EDITORIAL

The European Society of Cardiology 2009 guidelines on the prevention, diagnosis, and treatment of infective endocarditis

Key messages for clinical practice

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Introduction The recently published European Society of Cardiology (ESC) guidelines on the prevention, diagnosis, and treatment of infective endocarditis (IE)[1] recognize that IE is a changing disease, which, despite advances in diagnosis and treatment, remains very dangerous and challenging. In those at high risk due to a prosthetic valve, previous IE or congenital heart disease, morbidity and mortality remain close to 50%.[2]

Recent decades have seen *Staphylococcus aureus*, often acquired as a result of nosocomial infection or intravenous drug abuse, overtake oral streptococci as the most common pathogen in IE in developed nations.[3] IE is also increasingly frequent in the elderly[4] and in those with no previous documentation of valvular heart disease (VHD) (47% in a recent French study[5]).

With these changes in mind, the ESC guidelines committee has suggested that antibiotic prophylaxis should be reduced and that surgery should be performed earlier than previously recommended. They have also emphasized the important role of echocardiography in making an early diagnosis of IE, and monitoring its course.

Prevention of infective endocarditis Antibiotic prophylaxis to prevent IE in patients with high-risk cardiac lesions has been traditional cardiac and dental practice for over half a century, despite limited evidence of benefit. The efficacy of antibiotic prophylaxis for IE has never been demonstrated in a randomized controlled trial.

In line with recent guidelines published by the American Heart Association (AHA)[6] and the United Kingdom National Institute for Health and Clinical Excellence (NICE),[7] the ESC committee has suggested a dramatic reduction in the emphasis on antibiotic prophylaxis before dental and other invasive procedures (TABLE). Importantly, they suggest that prophylaxis is no longer indicated for native valve disease, nor for invasive respiratory, gastrointestinal or genitourinary procedures. This means that for the majority of patients, antibiotic prophylaxis is no longer recommended.

Innovative French guidelines in 2002[8] were the first to suggest a reduction in the practice of antibiotic prophylaxis, by restricting prophylaxis to those with the highest risk of the disease and its consequences. These also stressed the importance of general oral hygiene in the prevention of IE. Subsequent guidelines from the AHA in 2007 are very similar to the recent ESC publication, but include cardiac transplant recipients with VHD in the high-risk category and also recommend prophylaxis for invasive procedures of the respiratory tract needing mucosal incision or biopsy.

These changes are not, however, as far-reaching as the controversial guidelines published by the NICE in 2008. These suggested an end to the practice of antibiotic prophylaxis for dental procedures altogether, restricting prophylaxis very specifically to those with high-risk cardiac lesions, undergoing gastrointestinal or genitourinary procedures where there is suspected pre-existing infection (when antibiotics would be used anyway).

A careful approach by cardiologists, dentists, and general practitioners will be required to explain these changes to patients, many of whom

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TABLE Summary of current international guidelines for antibiotic prophylaxis in infective endocarditis

	American Heart Association, 2007	National Institute for Health and Clinical Excellence, 2008	European Society of Cardiology, 2009
high-risk patients	previous IE prosthetic valve unrepaired or incompletely repaired cyanotic congenital heart disease congenital heart disease repaired with prosthetic material (for 6 months after the procedure) valve disease in cardiac transplant recipients	previous IE prosthetic valve acquired valvular heart disease with stenosis or regurgitation structural congenital heart disease, including surgically corrected or palliated structural conditions; excluding isolated ASD, fully repaired VSD/PDA, endothelialized closure devices hypertrophic cardiomyopathy	previous IE prosthetic valve or prosthetic material used for valve repair cyanotic congenital heart disease (without surgical repair or with residual defects, palliative shunts or conduits) congenital heart disease repaired with prosthetic material (for 6 months if complete repair, indefinite if residual defect)
procedures requiring prophylaxis	dental procedures involving manipulation of gingival tissue, the periapical region of teeth, or perforation of the oral mucosa invasive procedures of the respiratory tract needing incision or biopsy of the mucosa	gastrointestinal and genitourinary procedures where there is suspected pre-existing infection	dental procedures requiring manipulation of the gingival or periapical region of the teeth or perforation of the oral mucosa

Abbreviations: ASD – atrial septal defect, IE – infective endocarditis, PDA – patent ductus artery, VSD – ventricular septal defect

have taken antibiotic prophylaxis before dental work for many years and have previously been warned about the significant dangers of IE. In this explanation to patients, it is important to understand the evidence (and its limitations) considered by the ESC committee.

The reasoning behind antibiotic prophylaxis is theoretical: bacteremia may provoke IE in patients with valvular abnormalities; invasive procedures may lead to bacteremia; and, in animal models, antibiotics before an induced bacteremia can reduce the risk of IE. However, whether results from animal models can be extrapolated to humans is unclear.

Daily oral activities (e.g., tooth brushing and chewing) cause transient streptococcal bacteremia, the cumulative result of which is an annual exposure thousand to million times greater than a single tooth extraction.[9] In animal models, the magnitude of bacteremia required to cause IE is 2 to 4 orders of magnitude greater than that caused by routine dental procedures[10] and a direct link between such procedures and IE has never been proven. A Cochrane Review from 2004 concluded that there was no evidence to support the use of penicillin prophylaxis in preventing IE.[11]

The only studies of the efficacy of antibiotic prophylaxis have been case-control analyses. A 2-year study of 275 patients in the Netherlands showed that most cases of IE are attributable to random bacteremia, not invasive procedures.[12] This study concluded that even if prophylaxis was entirely effective, then it would only prevent a very small number of IE cases. Similarly, a French study concluded that dental procedures were not associated with an increased risk of IE[13] and a study conducted in 54 hospitals in Philadelphia, United States, found that recent dental treatment was no more likely in IE patients than in controls.[14]

The results of these studies and the lack of a randomized controlled trial do not mean that antibiotic prophylaxis for IE is ineffective. However, they do suggest that a huge number of prophylaxis doses would be necessary to prevent a very small number of cases and that the risk of developing IE after an unprotected dental procedure is extremely low.[15] A sufficiently powered randomized controlled trial would be a massive undertaking, given the heterogeneity of the underlying cardiac disorders and invasive procedures involved. Until now, such a trial would have been deemed unethical, but more restrictive guidelines may now pave the way for its development.

As these studies suggest, the number needed to treat for effective prevention is extremely high and the use of antibiotics is certainly not without risk. Anaphylaxis to β-lactam antibiotics occurs in 15 to 40 of 100,000 uses and is potentially fatal in 1 to 3 of 100,000.[16,17] There are also concerns regarding the problem of antibiotic resistance, although this is less likely with single doses. With this in mind, the overall cost-effectiveness of routine antibiotic prophylaxis is questionable.

Diagnosis of infective endocarditis The changes suggested by the ESC with regard to the diagnosis of IE are less dramatic and reflect the fact that IE remains a diagnostic challenge. The guidelines reiterate the early involvement of a cardiologist and infectious diseases expert in a suspected case of IE, and emphasize the need for early echocardiography. Echocardiography should not be used indiscriminately, however, the exception being *Staphylococcus aureus* bacteremia, which has such potential for devastating consequences that routine echocardiography is justified in any case, irrespective of the presence or absence of other features of IE.

Where the clinical suspicion of IE is low, a negative transthoracic echocardiogram with good image quality is sufficient. However, in all other circumstances where there is a clinical suspicion of IE, transthoracic echocardiography is the initial imaging modality of choice, but should be promptly followed by transoesophageal imaging. Importantly, where the initial transoesophageal echocardiogram is negative, but suspicion for IE remains, imaging should be repeated after 7 to 10 days, or even earlier in *Staphylococcus aureus* bacteremia. Where the study is positive, follow-up echocardiography is mandatory to monitor the response to treatment and detect the development of complications.

Newer echocardiographic techniques, including three-dimensional imaging, as well as other imaging modalities such as multi-slice computed tomography, magnetic resonance, nuclear medicine, and positron emission tomography have yet to be sufficiently evaluated in IE, but may supplement (not replace) transthoracic and transoesophageal echocardiography.

Treatment of infective endocarditis Almost half of patients with IE will undergo surgery[18] and the new ESC guidelines provide recommendations for the first time regarding the timing of surgery. There is a particular emphasis on early surgery in those with heart failure, abscess, perivalvular complications, or embolism. The guidelines define "emergency" surgery as within 24 h, "urgent" surgery as within a few days and "elective" surgery as within 1 to 2 weeks of commencing appropriate antibiotic therapy.

Heart failure is the most common complication of IE, occurring in 50% to 60% of cases[19] and emergency surgery is indicated in aortic or mitral IE with refractory pulmonary edema or shock, either due to acute regurgitation, valve obstruction, or the formation of a fistula into a cardiac chamber or the pericardium. Urgent surgery is indicated, if heart failure persists or if echocardiographic features suggest hemodynamic compromise. In those patients with severe aortic or mitral regurgitation without heart failure, surgery can be performed on an elective basis.

Uncontrolled infection is the second frequent indication for surgery in IE.[18] In those patients with persisting fever and positive blood cultures after 7 to 10 days despite appropriate antibiotic therapy (and in whom extracardiac infection has been excluded), urgent surgery should be considered given the high risk of significant complications. Urgent surgery should also be considered in patients with locally uncontrolled infection and abscess, false aneurysm, fistula formation, or enlarging vegetation.

The third indication for surgery – prevention of embolism – is perhaps the most contentious. Embolic events complicate 20% to 50% of cases of IE (although this risk falls rapidly to 6%–21% following the initiation of appropriate antibiotic therapy) and are responsible for some of the most devastating consequences of IE. In the Euro Heart Survey, vegetation size was a reason (often accompanied by other indications) for surgery in 54% of patients with native valve IE, and in 25% of those with prosthetic valve IE.[18]

Several studies in recent years have shown that patients with vegetations exceeding 10 mm are at higher risk of embolism, and that this risk increases when the size exceeds 15 mm or the vegetation is particularly mobile.[20,21] However, it has never been demonstrated that the benefit of early surgery for large vegetations alone outweighs the risk of intervention. The new ESC guidelines suggest that, in the absence of embolism, urgent surgery is indicated for patients with aortic or mitral vegetations exceeding 10 mm in size and with other factors suggesting a poor prognosis (heart failure, persistent infection or abscess). Following 1 or more embolic events (which may be silent and detected radiologically), urgent surgery is indicated in the absence of these poor prognostic features.

A more difficult decision is in those patients with very large vegetations (>15 mm), but no other adverse clinical features. Early surgery may be considered, but the patient's other comorbidities must be taken into consideration.

Conclusions The demography and microbiology of IE have changed in recent decades, but it remains as devastating a condition. The ESC guidelines have been updated in this light, with 3 important messages. First, antibiotic prophylaxis should be restricted to those at the highest risk and is no longer indicated for native valve disease. Rather, there should be an emphasis on other preventative measures, particularly good oral hygiene and the avoidance of unnecessary invasive procedures. Secondly, transthoracic and transoesophageal echocardiography remain the imaging modalities of choice in IE and should be implemented early and regularly in the course of this elusive condition. Thirdly, surgery should be considered earlier in the course of the disease than previously suggested, particularly in those with heart failure, uncontrolled infection, and large or mobile vegetations.

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