INFECTIVE ENDOCARDITIS: A COMPARISON OF INTERNATIONAL GUIDELINES

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Infective endocarditis (IE) is an uncommon disorder that carries a significant morbidity and mortality. Despite advances in diagnostic techniques as well as antimicrobial and surgical treatment, escalating antibiotic resistance in IE pathogens and new patterns of disease ensure that the management of IE remains a challenge.

Since 1955, both national and international guidelines have evolved to aid the prophylaxis, diagnosis and treatment of this important disease. However, the nature of IE ensures that the evidence base from which these guidelines have traditionally been derived is limited to case-control cohort studies, animal data and expert consensus opinion. For both practical and ethical reasons, no large, well-designed, randomised controlled trial has been conducted on either prophylaxis or treatment of IE. Despite the absence of a strong evidence base, antibiotic prophylaxis before a range of dental and other surgical procedures in susceptible populations is universally practised in the developed world.

Recently, the European Society of Cardiology (ESC),¹ British Cardiac Society/Royal College of Physician (BCS/RCP)² and American Heart Association (AHA)³ have all released new guidelines on the diagnosis and treatment of IE, with the ESC and BCS/RCP also including guidance on IE prophylaxis. Revised guidelines on the subject of IE prophylaxis alone have also been published by the Société Française de Cardiologie (SFC).^{4,5} (Excerpts from the four guidelines on prophylaxis of IE have been summarised as webtables 1–4; to view these tables visit the Heart website— <http://heart.bmj.com/supplemental>.) The guidelines demonstrate concordance on a wide majority of issues, with some key exceptions. A discussion of the evidence behind these exceptions contributes to the consensus-building process important for guideline implementation.

Shifting patterns of disease have prompted this international guideline review process. Recent epidemiological trends include a rise in the incidence of staphylococcal skin flora observed as the culprit pathogen, both in community-acquired as well as iatrogenic nosocomial IE.^{6,7} In case series where *Staphylococcus aureus* has overtaken *Streptococcus viridans* as the principal cause of IE, a corresponding rise in morbidity and mortality has been observed. The rapid emergence of multi-drug resistance in streptococci, staphylococci and enterococci, the major bacterial causes of IE, is an additional cause for serious concern. Intravenous drug use-associated endocarditis and prosthetic valve endocarditis have also gained prominence as distinct and significant disease entities.

DETERMINING THE NEED FOR INFECTIVE ENDOCARDITIS PROPHYLAXIS IN THE INDIVIDUAL PATIENT

All four sets of guidelines follow the established approach when assessing the risk of endocarditis. The individual risk profile of each patient is considered separately from the risk of the procedure undertaken, facilitating decision-making on a patient-by-patient basis. In the absence of a robust evidence base for IE prophylaxis, “grey areas” are inevitable. In cases where IE prophylaxis might be considered optional, the 2004 SFC guidelines advocate that a full discussion of the risks and benefits of antibiotic prophylaxis be held with the patient before a final decision is reached.⁵

PROPHYLAXIS GUIDELINES: PATIENT RISK GROUPS

Revised guidelines commenting on IE at-risk groups from the ESC (2004), the SFC (2004) and the BCS/RCP (2004) remain in broad agreement with the existing AHA guidelines on the subject (1997).⁸ Populations of patients at high risk and moderate risk are estimated to have a raised relative risk of contracting IE during transient bacteraemia, and a worse prognosis should this occur (table 1). All four sets of guidelines identify patients with a previous history of IE, prosthetic heart valves, surgically created conduits and complex cyanotic congenital abnormalities as a comparatively short list of particularly high-risk groups. Similarly, the guidelines agree that acquired valvular heart

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disease, non-cyanotic congenital heart disease and hypertrophic cardiomyopathy represent a moderate-risk group for IE.⁵ Minor differences include the classification of mitral valve prolapse with valvular regurgitation or severe valve thickening as high-risk by the British guidelines, while the AHA, ESC and SFC define this as moderate risk for IE (table 1).

The generation of these categories is not based on firm scientific evidence. The actual risk of contracting IE associated with mitral valve prolapse with valvular regurgitation or severe valve thickening is estimated to be 0.05% per year. Predictors of increased risk for development of IE include male sex, age older than 45 years, the presence of a systolic murmur, and leaflet thickening and redundancy.⁹ Antibiotic prophylaxis for those patients with a systolic murmur has been calculated to be a cost-effective measure. However, no additional evidence is offered by the BCS/RCP authors, or is available from the literature, to explain why the risk of IE in patients with mitral valve prolapse and severe valve thickening or valvular regurgitation is deemed comparable to the IE risk represented by the presence of prosthetic valves or complex uncorrected congenital heart disease.

PROPHYLAXIS GUIDELINES: PROCEDURES DEEMED HIGH RISK

The principle of antibiotic prophylaxis for IE is best established in the case of dental procedures. Dental procedures generate bacteraemias with organisms that often cause endocarditis. Given the known morbidity and mortality of IE, at-risk patients should reasonably be treated with antibiotics before dental procedures to prevent endocarditis. Antibiotics also clearly prevent endocarditis in experimental animals. However, substantive proof of effectiveness of antibiotic prophylaxis before dental procedures in humans is as yet unavailable.¹⁰ Failures of compliance, apparent failures of prophylaxis, the failure of prophylaxis measures to reduce the overall incidence of IE and the observation that the great majority of IE cases are not linked to any form of invasive procedure have contributed to debate on the merits of this approach. Nevertheless, prophylaxis against endocarditis has been widely recommended and practised for the last half century.

The 1997 AHA, 2004 ESC, and 2004 BCS/RCP guidelines are unanimous when identifying certain dental procedures (which generally involve bleeding from hard or soft tissues, including

periodontal surgery, scaling, and professional teeth cleaning) as particularly high risk in terms of producing transient bacteraemia, requiring antibiotic prophylaxis when performed on patients considered at high or moderate risk of endocarditis. There is general agreement on the need for prophylaxis before various other urological, respiratory and gastrointestinal procedures associated with dissemination of organisms likely to adhere to valvular endothelial surfaces, especially when mucosal integrity is breached (table 2). All four guidelines are clear that the evidence base for these recommendations is limited to consensus opinion based on trials and clinical experience.

The 2004 SFC guidelines therefore differ in limiting IE antibiotic prophylaxis only to high-risk patient groups undergoing particularly high-risk procedures, proposing an individual risk assessment in other cases (webtable 3).⁵ In notable contrast, the BCS/RCP 2004 guidelines recommend extending routine prophylaxis to both high- and moderate-risk patients undergoing a range of procedures which the authors describe as “not high-risk”, but have been reported to be associated with bacteraemia and/or IE (webtable 4). These procedures include:

- ▶ transoesophageal echocardiography (TOE)
- ▶ percutaneous transluminal coronary angioplasty (with or without stenting)
- ▶ occlusive device implantation
- ▶ balloon valvuloplasty
- ▶ upper gastrointestinal (GI) endoscopy (with or without biopsy)
- ▶ circumcision
- ▶ cervical smears
- ▶ acupuncture, body piercing and tattooing.

A brief discussion of the evidence behind some of these recommendations may be of interest.

TRANSOESOPHAGEAL ECHOCARDIOGRAPHY

The oropharynx and stomach are colonised with a variety of bacteria, and it is postulated passage of the TOE probe causes minor trauma, resulting in transient bacteraemia. Two case reports describe endocarditis temporally related to a TOE procedure. Various studies have investigated the phenomenon of post-TOE bacteraemia, with the overwhelming majority describing incidences of <5%. Two small studies describe incidences of bacteraemia at 13–17% (non-significant increases). Overall, eight out of 11 studies (totalling 1063

Table 1 Cardiac conditions associated with increased risk of infective endocarditis (universal to all guidelines)
High risk
▶ Prosthetic heart valves
▶ Uncorrected complex congenital cyanotic heart diseases
▶ Previous infective endocarditis
▶ Surgically constructed systemic or pulmonary conduits
Moderate risk
▶ Acquired valvular heart diseases
▶ Mitral valve prolapse with valvular regurgitation or severe valve thickening
▶ Non-cyanotic congenital heart diseases (except for secundum type ASD) including bicuspid aortic valves
▶ Hypertrophic cardiomyopathy

Table 2 Diagnostic and therapeutic interventions associated with a high risk of endocarditis (universal to all guidelines)
▶ Dental procedures with the risk of gingival/mucosal trauma
▶ Bronchoscopy (rigid instrument)
▶ Cystoscopy during urinary tract infection
▶ Biopsy of urinary tract/prostate
▶ Tonsillectomy and adenoidectomy
▶ Oesophageal dilation/sclerotherapy
▶ Instrumentation of obstructed biliary tracts
▶ Transurethral resection of prostate
▶ Urethral instrumentation/dilation

patients) have recommended against routine use of prophylaxis before TOE, while three studies propose consideration of prophylaxis in high-risk populations (additional references appear on the *Heart* website—<http://heart.bmj.com/supplemental>). The AHA 1997 guidelines similarly suggest consideration of antibiotic prophylaxis in high-risk populations, while both the SFC 2004 and ESC 2004 guidelines specifically reject the need for routine prophylaxis. So far, the evidence for recommending routine antibiotic prophylaxis for both high- and moderate-risk patients before TOE appears limited. A recent commentary from Chambers *et al* also suggests that expert consensus within the UK is not uniformly in favour of the new BCS/RCP recommendations of TOE prophylaxis.¹¹

PERCUTANEOUS CORONARY INTERVENTION (WITH OR WITHOUT STENTING)

Only two case reports describe endocarditis temporally associated with percutaneous coronary intervention (PCI). Diagnostic cardiac catheterisation has been reported to be associated with endocarditis on a number of occasions. Although multiple studies have described the phenomenon of asymptomatic bacteraemia post-PCI, none have documented consequent IE. The incidence of positive blood cultures overall ranged from <1% in two large studies (total 9842 patients) to 5–18% in another three small studies (total patients 708)¹² (additional references appear on the *Heart* website). In one cohort of 370 PCI procedures, the incidence of clinically significant procedure-related bacteraemia was zero. Although 5.8% of all blood cultures taken in association with PCIs were positive, only 0.16% were concluded to be of clinical significance, and none were directly related to the cardiac procedure. Clinically non-significant bacteraemias were found to correlate significantly with the duration of the procedure, multiple skin punctures performed, use of multiple balloons, and obesity.¹² Although no studies on the effectiveness of prophylaxis before PCI have been reported, a small prospective double-blind randomised study investigated the incidence of bacteraemia during and following the procedure, in 145 consecutive patients undergoing cardiac catheterisation, together with the usefulness of antibiotic prophylaxis with cefazolin. Statistical analysis revealed no significant difference in the incidence of bacteraemia between the groups (5.07% vs 3.8%, cefazolin vs placebo). On the basis of this study, antibiotic prophylaxis was not recommended before cardiac catheterisation. The AHA 1997, ESC 2004 and SFC 2004 guidelines on IE prophylaxis do not recommend prophylaxis of IE peri-PCI. Overall, available evidence does not appear to link significant bacteraemia post-PCI with IE, or justify routine prophylaxis of IE during PCI on patients considered moderate- to high-risk.

UPPER GASTROINTESTINAL ENDOSCOPY (WITH OR WITHOUT BIOPSY)

Eight cases of IE originating from oropharyngeal or gastrointestinal organisms have been reported after upper GI endoscopy, of which two occurred in the context of biopsy. In multiple series, the reported rates of associated bacteraemia for upper GI endoscopy range from 2–5%. Bacteraemia is almost always clinically non-significant, and the risk of bacteraemia does not appear to rise with biopsy. Existing practice is to provide antibiotic prophylaxis to patients deemed high risk, as per guidelines from the AHA (1997), the British Society of

Gastroenterology (2001)¹³ and the American Society for Gastrointestinal Endoscopy (2003).¹⁴ While the new BCS/RCP guidelines would extend prophylaxis also to those considered moderate risk, the ESC 2004 and SFC 2004 guidelines take the opposite tack of not recommending routine antibiotic prophylaxis. Currently, an overview of the data does not appear to justify routine prophylaxis of IE during upper GI endoscopy of patients considered moderate- to high-risk.

DIAGNOSIS OF INFECTIVE ENDOCARDITIS: THE MODIFIED DUKE CRITERIA

The protean manifestations of IE make early diagnosis a difficult challenge. Both the AHA 2005 and BCS/RCP 2004 guidelines explicitly rely on the modified Duke criteria^{15–16} to aid diagnosis of IE. However, the ESC 2004 guidelines do not specify use of the modified Duke criteria as a means to clinical diagnosis, noting that diagnostic criteria may help but certainly do not guarantee accurate diagnosis or exclusion of this multifaceted disease.

The establishment of international registries¹⁷ for IE aims to target some of the logistic difficulties encountered when collecting and assessing evidence in IE. The use of different diagnostic criteria across international guidelines therefore has long-term implications on the reported incidence and outcome of IE. Less specific diagnostic criteria may mean that a cohort of patients is wrongly diagnosed as “possible IE”, leading to an apparent reduction in adverse outcomes.

It is important to note that the Duke criteria were designed primarily as an epidemiological and clinical research tool, before high-quality echocardiographic imaging became widely available. Despite recent revision, the Duke criteria still have limitations in certain subgroups, in particular prosthetic valve endocarditis, culture-negative endocarditis, and IE associated with implanted devices. Although various studies have attempted to assess the clinical value of the Duke criteria and recent modifications, the significance of these studies remains limited by small entry numbers.

TREATMENT OF INFECTIVE ENDOCARDITIS

In the current era of proliferating antibiotic resistance, all guidelines recommend early microbiology input to ensure treatment regimens are guided by organism sensitivities. Benzylpenicillin and gentamicin remain the mainstay of treatment for sensitive streptococci and enterococci.

Indications for surgical involvement are made on a multidisciplinary basis and decisions on whether and when to proceed to surgery are made on an individual patient basis. Indications for consideration of surgery include: the haemodynamic complications of IE (acute valvular regurgitation), failure of adequate antimicrobial treatment to control infection (ongoing bacteraemia or sepsis, local spread of infection, resistant or particularly virulent organisms), and embolic complications despite adequate medical treatment (large vegetations, cerebral or recurrent emboli).

Outpatient intravenous antibiotic treatment for IE with appropriate backup is cautiously supported by the AHA 2005 guidelines, but in the absence of similar experience in Europe and the UK, is not recommended by the ESC or BCS/RCP.

All guidelines advocate early and ongoing consultation between cardiologists, microbiologists and cardiothoracic surgeons in joint care of this group of patients, with adequacy of

treatment and early detection of potential complications essential to successful management.¹⁸

COMMENTARY

Infective endocarditis (IE) exemplifies an important but rare disease where robust guidelines are key to improving clinical outcome. The recent guidelines released by the BCS/RCP, ESC and AHA have assessed current available evidence on diagnosis and treatment of IE and are reassuringly clear, concise and consistent. On the subject of prophylaxis, the BCS/RCP guidelines on prophylaxis of IE advocate a more aggressive approach than the SFC, ESC and AHA, recommending expansion of the list of invasive procedures needing routine prophylaxis for IE.¹⁷ From reviewing the scientific evidence base, it is difficult to justify recommending routine prophylaxis for patients who are undergoing TOE, PCI and upper gastrointestinal endoscopy, even when they are categorised as being at moderate and high risk of IE. Factors to be considered include potential adverse reactions to the prophylactic antibiotic used, as well as the cost-benefit aspects of the recommended prophylaxis. In the long term, guideline validation and expansion of the evidence base by international registries and similar initiatives (for example, the International Collaboration on Endocarditis¹⁷) are crucial to further advances in the understanding and treatment of IE.

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