

## Review Article

# Infective Endocarditis Prophylaxis for Dental Procedures in 2009: What Has Changed?

PEPIE TSOLKA, DEMOSTHENES KATRITSIS

*Athens Euroclinic, Athens, Greece*

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*Address:*  
D. Katritsis

*Athens Euroclinic*  
9 Athanassiadou St.  
11521 Athens  
Greece  
*e-mail:*  
[dkatritsis@euroclinic.gr](mailto:dkatritsis@euroclinic.gr)

**T**here is now evidence that most cases of infective endocarditis are not attributable to an invasive procedure, and bacteremia resulting from daily activities is much more likely to cause infective endocarditis than bacteremia associated with a dental procedure. Thus, the usefulness of antibiotic prophylaxis in this setting has been questioned. In the recently revised American Heart Association (AHA) guidelines, infective endocarditis prophylaxis is no longer mandatory, i.e. a Class I recommendation, in any patient, even in the presence of native valve disease. It should be given, as a Class IIA recommendation, in patients with prosthetic valves or a history of endocarditis only prior to dental procedures that involve manipulation in gingival tissue or the periapical region of the teeth, or perforation of the oral mucosa. This review discusses the new guidelines and suggests recommendations for cardiac conditions about which data are virtually lacking.

## Conventional wisdom

The association between dental health and infective endocarditis was first considered as early as in 1909, when Horder noted that the mouth can be a potential source of infective agents capable of affecting the heart.<sup>1</sup> Indeed, turbulent blood flow produced by certain types of congenital or acquired heart disease may traumatize the

endocardium and endothelial surfaces.<sup>2</sup> Invasion of the bloodstream by microbes that can colonize this damaged site may result in clinical infection.<sup>3</sup> Oral mucosal surfaces are populated by a dense endogenous microflora, including species known to cause infective endocarditis.<sup>4</sup> More than 700 species of bacteria have already been identified, 400 of which were found in the periodontal pocket adjacent to teeth.<sup>5</sup> Trauma to oral mucosal surfaces, particularly the gingival crevice around teeth, releases these microbial species transiently into the bloodstream. At least 126 individual bacteria have been isolated in blood cultures after extractions or toothbrushing.<sup>4,6</sup> Transient bacteremia commonly occurs not only during dental procedures but also during routine daily activities.<sup>3,6</sup> Streptococci represent a significant proportion of the flora around the teeth, especially in the supragingival plaque, and they are frequently associated with infective endocarditis.<sup>2</sup> Mediators of bacterial adherence, such as the lipoprotein receptor antigen I (LraI) found in the *Streptococcus viridans* group, promote colonization of the traumatized endocardial or endothelial sites and, depending on several factors, may give rise to infective endocarditis.<sup>7</sup> Animal model data have shown that the rate of infection of damaged heart valves is dependent on the inoculum size of the bacterial challenge, with larger inocula yielding higher infection rates.<sup>8</sup>

The rationale for endocarditis prophylaxis in clinical practice, therefore, is that antibiotics, by limiting bacteremia, should be effective in preventing infective endocarditis associated with dental procedures in humans.<sup>2,9</sup> The first AHA document on this subject was published in 1955 and has been followed by 9 revisions outlining which patients, which procedures, and which antibiotics should be used to prevent infective endocarditis. The European Society of Cardiology<sup>10</sup> has produced similar, although less detailed, guidelines.

However, this long-standing clinical practice has been based primarily on expert opinion and support from a few case-controlled and descriptive studies. There has never been a controlled, randomized study that evaluated this strategy and many authors have questioned the efficacy of antimicrobial prophylaxis in patients who undergo dental procedures.<sup>11-18</sup>

### Primary reasons for revision of the guidelines

Up to now there has been no consistent association between interventional procedures, dental or non-dental, and the development of infective endocarditis. A study conducted in 54 Philadelphian hospitals in the USA found that preceding dental treatment was no more likely in patients with infective endocarditis than in controls.<sup>13</sup> In addition, the extent to which systemic antibiotics reduce the incidence, duration, nature, and magnitude of bacteremia from dental procedures is controversial,<sup>15,19</sup> and the value of prophylaxis is far from proven. Although early studies<sup>14,19</sup> demonstrated that infective endocarditis prophylaxis may be effective, later and much larger studies showed that most cases of infective endocarditis are not attributable to an invasive procedure, and that the protective efficacy of antibiotic prophylaxis was not significant.<sup>18,21,22</sup> In a recent study amoxicillin had a significant impact on bacteremia from a dental extraction.<sup>6</sup> However, 33% of patients undergoing extraction after prophylaxis showed evidence of bacteremia, including species related to infective endocarditis.<sup>6</sup> This lack of 100% efficacy alters the per-dose risk-benefit ratio, increasing the number needed to treat to avert a distant site infection. Of course, the lack of proof of efficacy is not necessarily the proof of lack of efficacy, but there are still no data unequivocally demonstrating a benefit of prophylaxis in this respect.

There is now substantial evidence that bacteremia resulting from daily activities, such as chewing food, brushing teeth, flossing, use of water irrigation devices and other activities, is much more likely to cause

infective endocarditis than bacteremia associated with a dental procedure.<sup>3,6</sup> Bacteria commonly gain entrance to the circulation through ulcerated gingival crevicular tissue that surrounds the teeth.<sup>4</sup> Although dental extractions are among the most likely of dental procedures to cause bacteremia, toothbrushing may disrupt a far larger surface area of gingival crevicular tissue. Incidence rates for bacteremia in adults range from 0% to 100% for single-tooth extractions,<sup>15,16,23-25</sup> and from 0% to 57% for toothbrushing.<sup>26-30</sup> Transient bacteremias usually clear within 10 minutes, and positive blood cultures can be detected for as long as 60 minutes after a dental procedure.<sup>6,17,23,26</sup> Lockhart et al<sup>6</sup> have recently shown a substantial incidence of bacteremia (23%) from brushing, involving species of bacteria causing infective endocarditis. These investigators randomized 290 subjects to toothbrushing, single-tooth extraction with amoxicillin prophylaxis, or single-tooth extraction with identical placebo. Ninety-eight bacterial species, 32 of which are reported to cause endocarditis, were identified. The cumulative incidence of endocarditis-related bacteria from all 6 blood draws was 23%, 33%, and 60% for the toothbrushing, extraction-amoxicillin, and extraction-placebo groups, respectively ( $p < 0.0001$ ). In addition, the brushing group had a larger percentage of positive cultures at 60 minutes (9% versus 2%, respectively).<sup>6</sup> This suggests that brushing poses a risk for bacteremia similar to that of a dental extraction, given professional guidelines that recommend toothbrushing at least twice per day. Therefore, there is the potential for bacteremia from toothbrushing alone to occur >200 times per year, compared with an average of fewer than 2 dental office visits per year per person in the United States.<sup>32</sup> Guntheroth<sup>33</sup> estimated that with normal physiologic use of the oral cavity, about 5376 minutes of transient bacteremias occur each month in the average person. Thus, based on the high frequency of physiologic bacteremias and the low incidence of dental procedures preceding the onset of infective endocarditis, the odds of a case of infective endocarditis occurring from physiologic “seeding” of oral bacteria are 1,000 times greater than after a dental procedure.<sup>32</sup>

The presence of dental disease may increase the risk of bacteremia associated with these routine activities. Maintenance of optimal oral health and hygiene may reduce the incidence of bacteremia from daily activities and is more important than prophylactic antibiotics for a dental procedure in reducing the risk of infective endocarditis. Thus, evidence is now moving from “procedure-related bacteremia” toward “cumulative bacteremia” as the more likely cause of most cas-

es of infective endocarditis. Continued episodic bacteremia due to poor dentition may pose a much greater risk for the development of infective endocarditis than a single dental procedure.

It has even been also suggested that the risk of a serious allergic reaction to amoxicillin may be greater than the risk of contracting infective endocarditis. Anaphylaxis to  $\beta$ -lactam antibiotics occurs in 15-40 of 100,000 uses (being potentially fatal in 1-3 of 100,000 uses),<sup>33,34</sup> and there are concerns about the problem of community-derived antibiotic resistance. A report from the Cochrane Collaboration in 2004<sup>35</sup> concluded that there is no evidence about whether penicillin prophylaxis is effective or ineffective against infective endocarditis in people at risk who are about to undergo an invasive dental procedure, and it is not clear whether the potential harm and costs of penicillin administration outweigh any beneficial effect.

Not surprisingly, therefore, there has been a trend towards a changed attitude in relation to endocarditis prophylaxis. The French were the first, in 2002,<sup>36</sup> to challenge accepted practice; they emphasized the importance of general and oral hygiene in populations at risk and recommended prophylaxis only to patients at high risk. The 2006 guidelines of the British Society for Antimicrobial Chemotherapy also recommended prophylaxis only for those at high risk and for whom infective endocarditis would result in high mortality.<sup>37</sup> Even more provocatively, the most recent guidance from the British National Institute for Health and Clinical Excellence (NICE)<sup>38</sup> suggested an end to the practice of antibiotic prophylaxis against infective endocarditis altogether. Although NICE identified patients at increased risk of developing infective endocarditis, they no longer advocate prophylaxis for dental or respiratory procedures, even for traditionally held high-risk groups. Antibiotics were recommended only in patients at risk undergoing gastrointestinal or genitourinary procedures at a site where there is suspected pre-existing infection. Such a radical view was not easily accepted by the cardiology community. Several cardiologists argued that they are a potentially dangerous departure from established (albeit non evidence-based) practice, which will unnecessarily expose patients to the devastating risks of infective endocarditis.<sup>39-41</sup>

### The new ACC/AHA guidelines

In 2007 the AHA Rheumatic Fever, Endocarditis, and Kawasaki Disease Committee convened a group of national and international experts in the field, in-

cluding experts in the prevention and treatment of infective endocarditis, from the American Dental Association, the Infectious Diseases Society of America and the American Academy of Pediatrics to review current practice and provide new recommendations. After several years of discussion and debate within the writing group, combined with input from experts from other learned societies, the new recommendations were released.<sup>42,43</sup> The product clearly represents a break from long-accepted and implemented clinical practice. Major changes compared to previous guidelines are:

1. Antibiotic infective endocarditis prophylaxis is no longer mandatory, i.e. a Class I recommendation, in any patient. It is a Class IIA recommendation, i.e. it is reasonable to give prophylaxis in high risk populations, but additional studies are needed to support this view.

2. Antibiotic infective endocarditis prophylaxis should be given only to high-risk patients prior to dental procedures that involve manipulation in gingival tissue or the periapical region of the teeth, or perforation of the oral mucosa. Prophylaxis is no longer needed for routine anesthetic injections through non-infected tissue, dental radiographs, placement of removable prosthodontic or orthodontic appliances, adjustment of orthodontic appliances, placement of orthodontic brackets, shedding of deciduous teeth or bleeding from trauma to the lips or oral mucosa.

3. High-risk patients are defined not on the basis of an increased risk for infective endocarditis, but rather on an increased risk of an adverse outcome should they develop endocarditis, as indicated in Table 1.

4. Antibiotic infective endocarditis prophylaxis is no longer indicated in patients with native valve disease, such as aortic stenosis, mitral stenosis, or mitral valve prolapse.

**Table 1.** High-risk cardiac conditions requiring infective endocarditis prophylaxis.

- Prosthetic cardiac valve.
- Previous infective endocarditis.
- Unrepaired cyanotic congenital heart disease.
- Completely repaired congenital heart defect with prosthetic material or device, whether placed by surgery or by catheter intervention, during the first 6 months after the procedure (endothelialization of prosthetic material occurs within 6 months after the procedure).
- Repaired congenital heart disease with residual defects at the site or adjacent to the site of a prosthetic patch or prosthetic device (which inhibit endothelialization).
- Cardiac transplantation with subsequent cardiac valvulopathy.

**Table 2.** Simplified scheme of prophylactic antibiotic regimens administered 30-60 min before dental procedures that involve manipulation in gingival tissue or the periapical region of the teeth, or perforation of the oral mucosa. Pediatric doses are given in parentheses. In patients allergic to cephalosporins, cephalexin, cefazolin and ceftriaxone should be avoided.

Amoxicillin 2 g po (50 mg/kg po) or 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)

Allergy to penicillins:

Cephalexin 2 g po (50 mg/kg po)

OR

Clindamycin 600 mg po (20 mg/kg po) or clindamycin 600 mg IM or IV (20 mg/kg IM or IV)

OR

Azithromycin or clarithromycin 500 mg po (15 mg/kg po)

OR

Cefazolin or ceftriaxone 1 g IM or IV 50 mg/kg IM or IV

po – per os, IM – intramuscularly, IV – intravenously. IM or IV should be given only if the patient is unable to take oral medication.

The recommended antibacterial regimens for dental procedures remain unchanged (Table 2).

Unavoidably, a certain degree of uncertainty, if not confusion, has emerged among both dental and cardiac care professionals – not to mention patients who might have been exposed to different practices in the past and are now advised they are no longer necessary. If antibiotic prophylaxis is ineffective, why select the high-risk group for prophylaxis? Why has no case of penicillin-allergy associated death been reported in the context of antibiotic infective endocarditis prophylaxis? Even if protection offered by antibiotics is not 100% effective, why not accept even a limited benefit?

Perhaps our expert advice should be that guidelines, however detailed, can never be a substitute for individualized clinical judgment, and this is particularly true when dealing with recommendations derived from limited data.

A reasonable approach might be as follows:

1. Dental procedures other than those indicated above do not require prophylaxis.

2. For high-risk cardiac patients subjected to indicated dental procedures, it is reasonable to follow the recent AHA guidelines and administer prophylaxis despite the absence of strong scientific evidence.

3. For patients with cardiac conditions about which data are virtually lacking, such as bicuspid aortic valves, coarctation of the aorta, native valve disease, or significant hypertrophic obstructive cardiomyopathy, and who are subjected to dental procedures as indicated, the situation should be discussed and patient preferences should be assessed. If doctors and patients feel more

comfortable they can continue using prophylaxis with the antibiotic schemes proposed by the AHA.

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