Infective Endocarditis in the 21st Century

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Abstract
Infective endocarditis (IE) continues to be a disease characterized by high mortality and morbidity that has not been affected by significant advances in the last century. Despite considerable improvements in diagnosis and medical and surgical therapy, mortality has remained high for the past 25 years, in contrast to the majority of cardiovascular diseases such as heart failure and acute coronary syndromes, which have demonstrated noticeable improvements in terms of prognosis. IE has an exceptionally varied clinical presentation, from a severely ill patient with symptoms of acute infection and sepsis to an apparently healthy individual with only occasional night sweats, weight loss, and low-grade fever. Clinical manifestations of IE can be caused by symptoms or complications of the infection or by its frequent non-infectious complications, such as vascular and immunologic phenomena. IE remains a deadly disease, frequently associated with a difficult diagnosis. Significant changes in epidemiology and microbiology have increased the differences between patients seen in the US and Europe and those in countries with a higher incidence of rheumatic heart disease, such as South America and India. Therefore, specific regional approaches to IE are necessary.

Keywords
Infective endocarditis, surgery in infective endocarditis, prosthetic valve endocarditis

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Infective endocarditis (IE) continues to be a disease characterized by high mortality and morbidity that has not been affected by significant advances in the last century. Despite considerable improvements in diagnosis and medical and surgical therapy, mortality has remained high for the past 25 years, in contrast to the majority of cardiovascular diseases such as heart failure and acute coronary syndromes, which have demonstrated noticeable improvements in terms of prognosis. The current in-hospital mortality for patients with IE is 15–20%, with one-year mortality approaching 40%. In a 16-year follow-up of patients discharged with the diagnosis of IE, only 5% of the patients remained alive free of a new episode of endocarditis and without valve replacement surgery.

As with most valvular heart diseases, studies of IE in the literature are mainly series of reports and/or case studies; there is a marked absence of prospective controlled studies on this disease, perhaps because of its relative rarity and clinical polymorphism. The only multicentric prospective registry of IE is the International Collaboration on Endocarditis–Prospective Cohort Study (ICE-PCS), in which 58 hospitals from 25 countries took part.

The purpose of this article is to review the epidemiology of IE, modern therapy, both clinical and surgical, and to discuss the need for IE prophylaxis.

A Difficult Diagnosis
Endocarditis has an exceptionally varied clinical presentation, from a severely ill patient with symptoms of acute infection and sepsis to an apparently healthy individual with only occasional night sweats, weight loss, and low-grade fever. Clinical manifestations in IE can be caused by symptoms or complications of the infection or by its frequent non-infectious complications, such as vascular and immunologic phenomena. Immunologic symptoms such as arthritis and glomerulonephritis are especially frequent because of the high quantity of circulating immunocomplexes in IE. Vascular complications such as mycotic aneurysms and septic emboli can lead to neurologic or peripheral symptoms as the initial manifestation of the disease.

IE is a great deceiver, mimicking several rheumatologic, hematologic, neurologic, and nephrologic diseases. Quite frequently, patients with suspected IE are referred from other specialists in internal medicine. In particular, the patient is quite frequently first seen by a rheumatologist because of arthritis, fever, high acute-phase proteins, and frequently a positive rheumatoid factor. This polymorphic presentation frequently leads to delays in the diagnosis of IE. In a study at our institution, The Heart Institute – University of São Paulo, the duration of symptoms until the diagnosis of IE was 49.6±64.5 days.2
**Infective Endocarditis**

| Major Criteria | Blood Culture Findings Positive for Infective Endocarditis |
|----------------|------------------------------------------------------------|
| Typical micro-organisms consistent with IE from 2 separate blood cultures |
| Viridans streptococci, Streptococcus bovis, HACEK, or Staphylococcus aureus |
| Community-acquired enterococci, in the absence of a primary focus |

Micro-organisms consistent with IE from persistently positive blood culture findings, defined as ≥2 positive culture findings of blood samples drawn >12 hours apart and ≥3 of >4 separate culture findings of blood (with first and last sample drawn ≥1 hour apart) |

Single positive blood culture for *Coxiella burnetii* or antiphase I IgG antibody titer ≥1:800

**Evidence of Endocardial Involvement**

New valvular regurgitation; worsening or changing of pre-existing murmur, not sufficient murmur indicating new partial dehiscence of prosthetic valve |

Echocardiographic findings positive for IE (TEE recommended in patients with prosthetic valves, rated at least possible IE by clinical criteria or complicated IE (paravalvular abscess); TTE as first test in other patients), defined as follows: oscillating intracardiac mass on valve or supporting structures, in the path of regurgitant jets, or on implanted material in the absence of an alternative anatomic explanation

Abscess

**Minor Criteria**

Predisposition, predisposing heart condition, or intravenous drug use |

Fever, temperature >38ºC |

Vascular phenomena, major arterial emboli, septic pulmonary infarcts, mycotic aneurysm, intracranial hemorrhage, conjunctival hemorrhages, and janeway lesions |

Immunologic phenomena: glomerulonephritis, Osler nodes, Roth spots, and rheumatoid factor |

Microbiologic evidence: positive blood culture finding but does not meet a major criterion or serologic evidence of active infection with organism consistent with IE |

**Echocardiographic minor criteria eliminated**

**Definitions of Infective Endocarditis**

**Definite Infective Endocarditis** |

Pathologic criteria |

Micro-organisms demonstrated by results of cultures or histologic examination of a vegetation, a vegetation that has embolized, or an intracardiac abscess specimen |

Pathologic lesions, vegetation, or intracardiac abscess confirmed by results of histologic examination showing active endocarditis

**Clinical criteria** |

2 major criteria |

1 major criterion and 3 minor criteria |

5 minor criteria

**Possible Infective Endocarditis** |

1 major criterion and 1 minor criterion |

3 minor criteria |

Firm alternative diagnosis explaining evidence of IE |

Resolution of IE syndrome with antibiotic therapy for ≤4 days |

No pathologic evidence of IE at surgery or autopsy, with antibiotic therapy for ≤4 days |

Does not meet criteria for possible IE

Adapted from Li et al., 2000. HACEK = *Haemophilus species, Aggregatibacter (formerly Actinobacillus) actinomycetemcomitans, Cardiobacterium hominis, Eikenella corrodens, Kingella kingae*. Ig = immunoglobulin; IE = infective endocarditis; TEE = transesophageal echocardiography.

In 1994, Durack and et al. proposed diagnostic criteria for IE, initially conceived to classify the complex clinical manifestations and findings in IE for scientific study purposes. These criteria were rapidly implemented in clinical practice, becoming widely known as the Duke criteria (see Table 1). These were the first criteria to include echocardiography as a morphologic parameter, significantly improving sensitivity and maintaining the same specificity as the previous criteria.

The Duke criteria characterize the probability of IE as ‘definite,’ ‘possible,’ or ‘excluded.’ The main criteria are identification of the causative organism and echocardiographic demonstration of endocardial involvement. Additional criteria include fever, vascular involvement, or a predisposing heart disease. Since the initial publication of the Duke criteria, several modifications have been proposed with the purpose of increasing their sensitivity. The extended Duke criteria of Li et al. are now generally accepted: these consider *Staphylococcus aureus* bacteremia to be a main criterion, as a positive blood culture for *S. aureus* is associated with endovascular infection in up to 15% of cases. However, whenever new parameters are introduced it must be kept in mind that increased sensitivity often comes at the price of diminished specificity. Thus, a current meta-analysis of 3,557 patients has shown that the rise in sensitivity brought about by the Li modifications is associated with a similar fall in specificity.

In summary, diagnostic criteria are not a substitute for rational clinical judgment, particularly when blood cultures are negative, when prosthetic valves or pacemaker electrodes are infected, or in the case of right-side endocarditis.

**Changes in Patient Characteristics of Infective Endocarditis—A Widening Gap**

Geographic differences in the epidemiology of IE are becoming more evident. In developing countries, due to the high incidence of rheumatic fever and poor dental care, IE is still a subacute or chronic disease occurring primarily in younger patients with rheumatic valvular abnormalities. In stark contrast, IE is changing rapidly in the US and Europe, presenting few of the classic clinical findings traditionally associated with IE. Forty years ago, approximately 50% of cases of IE in the US were superimposed on pre-existing rheumatic lesions compared with ≤5% in recent studies, with prosthetic valve endocarditis (PVE) detectable in one-fifth of patients.

An emerging population at risk for IE in developed countries consists of patients with healthcare-associated infections. Overall, IE was attributed to a healthcare-related exposure in nearly 25% of the patients. These findings confirm those of recent reports from small single-center studies and provide evidence that these population changes are occurring in many regions of the world. Thus, nosocomial endocarditis is on the rise in the developed world, while poor nations retain the classic profile of IE.

**Changes in Infective Agents**

Changes in the epidemiology of endocarditis in the developed world led to a change in infecting micro-organisms. While in South America, India, and South-East Asia endocarditis is still predominantly caused by *Streptococci* and linked to poor oral health, *S. aureus* is now the most
common cause of IE in the developed world. This shift is due in part to the global presence of risk factors for S. aureus-associated IE (i.e., intravenous drug use, healthcare contact, and invasive procedures). Given the growing antimicrobial resistance of S. aureus, including to vancomycin, the importance of this pathogen as a potentially lethal infection is a cause of concern.

As the population of the developed world grows older, there is a higher prevalence of S. bovis-associated IE, mainly in Europe. Recent trends also pointed to the fact that HACEK-associated IE was relatively uncommon in North America, and that most cases of Q fever and Bartonella-associated IE came from Europe. Whether these findings reflect differences in patient characteristics, regional healthcare access, diagnostic bias, or other factors is still to be determined.

These changes in patients and pathogens have important implications for the diagnosis and management of IE. As nosocomial endocarditis is on the rise, stricter measures for prevention of bloodstream infections must be enforced in hospitals. Elderly hospitalized patients must have careful diagnostic attention in the presence of fever and bacteremia.

Meanwhile, in the developing world, in addition to the rise in hospital-related endocarditis, streptococcal endocarditis related to poor oral hygiene and lack of access to dental care in rheumatic patients is still very much the case. Improvements in access to medical and dental care, associated with aggressive primary prophylaxis of rheumatic fever, have the potential to markedly reduce the incidence of IE in developing countries.

**Treatment—Principles and Practice**

The fundamental goal of therapy in IE is the eradication of the pathogen from the infected tissue. There are several specific and non-specific defense mechanisms of micro-organisms, such as biofilm formation and increasing tolerance or resistance to various antibiotics, which make IE a particularly difficult-to-treat infection, requiring long courses of high-dose intravenous antibiotics. Generally, native-valve endocarditis must be treated for a four-week period and prosthetic valve endocarditis must be treated for at least six weeks, if not longer.

Although most previously published guidelines indicated combination therapy with beta-lactams and gentamicin, this recommendation has recently been questioned in literature, particularly in terms of the treatment of staphylococcal infections. The benefit of aminoglycosides was seen in small randomized trials more than 20 years ago, showing that the combination of nafcillin and gentamicin led to a more rapid defervescence in IE patients. Recent meta-analyses show that the combination therapy with gentamicin is not clinically superior to beta-lactam monotherapy and may be nephrotoxic. In the American Heart Association (AHA) guideline, combination therapy with gentamicin is designated as optional for the treatment of staphylococcal infection. This contrasts with the finding from a Swedish registry that the survival of patients with culture-negative IE is significantly improved if they are given combination therapy with gentamicin.

As staphylococcal endocarditis is on the rise in Europe and the US, antistaphylococcal agents other than vancomycin are being studied. The lipopeptide daptomycin, for example, has been studied in a prospective, randomized trial in patients with right-heart endocarditis and has been approved for this indication. The most interesting discovery is that this agent, unlike vancomycin, was at least as effective as the combination of a beta-lactam antibiotic and gentamicin in the treatment of methicillin-resistant staphylococcal infection.

Daptomycin was significantly less nephrotoxic than a combination of vancomycin or a semi-synthetic penicillin with gentamicin. Daptomycin was found to elevate the serum creatinine kinase (CK) concentration; therefore, the latter should be monitored when daptomycin is given. In a small number of cases in this study, the minimal inhibitory concentration (MIC) of daptomycin was found to rise under treatment. Although this finding is of uncertain significance, it indicates the possible development of resistance and thus requires further careful evaluation. The oxazolidinone linezolide has also been used successfully in a number of cases of staphylococcal IE, but as yet there are no prospective data on this form of treatment.

**Is There a Low-risk Group in Infective Endocarditis?**

Based on expert opinion only, the AHA recently changed the guidelines for the prevention of IE on the assumption that there may be a ‘benign’ group, even if the existence of this group has never been demonstrated. Multinational surveys of IE demonstrate a consistently high in-hospital mortality of approximately 20%. Even in groups with higher incidence of the so-called ‘low-risk’ endocarditis—that is, streptococcal endocarditis of a native valve in young patients (the most common cases in the developing world)—the mortality rate remains 18–30%. The decrease in the incidence of streptococcal endocarditis in Europe and North America led to the false impression that this group is less affected and has a lower IE risk. The fact remains that in developing countries, where streptococcal disease is frequent, all patients with IE have a disease with high morbidity and mortality, even young rheumatic patients.

If the AHA were certain of the inefficacy of the prophylactic regimen for IE, it might well have stated that there is no indication for prophylaxis in any population. As the AHA chose to maintain prophylaxis in the ‘high-risk’ group, the opinion is that prophylaxis may still be of some benefit. In our view, the high-risk group encompasses all patients with IE, not only those with manifestations that are frequent in North America and Europe (i.e. prosthetic valve endocarditis and endocarditis in congenital heart disease). Thus, we chose to remain adherent to the older AHA guidelines, and we do recommend prophylaxis for all patients, including young rheumatic patients with native valves; however, for young rheumatic patients the maintenance of good oral health and access to dental care are more important than IE prophylaxis.

The ICE-Merged Database (ICE-MD) and ICE-PCS, the largest ever in IE, found several factors that were independently associated with in-hospital mortality. Some of these factors are clinical, such as increasing age, presence of pulmonary edema, and paravalvular complications. In addition, prosthetic valve IE and staphylococcal IE were associated with an increased risk for in-hospital death, whereas there was a decreased risk associated with viridans streptococcal IE. An elevated erythrocyte sedimentation rate (ESR) was associated with a
Infective Endocarditis

decreased risk for death, although the reason for this is unclear. Elevated ESR may be associated with more chronic infection, thereby signifying a more chronic clinical course.

Trends in Cardiac Surgery in Infective Endocarditis and Prosthetic Valve Endocarditis

In the ICE-PCS nearly 50% of patients had surgery, which indicates that the threshold for early surgical treatment has lowered. In other surveys of IE outside the US and Europe, 35% of patients required surgery. This may reflect the higher incidence of streptococcal endocarditis, which is less frequently related to the need for surgery. The ICE-PCS study has found that early surgery is critical in improving survival in patients with definite IE. This finding adds detail to recent reports supporting early surgical intervention and adds credibility to the practice of a combined medical and surgical approach from admission for patients with IE, specifically in those with congestive heart failure and prosthetic valve infections.

Despite improvements in clinical and surgical therapy, PVE carries a high mortality risk ranging from 20 to 80% of affected patients. PVE is still associated with a more difficult diagnosis, a more severe prognosis, and difficulties in therapeutic strategies. Both mechanical and bioprosthetic valves can be infected by the invading microorganism, and their rate of infection is similar at five years (5.7%). However, mechanical prosthetic valves seem to carry a higher risk for infection during the first three months. Several factors have been associated with bad prognosis in PVE, including age, staphylococcal infection, early PVE, congestive heart failure, stroke, and intracardiac abscess. Among them, complicated PVE and staphylococcal infections are the most powerful markers.

The best therapeutic option in PVE is still being discussed. Although a medical surgical strategy is said to represent the best therapeutic option, medical therapy can be sufficient in some patients. Although surgery is considered the best option when PVE causes severe prosthetic dysfunction or heart failure, current recommendations are not based on prospective randomized studies, and the best therapy for PVE in the absence of such complications is still debated. Surprisingly, surgery was performed in only 50% of patients with PVE in the Euro Heart Survey, similar to the rate for patients with NVE.

Conclusion

In conclusion, IE remains a deadly disease, frequently associated with a difficult and tricky diagnosis. Significant changes in epidemiology and microbiology have increased differences between patients seen in the US and Europe and those in countries with a higher incidence of rheumatic heart disease, such as South America and India. Therefore, specific regional approaches to IE are necessary.