

Current Challenges of Infective Endocarditis

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Despite advances in the diagnosis and treatment of infective endocarditis in the last two decades, mortality due to this disease continues to be high, ranging from 15% to 27%, as demonstrated by Casabé et al and other series.¹⁻³ Such mortality rate probably results from changes in the profile of infectious endocarditis, in which the disease presently takes more complex forms. Therefore, in order to change the prognosis of the disease, it is essential to identify predictors of mortality in the various populations.

Changes in the clinical spectrum of infectious endocarditis over the years are well-documented in the literature² and include an ageing population, changes in underlying heart disease, a trend shift from rheumatic valve disease toward degenerative, congenital and myxomatous valve disease, and a higher percentage of patients in whom no predisposing heart disease has been identified. Moreover, the number of patients with intravascular devices, heart prostheses and implantable pacemakers is increasing, and more patients are undergoing invasive medical procedures such as dialysis, surgery with cardiopulmonary bypass and prolonged intravenous cannulation. Lastly, urban populations have a growing number of intravenous drug abusers. All these factors are associated with a change in the spectrum of causative microorganisms. Examples of these changes are a decrease of around 35% in the number of infectious endocarditis cases caused by the *viridans* streptococci and an increase of 50% in those caused by *Staphylococcus aureus*. Other streptococci have also increased, with a sharp decrease in cases of infectious endocarditis presenting negative blood cultures to about 5%.⁴

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One of the changes in this spectrum stems from the gradual rise in *S. aureus* as the causative microorganism of infectious endocarditis, particularly in prostheses, as shown by Casabé et al.¹ This microorganism produces a serious, rapidly progressing, highly emboligenic toxic infectious condition with dissemination and spread of the infection, that quickly leads to valve deterioration and death from multiorganic failure. There are often no physical manifestations of infectious endocarditis at onset. Additionally, the high virulence of *S. aureus* probably explains the increasing number of valves that become infected in patients that have no history of heart disease (41% in Casabé's series). Recent publications have shown a spectacular rise in the frequency of bacteremias caused by *S. aureus* and associated with increased antibiotic resistance. This increase is partially explained by advances in therapies and medical procedures and by the increased use of invasive procedures, prostheses and intravascular stents, expanding the total population at risk.⁵ Intravenous drug abusers (four patients in this series) are also at high risk, with 74% infected by this microorganism and a predominance of tricuspid valve involvement (70%).⁶ These patients have a 3% to 25% risk of developing infectious endocarditis. As a result, some authors recommend echocardiograms in all patients with a bacteremia caused by *S. aureus* who do not respond quickly to antibiotic therapy.

Major improvements that have led to a change in the prognosis of infectious endocarditis include new techniques for bacteriological diagnosis and echocardiograms that allow visualization of the typical lesions of the disease and its complications. In terms of treatment, antibiotics and heart surgery have had a profound impact on the course and prognosis of the disease.

New microbiological techniques have helped minimize the percentage of negative blood cultures in patients who do not receive antibiotic therapy prior to diagnosis of the disease. The ICE (International Collaboration on Endocarditis) retrospective database, which includes nearly 2200 patients who meet the definite infectious endocarditis (Duke) criteria, reports only 2% of negative blood cultures.⁴ Current microbiological techniques that

use automated methods, longer incubation periods, enriched culture media and tissue culturing allow hard-to-grow microorganisms to be identified. Serological tests are now capable of identifying fastidious bacteria that cause a small percentage of the infectious endocarditis cases that would otherwise be hard to diagnose. New molecular techniques (polymerase chain reaction-amplified DNA sequential analysis) have proved to be extremely useful in improving the detection and identification of non-culturable causative agents of infectious endocarditis.⁷ Despite all these advances, the percentage of negative blood cultures in the different series still varies considerably, being between 2.5% and 31%.² Many of these patients were already receiving antibiotic therapy when the blood samples were drawn. Under these circumstances, antibiotic-neutralizing resins can improve diagnostic performance in a limited number of cases. This is one of the points that can be improved if the disease is suspected early on and all the currently available microbiological tools are used, as shown in the ICE retrospective database.⁴

Echocardiography is also a fundamental advance in the diagnosis of this disease. Transthoracic echocardiography was initially an important tool for the diagnosis of infectious endocarditis, but transesophageal echocardiography has a greater sensitivity and specificity, as it allows visualization of structures up to 1 mm in size (e.g., vegetations, valve perforations and small abscesses of 5 mm). It is also the best method for assessing prosthetic heart valves. The sensitivity of transesophageal echocardiography in detecting vegetations is between 87% and 100%, and the specificity between 91% and 100%.

Sensitivity, detecting abscesses is 80%-87%. The negative predictive value of transesophageal echocardiography is 98%.⁹ However, the examination does have limitations when the infection is in its earliest stages, when the vegetations have embolized or when there are previous, rheumatic or degenerative valve lesions that are sometimes impossible to identify. Caution is also needed in the study of prosthetic valves with added artifacts produced by the prosthetic material and by acoustic shadowing.

The introduction of antibiotics has caused the mortality of 100% to drop to figures below 30%. Although a wide variety of antibiotics are now available, the development of antibiotic resistance often limits the therapeutic options.

Prompt heart surgery to eradicate the infectious focus and correct the mechanical complications of infectious endocarditis that lead to heart failure is the other factor which has had a positive impact on the prognosis of the disease. The percentage of patients requiring surgery is 25%-40% in general hospitals and 50%-60% in tertiary medical centers. Operative mortality ranges between 8% and 16%.¹⁰

In terms of the clinical analysis of infectious endocarditis, general conclusions are hard to draw because of the low incidence of the disease and the fact that studies with a control group are not possible. The articles generally report observational studies conducted in only a few centers, and the results are influenced by regional, socioeconomic and population-related characteristics. A comparison of infectious endocarditis studies in countries with similar per capita investments in health discloses clear regional differences, even within Europe. This is observed, for instance, in the spectrum of causative agents and in the percentage of cases successfully handled by surgery.^{11,12} The incidence of infectious endocarditis is also higher in urban versus rural populations, possibly reflecting the impact of intravenous drug abuse and other socioeconomic factors. Community-acquired infectious endocarditis has different characteristics from cases treated in tertiary medical centers, which receive a high percentage of the patients referred for surgical treatment of their complications. This is the case of the patient population analyzed by Casabé et al.¹ In general, studies at tertiary centers include patients with much more complex conditions, a higher number of operations and a larger proportion of patients with prosthetic heart valves and implantable pacemakers.^{3,13}

Another component that has helped change our approach toward infectious endocarditis is the use of more accurate diagnostic criteria. Since 1994 echocardiographic findings specific to infectious endocarditis have been included in the main diagnostic criteria. As a result, patients not previously classified with definitive infectious endocarditis for lack of confirmation by histological study or necropsy are now included in the most recent clinical series.

The study population of Casabé et al has all the typical characteristics of patients at a tertiary referral center, in which the number of patients referred for surgical treatment of the disease is high.^{1,13} This could explain why 18% of blood cultures were negative, as many of these patients were already on antibiotics at the time of diagnosis. Furthermore, Casabé et al found a high number of infectious endocarditis in prosthetic valves (39% of them early) in relation to cardiopulmonary bypass surgery, and a high percentage of successful surgeries for infectious endocarditis (64%). This series is in every regard similar to our experience at the Hospital de la Universidad Católica de Chile (a tertiary medical center) between 1980 and 1999. We analyzed 261 consecutive episodes of infectious endocarditis and found 27% with negative blood cultures, 28% with prosthetic valve infectious endocarditis and 52% with successful surgical resolution.³

The mortality predictors identified in Casabé's series were uncontrolled sepsis and advanced heart failure.

These mortality predictors are common in tertiary center patients and basically reflect extremely advanced disease, higher virulence of the microorganisms and extensive valve damage.

Based on the above analysis, we conclude that the current approach to infectious endocarditis (although it could be perfected) is adequate, and that mortality is due to the extremely late diagnosis of the disease. Consequently, the medical community should become more familiar with changes in the epidemiological and clinical profile of the disease, so it can identify populations at risk. The ageing population, changes in cardiac risk factors, emerging populations of immunosuppressed patients and intravenous drug abusers, and a growing number of patients who have undergone invasive medical procedures or require endovascular devices, comprise a population susceptible to the development of a disease with entirely different clinical and epidemiological aspects.

Prophylaxis for infectious endocarditis would be the simplest, most cost-effective way to prevent the disease. However, antibiotic prophylaxis has not yet been demonstrated. The American Heart Association has stratified preexisting cardiac conditions according to the risk of complications and death if infectious endocarditis develops. It also has published antibiotic prophylaxis guidelines for specific patient groups undergoing certain procedures associated with different degrees of bacteremia, although there are not enough studies confirming the validity of these guidelines.¹³ Some studies are reopening the debate on the potential damage of indiscriminate use of antibiotics for infectious endocarditis prophylaxis, as the approach could be more harmful in the general population than any unproven benefits of prophylaxis.⁴

In conclusion, the predictors of poor outcome in infectious endocarditis treatment are well-defined and clearly related to late diagnosis of the disease. The medical community should be aware of changes in the characteristics of patients at risk of acquiring the condition. The present challenge consists of identifying these at-risk populations, in order to provide timely diagnosis of the disease and undertake appropriate, successful therapy.

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