THE CHANGING FACE OF INFECTIVE ENDOCARDITIS

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"Come and look, Madame Mahler. Even I have not seen streptococci in such a marvellous state of development. Just like seaweed."

Gustav Mahler's bacteriologist, Paris 1911

Almost 100 years since the death of the great Bohemian symphonic composer from complications of the disease, infective endocarditis (IE) continues to surprise, frustrate and perplex. Even in the modern era of advanced diagnostic imaging, improved antimicrobial chemotherapy and potentially curative surgery, IE remains an evolving disease with a persistently high mortality and morbidity. Despite these improvements in health care, the incidence of the disease has remained unchanged over the past two decades at approximately 1.7-6.2 cases per 100,000 patient years and may even be increasing. Almost all aspects of the disease, including its natural history, pre-disposing factors, sequelae and causative organisms are virtually unrecognisable compared with Osler's original descriptions from the nineteenth century. In particular, chronic rheumatic heart disease is now an uncommon antecedent, whereas degenerative valve disease of the elderly, mitral valve prolapse, intravenous drug abuse, preceding valve replacement or vascular instrumentation have become increasingly frequent, coinciding with an increase in staphylococcal infections and those due to fastidious organisms. Furthermore, previously undetected pathogens are now being identified with the disease and multi-drug resistant bacteria challenge conventional therapeutic regimes. This short article provides a concise review of current understanding of this difficult condition and an update of recent developments in medical and surgical management.

EPIDEMIOLOGY
A recent review of contemporary case series encompassing a total of 3784 episodes of IE between 1993 and 2003, demonstrated a median incidence of 3.6 per 100,000 population/year with a progressive increase in relation to age. The male-to-female ratio was 2:1 and median in-hospital mortality rate 16% (range 11-26%). Staphylococci and streptococci accounted for the majority of cases and notable trends included a rising prevalence of staphylococcal skin flora due to iatrogenic nosocomial infection, Staphylococcus aureus affecting intravenous drug users and Streptococcus bovis (mainly Streptococcus gallolyticus) in the elderly, often connected to underlying gastrointestinal neoplasia. These findings, particularly the increasing problem of IE affecting the elderly population, have been confirmed in other recent European series.

Nosocomial infection
Nosocomial infection accounted for endocarditis in 22% of one recent series with a mortality rate greater than 50%. Predominant pathogens were staphylococci and enterococci, often related to intravenous catheters or surgical procedures, and less than 50% had underlying structural heart disease. Particular risk groups in this category include the immunosuppressed with central venous catheters and those undergoing haemodialysis.
Intravenous drug users

Intravenous drug users predominate in series of young people and overall incidence of IE in this group is 1-5%/year. The tricuspid valve is infected in over 50% of cases and the majority have no known pre-existing cardiac disease. Repeated injections of impure material could, however, encourage cytokine production, valvular inflammation and fibronectin deposition on previously healthy valve tissue, thereby predisposing to infection. *Staphylococcus aureus* species predominate, although unusual infections including *Pseudomonas aeruginosa*, fungi, bartonella, salmonella and listeria may also be encountered, particularly in those who are HIV-positive, where outcome is inversely related to CD4 count.

Prosthetic valve endocarditis

Prosthetic valve endocarditis accounts for 10-15% of most series with an overall incidence of 0.1-2.3% per patient-year. Cases may be classified as early or late depending on whether infection arises within one year of surgery or later, and both mechanical valves and bioprostheses appear equally susceptible. Early infection peaks two months following surgery and is often due to *Staphylococcus epidermidis* or *Staphylococcus aureus*, whereas the spectrum of late infection mirrors that of native valve disease.

**PATHOPHYSIOLOGY**

A detailed discussion of the clinical features of IE is beyond the scope of this article and covered elsewhere. Both acute and insidious presentations are common and classical clinical signs often absent. Thus, a low index of clinical suspicion and early investigation of those at risk are decisive.

Recent advances in our understanding of the underlying pathophysiology, particularly in staphylococcal and streptococcal infection, provide insight into mechanisms of disease progression and offer the prospect of improved management and directed therapy. At cellular level, mechanical and inflammatory lesions promote microbial adherence to injured endothelium during transient bacteraemia (Figure 1). Parallel inflammation-induced expression of β1 integrins by endothelial cells facilitates adhesion of pathogens which carry fibronectin-binding proteins on their surface (eg. *Staphylococcus aureus*) thus providing a mechanism for the development of IE in those without pre-existent valve disease. Endothelial disruption also permits contact of blood with subendothelial factors (extracellular matrix proteins, thromboplastin and tissue factors) which promote coagulation. Pathogens associated with IE bind avidly to the resultant coagulum, initiating a cycle of monocyte activation, cytokine and tissue factor production, resulting in progressive enlargement of an infected vegetation. Subsequently, local extension and tissue damage may result in abscess formation and ultimately, septic emboli may disseminate to remote organs, notably the brain, spleen and kidney, with corresponding resultant clinical sequelae.
DIAGNOSIS

Blood cultures
Positive blood cultures remain the cornerstone of diagnosis and provide live bacteria for susceptibility testing. The first two sets of cultures are positive in more than 90% of cases. The need for sampling prior to antibiotic administration is self-evident though surveys of contemporary practice reveal consistent failure in this respect.\(^3\)\(^1\)\(^0\) Although IE caused by anaerobes is uncommon, cultures should be incubated in both aerobic and anaerobic atmospheres to detect organisms such as *Bacteroides* or *Clostridium* species. If there is a history of prior antibiotic treatment, diagnostic yield is increased by use of sodium polyanetholsulfonate or a dedicated adsorbent resin, both of which inactivate antimicrobial effects. When cultures remain negative at five days, subculture onto chocolate agar plates may allow identification of an atypical organism. Prolonged culture is associated with rising likelihood of contamination, however, and alternative techniques (or an alternative diagnosis) should be considered at this stage.

Culture negative infective endocarditis and atypical organisms
Negative blood cultures occur in 2.5-31% of all cases of IE, often delaying diagnosis and the onset of treatment with profound impact on clinical outcome. Negative cultures arise most commonly as a consequence of prior antibiotic administration but an increasingly common scenario is infection by fastidious organisms with limited proliferation under conventional culture conditions, or requiring specialised tools for identification.\(^1\)\(^1\) Such pathogens include *Coxiella*, *Legionella*, the HACEK group (*Haemophilus* species, *Actinobacillus actinomycetemcomitans*, *Cardiobacterium hominis*, *Eikenella corrodens*, and *Kingella kingae*), *Chlamydia*, *Bartonella*, *Tropheryma whippelii*, and fungi, including *Candida*, *Histoplasma* and *Aspergillus* species, and *Torulopsis glabrata*. These organisms may be particularly common in IE affecting patients with prosthetic valves, indwelling venous lines, pacemakers, renal failure and immunocompromised states. A summary of diagnostic techniques and treatment regimes in these difficult scenarios is provided in Table 1.

Echocardiography
Transthoracic and transoesophageal echocardiography are now ubiquitous and their utility in diagnosis and management of IE clearly recognised.\(^1\)\(^2\) Transoesophageal imaging has superior sensitivity and specificity, is cost-effective and recommended when clinical suspicion is high and a transthoracic study is negative, in all cases of prosthetic valve endocarditis and when complications are suspected or likely, particularly prior to surgery. The utility of both modes of investigation is diminished when applied indiscriminately, however, and appropriate application in the context of simple clinical criteria improves diagnostic yield.\(^1\)\(^3\)
Advances in imaging technology have had minimal impact at day to day clinical level. The use of harmonic imaging has improved study quality without altering sensitivity in the detection of vegetations while the roles of three dimensional
echocardiography and other alternative modes of imaging (CT, MRI and technetium scintigraphy) have yet to be formally evaluated.

Diagnostic criteria and their limitations
The original von Reyn diagnostic criteria, based upon clinical and microbiological features, have now been surpassed by the Duke criteria which emphasise the role of echocardiography. Many studies have now demonstrated the superiority of the Duke criteria and a scientific statement of The American Heart Association has concluded that they should be adopted as the primary diagnostic schema when IE is suspected. Nevertheless, clear deficiencies remain and sensitivity is diminished in those whose blood cultures are negative, those with infection affecting a prosthetic valve or pacemaker lead and those with IE affecting the right heart (particularly drug abusing patients).

Modified Duke criteria and new diagnostic techniques
In 1997, Lamas and Eykyn proposed a number of clinical amendments to the Duke criteria (“the St Thomas modifications”). Simultaneously, recognition of the role of Q-fever, a worldwide zoonosis caused by Coxiella burnetti and a particularly frequent cause of IE in France, increasing prevalence of staphylococcal infection and widespread use of transoesophageal echocardiography resulted in further modifications to the Duke criteria (Table 2).

HISTOLOGICAL/IMMUNOLOGICAL TECHNIQUES
Histological findings are included in the Duke diagnostic criteria and pathological examination of resected valvular tissue or embolic fragments remains the gold standard for the diagnosis of IE. Pathological examination may also guide antimicrobial treatment if the causative agent can be identified by means of special stains or immunohistological techniques. Electron microscopy has high sensitivity and may help to characterise new microorganisms, but is time consuming and expensive. Coxiella burnetti and Bartonella species may be easily detected by serological testing using indirect immunofluorescence or ELISA.

MOLECULAR TECHNIQUES
The polymerase chain reaction (PCR), utilising nucleic acid target or signal amplification, alone or in combination with sequence analysis, allows rapid and reliable detection of fastidious and non-culturable agents in blood and surgical material of patients with IE. It may also be of value when phenotypic characterisation is essential following isolation of two or more organisms in separate cultures (most commonly due to contamination with skin commensals during sampling or polymicrobial infection in intravenous drug abusers). The utility of the technique has recently been validated in series of patients undergoing valve surgery for IE and its incorporation as a major Duke diagnostic criterion has been proposed with widespread support. Although the technique offers several advantages, including extreme sensitivity, there are inherent limitations including the risk of sample contamination, false negatives due to the presence of PCR inhibitors in clinical samples and inability to provide information concerning
bacterial sensitivity to antimicrobial agents. Results therefore require careful interpretation and the technique seems unlikely to supersede blood cultures as a prime diagnostic tool. Future improvements include the possibility of quantitation by real-time PCR (eliminating the need for gel electrophoresis) with faster, more accurate results, and the investigation of common antimicrobial resistance genes enabling a targeted and cost-effective approach to antibiotic treatment.

**TREATMENT**

Successful outcome depends upon careful collaboration between the cardiologist, microbiologist and cardiac surgeon. Infective endocarditis is an evolving clinical entity and careful scrutiny for progression of disease and development of complications is mandatory. Although randomised controlled trials providing an evidence base to guide therapeutic decisions are virtually non-existent, detailed international guidelines provide robust recommendations.

**Antimicrobial chemotherapy**

Recommendations for the treatment of the most common causes of IE have been recently published and provide a detailed review of the multiple available antimicrobial regimes. Bactericidal antibiotics are essential and high serum concentrations are desirable to ensure diffusion into vegetations. Long-term treatment for 4-6 weeks is usually necessary to kill dormant bacteria within infected foci, although shortened courses of combination therapy may be considered in those with sensitive organisms. In-patient parenteral therapy is the traditional and preferred option, but outpatient therapy (ideally using once daily treatment regimes) may be appropriate in selected patients, particularly once the initial two-week period (when risk of complications is highest) has elapsed. Adverse reactions to potent combinations of antibiotics are common during these prolonged courses of treatment and careful clinical and laboratory monitoring is required. There is no evidence to support the use of oral "follow-on" therapy after completion of a course of intravenous treatment. Empirical broad-spectrum therapy should be commenced in subjects in whom IE is suspected after appropriate blood cultures have been performed. Once the infecting organism is established, an optimal treatment regime is determined based upon antibiotic susceptibility testing and the minimal inhibitory concentration of principal drugs for the pathogen. Minimal bactericidal concentration is outmoded and no longer required. Newer antimicrobial agents for the treatment of gram positive cocci (quinupristin/dalfopristin, linezolid and daptomycin) show promise, but require further study before their specific application in IE is clear.

**Resistant pathogens**

Bacterial resistance to conventional antibiotic regimes is increasingly recognised and presents a grave therapeutic challenge. Specialist advice is always necessary and early surgery may have a particular role. Streptococci may resist penicillin and other β-lactams due to decreased β-lactam affinity of their membrane-bound penicillin-binding proteins. Intermediate
resistance may be overcome using a β-lactam in synergy with an aminoglycoside and highly resistant strains remain susceptible to vancomycin. Methicillin-resistant staphylococci remain widely prevalent in most hospital environments and vancomycin resistance, mediated via chromosomal mutations affecting cell wall synthesis, is now an emerging problem. Innovative and often unlicensed combinations of old and new antibiotics may be required and outcome is invariably poor. Similar problems arise in the treatment of multidrug-resistant enterococci. Aminoglycosides have a potential role and streptomycin may be of particular value.

Special subsets
INTRACARDIAC PROSTHETIC MATERIAL
Infective endocarditis may affect prosthetic valves, permanent pacemakers or intracardiac defibrillators. Cases involving intracoronary stents or closure devices have been reported, though remain extremely rare. A 4-6 week course of antibiotics is recommended and all infected material should be explanted when possible. Repeat surgery is recommended for all those with early prosthetic valve endocarditis and for the development of complications in those with a late presentation.

INTRAVENOUS DRUG USERS
A methicillin sensitive Staphylococcus aureus is the causative organism in the majority of cases and antibiotic regimes should reflect this. Treatment will include either penicillinase-resistant penicillins or vancomycin, depending on the likelihood of methicillin resistance. Polymicrobial infection is common and Pseudomonas aeruginosa and Candida species should be considered in those who fail to respond to treatment. Short course combination therapy and oral regimes may be considered in those with IE localised to the right heart.

Anti-platelet and anticoagulant therapy
Despite experimental evidence to suggest a beneficial role of aspirin in reducing embolic complications and attenuating microbial virulence, a recent randomised trial in left sided IE demonstrated no significant benefits and increased risk of bleeding.27 Similarly, anticoagulant therapy carries significant hazard in IE and should be avoided unless essential.28

Surgery
Surgery for IE is potentially life saving29 and required in 25-30% of cases during acute infection and in 20-40% during convalescence.30 Assessment of the impact of surgery on outcome is difficult since patients referred for surgery are frequently those with severe complications related to virulent organisms. Conversely, the sickest patients (frequently the elderly with attendant co-morbidity) are often deemed unfit for surgery. Nevertheless, overall surgical mortality in active IE is 8-
16%, with actuarial survival rates of 75% and 61% at 5 and 10 years, respectively.\textsuperscript{31} Clear indications for surgery\textsuperscript{25} include, (i) haemodynamic decompensation due to acute valvar regurgitation, (ii) persistent fever and bacteraemia despite appropriate antibiotic therapy, (iii) development of abscesses or fistulae due to local spread of infection, and (iv) involvement of microorganisms highly resistant to treatment (eg. fungi, \textit{Brucella}, \textit{Coxiella}) or (v) with potential for rapid tissue destruction (eg. \textit{Staphylococcus lugdunensis}). A low threshold for surgery is also recommended in early prosthetic valve endocarditis, particularly when associated with \textit{Staphylococcus aureus} infection, and in those with complications arising from a late presentation.\textsuperscript{32} Surgery may be considered in patients with large vegetations of high embolic potential (notably those >10mm or on the mitral valve), those increasing in size despite antibiotic therapy and those >20mm on the tricuspid valve after recurrent pulmonary emboli. In the difficult scenario where cerebral embolism causes neurological deficit, surgery should be considered early (within 72 hours) once cerebral haemorrhage has been excluded. If this is impractical, surgery should be deferred for 3-4 weeks in those with cerebral infarction and for longer in those with intracerebral haemorrhage.\textsuperscript{33} After complete excision of all infected tissue, valve replacement with a mechanical or biological prosthesis is required in the majority of patients. Use of a homograft has particular attractions in those with IE affecting the aortic valve, especially when complicated by abscess formation,\textsuperscript{34} though uptake in contemporary series was lower than anticipated,\textsuperscript{3} reflecting the need for particular surgical expertise and possible difficulties with valve procurement. Good results from conservative valve preservation techniques, particularly mitral valve repair and the Ross procedure, have also been reported in several series though technical expertise is required and experience to date limited. Final outcome has little relation to the duration of previous antibiotic therapy and surgery should not be delayed when clearly indicated in the vain hope that a sterile operative field can be achieved.\textsuperscript{31} The duration of post-operative antibiotic therapy is determined by the results of valve culture. In patients with negative valve cultures, pre-operative plus post-operative antimicrobial therapy should equal a full course of recommended treatment. Patients with positive valve cultures and most of those with prosthetic valve endocarditis should receive a full course of treatment following surgery. Survivors of surgery are a high risk group for recurrent IE and vigorous prophylaxis is essential in this group.
PROPHYLAXIS
The efficacy of antibiotic prophylaxis in the prevention of IE remains controversial. Case control studies indicate that prophylaxis prevents only a limited number of cases and randomised controlled trials have never been undertaken (nor are they likely), since the number of patients required would be excessive and ethical issues prevent use of a placebo group. Overall uptake of prophylaxis and levels of patient education are poor and bacteraemia related to daily transfer of organisms from mouth to blood is more often implicated than dental or other surgical procedures. Current recommendations therefore maintain the principle of antibiotic prophylaxis while limiting indications to cases with the highest ratio of individual benefit to individual and collective risk (Table 3). General preventive measures (good dental care and skin hygiene, avoidance of unnecessary procedures and instrumentation) remain essential and recommended antibiotic regimes are widely available.

INTERNATIONAL COLLABORATION
To date, knowledge of the clinical features and natural history of IE has relied largely on small, uncontrolled, outdated studies; modern, well designed registries and trials reflecting current disease patterns are long overdue. The recently elaborated International Collaboration on Endocarditis (ICE) will contribute significantly to both our current and future knowledge of IE, allowing the development of new diagnostic and therapeutic strategies. Since its inception in 1999, 39 sites in 16 countries have become involved in this project headed by an international steering committee. The initial merger of existing databases has yielded a primary group of 2200 well characterised patients with definite IE by the Duke criteria, allowing the assessment of regional differences in presentation and outcome. Indeed, analysis of the dataset has already enabled valuable insight into emerging epidemiological patterns of the disease and its clinical presentation. Although databases from specialised units have the potential for referral bias and consequent over-reporting of seriously ill patients and those with uncommon disease manifestations, the ICE infrastructure will allow prospective recording of all new cases of IE, including a minimum standardised clinical dataset, with re-analysis of microbiological samples and echocardiographic studies in core laboratory facilities. In future, this platform will provide the basis for sorely needed adequately sized randomised clinical trials in the management and treatment of IE.

NEW DEVELOPMENTS
A number of exciting developments offer the prospect of improved prevention and treatment of IE. Vaccines targeted at specific bacterial adhesins may inhibit valve colonisation and encouraging results have been obtained with anti-streptococcal and anti-staphylococcal vaccination in vitro and with haemodialysis patients in vivo. Newer antibacterial agents with novel effects may digest the essential gram-positive peptidoglycan by triggering of bacteriophage-encoded bacteriolytic enzymes or attenuate the invasive properties of Staphylococcus aureus by reducing secretion of haemolysins and toxins. Finally, modified biomaterials in
development may reduce the risk of IE in patients with artificial heart valves or other intra-cardiac prosthetic material. Despite these advances, however, the changing face of IE seems set to challenge the endeavours of cardiologists, microbiologists and cardiac surgeons for many decades yet.
LEGEND TO FIGURE 1

Early steps in bacterial valve colonisation

(A) Colonisation of damaged epithelium: exposed stromal cells and extracellular matrix proteins trigger deposition of fibrin-platelet clots to which streptococci bind (upper panel); fibrin-adherent streptococci attract monocytes and induce them to produce tissue-factor activity (TFA) and cytokines (middle panel); these mediators activate coagulation cascades, attract and activate blood platelets, and induce cytokine, integrin, and TFA production from neighbouring endothelial cells (lower panel), encouraging vegetation growth.

(B) Colonisation of inflamed valve tissues: in response to local inflammation, endothelial cells express integrins that bind plasma fibronectin, which microorganisms adhere to via wall-attached fibronectin-binding proteins, resulting in endothelial internalisation of bacteria (upper panel); in response to invasion, endothelial cells produce TFA and cytokines, triggering blood clotting and extension of inflammation, and promoting formation of the vegetation (middle panel); internalised bacteria eventually lyse endothelial cells by secreting membrane-active proteins – eg. haemolysins (lower panel).

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REFERENCES


Table 1: Investigation and management of rare causes of culture negative endocarditis

<table>
<thead>
<tr>
<th>Pathogen</th>
<th>Diagnostic procedure</th>
<th>Proposed therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Brucella</em> spp</td>
<td>Blood cultures; serology; culture, immunohistology and PCR of surgical material</td>
<td>Doxycycline plus rifampin or cotrimoxazole (treatment for &gt;3 months)</td>
</tr>
<tr>
<td><em>C Burnetti</em></td>
<td>Serology (IgG phase I in 800); tissue culture, immunohistology and PCR of surgical material</td>
<td>Doxycycline plus hydroxychloroquine or doxycycline plus quinolone (&gt;18 months treatment)</td>
</tr>
<tr>
<td><em>Bartonella</em> spp</td>
<td>Blood cultures; serology; culture, immunohistology and PCR of surgical material</td>
<td>β lactams or doxycycline plus aminoglycoside (&gt;6 weeks treatment)</td>
</tr>
<tr>
<td><em>Chlamydia</em> spp</td>
<td>Serology; culture, immunohistology and PCR of surgical material</td>
<td>Doxycycline or new fluoroquinolones (long term treatment, optimum duration unknown)</td>
</tr>
<tr>
<td><em>Mycoplasma</em> spp</td>
<td>Serology; culture, immunohistology and PCR of surgical material</td>
<td>Doxycycline or new fluoroquinolones (&gt;12 weeks treatment)</td>
</tr>
<tr>
<td><em>Legionella</em> spp</td>
<td>Blood cultures; serology; culture, immunohistology and PCR of surgical material</td>
<td>Macrolides plus rifampicin or new fluoroquinolones (&gt;6 months treatment)</td>
</tr>
<tr>
<td><em>T whipplei</em></td>
<td>Histology and PCR of surgical material</td>
<td>Cotrimoxazole or β lactam plus aminoglycoside (long-term treatment, optimum duration unknown)</td>
</tr>
</tbody>
</table>

Adapted with permission from reference 11
### Table 2: Duke criteria for the diagnosis of infective endocarditis and proposed modifications

<table>
<thead>
<tr>
<th>Duke criteria</th>
<th>Suggested modifications</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pathological criteria</strong></td>
<td>Microorganisms demonstrated by culture or histological examination</td>
</tr>
<tr>
<td>Active endocarditis demonstrated by histological examination</td>
<td></td>
</tr>
<tr>
<td><strong>Major criteria</strong></td>
<td></td>
</tr>
<tr>
<td>Positive blood cultures</td>
<td>To be added:</td>
</tr>
<tr>
<td>- typical microorganisms consistent with endocarditis from two separate blood cultures</td>
<td>- positive serology for <em>Coxiella burnetti</em></td>
</tr>
<tr>
<td>- microorganisms consistent with endocarditis from persistently positive blood cultures</td>
<td>- bacteraemia due to <em>Staphylococcus aureus</em></td>
</tr>
<tr>
<td>Evidence of endocardial involvement</td>
<td>- positive molecular assay for specific gene targets and universal loci for bacteria and fungi</td>
</tr>
<tr>
<td>- echocardiography: oscillating structures, abscess formation, new partial dehiscence of prosthetic valve</td>
<td>- positive serology for <em>Chlamydia psittaci</em></td>
</tr>
<tr>
<td>- new valvar regurgitation</td>
<td>- positive serology for <em>Bartonella</em> species</td>
</tr>
<tr>
<td><strong>Minor criteria</strong></td>
<td></td>
</tr>
<tr>
<td>- predisposing heart disease</td>
<td>To be omitted:</td>
</tr>
<tr>
<td>- fever &gt;38°C</td>
<td>Suspect echocardiography (no major criterion)</td>
</tr>
<tr>
<td>- vascular phenomena</td>
<td>To be added:</td>
</tr>
<tr>
<td>- immunological phenomena</td>
<td>Elevated CRP, elevated ESR, splenomegaly,</td>
</tr>
<tr>
<td>- microbiological evidence (no major criterion)</td>
<td>haematuria, clubbing, splinter haemorrhages,</td>
</tr>
<tr>
<td>- suspect echocardiography (no major criterion)</td>
<td>petechiae and purpura</td>
</tr>
<tr>
<td><strong>Identified IE organism from metastatic lesions</strong></td>
<td>Identified IE organism from metastatic lesions</td>
</tr>
<tr>
<td><strong>Categories</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Definite:</strong></td>
<td>Pathological criteria positive</td>
</tr>
<tr>
<td>or 2 major criteria positive</td>
<td></td>
</tr>
<tr>
<td>or 1 major and 2 minor criteria positive</td>
<td></td>
</tr>
<tr>
<td>or 5 minor criteria positive</td>
<td></td>
</tr>
<tr>
<td><strong>Possible:</strong></td>
<td>All cases which cannot be classified as definite or rejected</td>
</tr>
<tr>
<td>1 major and 1 minor criterion positive</td>
<td></td>
</tr>
<tr>
<td>3 minor criteria positive</td>
<td></td>
</tr>
<tr>
<td><strong>Rejected:</strong></td>
<td>Alternative diagnosis</td>
</tr>
<tr>
<td>Resolution of the infection with antibiotic treatment for ≤ 4 days</td>
<td></td>
</tr>
<tr>
<td>No histological evidence</td>
<td></td>
</tr>
</tbody>
</table>

**Abbreviations:** CRP, C reactive protein; ESR, erythrocyte sedimentation rate; IE, infective endocarditis.

Reproduced from reference 17
Table 3: Summary of current recommendations for prophylaxis of infective endocarditis

Cardiac conditions conferring risk of infective endocarditis

<table>
<thead>
<tr>
<th>Group A: High risk</th>
<th>Group B: Lower risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Valvular prosthesis (mechanical, homograft or bioprosthesis)</td>
<td>Valvular disease; aortic regurgitation, mitral regurgitation, mitral stenosis, aortic stenosis</td>
</tr>
<tr>
<td>Cyanotic congenital heart disease and pulmonary-systemic shunts</td>
<td>Mitral valve prolapse with mitral regurgitation or valve thickening</td>
</tr>
<tr>
<td>History of infective endocarditis</td>
<td>Bicuspid aortic valve</td>
</tr>
<tr>
<td>History of infective endocarditis</td>
<td>Non-cyanotic congenital heart disease</td>
</tr>
<tr>
<td>History of infective endocarditis</td>
<td>Obstructive hypertrophic cardiomyopathy (with murmur)</td>
</tr>
</tbody>
</table>

Indications for antibiotic prophylaxis: oral or dental procedures

<table>
<thead>
<tr>
<th>Procedural risk</th>
<th>Group A: High risk</th>
<th>Group B: Lower risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>High procedural risk</td>
<td>Recommended</td>
<td>Optional**</td>
</tr>
<tr>
<td>Low procedural risk</td>
<td>Not recommended</td>
<td>Not recommended</td>
</tr>
</tbody>
</table>

Indications for antibiotic prophylaxis: non-oral or dental procedures*

<table>
<thead>
<tr>
<th>Procedural risk</th>
<th>Group A: High risk</th>
<th>Group B: Lower risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very high procedural risk</td>
<td>Recommended</td>
<td>Recommended</td>
</tr>
<tr>
<td>High procedural risk</td>
<td>Recommended</td>
<td>Optional**</td>
</tr>
<tr>
<td>Low procedural risk</td>
<td>Optional**</td>
<td>Not recommended</td>
</tr>
<tr>
<td>Negligible procedural risk</td>
<td>Not recommended</td>
<td>Not recommended</td>
</tr>
</tbody>
</table>

*Diagnostic and therapeutic interventions likely to produce bacteraemia: bronchoscopy (rigid instrument), cystoscopy during urinary tract infection, biopsy of urinary tract/prostate, tonsillectomy and adenoidectomy, oesophageal dilation/sclerotherapy, instrumentation of obstructed biliary tract, transurethral resection of prostate, lithotripsy, gynaecological procedures in the presence of infection

**Factors determining whether antibiotic prophylaxis is prescribed when deemed optional: For: age >65 years, cardiac, renal, respiratory and hepatic insufficiency, diabetes mellitus, acquired, constitutional or therapeutic immunosuppression, oral or dental condition, inadequate oral or dental hygiene, important bleeding (intensity, duration), technically difficult or prolonged procedure, patient's opinion after receiving information
Against: allergy to several antibiotics, patient's opinion after receiving information
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