

## Diagnosis and treatment of infective endocarditis in intensive care

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### Abstract

**Infective endocarditis (IE) is an infectious microbial disease of the heart valvular endothelium. The characteristic lesion consists of the presence of vegetations that can settle in the valvular veils, tendon cords or mural endocardium.**

**Hospital mortality in patients with severe sepsis or septic shock has been between 20 and 50%, a**

**fact probably underestimated and overshadowed by a late referral to the intensive care unit, even though clear criteria for entry into the unit have been established for patients with this situation.**

**The objective of this study was to know the characteristics, evolution and prognosis of patients with infective endocarditis who required treatment in the Intensive Care Unit.**

**Key words:** Infectious endocarditis, diagnosis, treatment, microbiology, critical care.

### Introduction

Infectious endocarditis (IE) is a disease caused by a microbial infection of the cardiac endothelium. The vegetation, with involvement of the heart valves and endocardium, are characteristic. It has an incidence of 1.6-6.0 cases/100,000 patient-year in the general population and 11.6 cases/100,000 patient-year in addicts to parenteral drugs. The majority of patients who develop IE have a previous injury of the cardiac endothelium. IE is a rare disease, with a particularly difficult identification and diagnosis, which requires the assistance of different specialists for its diagnosis and treatment, such as intensive care specialists, infectious disease specialists, microbiologists, cardiologists and surgeons. There have been significant changes in epidemiological and microbiological patterns since many of the common bacteria are becoming poten-

tially resistant to medication as antibiotics. It is also important to clarify the presence of a higher proportion of older and multi-pathology patients who require treatment, with aggressive germ infection and acute presentation. (1)

Hospital mortality in patients with severe sepsis or septic shock has been between 20 and 50%, a fact probably underestimated and overshadowed by a late referral to the intensive care unit, even though clear criteria for entry into the unit have been established for patients with this condition. In the case of endocarditis, a large and recent series of analysis in our country show an in-hospital mortality of 29.5%. (2)

In this way, the need for a multidisciplinary management of IE patients is important, and the intensive care unit is the place where this demand is strong, since it is the high frequency of serious complications that occur during the course of the infection. The patients that enter with IE usually come from different hospital services such as emergencies, cardiology or internal medicine, since the severity of these patients requires the help of this special unit. (3)

The objective of our study was to analyze the differential characteristics of patients with IE who required admission to intensive care, as well as the evolution and prognosis of the inpatients according to objective criteria and severity scores, identifying the variables that were associated with the entry into the unit and the death of the patients.

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## Epidemiology

The epidemiological profile of IE has changed considerably in recent years, especially in industrialized countries as microorganisms have achieved drug resistance that makes more difficult to cure the disease. Although IE has always been a disease that has mainly affected young adult patients with well-identified valve diseases, currently older patients suffering from health care procedures, both in patients without prior valvular disease and in patients with valves prosthetic. (4)

To understand epidemiology, it is necessary to see IE as a set of clinical situations that are sometimes very different from one another. In an attempt to avoid overlap, the following four IE categories should be separated according to the location of the infection and the presence or absence of intracardiac foreign material: 1) IE on left native valve, 2) IE on left prosthetic valve, 3) right IE, and 4) related IE with the devices. In relation to the type of acquisition of the disease, the following situations can be identified: IE acquired in the community, IE associated with healthcare (nosocomial and non-nosocomial) and IE in injecting drug addicts. (5)

## Diagnosis

The diverse nature and epidemiological profile of the evolution of IE ensure that its diagnosis remains a challenge in intensive care medicine. The clinical history of IE is highly variable according to the microorganism causing the infection, the presence or absence of pre-existing heart disease in the patient, mainly valvulopathies and the presentation and manifestation of the disease. Thus, IE should be suspected in a variety of very different clinical situations, the most frequent being a rapidly progressive acute infection, but also as a chronic subcutaneous disease with fever and without specific symptoms, which may disrupt or confuse the initial assessment.

The characteristics for suspicion in situ the disease would be: 1) suspicions of regurgitate heart murmur along with embolism events of unknown origin. The aforementioned sepsis of unknown origin was probably the cause of IE. 2) The patient had fever. 3) The patients most susceptible to IE are those who have cardiac prosthesis such as valves or pacemakers, or who suffered the disease previously after the intervention, manifesting it now again. This case is very common in immunosuppressed patients. 4) Predisposition to pathogenic diseases and evidence of heart failure.

Therefore, patients may come to a variety of specialists who may think of a range of other diseases, including chronic infection, rheumatic and auto-

immune diseases. Prompt intervention of a cardiologist and infectious disease specialist are strongly recommended to guide management.

## Microbiology and microbial diagnosis

This is possibly the most important category for the diagnosis of IE, accounting for 85% of the disease. The causative microorganisms are usually Staphylococci, Streptococci and Enterococci.

### *Infectious endocarditis caused by Streptococci and Enterococci*

The oral Streptococci form a powerful group of very diverse microorganisms where we can differentiate different species such as *S. sanguis*, *S. mitis*, *S. salivarius*, *S. mutans* and *Gemella morbillorum*. These microorganisms are almost always susceptible to antibiotics, especially penicillin. Members of the *S. milleri* or *S. anginosus* group (*S. anginosus*, *S. intermedius* and *S. constellatus*) should be distinguished as they tend to form abscesses and cause disseminated infection via the bloodstream, often requiring longer duration of antibiotic therapy. In addition, "defective" nutritionally variant Streptococci recently reclassified into other species (*Abiotrophia* and *Granulicatella*) should also be distinguished, as they often tolerate penicillin. Group D Streptococci form the *S. bovis*/S complex. *Equinus*, which includes the commensal species of the human intestinal tract and until recently were called *Streptococcus bovis*. They are usually susceptible to penicillin G, as are oral Streptococci. Among Enterococci, *Enterococcus faecalis*, *E. faecium* and, to a lesser extent, *E. durans* are the three species that cause IE. (6)

### *Staphylococcal infective endocarditis*

Traditionally, IE by Staphylococci in native valve is due to *S. aureus*, which is most often susceptible to oxacillin, at least in the community-acquired IE. In contrast, IE by *Staphylococcus aureus* is most frequently due to coagulase negative Staphylococci with oxacillin resistance. (5)

### *Brucella*

Brucellosis is a zoonosis of global distribution that very rarely causes endocarditis. IE by *Brucella* is a subacute presentation entity characterized by extensive valve destruction and the production of myocardial abscesses, which usually require combined medical and surgical treatment. Without timely treatment, it evolves towards heart failure and death. (7) IE by *Brucella* generally requires a combined treatment (medical and surgical), since mortality without surgical treatment is estimated at

more than 80%, although successful results have been reported with medical treatment alone.

#### *Pneumococcal*

Due to the low frequency of infection by Pneumococci, no comparative studies are available to evaluate different therapeutic regimens, so the information given here follows exclusively from the analysis of retrospective series and the opinion of experts. It is always necessary to confirm that Pneumococcus is sensitive to penicillin (MIC<0.06 mg/ml). While awaiting sensitivity results, it is advisable to initiate empirical treatment with third generation cephalosporins (ceftriaxone or cefotaxime). In case of high local incidence of penicillin resistant Pneumococcus, it is recommended to associate vancomycin in the initial empirical treatment until the final sensitivity is available. (8)

#### *Legionella*

In general, they are patients with prosthetic valve and who acquired the infection in the post surgical period within the hospital setting. Antibiotic treatment consists of the combination of erythromycin and oral rifampicin during the first two months, and continues another six months to one year with the same oral combination. Combined medical-surgical treatment should always be considered. (9)

#### *Chlamydia*

Chlamydia psittaci is the causative agent of IE in most of the rare cases reported, although some authors mention *C. trachomatis* and even *C. pneumoniae*. The combination of tetracycline plus rifampicin for an average period of 6 weeks (in some cases followed by prolonged periods of doxycycline treatment, waiting for the decrease in antibody titers) was successful in approximately 70% of cases. In almost half of the patients the surgical treatment was associated. (10)

#### *Coxiella burnetti*

In the majority of patients there is a predisposing factor or prosthetic valve as antecedent. In general, tetracyclines have been used in combination with trimethoprim-sulfamethoxazole or rifampicin at varying periods according to the decrease in antibody titres. However, in approximately half of the cases, surgical treatment was required. Although it has been reported on the successful treatment of endocarditis with ciprofloxacin and in general the use of quinolones in the pneumonic forms of the disease has been proven, more experience is required for the recommendation of its use in this situation. (11)

#### *Microbiological diagnosis*

The diagnosis of these microorganisms is carried out by means of different laboratory and culture techniques.

##### *a. Hemocultures*

Positive blood cultures remain the most effective technique for the diagnosis of IE. Normally, three series (at least one aerobic and one anaerobic between them), each with 10 ml of blood obtained from a peripheral vein using a meticulous technique of sterilization, are almost always enough to identify the usual microorganisms. Central venous catheter samples should be avoided, because of the high risk of contaminants (false positives, usually Staphylococci) and of corrupting the results.

Although anaerobic IE is uncommon, blood cultures should be incubated in aerobic and anaerobic atmospheres to detect organisms such as Bacteroides or Clostridium species. When the culture remains negative on the fifth day, the subculture on chocolate agar plates will allow the identification of a demanding organism. (12)

##### *b. Histological/immunological techniques*

The pathological recognition of valvular tissue or embolic fragments remains a very useful technique for the diagnosis of IE and can guide antimicrobial treatment if the causative agent can be identified by means of special strains or immunohistological techniques. Electron microscopy has high sensitivity and may help characterize new microorganisms, but it can be time consuming and expensive. *Coxiella burnetti* and *Bartonella* species can be easily detected with serological testing using indirect immunofluorescence or an enzyme-linked immunosorbent assay (ELISA), and recent data have shown a similar utility for Staphylococci. Immunological analysis of the urine allows the detection of degradation products of microorganisms, and the detection of *Legionella* species by ELISA using this technique has been demonstrated. The incorporation of methods into the accepted diagnostic criteria awaits the prospective validation. (13)

##### *c. Molecular biological techniques*

Cardio-pulmonary reanimation (CPR) techniques allow the rapid and reliable detection of demanding organisms and non-cultivable agents in patients with the disease. Although there are several advantages such as extreme sensitivity, intrinsic limitations include the lack of reliable application in all blood samples, the risk of contamination, false negatives because of the presence of PCR inhibitors in clinical samples, inability to provide infor-

information on bacterial sensitivity to antimicrobial agents and persistent positivity despite clinical recovery. PCR of excised valvular tissue or embolic material should be performed in patients with negative blood cultures who undergo valvular surgery or embolectomy. (14)

### **Treatment**

All patients with IE due to bacterial infection should receive hospital treatment for at least 2 weeks, during which the potential occurrence of cardiac or extracardiac complications will be monitored. After this hospital period, patients may be candidates to continue out-of-hospital parenteral antibiotic therapy, without forgetting the severity of the disease. The recommended treatment for IE is based on results consistent with a large number of studies. (15)

The use of intravenous bactericidal antibiotics that reduce failures and recurrences are the most common techniques or treatments (**Table 1**). The duration of treatment is 4-8 weeks, since the germs are within the matrix of platelets and fibrin in large concentrations, with relatively low rates of metabolism and cell division and therefore with reduced susceptibility to beta-lactams and others antibiotics active against the cell wall. Treatment will begin at the time of diagnosis, continuing during hospital intensive care days. (16)

The recommendations on the management of anticoagulant treatment of patients with IE are based on a low level of evidence, and the multidisciplinary team of endocarditis must make the decisions in an individualized way. The role of bridging with unfractionated heparin or low molecular weight heparin for patients with IE has not been studied, although it may have reasonable advantages in special situations. The available evidence does not

support the initiation of antiplatelet therapy in patients diagnosed with IE, despite the promising results obtained in the experimental studies. Some cohort studies indicate a possible reduction in the rate of embolic complications or the development of IE in subgroups of patients already receiving antiplatelet therapy, although the data are contradictory. (17)

One must remember that mycotic infection has poor prognosis and most require surgical treatment. The first choice of medical treatment is amphotericin B for 6 weeks. This antimycotic does not penetrate well in the vegetations, so some authors recommend adding 5-fluorocytosine that acts synergistically. Fluconazole may be useful in the case of susceptible fungi.

The practitioner should always remember that prophylaxis is the best method. The performance of diagnostic or therapeutic procedures that may induce bacteremia in children with heart disease increases the risk of developing IE and is performed under antibiotic protection. There is no conclusive evidence of its effectiveness. It is recommended to administer the drug one hour before the procedure and not more than 6 hours later to achieve therapeutic concentrations of the antibiotic before bacteremia and to avoid resistance.

### **Conclusions**

A high proportion of patients with endocarditis require admission to the Intensive Care Unit, presenting a much more unfavorable prognosis. Infection with bacteria or fungi, heart failure, and cerebral embolism are predictors of in-hospital mortality. The union of different disciplines like intensive care medicine, microbiology or cardiology, can be fundamental for the early diagnosis and treatment.

**Table 1.** Antibiotic treatment in patients with IE

Germ	Antibiotic	Dosage	Weeks	Prosthetics
Streptococci (susceptible to penicillin)	Penicillin G or ceftriaxone	50,000 U/kg/6h 100 mg/kg/24h	4 weeks	No
Streptococci (relatively resistant to penicillin)	Penicillin G or ceftriaxone plus gentamicin	50,000 U/kg/4h 100 mg/kg/24h 1 mg/kg/8h	2 to 4 weeks	No
Enterococci, Strep. viridans, Abiotrophia sp., Streptococci (resistant to penicillin)	Penicillin G plus gentamicin	50,000 U/kg/4h 1 mg/kg/8h	4 to 6 weeks	No
Streptococci, Enterococci, or Abiotrophia	Vancomycin or vancomycin plus gentamicin	20 mg/kg/12h 20 mg/kg/12h 1 mg/kg/8h	4 to 6 weeks	Yes
Enterococci Streptococci, or Abiotrophia	Vancomycin plus gentamicin	20 mg/kg/12h 1 mg/kg/8h	6 weeks	Yes
Allergic to beta-lactam or resistant to methicillin	Vancomycin	20 mg/kg/12h	6 weeks	Yes

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