



## TECHNICAL REPORT

# Epidemiology and Diagnosis of Health Care–Associated Infections in the NICU

## abstract

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Health care–associated infections in the NICU are a major clinical problem resulting in increased morbidity and mortality, prolonged length of hospital stays, and increased medical costs. Neonates are at high risk for health care–associated infections because of impaired host defense mechanisms, limited amounts of protective endogenous flora on skin and mucosal surfaces at time of birth, reduced barrier function of neonatal skin, the use of invasive procedures and devices, and frequent exposure to broad-spectrum antibiotics. This statement will review the epidemiology and diagnosis of health care–associated infections in newborn infants. *Pediatrics* 2012;129:e1104–e1109

## INTRODUCTION

Health care–associated infections are infections acquired in the hospital while receiving treatment of other conditions. They are common occurrences in patients of all ages and are estimated to result in 2 million infections, 90 000 deaths, and \$28 to \$45 billion in excess health care costs annually.<sup>1,2</sup> In the Pediatric Prevention Network national point prevalence survey, 11.2% of NICU patients had a health care–associated infection on the day of the survey.<sup>3</sup> Although there are no recent estimates of the cost of health care–associated infections in the NICU, Payne et al<sup>4</sup> estimated that health care–associated bloodstream infections added almost \$100 million to the cost of treating infants with birth weights from 500 to 1499 g in 1999 dollars. Because this finding represented the excess costs associated with only one type of infection in one gestational age cohort, it provides just a glimpse of the financial impact of health care–associated infections in the NICU. This financial estimate does not include the potential morbidity and mortality concerns for the infant and the effect that the prolonged hospital stay has on the family and resource utilization within the hospital. Reducing health care–associated infections in the NICU would have benefits to infants, families, and the health care delivery system. The purpose of this technical report was to review the epidemiology and diagnosis of health care–associated infections in the NICU. A companion policy statement addresses strategies for the prevention of health care–associated infections.

## EPIDEMIOLOGY

Newborn infants hospitalized in a NICU have host factors that not only make them more vulnerable to acquisition of health care–associated

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### KEY WORDS

antibiotics, health care–associated infection, neonate, newborn, NICU, nosocomial infection

### ABBREVIATIONS

CDC—Centers for Disease Control and Prevention

CPAP—continuous positive airway pressure

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The guidance in this report does not indicate an exclusive course of treatment or serve as a standard of medical care. Variations, taking into account individual circumstances, may be appropriate.

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infections but also increase their risk of developing more serious illnesses. Whether an infant is born preterm or at term, many components of their innate and adaptive immune systems exhibit diminished function when compared with older children and adults. Infants with birth weights less than 1500 g (very low birth weight) have rates of health care–associated infections 3 times higher than those who weigh greater than 1500 g at birth. However, the increased susceptibility to infection in infants of very low birth weight is multifactorial and related to both the developmental deficiencies in the innate and adaptive immune systems and a greater likelihood of a critical illness requiring invasive monitoring and procedures. Furthermore, the immunologic deficiencies can be exacerbated by the critical nature of many of the illnesses affecting newborn infants.<sup>5</sup>

Colonization of mucous membranes and the skin occurs rapidly after birth. Newborn infants delivered vaginally are colonized with maternal bacteria acquired from the birth canal. In most instances, those organisms do not cause invasive disease; however, in critically ill newborn infants, this colonization can potentially lead to systemic infection when skin or mucosal surfaces are compromised. The stratum corneum of the skin is poorly developed before 26 weeks' gestation, and ill neonates are at increased risk of developing skin and mucosal injury (eg, by suctioning or invasive procedures), allowing invasive bacteria access to deeper tissues or vascular spaces. Furthermore, mucosal surfaces and skin of infants in the NICU are more likely to be colonized with Gram-negative enteric rods, staphylococci, enterococci, and *Candida* species. NICU-acquired microbes are more likely to be pathogenic and resistant because of frequent exposure of hospitalized infants to antibiotic agents.

Data describing the epidemiology and incidence of health care–associated infections in NICUs can be obtained from 4 sources: (1) the National Health-care Safety Network (previously known as the National Nosocomial Infections Surveillance system) at the Centers for Disease Control and Prevention (CDC); (2) the Pediatric Prevention Network at the National Association of Children's Hospitals and Related Institutions; (3) the Vermont Oxford Network; and (4) the National Institute for Child Health and Human Development Neonatal Research Network.

In addition to preterm birth,<sup>6,7</sup> risk factors associated with an increased rate of health care–associated infections include the presence of invasive devices (intravascular catheters, endotracheal tubes, orogastric tubes, urinary catheters, and drains), exposure to broad-spectrum antibiotic agents, parenteral nutrition,<sup>8</sup> overcrowding and poor staffing ratios, administration of steroids and histamine<sub>2</sub>-receptor antagonists, and acuity of underlying illness. Furthermore, the lower the birth weight, the more invasive technology is used.<sup>6,7</sup>

Parenteral nutrition is commonly administered to the sickest infants through central venous catheters or peripherally inserted central catheters. The relationship between central line use and increased risk of infection has been demonstrated in multiple studies<sup>9–11</sup>; administration of lipids may be an independent risk factor for bacterial or fungal sepsis.<sup>10</sup>

The most common type of health care–associated infection within the NICU is a catheter-associated bloodstream infection.<sup>3</sup> Within the first 30 days after birth, coagulase-negative *Staphylococcus* species, *Staphylococcus aureus*, *Enterococcus* species, and Gram-negative enteric bacteria are the most common etiologic agents. After 30 days of age, coagulase-negative *Staphylococcus* species remain the most common

pathogens; however, fungi, particularly *Candida* species and *Malassezia furfur*, have been noted with increasing frequency.<sup>3</sup> Central-line–related infections are, in large part, a result of problems with poor technique at the time of placement and ongoing care of the catheter site. Data suggest that the hub is a common source of contamination and subsequent infection.<sup>12</sup> Not surprisingly, the occurrence of catheter-associated bloodstream infections is highly related to the duration of catheter use and the number of times the catheter or hub is entered or opened.

Health care–associated lower respiratory tract infections and ventilator-associated pneumonia are of extreme importance for hospitalized infants because of their frequency and potential severity. Health care–associated pneumonia represents 6.8% to 32.3% of health care–associated infections in the NICU and is the second most frequent hospital-acquired infection in critically ill neonates.<sup>7,13,14</sup> The most recent National Healthcare Safety Network data indicate a pooled mean rate of ventilator-associated pneumonia from 0.7 to 2.2 per 1000 ventilator days.<sup>7</sup> However, rates varied among NICUs, with 90% of NICUs reporting rates between 2.1 and 7.3 per 1000 ventilator days. Variations in incidence likely reflect, in part, difficulty in making this diagnosis in infants with chronic lung disease. As with most health care–associated infections, birth weight and gestational age correlate inversely with the incidence of ventilator-associated pneumonia. Many of the risk factors for the development of health care–associated pneumonia in NICU patients are similar to those previously identified in adult patients, such as prolonged duration of mechanical ventilation, severe underlying cardiopulmonary disease, prolonged intravenous alimentation, and previous thoracoabdominal surgery.

Most bacterial health care–associated lower respiratory tract infections occur by aspiration of bacteria that colonize the oropharynx or the upper gastrointestinal tract. On rare occasions, health care–associated pneumonias may result from contiguous spread or a primary infection at a distant site. Under normal circumstances, the filtration system of the upper airway and the mucociliary clearance system of the large airways protect the lower respiratory tract from bacteria that may be present in the patient's environment or that reside in the upper respiratory tract. Endotracheal tubes bypass these initial host barrier defense mechanisms, providing direct access of bacteria and other pathogens to the lower respiratory tract. Uncuffed endotracheal tubes provide even easier access of microorganisms to the lower respiratory tract.<sup>15–17</sup> The aspiration of contaminated materials may be obvious or, more commonly, may be subclinical.<sup>15–18</sup> By using pepsin as a marker for aspiration, microaspiration has been detected in up to 92.8% of ventilated neonates.<sup>18,19</sup> Methylxanthines and bronchopulmonary dysplasia increase the frequency of microaspiration. Microaspiration is also more frequent in infants with severe bronchopulmonary dysplasia compared with those with moderate bronchopulmonary dysplasia.<sup>18,19</sup> Neonates who have either impaired swallowing mechanisms or anatomic abnormalities that prevent adequate protection of their airway are also at increased risk of aspiration.<sup>15,16,20</sup>

Dense bacterial polysaccharide biofilm can coat the endotracheal tubes, and polymicrobial flora become embedded into this film. Endotracheal suctioning can dislodge these aggregates of bacteria, providing a large bacterial inoculum directly into lower airways. Nasal continuous positive airway pressure (CPAP) does not bypass many of

the protective barriers, does not require endotracheal suctioning, and reduces mechanical disruption of respiratory mucosa. This likely explains the lower risk of health care–associated pneumonia in neonates using nasal CPAP versus those treated with endotracheal intubation (1.8 vs 12.8 per 1000 nasal CPAP or ventilator days).<sup>21</sup> However, CPAP has been associated with an increased risk of Gram-negative infections.<sup>22</sup>

Skin and soft tissue infections are commonly observed in NICU patients. Neonates, especially those born preterm, have fragile skin, which is easily traumatized. Cellulitis, abscesses, and skin abrasions are frequently noted at sites of percutaneous puncture (langets and scalp electrodes), in diaper or bandage areas, and at surgical incision sites. *S aureus* is by far the most common microorganism responsible for all skin and soft tissue infections in the NICU. The recent emergence of methicillin-resistant *S aureus*, both endemic health care–associated and community-associated strains, has made management of these infections complicated. Gram-negative enteric rods and yeasts are less commonly associated with skin and soft tissue infections than *S aureus*, but they are associated with surgical procedures, particularly those affecting the gastrointestinal tract.

### **DIAGNOSIS OF CENTRAL LINE–ASSOCIATED BLOODSTREAM INFECTIONS**

The presence of a central venous catheter is a major risk factor for bloodstream infection. Coagulase-negative staphylococci are responsible for nearly 50% of catheter-related bloodstream infections. Other pathogens include Gram-negative organisms (~20%), *S aureus* (4% to 9%), *Enterococcus* species (3% to 5%), and *Candida* species (~10%).<sup>23</sup> Coagulase-negative

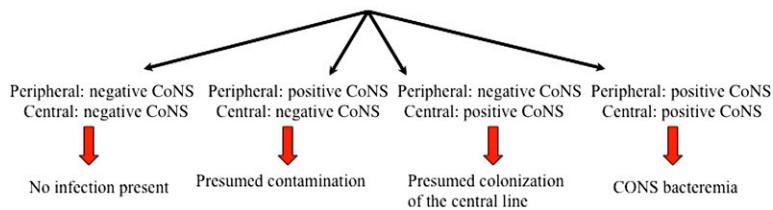
staphylococci are skin commensals; therefore, interpretation of a blood culture result positive for this organism is difficult. The diagnosis is made even more problematic by the non-specific signs of sepsis in the neonate. It is noteworthy that the databases of the National Healthcare Safety Network, Vermont Oxford Network, and the National Institute for Child Health and Human Development Network include infants with a single positive blood culture and clinical signs as “proven cases” of central line–associated bloodstream infection. Although many experts recommend obtaining both central line and peripheral blood cultures when evaluating neonatal patients for central line–associated bloodstream infection, a single blood culture sample is commonly obtained. In those situations, it may be difficult to determine whether the coagulase-negative *Staphylococcus* is the responsible pathogen or a contaminant, and the clinician will need to make a judgment on the basis of the laboratory data and response to treatment. The Infectious Diseases Society of America recommends that paired samples be drawn from the catheter and a peripheral vein (level of evidence: A-II).<sup>24</sup> Although this action may not be possible for all neonates, paired samples should be obtained whenever feasible. Neonates with a suspected central line–associated bloodstream infection should be treated with broad-spectrum antibiotic agents to cover both Gram-positive and Gram-negative pathogens. An algorithm for interpreting a positive blood culture result for coagulase-negative staphylococci is shown in Fig 1.

### **DIAGNOSIS OF HEALTH CARE–ASSOCIATED PNEUMONIA**

Health care–associated pneumonia can have adverse clinical consequences, both from the infection itself and from

### Clinical Signs and Symptoms of Sepsis

Draw *central and peripheral blood cultures* and begin broad-spectrum antibiotics



**FIGURE 1**

Algorithm for interpreting a positive blood culture result for coagulase-negative staphylococci (CONS).

its therapies. Health care–associated pneumonias in infants may result in increased exposure to broad-spectrum antibiotic agents, need for reintubation, increased duration of assisted ventilation, increased length and cost of hospitalization, secondary infections including sepsis, and even death.

The optimal method of diagnosing health care–associated pneumonia in neonates remains to be established. In neonates with underlying pulmonary disease, it may be difficult to differentiate between preexisting lung disease and health care–associated pneumonia or tracheitis. In general, the diagnosis of health care–associated pneumonia is made on the basis of evidence of respiratory decompensation with new and persistent infiltrates on a chest radiograph. Clinical signs suggesting that a health care–associated bacterial pneumonia has developed in an infant receiving mechanical ventilation include changes in the patient's respiratory status that are unexplained by other events and a significant increase in the quantity and quality of respiratory secretions. However, signs such as fever, leukocytosis, and changes in the quality and quantity of tracheobronchial secretions may occur for reasons other than the development of a health care–associated lower respiratory tract infection. Unfortunately, relying on clinical changes and chest radiographic findings for the diagnosis in a NICU

setting may overestimate the true incidence of health care–associated pneumonia. Infants with atelectasis, congenital heart disease, bronchopulmonary dysplasia, pulmonary hemorrhage, pulmonary edema, and surgical procedures affecting the chest may have radiographic changes that are similar to changes seen with pneumonia. The National Healthcare Safety Network and CDC definition requires at least 48 hours of mechanical ventilation accompanied by new and persistent radiographic infiltrates after the initiation of mechanical ventilation. In addition to these criteria, infants younger than 1 year old must exhibit worsening gas exchange and at least 3 of the following: (1) temperature instability with no other recognized cause; (2) leukopenia (white blood cell count  $<4000/\text{mm}^3$ ); (3) change in the character of sputum or increased respiratory secretions or suctioning requirements; (4) apnea, tachypnea, nasal flaring, or grunting; (5) wheezing, rales, rhonchi, or cough; or (6) bradycardia ( $<100$  beats/min) or tachycardia ( $>170$  beats/min).<sup>25</sup> Baltimore,<sup>26</sup> however, has pointed out that the CDC definitions were developed for epidemiologic surveillance and have not been validated for clinical diagnosis.

Laboratory tests, such as Gram stain or bacterial culture, documenting the presence of inflammation and pathogenic microorganisms in lower respiratory

tract secretions may be helpful in establishing the presence of a health care–associated lower respiratory tract infection. However, in most cases, presence of bacteria in specimens obtained by suctioning the endotracheal tube represents colonization rather than an invasive infection, even when the culture is obtained immediately after intubation. In addition, the correlation between culture results obtained from endotracheal suction specimens and those from samples obtained directly from the lungs, pleural cavity, or blood is poor.<sup>27,28</sup>

When it is likely that a health care–associated bacterial pneumonia is present, a number of procedures can assist in establishing the etiologic agent. A Gram stain of a specimen obtained by suctioning through the endotracheal tube can provide evidence of an inflammatory (and potentially infectious) process in the lower respiratory tract.<sup>29</sup> The presence of an abundance of polymorphonuclear neutrophils or a significant increase in polymorphonuclear neutrophils from a previous Gram stain of the same secretions, regardless of the presence of a predominant bacterial organism, is supportive evidence that pneumonia is present but also may represent tracheitis. The presence of a single organism obtained by culture that is consistent with an organism identified on the Gram stain increases the likelihood that this agent is causally related to the health care–associated bacterial pneumonia.<sup>29</sup>

Numerous efforts have been made to develop techniques for obtaining specimens from the lower respiratory tract that can identify the bacteria responsible for the health care–associated pneumonia without interference by upper airway contamination. Transtracheal aspiration, transthoracic needle aspiration and biopsy, and bronchoscopy have been used in older children and

adults to obtain samples directly from the lower respiratory tract, but these procedures are generally contraindicated in neonates. Moreover, there is a high rate of false-positive results in children who have underlying pulmonary conditions that might be confused with pneumonia by their clinical and radiographic appearances.

Bronchoalveolar lavage is a reliable method for obtaining lower respiratory tract secretion samples in older children and adults.<sup>30–32</sup> However, its role in diagnosing ventilator-associated pneumonia in older children and adults has not been established, and experience in preterm infants is limited. In intubated neonates, tracheal aspirates may provide information similar to that which can be obtained by bronchoalveolar lavage. However, for neonates with rapidly progressing lower respiratory tract disease or in whom a diagnosis is not established with routine tracheal aspirate, a bronchoalveolar lavage may be indicated (if technically feasible).<sup>33–35</sup> The aspirated fluid can be centrifuged, and the pellet can be examined immediately for bacteria (Gram stain or acridine orange) and fungi (KOH or Calcofluor). Cultures and other molecular diagnostic testing (eg, direct fluorescent antibody assay, polymerase chain reaction assay) can be performed for aerobic bacteria, fungi, and viruses. The differential count of white blood cells from bronchoalveolar lavage fluid may also be helpful. Infants with bacterial or fungal infections are more likely to have a high proportion of granulocytes in bronchoalveolar lavage fluid.<sup>33,36</sup>

Isolation of the same bacterial pathogen from the blood and the lower respiratory tract usually confirms that this organism is the agent responsible for the health care–associated pneumonia. However, only approximately 2% to 5% of patients with health care–associated bacterial pneumonia have positive blood cultures.<sup>36</sup>

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