Nosocomial infective endocarditis in critically ill patients: a report of three cases and review of the literature

Samir H. Haddad a, Yaseen M. Arabi a, Ziad A. Memish b, c, *, Abdullah A. Al-Shimemeri a

a Department of Intensive Care, King Fahad National Guard Hospital, P.O. Box 22490, Riyadh 11426, Kingdom of Saudi Arabia
b Department of Medicine, King Fahad National Guard Hospital, P.O. Box 22490, Riyadh 11426, Kingdom of Saudi Arabia
c Infection Prevention and Control Program, King Fahad National Guard Hospital, P.O. Box 22490, Riyadh 11426, Kingdom of Saudi Arabia

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Summary Nosocomial infective endocarditis (NIE) is a relatively uncommon but nevertheless a serious complication affecting critically ill hospitalized patients who are frequently exposed to life-saving invasive procedures. We report three cases of NIE in a tertiary-care hospital encountered during a period of two years. The first case developed in a 50% burn-injured patient; the second in a liver transplant recipient; and the third in a renal transplant recipient. All patients met indications for cardiac surgical intervention, however, the patient who had received a liver transplant (case 2) was considered a poor candidate and unfit for surgery; she subsequently died. The other two patients underwent open-heart surgery. The burns patient (case 1) survived; conversely, the renal transplant recipient (case 3) died postoperatively. We have reviewed the literature concerning NIE in critically ill patients and describe the epidemiology, microbiology and clinical features of this uncommon infection and comment on its diagnosis and management.

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Introduction
Nosocomial infections are an ever-increasing problem, with an estimated 2.5 million cases affecting more than two million patients every year in the United States, at a cost of $4.5 billion. Currently, between 5—10% of patients admitted to acute care hospitals acquire one or more infections. Nosocomial infections affect a large percentage of critically ill patients admitted to intensive care units (ICUs). It is the requirement for multiple life-saving invasive procedures, such as central venous access,
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endotracheal intubation, and indwelling urinary catheters which cause defects in the intrinsic barriers to microbial invasion and increase susceptibility to infection. Studies have shown that 21.2–35.6% of ICU patients develop an infection during their stay in ICU. Using the standard definitions for nosocomial infections, several reports have revealed that pneumonia is the most common nosocomial infection, followed by urinary tract infections and bloodstream infections. Nosocomial infective endocarditis (NIE), both in native and prosthetic valves, is a less common infection. However, it is a well known complication, developing in seriously ill hospitalized patients who require numerous invasive procedures. Few studies have reported on hospital-acquired infective endocarditis, and only one has focused on NIE in ICU patients. Finally, studies that have reviewed cases of NIE in solid organ transplant recipients and in burns patients are also limited.

We report three cases of hospital-acquired infective endocarditis; two in solid organ transplant recipients and one following a major burn injury, in a mixed medical/surgical tertiary care ICU (King Faisal National Guard Hospital, Riyadh, Kingdom of Saudi Arabia). These cases were encountered over a two-year period from 2000–2001. During this time there were 1298 admissions to the ICU, constituting 0.23% of all ICU admissions.

Case reports

Patient 1

A 33-year-old woman was admitted with 50% total body surface area full thickness burns. Both burn wounds and airway became colonized with methicillin-resistant Staphylococcus aureus (MRSA). In her fifth month of hospitalization and on the second postoperative day of burn wound debridement with skin grafting, she developed a high fever of 39.5°C. Two blood cultures grew MRSA. Antibiotic therapy was started with intravenous vancomycin. Repeat blood cultures five days after antibiotic treatment remained positive for MRSA. The patient improved and was discharged later from the hospital.

Patient 2

A 48-year-old female with a liver transplant was readmitted to the ICU for septic shock in her third month of hospitalization. Central venous line sepsis was suspected. Two peripheral blood cultures and the tip of central line grew methicillin-sensitive Staphylococcus aureus. Intravenous cloxacillin was administered. A TTE showed thickened mitral and aortic valves with mitral and aortic regurgitation. Although rifampin was added and all intravascular devices were changed she developed persistent Staphylococcus aureus bacteremia and daily blood cultures remained positive for the same organism for five consecutive days. A TEE showed a mitral valve vegetation with an annular abscess and perforation. Early surgical intervention was entertained for the treatment of the paravalvular abscess. However, she was considered a poor candidate for cardiac surgery because of her poor general condition with multi-organ failure and she subsequently died.

Patient 3

A 52-year-old male renal transplant recipient was readmitted with a presumptive diagnosis of cytomegalovirus chorioretinitis six weeks after discharge. On the second hospital day he was admitted to ICU for confusion and change in his mental status. A CT scan of the head revealed a hemorrhagic cerebral infarct. A pansystolic heart murmur was detected. Infective endocarditis complicated by an embolic cerebral infarct was suspected. A TTE was suggestive of endocarditis. A TEE was performed and showed a large vegetation with rupture of the mitral valve. As all blood cultures were negative, the diagnosis of culture-negative endocarditis was made. Antibiotic therapy was started with intravenous ceftazidime, clindamycin, and gentamicin. Considering the large vegetation size and the negative blood cultures with lack of response to the antibiotic therapy, fungal endocarditis was suspected. Empiric antifungal therapy was initiated with amphotericin B. Although the patient was in serious general condition and had multi-organ failure, he underwent open-heart surgery for mitral valve replacement. He died on the second postoperative day. The pathology of the mitral valve vegetation specimen showed fungal infective endocarditis. The culture specimen grew Aspergillus spp.
Discussion

Nosocomial infective endocarditis continues to be considered a serious problem and a life-threatening disease. Although significant progress has been made in both diagnosis and treatment, NIE is still associated with prolonged hospital stay, increased morbidity, mortality and medical costs.

Definition

Nosocomial infective endocarditis is defined as acute IE occurring 48 to 72 hours or more post-admission to hospital and/or endocarditis directly relating to a hospital-based procedure performed during a previous hospital stay within eight weeks of admission. Early prosthetic valve endocarditis (PVE) is therefore included, based on the latter definition. However, others usually exclude cases of early PVE from NIE and define them as IE occurring within the first year after valve replacement and thought to be acquired in the operating room or during the perioperative period.

Epidemiology

Nosocomial infective endocarditis has been considered to be a rather infrequent hospital-acquired infection representing 0.1% of nosocomial infections. It is encountered as a rare entity in critically ill patients. However, the exact incidence of NIE in ICU settings is not well known. In the only existing study of NIE in the ICU, NIE was identified in 0.8% of patients admitted to a medical ICU. Approximately 7.5% to 29% of all cases of IE seen in tertiary hospitals have been nosocomially acquired, compared to 14% to 25% in community hospitals. Over the past few decades, there has been a worldwide increase in the number of cases of NIE. Fernandez-Guerrero et al. found that NIE accounted for 9.3% of all episodes of IE diagnosed over a 15-year period (1978–1992) in a tertiary-care hospital with a ten-fold increase in the number of cases of NIE in comparison to the historical control cases of IE treated at the same hospital from 1960 to 1975. This increase in the incidence of NIE is attributed to various reasons including the widespread use of invasive procedures, the growing population of elderly patients with degenerative valvular heart disease and/or prosthetic valves, and the improvement in the diagnosis of IE with new diagnostic schema (the Duke criteria).

Patient characteristics

Overall, more than 60% of patients with NIE are male and they are often elderly. Approximately two thirds of the patients are over the age of 60 years. Their mean age (55 ± 3.2 years to 65 ± 9 years) is also greater than that of patients with community-acquired infective endocarditis (only 21–29.5% of the latter are >60 years with a mean age of 47.8 ± 1.5 years).

Source of infection

Most cases of NIE are secondary to device-related bacteremia. Central venous catheters account for an estimated 90% of all catheter-related bloodstream infections. Therefore, the most common source of infection resulting in NIE is an intravascular catheter or another intravascular device, being implicated in 45.5–56.5% of episodes of NIE. Cases of catheter-related NIE (CR-NIE) have been associated with all kinds of intravascular devices; 9.1–48% of episodes of CR-NIE were associated with central venous catheters, 6–22.7% with peripheral venous catheters, 2–9% with central arterial catheters (pulmonary artery catheters) and a substantially lower incidence with peripheral arterial catheters and hemodialysis catheters. The duration of catheterization was a major risk factor for CR-NIE. In all cases of CR-NIE reported by Fernandez-Guerrero et al., the implicated catheters had been in place for >78 hours (5–10 days in 68% of cases). Other sources of infections resulting in NIE have been: surgical wounds; surgical procedures or instrumentation of the genitourinary tract, heart, gastrointestinal or tracheal tract; and skin and soft tissue lesions. The portal of entry could not be identified in 0–17% of cases of NIE.

Microbiology

The most frequently isolated pathogens in NIE are staphylococci (77.4%), both S. aureus and coagulase-negative staphylococci. In more recent reports, the organism causing NIE has been predominantly S. aureus, being responsible for 52–57% of cases. The link between intravascular catheters and nosocomial S. aureus endocarditis is well known and has been emphasized. Ninety-one
 percent of nosocomial S. aureus endocarditis is associated with an intravascular device as the most probable portal of entry.6—10,11 Although not all patients with intravascular device-associated S. aureus bloodstream infections develop endocarditis, the risk of developing this complication in such patients is marked. In 1997, a prospective study of patients with S. aureus bloodstream infections by Fowler et al. reported that 16 (23%) of 69 patients with intravascular catheter-associated bloodstream infections had endocarditis.22 The identification of catheter-related S. aureus bacteremia has significant clinical implications. Recently, Rosen et al. recommended the use of TEE for all patients with clinically uncomplicated (i.e. no clinical evidence of endocarditis) catheter-related S. aureus bacteremia, to determine the duration of antibiotic therapy. Considering the overall cost, he reported that the use of TEE was cost effective in determining the choice between two or four weeks’ empirical antibiotic treatment.23

The second most common pathogen implicated in NIE is Enterococcus spp, causing 5—30% of cases.8,9,20 Entercoccal endocarditis frequently originates from the genitourinary tract, which is suspected to be the source of infection in 14—70% of cases of NIE.24 Recent reports have documented a steady increase in the incidence of nosocomial enterococcal bloodstream infections.25—27 However, enterococcal endocarditis develops in a minority of patients with enterococcal bacteremia. Elderly patients and those with underlying vascular disease seem to be at higher risk. Particularly alarming are cases of NIE caused by strains of Enterococcus faecalis highly resistant to aminoglycosides,24 or by multiresistant Enterococcus faecium.14,29,30

Fungal IE is a rare infection representing <10% of IE cases.31 However, Gilmore and Fenelon observed an increase in the incidence of fungal endocarditis in the last decade.22 Candida spp, (both C. albicans and non-albicans Candida), are the most common pathogens involved in fungal NIE, followed by Aspergillus spp. Predisposing factors for fungal endocarditis include prolonged antibiotic therapy, immunosuppressive therapy, central venous catheters (mainly for total parenteral nutrition), pacemaker implantation, disseminated fungal infection, previous cardiac surgery, prior or concomitant bacterial endocarditis, and prosthetic heart valves. Whenever Aspergillus spp, Histoplasma spp, and Mucor spp are implicated, they rarely grow on routine fungal isolator media. Case 3 is a typical presentation. A kidney transplant recipient receiving immunosuppressive therapy (cyclosporin and prednisone) diagnosed initially with culture-negative endocarditis, however the histopathology and the culture confirmed Aspergillus to be the causative pathogen. Thus, fungal infection should be considered in critically ill immunocompromized patients with culture-negative NIE.

Although Gram-negative bacteremia is common in the hospital setting, Gram-negative bacilli are infrequently involved in NIE, most likely because of their decreased capability to adhere to heart valves.22 Pseudomonas aeruginosa is the most frequent Gram-negative organism implicated in NIE. Patients on hemodialysis are at higher risk of developing Pseudomonas IE.

In a much earlier study, culture-negative IE accounted for 5% of cases.32 Culture-negative NIE was attributed to prior administration of antimicrobials, before blood cultures were drawn, especially in patients who had been hospitalized for prolonged periods. In certain cases of fungal NIE, such as Curvularia spp, Pencillium spp, and Phycomyces spp, blood cultures were always negative. The risk of fungal IE is increased in solid organ transplant recipients. Paterson et al. found that fungal infections were responsible for 28% of the 46 cases of IE in solid organ transplant recipients.11

Risk factors and cardiac involvement

Patients with predisposing heart conditions, such as degenerative valvular disease, rheumatic valvulopathy, prosthetic valves, and previous endocarditis, are at high risk of developing NIE. Immunosuppressed patients appear to be at especially high risk. Forty percent of patients with NIE had no known preexisting valvular disease. The predomiance of left-sided NIE (mitral and aortic valves) is attributed to the dominance of underlying valvar lesions, as well as preexisting prosthetic cardiac valves in the left side of the heart. Right-sided infections, mainly tricuspid valve NIE, are rare and occur mostly in patients whose endocarditis is associated with an intravascular device such as pacemaker or intravascular catheter.

Clinical features and diagnosis

In general, symptoms found at presentation in patients with NIE are similar to those noted in patients with community-acquired infective endocarditis (CIE). The most common clinical manifestations are: fever, hypotension, new/changing cardiac murmurs, chills, congestive heart failure with pulmonary edema, tachycardia, and renal failure.

The clinical diagnosis of IE is surprisingly difficult. This is due both to the inaccessibility of intra-cardiac vegetations and to the highly variable and sometimes non-specific nature of the clinical
manifestations leading to a wide differential diagnosis. History, physical examination and laboratory findings are important. In critically ill patients hospitalized in the ICU, diagnosing NIE can be even more difficult. The classical manifestations of endocarditis are not usually seen in critically ill patients. Central nervous system signs of endocarditis are often blunted due to sedation. Fever and bacteremia are frequently attributed to other possible co-existing hospital-acquired infections. Finally, acute renal failure is common in ICU patients and attributed to different mechanisms.

Echocardiographic diagnosis

Echocardiography is recognized as the method of choice for the non-invasive identification of valvular vegetations in patients with IE. It also gives valuable information on associated complications, such as abscesses or perforations, as well as on cardiac function. Echocardiographic detection of valvular vegetation and/or an associated complication in patients with active IE not only confirms the diagnosis but also guides the timely institution of appropriate therapy, including the need for surgical intervention, and helps in determining prognosis.

In the diagnosis of IE and its complications, transesophageal echocardiography (TEE) is much more sensitive than transthoracic echocardiography (TTE) and has increased diagnostic accuracy. Although this is, in general, well known, it is probably more evident in ICU patients. The use of TTE is often limited in ICU patients for many reasons, including mechanical ventilation, chest wall edema, subcutaneous emphysema, and dressings. TEE has been recommended in all patients with intravascular device-associated S. aureus bloodstream infections.

Outcome

Remarkable progress has been made in the management of NIE during the last few decades, leading to a decrease in the mortality rate from 82% in the 1960s to between 40.9—56.5% in the 1990s. The mortality rate is higher in more elderly patients compared with younger (50% vs. 25%), in S. aureus and fungal IE, and in NIE compared with CIE (40.9—56.5% vs. 18—26.5%). Although it is well known that the outcome of patients with NIE is poor, it is difficult to make accurate estimates of mortality in the subgroup of critically ill patients with NIE. Gouello et al. reported an overall mortality of 68%, and death was directly associated with NIE in 36% of cases.

Surgical management is more frequently indicated in critically ill patients with NIE than in other patients with IE, and the majority of ICU patients with NIE meet indications for cardiac surgery. However, most of these patients are in poor general condition, at high risk for major operations and therefore considered unfit for cardiac surgery. Consequently, surgery can be undertaken only in a few, selected patients. In the series of Gouello, of the 16 cases with surgical indications, only five patients underwent surgery, and 11 did not as they were unfit. The mortality rate was higher in the group of patients in whom cardiac surgery was indicated but could not be operated on because of poor general conditions, than the group of patients who underwent surgery (nine out of 11 vs. two out of five).

In fact, this difference in mortality could be easily explained by the more serious illnesses and poorer condition of patients who were not candidates for cardiac surgery. Although surgery is promising, the benefit is difficult to evaluate and timing is unclear.

NIE in special populations

Solid organ transplant recipients, because of multiple invasive procedures, prolonged hospitalization and immunosuppressive therapy, are at high risk of developing infectious complications such as bacteremia and, uncommonly, IE. Paterson et al. found a prevalence of IE of 1.7% in a cohort of liver transplant recipients. They quoted a study that reported a prevalence of IE of 6% among heart transplant recipients. Although previously reported cases in kidney transplant recipients are relatively numerous, they found no data from which the prevalence of endocarditis could be calculated among these patients.

Solid organ transplant recipients with IE vary from other patients with IE in many aspects. Their mean age is lower (46 years; range 12—67 years). Most patients have no history of valvular disease or abnormality. The majority of cases are nosocomially-acquired (74% NIE vs. 26% CIE). The spectrum of causative organisms is evidently different: bacterial in 71% and fungal in 28%. Staphylococcus aureus and Aspergillus fumigatus are the most common organisms, being responsible for about 50% of cases (31% and 18% respectively). Finally, among these patients the mortality rate is high (64%).

NIE is an uncommon but grave complication following major burn injury. Burn wound manipulation is the most likely source of bacteremia and consequently NIE. Staphylococcus aureus and Gram-negative bacilli are the most frequently implicated organisms. Presentation is characteristi-
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The incidence of nosocomial infective endocarditis (NIE) in critically ill patients is reported to be high, with persistent fever and positive blood cultures as common features. The diagnosis of NIE in critically ill patients can be challenging due to the multiple confounding symptoms and signs that may mimic other critical conditions such as intra-abdominal abscess, pneumonia, and other septic conditions. Patients with NIE often present with high clinical suspicion but limited diagnostic tests, such as negative blood cultures, and the clinical picture may be as well as the management. Underlying immunosuppression appears to predispose to this infection. Unusual organisms such as Aspergillus spp, although rare, can be responsible and should be considered in critically ill patients with high clinical suspicion of NIE but with negative blood cultures. More importantly, the prior administration of antimicrobials before blood cultures are drawn is a more likely etiology of culture-negative endocarditis in the critical case. Although the majority of critically ill patients with NIE meet indications for surgery, many of them are considered too ill and unsuitable for cardiac surgery. But patients who undergo surgical intervention appear to have a better outcome. Finally, because of its high mortality, prevention needs to be emphasized; patients at risk should be identified and measures for prophylaxis and care of intravascular devices and other invasive procedures must be implemented. Confident interest: No conflicting interest declared.

Conclusion

In summary, NIE in critically ill patients represents an unique entity. Considering its rare occurrence and the multiple confounding symptoms and signs in this group of patients, the diagnosis can be difficult, delayed, or even missed. NIE in critically ill patients has serious consequences leading to multi-organ failure, which can further complicate the clinical picture as well as the management. Underlying immunosuppression appears to predispose to this infection. Unusual organisms such as Aspergillus spp, although rare, can be responsible and should be considered in critically ill patients with high clinical suspicion of NIE but with negative blood cultures. More importantly, the prior administration of antimicrobials before blood cultures are drawn is a more likely etiology of culture-negative endocarditis in the critical case. Although the majority of critically ill patients with NIE meet indications for surgery, many of them are considered too ill and unsuitable for cardiac surgery. But patients who undergo surgical intervention appear to have a better outcome. Finally, because of its high mortality, prevention needs to be emphasized; patients at risk should be identified and measures for prophylaxis and care of intravascular devices and other invasive procedures must be implemented. Conflict of interest: No conflicting interest declared.

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