocrates Online Formulary. Amoxicillin manufacturing pricing. Available at <https://online.epocrates.com/noFrame/showPage.do?method=drugs&MonographId=139>. Accessed August 31, 2008.
14. Pham P, Bartlett JG. John Hopkins Antibiotic Guide: Natural Penicillin. 03-12-2008. Available at <http://prod.hopkinsabxguide.org/antibiotics/antibacterial/natural-pcns/penicillin.html?contentInstanceId=25488>. Accessed August 31, 2008.
15. MacMahon SW, Hickey AJ, Wilcken DE, Wittes JT, Feneley MP, Hickie JB. Risk of infective endocarditis in mitral valve prolapse with and without precordial systolic murmurs. *Am J Cardiol*. 1987;59(1):105–108.
16. Rossi EG, Grinberg M, Mansur AJ, Bellotti G, Pileggi F, Jatene A. Mitral valve prolapse in infective endocarditis. Incidence and characteristics. *Arq Bras Cardiol*. 1990;54(2):101–104.
17. Frary CJ, Devereux RB, Kramer-Fox R, Roberts RB, Ruchlin HS. Clinical and health care cost consequences of infective endocarditis in mitral valve prolapse. *Am J Cardiol*. 1994;73(4): 263–267.
18. Devereux RB, Frary CJ, Kramer-Fox R, Roberts RB, Ruchlin HS. Cost-effectiveness of infective endocarditis prophylaxis for mitral valve prolapse with or without a mitral regurgitant murmur. *Am J Cardiol*. 1994;74(10):1024–1029.
19. Daly CG, Currie BJ, Jeyasingham MS et al. A change of heart: the new infective endocarditis prophylaxis guidelines. *Australian Dental Journal*. 2008 Oct;53(3):196–200.