Acute bivalvular left-sided methicillin-resistant *Staphylococcus aureus* endocarditis with cardiac, cerebral, renal and septic complications [48]

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**ABSTRACT**

Infective endocarditis (IE) is now rare in developed countries, but its prevalence is higher in elderly patients with prosthetic valves, diabetes, renal impairment, or heart failure. An increase in health-care associated IE (HCAIE) has been observed due to invasive maneuvers (30% of cases). Methicillin-resistant *Staphylococcus aureus* (MRSA) and *Enterococcus* are the most common agents in HCAIE, causing high mortality and morbidity.

We review complications of IE and its therapy, based on a patient with acute bivalvular left-sided MRSA IE and a prosthetic aortic valve, aggravated by congestive heart failure, stroke, acute immune complex glomerulonephritis, *Candida parapsilosis* fungémia and death probably due to *Serratia marcescens* sepsis. The HCAIE was assumed to be related to three temporally associated in-hospital interventions considered as possible initial etiological mechanisms: overcrowding in the hospital environment, iv quinolone therapy and red blood cell transfusion. Later in the clinical course, endocardite aguda bi-valvular esquerda por *Estafilococo aureus* meticilino-resistente com complicações cardíaca, cerebral, renal e sepsis

**RESUMO**

Em países desenvolvidos a endocardite infecciosa (EI) é actualmente pouco frequente, mais prevalente em idosos com próteses valvulares, diabetes, insuficiência renal e insuficiência cardíaca. Manobras invasivas causaram um aumento das endocardites associadas a cuidados hospitalares (HCAIE) (30% dos casos), sendo o *Estafilococo aureus meticilino-resistente* e o *Enterococo* os agentes infecciosos mais comuns nestes casos, condicionantes de maiores mortalidade/morbilidade.

Os autores revêem as complicações da EI e sua terapêutica, baseados numa doente com EI aguda bi-valvular esquerda e com prótese valvular aórtica, complicada de insuficiência cardíaca, embolia cerebral, glomerulonefrite aguda pós-infecciosa a imunocomplexos, fungémia por *Candida*
**INTRODUCTION**

*Staphylococcus* aureus (SA) is a major cause of infective endocarditis (IE) in all age-groups, accounting for around 55% of cases, and is more common in patients with prosthetic valves or abnormal native valves\(^{(1)}\). SA IE usually presents as a highly toxic, febrile illness, with frequent focal metastatic infection and a high rate of heart failure and central nervous system complications. New heart murmurs or modification of previous ones are heard initially in 30-45% of patients and eventually in 75-85% of cases as a consequence of progressive valve damage.

Left-sided IE due to SA in non-intravenous drug abusers has a very high mortality rate in those aged over 50 years and with significant underlying diseases and when severe complications occur, such as major neurological events, valve dysfunction with heart failure, and renal failure due to acute glomerulonephritis. However, in a report from Spain, Lopez et al. \(^{(2)}\) described more frequent valvular impairment (regurgitation and perforation) due to left-sided SA endocarditis in younger patients, the *worse prognosis* in older patients being due to comorbidities and higher surgical mortality.

Patients with IE due to MRSA are significantly more likely to present renal failure and to experience bacteremia than those with IE due to methicillin-susceptible SA (MSSA). Risk factors for death due to IE include severity of illness at onset of bacteremia, MRSA infection and atrioventricular block. MRSA as the infecting microorganism in cases of IE is a risk factor that should be considered for possible prompt valve resection\(^{(3)}\).

Health-care associated IE (HCAIE) is increasingly being reported in developed countries, due to increasing age of patients, comorbidities (diabetes, renal impairment, previous heart valve disease, and immunosuppressive states), and the growing number of invasive maneuvers with their high risk of bacteremia\(^{(4)}\).

We report a case of an elderly female patient with previous left-sided bivalvular fibrocalcifying disease, a prosthetic aortic valve, red cell blood transfusion one week before, and hospitalization for acute pulmonary infection treated with iv quinolone, who developed acute left-sided bivalvular IE...
An 83-year-old woman was admitted to our infirmary on November 12 2009 due to acute hypoxemic respiratory infection (PaO₂ 35.2 mmHg) of one week’s duration, ten days after a red cell transfusion in the emergency ward for iron deficiency anemia of undiagnosed etiology (Hb 8.1 g/dl), presumably related to warfarin therapy. The patient complained of fever, cough productive of purulent sputum, left thoracic pain and progressive dyspnea.

Her past medical history included a biological aortic valve prosthesis due to fibrocalcifying disease (November 2004), ischemic/hypertensive cardiomyopathy, chronic atrial fibrillation, secondary pulmonary hypertension, ischemic stroke without sequelae, acute bronchopneumonia and iron deficiency anemia due to hemorrhagic gastritis (May 2009). Her father had died from acute rickettsiosis and her mother from ischemic stroke.

On observation, her temperature was 38.5 °C, blood pressure 124/68 mmHg, heart rate ~120 bpm, and respiratory rate 26/min. An aortic systolic ejection murmur (III/VI) was audible, with no other abnormal sounds. There were bilateral diffuse rhonchi on lung auscultation. Abdominal semiology was normal and there was no leg edema.

Laboratory blood tests (Table I) revealed anemia of chronic disease; leukocytosis with neutrophilia; INR 2.3; elevated CRP; hypoxemia; hypoalbuminemia (2.56 g/dl); and normal urea and creatinine, with calculated GFR of 62.3 ml/min. Urinary sediment showed 75 WBCs/μl, but urine culture was negative, as was urinary antigen for *Pneumococcus* and *Legionella pneumophila*. The chest X-ray showed cardiomegaly and bilateral peribronchitis.

After the first day on iv therapy with levofloxacin, the patient was afebrile and improving rapidly, and her WBCs were normal on the 6th day of therapy (Table I). During the night of the 8th to 9th day of hospitalization she developed high fever (39 °C), chills, vomiting, abdominal pain and headache, and a de novo mitral systolic murmur (III/VI) was audible. Conjunctival petechiae and finger splinter hemorrhages were detected, but retinoscopy was normal. No hepatomegaly or splenomegaly were observed. Blood tests on the following morning showed recurrent and higher leukocytosis (Table I), and urinary sediment revealed many erythrocytes but no proteinuria. Blood cultures were taken and MRSA was subsequently isolated, susceptible to gentamicin, vancomycin, teicoplanin and linezolid. Transesophageal echocardiography performed on the same day revealed a small vegetation on the fibrocalcified native mitral valve, but apparently not on the biological prosthetic aortic valve. One day later right hemiparesis occurred due to left frontal-parietal ischemic stroke. Cardiologists did not advise surgery then or later on due to comorbidities and complications in an 83-year-old patient.

Therapy with vancomycin, gentamicin and rifampicin was initiated on the day of diagnosis of endocarditis, subsequently changed to linezolid when renal failure ensued, revealed by blood tests on the 14th day of hospitalization (plasma urea 147 mg/dl and creatinine 1.9 mg/dl) (Table I), which was at first presumed to be due to drug iatrogeny. However, diuresis becomes progressively lower and on December 22 2009 (the 22nd day of hospitalization) the patient was in anuria with acute elevation of renal function markers (Table I) and heart failure (NYHA class III). C3 was lower than normal, which persisted throughout
Although three transthoracic echocardiograms performed during the six weeks of therapy showed no new abnormal echocardiographic signs, transesophageal echocardiography performed subsequently showed an apparently new aortic valve infection with suspected perivalvular abscess cavity (Figure 4). However, urgent heart surgery was refused by a cardiovascular surgeon, because: (1) after serial review of all echocardiograms it was considered that bivalvular endocarditis had been present from the beginning, and that after six weeks of antibiotic therapy and with no clinical or laboratory signs of active infection, the image of an abscess cavity probably corresponded to an already epithelialized sequelar cavity; (2) the serious clinical situation of the patient would result in postoperative death.

Meanwhile, Candida parapsilosis was isolated from a blood culture taken on December 21, 2009 (one positive and two negative blood samples, susceptible to fluconazole, voriconazole, amphotericin B and caspofungin), for which iv fluconazole was initiated as soon as the result was known (January 2, 2010). Serial blood cultures were no longer positive for MRSA after the first week of therapy.

Assuming that renal function would not recover, the temporary hemodialysis catheter was replaced in the nephrology unit by a permanent tunneled catheter inserted through the lumen of the previous one. On the same day, several hours after the procedure, severe clinical worsening occurred: on the following day the patient presented in septic shock and profound lactic acidosis (pH 6.942; cHCO3- 4.6 mmol/l; anion gap 17.5 mmol/l; cLactate 12.7 mmol/l), and was transferred to the intensive care unit. Assisted ventilation was required, and iv vancomycin and piperacillin-tazobac-
tam antibiotic therapy were prescribed as well as circulatory support with vasoactive amines, but the patient died three days later due to multiorgan failure. *Serratia marcescens* (susceptible to piperacillin-tazobactam) was later isolated from blood cultures obtained during this period, and two other blood cultures dated December 30 2009 and January 5 2010 were positive for *C. parapsilosis*, although this result was known only after the patient’s death. Her family did not authorize necropsy.

**DISCUSSION**

In developed countries, IE is a rare disease, with an incidence of 3-10 cases/100,000 population per year. A higher prevalence has been observed in the elderly[1]. While rheumatic heart disease remains the predominant risk factor in developing countries, in developed countries newer predisposing factors have arisen, such as valve prostheses, degenerative valve sclerosis and intravenous drug abuse[2].
and even esthetic procedures such as body piercing have been implicated in the development of IE in individuals with or without previous heart disease. The incidence of HCAIE is increasing, representing up to 30% of total cases, which are mostly related to invasive maneuvers, such as intravenous catheters, hyperalimentation lines, pacemakers, and dialysis access, with a consequent high risk of bacteremia. Aseptic measures during these procedures are therefore very important.

Changes in the conditions associated with IE have altered the frequency of the etiological microorganisms, with the incidence of streptococcal IE decreasing and that of staphylococcal IE increasing. In fact, HCAIE, besides being associated with older age, diabetes, renal impairment and heart failure, has also been associated with MRSA and Enterococcus. In a smaller proportion of cases Candida (4%) and Gram-negative bacilli (5%) may be the agents responsible for HCAIE. Mortality and morbidity remain unacceptably high and recent health care exposure has been identified as an independent predictor of mortality.

Prosthetic valve IE represents 10-30% cases of IE in most developed countries. The risk of early-onset IE is greater for mechanical heart valves, but later becomes similar for mechanical devices and bioprostheses. *Staphylococcus aureus* and coagulase-negative *Staphylococcus* are now the most common cause of prosthetic valve endocarditis and are associated with a poor prognosis. Prosthetic valve endocarditis is associated with high mortality despite diagnostic and therapeutic improvements. Early prosthetic valve endocarditis (first eight weeks after surgery) usually presents with a more acute clinical picture than late prosthetic valve endocarditis (more than one year after surgery), but these considerations can be modified in HCAIE.

Unexplained fever in a patient with a prosthetic valve should prompt immediate and careful evaluation for prosthetic valve endocarditis. Frequently, new or changing murmurs and congestive heart failure are detected. Blood cultures (only a small percentage of patients with no previous antibiotic therapy will have sterile blood cultures) and echocardiograms (preferably transesophageal) are of crucial importance in diagnosis. Serial echocardiograms throughout the clinical course
are of utmost importance for evaluation of the severity of IE and for the detection of valve destruction by abscesses, a not uncommon occurrence in SA valve infections. Real-time polymerase chain reaction of bacterial rDNA from surgically removed heart valves is a recent diagnostic method that is especially useful in patients with culture-negative IE.

IE’s clinical course may present with various complications, as was well illustrated in our patient’s case. Heart failure is the most frequent severe complication of IE and congestive heart failure and neurological events have the strongest influence on the clinical course and prognosis of IE. Congestive heart failure is usually due to infection-induced valve damage, and aortic valve infection is more frequently associated with congestive heart failure than is mitral valve infection. Cavities visualized on ultrasonography are a sign of perivalvular abscess formation.

Systemic emboli are among the most common clinical sequelae of IE, occurring in up to 40 per cent of patients, and can often predate the diagnosis. There is a trend towards a higher risk of subsequent systemic embolism in patients with a vegetation >10 mm. Neurological manifestations occur in 30-40% of patients, embolic stroke being the most common and clinically important. They are more frequent when IE is caused by SA and are associated with increased mortality.

Other neurological complications include intracranial hemorrhage resulting either from hemorrhage into an infarct or from rupture of a mycotic aneurysm, cerebral abscesses, purulent meningitis, severe headaches, seizures and encephalopathy. Rapid treatment with antibiotics is of major importance, since the rate of embolic neurological events decreases significantly after it is begun. Despite antibiotics having been initiated as soon as a diagnosis of IE was confirmed, our patient still suffered a neurological event which affected prognosis as well as clinical and surgical options.

Renal events in IE include renal infarcts due to septic embolism occluding interlobular arteries and arterioles (particularly in SA endocarditis), renal cortical necrosis, antibiotic-induced interstitial nephritis, renal abscesses and glomerulonephritis that may or may not be secondary to immunoglobulin and complement deposition in mesangial and subendothelial locations. Renal biopsy specimens may reveal focal and segmental or diffuse proliferative lesions, often associated with infiltrating cells, typically monocytes/macrophages, and
sometimes a neutrophilic exudate. Crescents are often associated with proliferative lesions. Rarely, rapidly progressive exudative glomerulonephritis develops, leading to end-stage renal failure unresponsive to antibiotic therapy. Immunostaining reveals granular C3 deposition, which is often but not always accompanied by IgG or IgM (3). Persistent circulating immune complexes and C3 depletion, despite antibiotic treatment, have been shown to indicate the failure of therapy and a high probability of persistent infection and glomerulonephritis (3).

Renal insufficiency as a result of immune complex-mediated glomerulonephritis occurs in less than 15% of cases. Patients with IE due to MRSA are significantly more likely to have complicating renal insufficiency and to experience persistent bacteremia than those with IE due to MSSA. Patients may develop endocarditis-related glomerulonephritis despite appropriate antibiotic therapy, and the development of renal failure may be delayed until several days after antibiotic therapy is initiated. Patients presenting with advanced renal failure usually have a poor outcome (3).

Rarer complications are vertebral osteomyelitis, acute septic arthritis, and metastatic abscesses in the spleen and soft tissues. Additionally, all measures associated with hospital treatment of IE can by themselves cause their own complications (hospital infections) (9).

Mortality from prosthetic valve IE is extremely high (20-30% of cases) (6). Our patient clearly illustrates several risk factors associated with increased mortality during the clinical course of IE: congestive heart failure, renal failure, neurological events, old age and comorbidities (previous heart disease and pulmonary hypertension), as well as exposure in an overcrowded infirmary.

Treatment of prosthetic valve IE relies on a combination of prolonged antimicrobial therapy and, in about half of patients, valve surgery (abscess drainage and/or removal of endovascular prosthetic material for treatment of uncontrolled sepsis) (1, 3). Recommended antimicrobial therapy for prosthetic valve IE due to MRSA is an association of vancomycin plus rifampin for 6-8 weeks plus gentamicin for two weeks (or an alternative drug in gentamicin-resistant SA) (6). By contrast, vancomycin has worse results in the treatment of endocarditis due to MSSA than beta-lactam antibiotics.

When assessing treatment outcomes, it is important to bear in mind the recent emergence of multiple MRSA phenotypes with reduced susceptibility to glycopeptides. Minimum inhibitory concentrations (MICs) of vancomycin for MRSA in these cases can be higher than usual (1-2 μg/ml). These strains are vancomycin-intermediate SA (VISA) with MICs between 4-8 μg/ml, heterogeneous VISA (hVISA), which contains a subpopulation of cells with reduced susceptibility to vancomycin (MICs ≥4 μg/ml), and vancomycin-resistant SA (VRSA) (MICs ≥16 μg/ml). Also to be considered is the occurrence of MRSA in a community setting with silent acquisition in patients who were previously in a healthcare environment, or household contacts, as well as truly community-acquired MRSA with Panton-Valentine leukocidin genes (10). At our hospital we have no facilities to investigate this issue.

Not all novel pharmaceutical molecules such as lisostaphin, quinupristin-dalfopristin, linezolid, daptomycin and tigecycline are valid proven options for left-sided acute MRSA endocarditis, although they exhibit comparable in vitro activity against MRSA. The oxazolidinone linezolid appeared to be effective in several recent studies (10).

Since a considerable proportion of prosthetic valve IE patients may require surgery, careful planning and individualization of intervention timing is essential. The optimal time to perform surgery is before severe hemodynamic disability or spread of the infection to perivalvular tissue have occurred. The most frequent indications for surgery are heart failure, uncontrolled infection and prevention of embolic events (9).

The risks associated with surgery are higher for patients with prosthetic valve endocarditis than for those with native valve IE, but the recommendations for surgery are essentially the same for both forms of endocarditis.

It has long been known that if not contraindicated for any reason, combined medical and surgical treatment significantly improves
outcome, with mortality rates of SA prosthetic valve endocarditis diminishing from 70% to 25% of cases (8). Some authors consider that SA prosthetic valve IE alone may be an indication for valve replacement surgery. However, as Paterick et al. (9) clearly advise, surgery is not indicated if complications or comorbid conditions suggest that the possibility of recovery is remote.

Unfortunately, in the case of our patient we were initially only able to diagnose native mitral valve endocarditis, and the patient also presented complications that despite being to some extent reasons to perform surgery, were also a contraindication, due to their severity. The neurological event that our patient suffered affected the planning of surgical treatment. When central nervous system complications occur, timing for surgical treatment cannot be precisely defined. It should usually be performed after two or four weeks, respectively, if an embolic or hemorrhagic event has occurred, and ideally in the absence of heart failure (9). Anuria due to immune complex acute glomerulonephritis also made immediate surgery impossible.

During the clinical evolution our patient presented with two hospital infections: (1) positive blood culture for Candida parapsilosis on the 39th day of hospitalization after a prolonged course of several parenteric antibiotics, but not known until the 56th day, at which time iv fluconazole was initiated; (2) septic shock due to septicemia from Serratia marcescens infection, probably occurring after the insertion of a tunnelized hemodialysis catheter through a previous one. S. marcescens was isolated in blood cultures taken two days before the patient died. S. marcescens, a Gram-negative Enterobacteriacea, is an opportunistic pathogen in humans, responsible for hospital outbreaks, particularly in the ICU. Serratia is responsible for about 2% of nosocomial bacteremias and infections of the lower respiratory tract, urinary tract, surgical wounds, and skin and soft tissues. S. marcescens infections should be treated with an aminoglycoside plus an anti-Pseudomonas beta-lactam.

In conclusion, we considered several possible mechanisms of MRSA HCAIE occurrence in our patient: (1) acute IE due to MRSA is usually HCAIE acquired inside hospitals and nursing and residential homes, where there is frequent use of antibiotics such as macrolides, cephalosporins, quinolones, and to some extent aminoglycosides (10); (2) intravenous procedures utilized several times in the environment of our hospital (emergency ward and infirmary); (3) in general, inadequate ward or unit staff, or staff training, overcrowding of patients, lack of isolation facilities, frequent relocation of patients and staff, and poor attention to infection control procedures increase the risk of nosocomial infections. It is also suggested that some MRSA infections presenting from the community are sometimes associated with silent acquisition after patients have been in an inpatient environment for more than five days within the past year (10); (4) although very rare, there is a risk of SA infection and even of death after red blood cell transfusion (as reported by the FDA and other sources) (11).

The antibiotic association utilized at the beginning was decided based on the possibility of prosthetic valve HCAIE. Unfortunately the first diagnosis was an isolated infection of a native valve, with several acute and serious complications occurring sequentially, that made it impossible to proceed with prosthetic valve surgery. This case is presented to illustrate how the evolution of a case of acute IE due to MRSA can be difficult to control and to treat.

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