# Nosocomial Infections in Neurocritical Care

*Rafael Ortiz, MD, and Kiwon Lee, MD*

**Corresponding author**
Kiwon Lee, MD
Department of Neurology, Thomas Jefferson University,
900 Walnut Street, Philadelphia, PA 19107, USA.
E-mail: kiwon.lee@jefferson.edu

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Development of nosocomial infections is a commonly encountered problem for critically ill patients. Approximately half of all nosocomial pneumonias in the neurointensive care unit (NICU) are associated with ventilator-associated pneumonia. Prompt diagnosis with appropriate specimen analysis is required in order to prevent increased morbidity. Catheter-related blood stream infection imposes financial as well as medical implications. Multifaceted interventions are helpful to ensure adherence with evidence-based infection control guidelines. Urosepsis occurs in approximately 16% of patients. Colonized patients without evidence of infection do not require treatment, but the indwelling catheter should be changed. NICU patients have increased risk of developing cerebrospinal fluid infection due to frequent placement of external ventricular drains. The incidence of ventriculostomy-related meningitis or ventriculitis is approximately 8%. It is unclear whether the duration of ventricular catheter has any relationship with the risk of infection. Patients often receive multiple antibiotics, leading to an increased risk of developing *Clostridium difficile* colitis, which needs prompt diagnosis and appropriate antimicrobial therapy.

## Introduction

Patients who are admitted to the neurointensive care unit (NICU) are at increased risk of developing infections. There are numerous catheters and indwelling drains and tubes that predispose acutely ill patients to often inevitable nosocomial infections while staying in the unit. Acquired infections can be caused by either endogenous organisms that are part of the patient's own normal flora, or exogenous organisms transmitted from the hospital [1]. Despite infection control effort, spread of infection often originates from the hands of caring hospital staff. Not uncommonly, the normal colonized flora may become virulent pathogens. The pharyngeal flora often includes enteric organisms, and fecal and skin flora also may transform themselves into drug-resistant hospital-acquired strains [2]. Patients with acute head trauma have defects in the cellular arm of the immune system that further increase the risk of nosocomial infections, including deficiencies in neutrophil superoxide release, immunoglobulin production, and T-cell function [1,3]. The use of corticosteroids to treat patients with acute brain injury may also increase the risk of infection [4]; therefore, the use of steroids should be avoided for patients with cytotoxic brain edema (eg, ischemic stroke and intraparenchymal hemorrhage).

## Respiratory Infection

A significant number of patients with acute brain injury require endotracheal intubation and mechanical ventilation support for airway protection. Approximately half of all nosocomial pneumonias are associated with mechanical ventilation, a condition known as ventilator-associated pneumonia (VAP) [1,5]. Between 10% and 20% of patients who are mechanically ventilated for more than 48 hours will develop VAP [6]. The risk of developing VAP is about 1% to 3% per day in intubated patients [1,7]. Critically ill patients who develop VAP are twice as likely to die as those who do not. VAP prolongs ICU length of stay by over 6 days, and patients who develop VAP incur over $10,000 in additional health care expenses, not including cost of physician charges [6,8].

### Microbiology

Although gram-negative pathogens have been traditionally implicated in VAP, several surveys suggest that *Staphylococcus aureus* is now as common a pathogen as *Pseudomonas aeruginosa* [9,10]. Given the fact that more than 50% to 70% of *S. aureus* are methicillin-resistant (MRSA), as many as 10% to 12% of all cases of nosocomial pneumonia may be due to MRSA [8]. Antimicrobial resistance remains a major problem with gram-negative infections as well. It has been reported that approximately 15% percent of *P. aeruginosa* are

now resistant to carbepenems such as imipenem and meropenem, both of which are very broad-spectrum antimicrobials [11]. A central tenet in care remains the collection of local antibiotic resistance data so one can make appropriate initial selections when choosing which agents to employ for therapy. Considering the high prevalence of the problems, appropriate prevention of VAP should be of paramount importance in ICU management. Basic methods of prevention may include hand hygiene, avoidance of endotracheal intubation with use of noninvasive ventilation when appropriate [12,13], limiting the use of sedatives [14], early extubation as soon as possible without delays, appropriate patient positioning in bed [15,16], and avoidance of unnecessary packed erythrocyte transfusion [17].

**Diagnosis**

When establishing a diagnosis, it is important to consider the following questions. 1) Does the patient have pneumonia? 2) If the patient has pneumonia, what is the responsible pathogen? [18]. The new guidelines recommend a chest radiograph, an assessment of oxygenation, blood cultures, and sampling of the lower respiratory tract as part of the initial evaluation. The gold standard for establishing the diagnosis requires quantitative cultures of deep specimens obtained by bronchoalveolar lavage or bronchoscopy-protected brush specimens [5]. Given the widespread use of broad-spectrum empiric antibiotic treatment, the utility of invasive diagnostic testing of this type in routine clinical practice remains controversial [1].

**Treatment**

A balance needs to be established between the initial need to use broad antibiotic coverage to ensure that the culprit pathogen is treated, and the recognition that prolonged use of broad-spectrum agents promotes antimicrobial resistance [8,19]. In general, early infections (less than 3 days) require coverage for *S. aureus*, *Haemohphilus influenzae*, *Streptococcus pneumoniae*, and nonpseudomonal gram-negative rods with intravenous B-lactam (cefotaxime, ceftriaxone) plus either intravenous macrolide (azithromycin) or intravenous fluoroquinolone. Patients with late infections require double coverage for resistant *Pseudomonas* or *Acinetobacter* with selected intravenous antipseudomonal B-lactam (cefepime, imipenem, meropenem, piperacillin/tazobactam) plus intravenous antipseudomonal quinolone (ciprofloxacin), and treatment with vancomycin for MRSA. Vancomycin is administered by weight-based dosing (at 15 mg/kg every 12 hours), and the trough levels should be maintained at 15 to 20 g/mL [8,18]. Linezolid is an alternative treatment for MRSA [20,21]. Multiple studies have revealed that inappropriate initial therapy independently increases the risk for mortality in VAP between three and sevenfold [8,22]. Treatment can be modified, if necessary, after the results of cultures and sensitivities become available [1]. A French multicenter study of 197 patients who were randomized to either 8 or 15 days of treatment for bronchoscopically confirmed VAP concluded that the longer antibiotic course was not better in terms of mortality, relapse, superimposed infection, or length of stay, and only resulted in fewer antibiotic-free days as well as increased recurrent infections with antibiotic-resistant organisms. However, there was an increase in recurrences of nonfermenting gram-negative rod infections (eg, *P. aeruginosa*) in patients who received only 8 days of therapy [23•]. The duration of treatment with an effective agent should range from 7 to 14 days depending on the circumstances [1].

## Bloodstream Infection

Every patient in an ICU has intravenous catheters for administration of medications and fluids and for blood draws. In most cases, a central venous catheter (CVC) is inserted in either the subclavian, femoral, or internal jugular veins. Catheter-related bloodstream infections (CR-BSIs) are associated with significant morbidity, mortality, and costs. Assuming an average CR-BSI rate of 5.3 per 1000 catheter-days and an attributable mortality of 18, as many as 28,000 ICU patients die of CR-BSIs annually in the United States [24•,25–27].

**Microbiology**

Bacteremia can result from infection anywhere in the body, but is most often associated with infection arising from an intravenous or intra-arterial catheter [1]. The organisms most frequently involved in CR-BSI include *S. epidermis* (37%), *S. aureus* (13%), *Enterococcus* (13%), *Klebsiella-Enterobacter* (11%), *Candida* spp. (8%), and *Serratia* (5%) [1].

Routing replacement of CVCs every 3 days did not prevent BSI in a prospective study of 160 patients. Exchange over a guidewire was associated with an increased risk of infection [28]. A consensus statement found that although subclavian CVCs have a slightly lower risk of infection than femoral or internal jugular lines, this risk is offset by an increased risk of mechanical complications such as pneumothorax [1].

Several of the actions that must be implemented by the health care professionals taking care of patients with CVCs include hand washing; sterilization of procedure site; draping patient in sterile fashion; use of hat, mask, and sterile gown; use of sterile gloves; and application of sterile dressings. Multifaceted interventions that helped to ensure adherence with evidence-based infection control guidelines nearly eliminated CR-BSIs in a prospective observation in a surgical ICU [24•].

**Diagnosis**

The diagnosis of CR-BSI is made after two sets of blood cultures are obtained from the catheter and a distant venous puncture site. Positive blood and catheter

tip cultures in the appropriate clinical setting of unexplained fever in a patient with an intravascular catheter in place for more than 48 hours are required for diagnosis. Once the diagnosis is made, and/or if signs of sepsis, purulence, and erythema are seen, the catheter should be removed.

**Treatment**
The preferred regimen for empiric coverage is ceftazidime, 2 g every 8 hours and vancomycin, 1 g every 12 hours. Further treatment is dictated by the results of the blood cultures. In cases of septic shock, double coverage with an agent with antipseudomonal activity should be started [1].

## Urinary Tract Infection

Most patients who are hospitalized in ICUs receive an indwelling urinary catheter to monitor urinary output. The incidence of urosepsis, which is defined as an inflammation of the upper urinary tract that causes sepsis and bacteremia, occurs in approximately 16% of the ICU patient population [29,30].

**Microbiology**
The insertion of a catheter allows organisms to gain access to the bladder. The catheter induces an inflammation of the urethra, allowing bacteria to ascend into the bladder in the space between the urethral mucosa and the catheter. This route of infection is predominant in women because of the short urethra and the contamination with the anal flora. Intraluminal contamination is less frequent and is related to reflux of pathogens from the drainage system into the bladder [29]. The isolated pathogens among ICU patients with bacteriuria are essentially *Escherichia coli* (39%), *P. aeruginosa* (22%), *Enterococcus* spp. (15%), *Actinobacter acinus* (11%), *Klebsiella* spp. (11%), and *Proteus* spp. (11%) [31].

The longer the catheter is left in place, the higher the rate of infection. Even if the catheter is maintained as an absolutely closed system, the rate of development of significant bacteriuria inevitably seems to be about 3% to 5% per day. After 10 days, nearly 50% of all catheterized patients have acquired significant bacteriuria [1,32]. There are no effective means for preventing nosocomial urinary infections other than removing the catheter as soon as possible.

**Diagnosis**
Routine daily monitoring of the urine from all catheterized patients is not an efficient way to decrease the incidence of symptomatic bacteriuria [33]. Leukocyte esterase activity is an indicator of pyuria, and urinary nitrite production an indicator of bacteriuria. Because asymptomatic bacterial colonization is extremely common, treatment generally should be reserved for patients with pyuria (> 10 cells/$mm^3$) and fever, or leukocytosis [1].

**Treatment**
Asymptomatic bacteriuria does not require treatment [29,34]. Uncomplicated urinary infections diagnosed early in the ICU stay can be treated with trimethoprim/sulfamethoxazole, 160/800 mg or ciprofloxacin, 100 mg twice a day for 3 to 7 days. In the event of severe sepsis, third-generation cephalosporins are the most widely recommended antibiotics, but the spectrum must be narrowed as soon as possible. The duration of treatment, usually 14 days, has not been validated as a standard duration for ICU patients, and seriously ill patients may require more than one antibiotic therapy [29,35].

Candiduria represents from 3% to 15% of catheter-associated urinary infections in the ICU [31,36]. *Candida albicans* and *C. glabrata* are found in 46% and 31% of cases, respectively [37]. Colonized patients without evidence of infection do not require treatment, but the indwelling catheter should be changed or removed. Parenteral fluconazole for 14 days is the best option for treating a candiduria due to *C. albicans*, and voriconazole may be more effective against non–*C. albicans* species [38]. There are data indicating that bladder irrigation of critically ill patients does not confer a survival advantage [29].

## Ventricular Catheterization–related Infection

The main drawback in the use of ventricular catheters used for intracranial pressure monitoring and cerebrospinal fluid (CSF) drainage is the risk of ventriculitis and meningitis. Proposed risk factors for increasing the rate of infection include prolonged duration of ventricular catheter use, underlying diagnosis consistent with severe brain injury, concurrent infection in other body system, neurosurgical interventions and operations, cerebrospinal fluid leakage, catheter exchange, and technique of catheter placement [39–43]. The incidence of ventriculostomy-related meningitis or ventriculitis is approximately 8% [1,42]. A randomized control trial found no significant effect on the infection rate with routine catheter changes after 5 days of use [44]. A recent retrospective study concluded that the relationship between duration of catheterization and infection was not linear [39]. There was an extremely low daily infection rate that was present over the initial 4 days, but the rate of infection then remained relatively constant even with prolonged catheter use. To date, it is unclear whether the duration of ventricular catheter has any meaningful relationship with the risk of infection.

**Microbiology**
Infection results from direct spread of skin flora along the catheter tract or via direct inoculation when the system is flushed or irrigated with a contaminated syringe. Gram-positive cocci consistent with skin flora comprise the majority of the microorganisms cultured from cerebrospinal fluid (*S. epidermidis*, *P. acnes*, *S. aureus*) [1,39].

**Table 1. Nosocomial infections in the neurointensive care unit**

| | Pathogen | Empiric treatment |
|---|---|---|
| Respiratory infection | | |
| Early (< 3 d) | *Staphylococcus aureus*, *Haemophilus influenza*, *Streptoccocus pneumoniae*, gram-negative rods | Intravenous B-lactam (cefotaxime, ceftriaxone) plus intravenous macrolide (azithromycin) or intravenous fluoroquinolone |
| Late | *Pseudomonas*, *Acetinobacter*, methicillin-resistant *S. aureus* | Intravenous antipseudomonal B-lactam (cefepime, imipenem, meropenem, piperacillin/tazobactam) plus intravenous antipseudomonal quinolone (ciprofloxacin) and vancomycin |
| Bloodstream infection | *S. epidermidis*, *S. aureus*, *Enterococcus*, *Klebsiella-Enterobacter*, *Candida*, *Serratia* | Ceftazidime and vancomycin |
| Urinary tract infection | *Escherichia coli*, *Pseudomonas aeruginosa*, *Enterococcus*, *Actinobacter*, *Klebsiella*, *Proteus* | Uncomplicated infections treated with trimethoprim/sulfamethoxazole or ciprofloxacin; severe sepsis treated with third-generation cephalosporins |
| | *C. albicans* | Fluconazole |
| | *C. glabrata* | Voriconazole |
| Ventricular drainage infection | *S. epidermidis*, *P. acnes*, *S. aureus* | Ceftazidime and vancomycin |
| Gastrointestinal infection | *Clostridium difficile* | Oral metronidazole |

Although several series have demonstrated significant benefit from the use of prophylactic antibiotics [45,46], this finding has not been duplicated in other studies.

**Diagnosis**

The diagnosis is based on the presence of systemic signs of infection (fever and plasma leukocytosis) or deterioration in the level of consciousness, in conjunction with positive CSF aerobic and anaeorobic cultures and increased CSF leukocyte cell counts. Many NICU patients have a baseline central nervous system inflammation with abnormal CSF (increased leukocytes, increased protein). In these cases, it would be useful to follow the trend of the CSF leukocyte count to the erythrocyte count ratio as well as the trend of the absolute leukocyte number while final culture results are pending. In subarachnoid hemorrhage patients, however, the ratio often varies each day, and the rise in the absolute CSF leukocyte count may not necessarily indicate an active CSF infection.

**Treatment**

The preferred regimen for empiric coverage includes intravenous ceftazidime, 2 g every 8 hours and vancomycin, 1 g every 12 hours. This regimen should be adjusted after the final CSF culture results are obtained. The infected ventricular catheter should be removed. Because penetration of the blood-brain-barrier by vancomycin is not always effective, an adjunctive treatment option includes the use of intrathecal vancomycin and aminoglycosides. Treatment should be instituted for at least 14 days. Theoretically, antibiotic-impregnated catheters may further reduce the risk of infection, but this has not been validated in a large series.

## Nosocomial Gastrointestinal Infection

Nosocomial gastroenteritis usually presents with diarrhea and fever. More severe cases are associated with plasma leukocytosis and abdominal tenderness.

**Microbiology**

Treatment with antibiotics is the main risk factor for *Clostridium difficile* colitis, although it can also be transmitted from patient to patient by health care personnel. Second- and third-generation cephalosporins and clindamycin are the most common antibiotics prescribed for nosocomial gastrointestinal infection prior to the advent of *C. difficile* [1,47].

**Diagnosis**

The detection of *C. difficile* toxins in the stool can be made by a laboratory test (cytotoxicity assay) where the toxins can be easily observed by microscopic examination. The *C. difficile* cytotoxin assay may be positive in only 30% to 60% of the cases confirmed by colonoscopy, which may reveal mucosal inflammatory changes and pseudomembranous lesions.

**Treatment**

Empiric treatment with metronidazole, 500 mg orally every 6 hours for 10 days is indicated when there is any clinical suspicion. Vancomycin, 250 mg orally every 6 hours is usually reserved for resistant infections [1].

## Conclusions

Nosocomial infections in the NICU are serious problems that may prolong length of stay and worsen patients'

outcome. Health care providers should be aware of the common ICU pathogens and be able to provide appropriate and prompt treatment. Table 1 summarizes the most common pathogens observed in a NICU, along with treatments. Basic rules of hand washing and sterile precautions should be followed as well in order to avoid the infection and improve the quality of patient care. It is important to initiate broad-spectrum antibiotic coverage for patients with a clinically suspected nosocomial infection in the ICU, keeping in mind that a regimen of "de-escalation" should be instituted as soon as the final culture results are available in order to prevent antimicrobial resistance.

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