

Infective Endocarditis: Rationale for Revised Guidelines for Antibiotic Prophylaxis

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Infective endocarditis is an uncommon but serious and often life-threatening condition. While developments in cardiac imaging, therapeutics and surgical techniques have led to improved outcomes in individual patients, the overall incidence of infective endocarditis has remained relatively stable from 1950 through 2000, i.e., about 3.6 to 7.0 cases per 100,000 patient-years.¹ The predisposing risk factors have changed over time with the emergence of intravenous drug abuse, intravascular prostheses, nosocomial exposure, hemodialysis, and age-related valvular sclerosis as more prevalent than rheumatic heart disease, especially in the developed countries.² In addition to the risk factors, studies show that the causative flora implicated in infective endocarditis have also evolved, with *Staphylococcus aureus* emerging as the predominant pathogen, while a recent population-based study disputes this.³

Infective endocarditis is characterized by the presence of vegetations composed of platelets, fibrin, microorganisms, and inflammatory cells. The pathogenesis of infective endocarditis involves a complex sequence or confluence of events.⁴ Endothelial damage caused by turbulent blood flow seen in congenital or acquired heart disease causes platelets and fibrin deposition leading to formation of non-bacterial thrombotic endocarditis (NBTE). In this setting an episode of bacteremia could result in bacterial adherence to NBTE, bacterial proliferation within the NBTE, and formation of vegetations, the typical lesions of infective endocarditis (figure 1).

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Empiric Approach to Infective Endocarditis Prophylaxis:

Caution is the Watchword!

Prevention of infective endocarditis, potentially a life-threatening condition, has been given serious consideration by the entire medical community including physicians, surgeons, and dentists. Guidelines for preventing infective endocarditis related to medical procedures have been developed by professional societies like the American Heart Association (AHA) since the 1950s. The guidelines were empiric, formulated based more on pathophysiology and expert opinion and less on clinical evidence. Since both endothelial injury and a precipitating event causing bacteremia are requisite for development of infective endocarditis, patients with risk factors for endothelial injury undergoing medical procedures which can cause transient bacteremia were construed to be at high risk for developing infective endocarditis. Since certain groups of bacteria (eg, Streptococci, Staphylococci, Enterococci) are commonly known to adhere to nonbacterial thrombotic endocarditis (NBTE) causing infective endocarditis, procedures which caused bacteremia from these organisms were considered as high risk procedures. Prevention of bacteremia

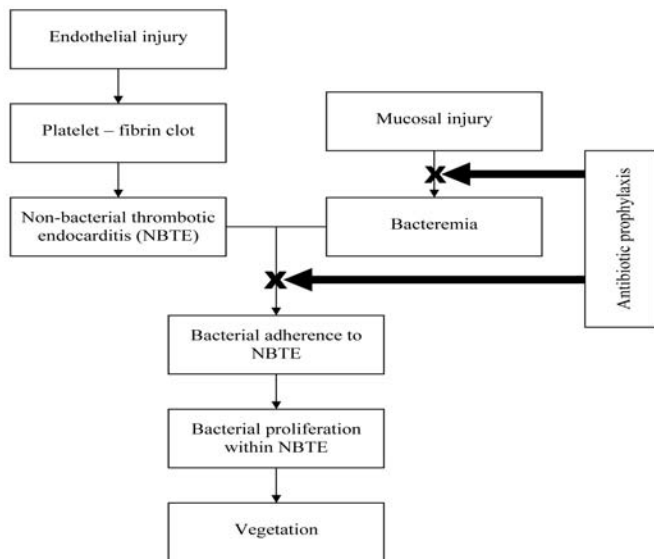


Figure 1. Pathogenesis of infectious endocarditis and rationale for antibiotic prophylaxis.

with appropriate antibiotics could in theory prevent or reduce bacteremia and prevent bacterial colonization of NBTE and thereby minimize the risk of infective endocarditis (figure 1). The bone of contention among the various guidelines and revisions is defining the patient population at high risk for cardiac endothelial injury and procedures with high risk for bacteremia.

Evidence-Based Approach to Infective Endocarditis Prophylaxis: Do no Harm!

While in theory, use of appropriate antibiotic prophylaxis for bacteremia causing procedures in patients with cardiac risk factors should lead to decreased incidence of infective endocarditis, this has not borne out in studies. Several factors contribute to the failure of this seemingly sound empirical approach. It is common knowledge, and studies have shown, that procedures like dental extraction cause bacteremia, but so do everyday activities like brushing teeth. While the degree of bacteremia caused by routine activities at a particular point in time may or may not be on the same magnitude as dental procedures, the overall burden of bacteremia over extended periods of time from daily activities would definitely surpass the transient bacteremia seen after medical procedures. The cumulative exposure to bacteremia from routine daily activities in 1 year may be as high as 5.6×10^6 times greater as that resulting from a single tooth extraction.⁵ Studies have shown only a small fraction, if any, of the infective endocarditis cases were probably caused by dental procedures.^{6,7} Another weak link is the efficacy of antibiotic prophylaxis in preventing or reducing bacteremia, as this is the main argument for empiric approach. The evidence for bacteremia reduction or prevention by antibiotic prophylaxis is conflicting.⁸⁻¹¹ Even studies which show reduction in bacteremia do not show reduction in infective endocarditis.^{8,9} While studies in dental procedures have failed to show a clear benefit for antibiotic prophylaxis, studies in other procedures (respiratory, gastrointestinal, and genitourinary) are very limited.

Table 1. Comparison of guidelines for infective endocarditis prophylaxis (1997–2008).

Guidelines	AHA 1997 ¹⁷	SPILF/SFC 2002 ¹⁸	ESC 2004 ¹⁹	BSAC 2005 ²⁰	AHA 2007 ⁴	NICE 2008 ²¹
Risk groups described based on cardiac conditions*	High, moderate, negligible	High, low	High, moderate	High	High	High
Risk groups where prophylaxis is recommended or optional†	High, moderate	High, low	High, moderate	High	High	-
Dental	Yes	Yes	Yes	Yes	Yes	No
Respiratory	Yes	Yes	Yes	Yes	Yes	No
Procedures with recommendation for prophylaxis‡						
Gastrointestinal	Yes	Yes	Yes	Yes	No	No
Genitourinary	Yes	Yes	Yes	Yes	No	No
Infected skin/musculoskeletal	Yes	N/A	N/A	N/A	Yes	N/A
Antiseptic rinse	Yes	Yes	Optional	Yes	No	No

*Individual guidelines have classified cardiac conditions into different groups based on their risk for IE. The cardiac conditions included, as well as the risk groups described, differ among individual guidelines. We have tabulated the risk groups described by these guidelines.

†In the setting of a procedure causing bacteremia.

‡In patients with cardiac risk factors.

Yes: Prophylaxis recommended when criteria met; No: Prophylaxis not recommended; N/A: No specific recommendation. Bold typeface used to emphasize the change in recommendations from yes to no.

AHA, American Heart Association; BSAC, British Society for Antimicrobial Chemotherapy; ESC, European Society of Cardiology; NICE, National Institute for Health and Clinical Excellence; SPILF/SFC, Société de Pathologie Infectieuse de Langue Française/ Société Française de Cardiologie.

Table 2. American Heart Association infective endocarditis prophylaxis recommendations.

Cardiac conditions in which prophylaxis is reasonable

- Prosthetic cardiac valve or prosthetic material used for cardiac valve repair
- Previous infective endocarditis
- Congenital heart disease (CHD)
 - Unrepaired cyanotic CHD, including shunts and conduits
 - Completely repaired congenital heart defect with prosthetic material or device, during the first 6 months after the procedure
 - Repaired CHD with residual defects at or adjacent to site of prosthetic patch or device inhibiting endothelialization
- Post-cardiac transplant valvulopathy

Procedures for which prophylaxis is reasonable (only in patients with above listed high risk cardiac conditions)

- All dental procedures that involve manipulation of gingival tissue or the periapical region of teeth or perforation of oral mucosa
- Invasive procedure of the respiratory tract that involves incision or biopsy of respiratory mucosa
- Procedures involving infected skin, skin structures, or musculoskeletal tissue

Antibiotic prophylaxis solely to prevent infective endocarditis is not recommended for gastrointestinal or genitourinary tract procedures

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Evidence on the cost effectiveness of antibiotic prophylaxis for at-risk patients undergoing interventional procedures is contradictory as well.¹²⁻¹⁶ Without any clear evidence of benefit, the traditional empiric approach for antibiotic prophylaxis has been in vogue, thus far, primarily thanks to the apprehension about the serious nature of infective endocarditis among physicians, as well as among patients, reinforced by past recommendations from professional societies. Emergence of antibiotic resistance as a significant public health concern combined with the risk of antibiotic-related adverse effects, albeit infrequent, such as anaphylaxis or *Clostridium difficile* colitis, has prompted a steady move towards an evidence-based approach to infective endocarditis prophylaxis. This is reflected in the recommendations of different professional societies in the last decade (table 1).^{4,17-21}

AHA 2007 Guidelines

The current AHA guidelines depart from the 1997 revision in several aspects.^{4,17} The potential role of daily activities in infective endocarditis causation and the very low yield for antibiotic prophylaxis (cases of infective endocarditis prevented) have been recognized. Prophylaxis has been restricted to only a small number of cardiac conditions with very high risk for adverse outcomes from infective endocarditis (table 2). The conditions included are not based on the likelihood of occurrence of infective endocarditis but rather based on the likelihood of adverse outcomes if infective endocarditis occurs in patients with these conditions. As far as the procedures deemed high risk, the major departure from the past is the removal of indication for infective endocarditis prophylaxis for all gastrointestinal and genitourinary procedures. The dental and respiratory procedures requiring prophylaxis have been clarified as those involving manipulation of gingival tissue or the periapical region of teeth, or perforation of oral mucosa and incision or biopsy of respiratory mucosa, respectively. The 2007 AHA recommendations for antibiotic prophylaxis are summarized in table 3.

National Institute for Health and Clinical Excellence (NICE) Guidance

NICE guidelines published in 2008 made an even more radical departure from the past.²² They do not recommend antibiotic prophylaxis for dental, or non-dental procedures (eg, respiratory, gastrointestinal, and genitourinary).²¹ If a person at risk for infective endocarditis is receiving antibiotic therapy because they are undergoing a gastrointestinal or genitourinary procedure at a site with a suspected infection, antibiotics used should cover organisms that cause infective endocarditis (presumably Enterococci). The guidelines do not make explicit recommendations about procedures involving infected skin and musculoskeletal tissues. Chlorhexidine mouthwash prior to dental procedures is not recommended. A list of cardiac conditions at high risk for developing infective endocarditis is provided primarily for advocating importance of maintaining oral hygiene and increased vigilance for incidence of infective endocarditis (table 4).

The AHA guidelines (2007)⁴ and the NICE guidance (2008),²¹ as well as the British Society for Antimicrobial Chemotherapy (BSAC) guidelines (2005), represent significant departure from the traditional approach to infective endocarditis prophylaxis and have been received with initial apprehension among the medical community.²³⁻²⁵ Recently more professional societies have incorporated the recommendations of AHA guidelines into their advisory statements.^{26,27} The cause for dissent arises from two important aspects, one being the major departure from traditional recommendations. The second, and probably the most intriguing aspect, is that two professional societies (BSAC and AHA) and NICE have come with three significantly different sets of recommendations, even though all three recognize the paucity of evidence and aim to narrow the indication for prophylaxis. Based on the same body of evidence (lack of evidence for benefit in dental procedures and lack of good epidemiological data for non-dental procedures), BSAC recommends prophylaxis for dental and

Table 3. Antibiotic prophylactic regimens (AHA 2007)*.

Dental/respiratory procedures†

Situation	Agent	Regimen: single dose 30 to 60 min before procedure	
		Adults	Children
Oral	Amoxicillin	2 g	50 mg/kg
Unable to take oral medication	Ampicillin	2 g IM or IV	50 mg/kg IM or IV
	OR cefazolin or ceftriaxone	1 g IM or IV	50 mg/kg IM or IV
Allergic to penicillins or ampicillin-oral	Cephalexin‡¶	2 g	50 mg/kg
	OR clindamycin	600 mg	20 mg/kg
	OR azithromycin or clarithromycin	500 mg	15 mg/kg
Allergic to penicillins or ampicillin and unable to take oral medication	Cefazolin or ceftriaxone¶	1 g IM or IV	50 mg/kg IM or IV
	OR clindamycin	600 mg IM or IV	20 mg/kg IM or IV

Gastrointestinal/genitourinary procedures

Use of antibiotics solely for prophylaxis **not** recommended. For procedures involving infected tissue add enterococcal coverage (e.g., amoxicillin, ampicillin, piperacillin or vancomycin) to the therapeutic regimen.

Infected skin and musculoskeletal tissue

Include an agent active against Staphylococci and β -hemolytic streptococci (e.g., anti-staphylococcal penicillin or cephalosporin; clindamycin or vancomycin in penicillin allergic patients) in the therapeutic regimen.

* For patients with cardiac conditions described in table 2.

† For dental and respiratory procedures discussed in table 2.

‡ Or other first- or second-generation oral cephalosporin in equivalent adult or pediatric dosage.

¶ Cephalosporins should not be used in an individual with a history of anaphylaxis, angioedema, or urticaria with penicillins or ampicillin. IM, intramuscular; IV, intravenous.

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non-dental (including gastrointestinal and genitourinary), AHA recommends prophylaxis for only dental and respiratory procedures and not gastrointestinal or genitourinary procedures, and NICE recommends prophylaxis for none of the procedures. While these three guidelines differ in their details, they all point toward a general trend against empiric use of antibiotic prophylaxis for infective endocarditis. With the rampant increase in incidence of multi-drug resistant organisms, an evidence-based approach to antibiotic prophylaxis is a healthy trend. Establishing the efficacy and safety of antibiotic prophylaxis with well-designed prospective studies, a yardstick used for acceptance of most medical interventions, should be required for antibiotic prophylaxis as well, considering the significant public health concerns discussed earlier. Subsequent to publishing these guidelines, a Cochrane database review on antibiotics for prophylaxis of bacterial endocarditis in dentistry showed no evidence as to whether penicillin prophylaxis is effective or ineffective against bacterial endocarditis in people at risk who are about to undergo an invasive dental procedure.²⁸

Conclusion

With the NICE guidance, infective endocarditis prophylaxis

has come full circle. In the latter half of the 20th century, regular revisions for infective endocarditis prophylaxis guidelines added more cardiac risk conditions and risk groups, more at risk procedures and more antibiotic regimens, adding to the complexity faced by a primary physician in both applying these recommendations to an individual patient and also in explaining the benefits and potential harm to the patient. This created potential for misgivings in physician-patient relationships and medico-legal pitfalls. The newer guidelines are much simpler to follow and could potentially overcome this serious concern. However, explaining these drastic changes to a returning patient and to referral physicians who are more accustomed to old recommendations would be equally challenging, if not more. The upcoming European Society of Cardiology guidelines, expected in 2009 and predicted to be on similar lines to the NICE guidelines, will hopefully help in settling this issue (<http://www.escardio.org/guidelines>). One of the bright spots in the AHA guidelines is the reduction in the use of prophylactic antibiotics in cases where it can be avoided without serious adverse outcomes. Limited use of prophylaxis will likely reduce the unwanted selection of antibiotic-resistant strains and their unintended consequences such as *C. difficile*-associated colitis.

Table 4. NICE guidance for infective endocarditis prophylaxis.

Cardiac conditions at high risk for infective endocarditis:

- Acquired valvular heart disease with stenosis or regurgitation
- Valve replacement
- Structural congenital heart disease, including surgically corrected or palliated structural conditions, but excluding isolated atrial septal defect, fully repaired ventricular septal defect or fully repaired patent ductus arteriosus, and closure devices that are judged to be endothelialized
- Previous infective endocarditis
- Hypertrophic cardiomyopathy

Antibiotic prophylaxis is not recommended:

- For people undergoing dental procedures
- For people undergoing non-dental procedures at these sites (upper and lower gastrointestinal; genitourinary tract - urological, gynecological and obstetric procedures, and childbirth; upper and lower respiratory tract – includes ear, nose and throat procedures and bronchoscopy)

Chlorhexidine mouthwash is not recommended for infective endocarditis prophylaxis for dental procedures.

Infections in patients at risk for infective endocarditis should be promptly treated to reduce risk of infective endocarditis developing. Antibiotic therapy used for gastrointestinal or genitourinary procedures at a site with suspected infection in patients at risk of infective endocarditis, should cover organisms causing infective endocarditis.

Patients should be educated on benefits and risks of antibiotic prophylaxis, recommendations against antibiotic prophylaxis, importance of oral hygiene, symptoms of infective endocarditis and risks of invasive procedures including non-medical procedures like body piercing and tattooing.

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