

Editorial

Prevention of Infective Endocarditis: Between Progress in Scientific Knowledge and the Lack of Randomized Trials

Prevención de la endocarditis infecciosa: entre el avance en los conocimientos científicos y la falta de ensayos aleatorizados

Carlos Falces^a and José M. Miró^{b,*}

^aServicio de Cardiología, Hospital Clínic, IDIBAPS, Universidad de Barcelona, Barcelona, Spain

^bServicio de Enfermedades Infecciosas, Hospital Clínic, IDIBAPS, Universidad de Barcelona, Barcelona, Spain

Article history:

Available online 5 October 2012

Physicians and dentists have traditionally prescribed antibiotic prophylaxis to prevent infective endocarditis (IE) in certain patient groups. However, the latest guidelines reveal the lack of sufficient clinical evidence to endorse the general practice of prophylaxis.¹ Indeed, in only a few years, the “pendulum” has swung from recommending antibiotic prophylaxis for a number of procedures and types of heart disease to restricting its use considerably at the present time.²

IE is a rare disease that continues to produce high morbidity (cardiac surgery rates of 50%) and mortality (approximately 20%) in the 21st century despite major medical and surgical advances in its diagnosis and treatment.³ The recommendation to administer antibiotics before a medical or dental procedure that could cause transient bacteremia in patients at risk of IE has been widely disseminated for decades.² Expert committees have based their efforts on a logical sequence of premises: IE causes high morbidity and mortality; there is evidence that certain heart diseases predispose patients to IE; certain procedures lead to transient bacteremias that can cause IE, and experimental animal models have shown the efficacy of antibiotic prophylaxis in preventing the disease. Based on these reasonings, for years it was thought that prophylaxis in humans should be effective for prevention in dental, gastrointestinal, and genitourinary procedures in patients with certain heart diseases.² A review of the scientific evidence confirms the validity of the first 4 fundamentals, but raises questions about the last one on antibiotic prophylaxis in humans.² As a result, the current recommendations of the scientific societies have greatly restricted the indications for antibiotic prophylaxis^{4,5} and have even proposed that prophylaxis not be used.⁶ This has led to strong debate in the medical field. In the case of prophylaxis for dental procedures, a review of clinical studies found no evidence about whether prophylaxis was effective or not.⁷ In addition, IE has experienced etiologic changes in recent decades and is no longer predominantly caused by *viridans* group streptococci, but rather by nonoral microorganisms such as *Staphylococcus aureus*, which

further reduces support for antibiotic prophylaxis as previously conceived.³

There are arguments for and against antibiotic prophylaxis to prevent IE. The American Heart Association began to issue prophylaxis recommendations more than 5 decades ago based on several factors: bacteremias can cause IE, the causative microorganisms are part of the normal oral flora, there are many case reports of a temporal relationship between dental procedures and the development of IE, and the risk of adverse effects of antibiotics is low for a disease with very high morbidity and mortality; nevertheless, antibiotic prophylaxis has not prevented endocarditis in some well-documented cases.⁸ The frequency of bacteremia during common dental procedures is known to be high, but most cases are transient and also occur spontaneously because of activities of daily living, such as teeth brushing or chewing gum.⁹ Therefore, the number of bacteremias experienced by an individual is much higher due to daily activities than to dental procedures and the use of prophylaxis would prevent only a few cases. Additionally, a relationship with previous dental procedures is not identified in most cases of IE. Since the early 20th century, it has been known that bacteremias are more common and can occur spontaneously in individuals with poor oral hygiene or periodontal disease. As a result, adequate oral hygiene and regular dental visits are considered key prevention measures, probably with greater impact than antibiotic prophylaxis.

The data used to prepare the previous guidelines are based on experimental or case-control studies,¹⁰ and no randomized control studies have been carried out to evaluate the usefulness of antibiotic prophylaxis. The efficiency of prophylaxis has been questioned, as an extremely high number of patients would need to be treated to prevent a very few cases of IE,¹¹ which is impossible.

The current clinical practice guidelines from the American Heart Association⁴ and the European Society of Cardiology⁵ have significantly restricted prophylaxis indications by limiting the recommendation to patients at a higher risk of IE (Table 1) or those who would have more severe disease and by reducing the procedures for which the indication is recommended (Table 2). The recommended antibiotic regimens in these cases are listed in Table 3. More sweepingly, the British National Institute of Clinical Excellence recommends that systematic prophylaxis not be

SEE RELATED ARTICLE:

<http://dx.doi.org/10.1016/j.rec.2012.04.007>, Rev Esp Cardiol. 2012;65:1134–5.

* Corresponding author: Servicio de Enfermedades Infecciosas, Hospital Clínic, Villarroel 170, 08036 Barcelona, Spain.

E-mail address: jmmiro@ub.edu (J.M. Miró).

Table 1
Patients for Whom Antibiotic Prophylaxis Is Recommended

Patients with a prosthetic valve or prosthetic material used for heart valve repair
Patients with a history of endocarditis
Patients with congenital heart diseases
Cyanotic congenital diseases not surgically repaired
Diseases repaired with prosthetic material during the first 6 months
Diseases repaired with prosthetic or paraprosthetic residual defects

Adapted from Habib et al.⁵**Table 2**
Procedures in Which Antibiotic Prophylaxis Is Recommended

<i>Dental procedures</i>
Prophylaxis recommended in all procedures that involve handling the mucosa in the gingival or periapical region of the tooth or perforation of the oral mucosa
Antibiotic prophylaxis not required: anesthesia injections through uninfected tissue, dental x-rays, placement of removable endodontic or prosthodontic apparatus or supports, loss of primary teeth and bleeding due to trauma to the lips or oral mucosa
<i>Respiratory tract</i>
Not recommended in respiratory tract procedures, except in invasive procedures to treat an infection that must be treated
<i>Gastrointestinal tract</i>
Not recommended, unless infectious processes are present at the time of the procedure
<i>Genitourinary tract</i>
Not recommended in elective procedures (colonization or infection must first be treated)

Adapted from Habib et al.⁵

administered for any indication, in view of the lack of scientific evidence.⁶ Instead, National Institute of Clinical Excellence recommended that patients be educated on the importance of good oral hygiene and on the need to be familiar with the risk of invasive procedures and understand the symptoms of IE that would warrant early consultation. In the United Kingdom, this recommendation has led to a 78.6% decrease in prophylaxis prescriptions, although a significant increase in IE cases has not been reported after 2 years of follow-up.¹²

Changes to the guidelines have meant that dentists and clinicians have difficulty in explaining to patients that a recommendation they have heard for many years is no longer current in the United Kingdom for patients with a prior history of endocarditis, who should also not receive prophylaxis according to the National Institute of Clinical Excellence guidelines. This has led to confusion among the health community and public at large.

In our opinion, the decrease in the number of prophylactic indications in the current guidelines reveals the need for health professionals to pool scientific skills, the lack of evidence on

Table 3
Recommended Antibiotics for Adults Undergoing High-risk Dental Procedures in the Recommended Cases

Regimen of choice	Amoxicillin (2 g, oral solution), single dose 30-60 min before the procedure
In cases of oral intolerance	Cephalexin (2 g) or cefazolin or ceftriaxone (1 g), single intravenous dose 30-60 min before the procedure
In cases of penicillin allergy	Clindamycin (600 mg, oral or intravenous)

prophylaxis, and the need for adequate clinical discretion with patients. In recent decades, considerable progress has been made in our understanding of IE through basic and experimental research, epidemiology, and clinical management of patients, which represents a good example of translational research. In the case of prophylaxis, however, there is no evidence based on randomized clinical trials showing the efficacy of the measures or completely proving their ineffectiveness. Due to the characteristics of this rare condition and the historical trend of prophylactic recommendations, these kinds of randomized studies will probably never be performed. In this context, we consider that the European Society of Cardiology recommendations⁵ currently in effect in Spain are adequate, as they combine a scientific understanding of the topic with prudence in recommending prophylaxis for high-risk patients and not recommending it for any others.

Knowledge of and compliance with the clinical practice guidelines vary widely among dentists. While some countries have seen a high degree of familiarity and acceptance of the guidelines,¹³ in the past decade dentists in Spain have shown a lack of understanding of the prophylactic indications, with low compliance with the current recommendations.¹⁴ In an article published in *Revista Española de Cardiología*, Torres et al.¹⁵ reported no substantial change in the situation, with little understanding of the recommendations (93% of those surveyed were unaware of the documents on IE prevention) and a low acceptance of the current restrictions recommended in the guidelines. Some confusion is also evident, as some believe the message from the cardiologic community is imprecise and variable; this is understandable in view of the major changes made in prophylactic indications in recent years. The article rightly concludes that there is a communication problem between the various professionals related to the issue and that work should be done to improve professionals' understanding of and adherence to the guidelines.

Information resources (e.g. brochures, videos, and websites) to explain the recommendations and facilitate professionals' work can improve implementation of the measures. An example of this would be the preparation of a patient document on current recommendations drawn up jointly by the dentistry and cardiology societies similar to the one written in Catalonia.¹⁶

IE prevention is an objective that should involve the entire health community, scientific societies, health administration, primary care physicians, cardiologists, dentists, infectious disease specialists, internists, epidemiologists, pharmacists, and nurses. Coordination and communication among all of these parties are essential to achieving adequate implementation of the guidelines and recommendations. Torres et al.¹⁵ shows that we are still far from achieving this objective.

ACKNOWLEDGEMENTS

The authors thank the other members of the Endocarditis Study Group at the *Hospital Clínic de Barcelona* for their assistance: A. del Río, J.M. Pericás, X. Castañeda, C. Cervera, A. Moreno, J.M. Gatell (*Servicio de Enfermedades Infecciosas*), F. Marco, C. García de la María, Y. Armero, M. Almela, J. Vila (*Servicio de Microbiología*), C.A. Mestres, R. Cartañá, L. Mont, S. Ninot, J.L. Pomar, M. Azqueta, M. Sitges, J.C. Paré, M. Heras (*Instituto Clínic del Tórax*), J. Ramírez, T. Ribalta (*Departamento de Anatomía Patológica*), M. Brunet (*Servicio de Toxicología*), D. Soy (*Servicio de Farmacia*), and G. Fita, and I. Rovira (*Servicio de Anestesia*).

CONFLICTS OF INTEREST

None declared.

REFERENCES

1. Falces C, Garcia de la Mària C, Mestres CA, Del Río A, Marco F, Moreno A, et al. Profilaxis antibiòtica de la endocarditis infecciosa: a quién y cuándo se debe recomendar. *Rev Esp Anestesiol Reanim.* 2009;56:135–8.
2. Duval X, Lepout C. Prophylaxis of infective endocarditis: current tendencies, continuing controversies. *Lancet Infect Dis.* 2008;8:225–32.
3. Murdoch DR, Corey GR, Hoen B, Miró JM, Fowler Jr VG, Bayer AS, et al. Clinical presentation, etiology, and outcome of infective endocarditis in the 21st century: the International Collaboration on Endocarditis-Pro prospective Cohort Study. *Arch Intern Med.* 2009;169:463–73.
4. Wilson W, Taubert K, Gewitz M, Lockhart P, Baddour L, Levison M, et al. Prevention of infective endocarditis. Guidelines from the American Heart Association. *Circulation.* 2007;116:1736–54.
5. Habib G, Hoen B, Tornos P, Thuny F, Prendergast B, Vilacosta I, et al. The Task Force on the prevention, diagnosis and treatment of infective endocarditis of the European Society of Cardiology. Guidelines on the prevention, diagnosis and treatment of infective endocarditis. *Eur Heart J.* 2009;30:2369–413.
6. Centre for Clinical Practice at NICE (UK). Prophylaxis against infective endocarditis: antimicrobial prophylaxis against infective endocarditis in adults and children undergoing interventional procedures [Internet]. London: National Institute for Health and Clinical Excellence (UK); 2008 [accessed 10 May 2012]. Available at: <http://www.nice.org.uk/CG064>.
7. Oliver R, Roberts GJ, Hooper L, Worthington HV. Antibiotics for the prophylaxis of bacterial endocarditis in dentistry. *Cochrane Database Syst Rev.* 2008; 8:CD003813. <http://dx.doi.org/10.1002/14651858.CD003813.pub3>.
8. Durack DT, Kaplan EL, Bisno AL. Apparent failures of endocarditis prophylaxis. Analysis of 52 cases submitted to a national registry. *JAMA.* 1983;250:2318–22.
9. Corner L, Larsen T, Filian M, Holmstrup P. Incidence of bacteremia after chewing, tooth brushing and scaling in individuals with periodontal inflammation. *J Clin Periodontol.* 2006;33:401–7.
10. Strom BL, Abrutyn E, Berlin JA, Kinman JL, Feldman RS, Stolley PD, et al. Dental and cardiac risk factors for infective endocarditis: a population-based, case-control study. *Ann Intern Med.* 1998;129:761–9.
11. Duval X, Alla F, Hoen B, Danielou F, Larrieu S, Delahaye F, et al. Estimated risk of endocarditis in adults with predisposing cardiac conditions undergoing dental procedures with or without antibiotic prophylaxis. *Clin Infect Dis.* 2006; 42:e102–7.
12. Thornhill MH, Dayer MJ, Forde JM, Corey GR, Hock G, Chu VH, et al. Impact of the NICE guideline recommending cessation of antibiotic prophylaxis for prevention of infective endocarditis: before and after study. *BMJ.* 2011;342:d2392. <http://dx.doi.org/10.1136/bmj.d2392>.
13. Zadik Y, Findler M, Livne S, Levin L, Elad S. Dentists' knowledge and implementation of the 2007 American Heart Association guidelines for prevention of infective endocarditis. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod.* 2008;106:e16–9.
14. Tomas-Carmona I, Diz-Dios P, Limeres-Posse J, Outumuro-Rial M, Caamaño-Duran F, Fernández-Feijoo J, et al. Pautas de profilaxis antibiòtica de endocarditis bacteriana recomendadas por los odontólogos en España. *Med Oral.* 2004;9:56–62.
15. Torres F, Renilla A, Flórez JP, Secades S, Benito EM, De la Hera JM. Grado de conocimiento de la profilaxis de endocarditis infecciosa entre los dentistas españoles. *Rev Esp Cardiol.* 2012;65:1134–5.
16. Noves normes de prevenció de l'endocarditis infecciosa. Barcelona: Societat Catalana de Cardiologia i Societat Catalana d'Odontostomatologia; 2009 [accessed 14 May 2012]. Available at: <http://www.catcardio.cat/pdfs/fitxa%203.pdf>.