Health care–associated infections in the neonatal intensive care unit

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Neonates represent a unique and highly vulnerable patient population. Advances in medical technology that have occurred over the last few decades have improved the survival and quality of life for neonates, particularly those infants born with extreme prematurity or with congenital defects. Although immunologic immaturity and altered cutaneous barriers play some role in the vulnerability of neonates to nosocomial infections, clearly, therapeutic interventions that have proven to be lifesaving for these fragile infants also appear to be associated with the majority of infectious complications resulting in neonatal morbidity and mortality. Rates of infections in neonatal intensive care units (NICUs) have varied from 6% to 40% of neonatal patients, with the highest rates in those facilities having larger proportions of very low-birth-weight infants (birthweight ≤1000 grams) or neonates requiring surgery. Efforts to protect the vulnerable NICU infants include the following: (1) optimal infection control practices, especially good hand hygiene and good nursery design; (2) prudent use of invasive interventions with particular attention to early removal of invasive devices after they are no longer essential; and (3) judicious use of antimicrobial agents, with an emphasis on targeted (narrow spectrum) rather than broad-spectrum antibiotics and appropriate indications (proven or suspected bacterial infections). (Am J Infect Control 2005;33:268-75.)

As with other settings in which critically ill patients receive care, infants hospitalized in neonatal intensive care units (NICU) are at risk for health care-associated infections because of their profound physiologic instability and exposure to invasive devices and broad-spectrum antibiotics.[1-3] However, this group of infants has some unique host risk factors that make them particularly vulnerable for acquiring health care-associated infections, as well as experiencing more severe illness as a result of these infections. Whether the infant is born prematurely or at full term, many components of the immune system exhibit diminished functional capacity (quantitative and qualitative) when compared with older children and adults[4] (Table 1). Most of the differences are based merely on an age-related intrinsic immaturity, which is more profound the earlier during gestation that the infant is born. In addition, the protected environment of intrauterine life prevents any significant immunologic exposure that would be necessary to prime many valuable protective immune responses. For these reasons, the newborn infant depends heavily on passively acquired maternal antibodies received from their mother by transplacental passage.[5] These passively acquired antibodies are primarily immunoglobulin G (IgG). Transmission of the antibodies to the fetus begins approximately mid-gestation (24-26 weeks gestation), with levels of IgG antibodies in the fetus not reaching adult levels until near full term. Infants born prematurely will have IgG antibody levels that are significantly lower than older children and adults.[5] These passively acquired antibodies represent the mother's prior experience and therefore may not always provide adequate protection against microorganisms to which the infant will be exposed in the NICU. The sick premature infant as well as full-term neonate may exhibit an iatrogenic hypo-gammaglobulinemia as a result of frequent blood drawing, which removes available maternally derived antibodies before the infant is capable of producing adequate antibodies for immunologic protection.

The sterile environment of the uterus results in the delivery of an infant devoid of protective endogenous microbial flora. Colonization of mucous membranes and skin occurs rapidly after birth. In healthy newborns, the majority of microbial flora that colonizes the mucosal surfaces and the skin is acquired from the infants' mother and other family members. However, neonates hospitalized within a NICU setting are likely to have their endogenous microbial flora result from endemic microorganisms present in the NICU and modified by frequent exposure to antibiotics[8,9] and contacts with health care workers.[10] There is a higher frequency of colonization by NICU patients with antibiotic-resistant bacteria (gram-negative enteric rods and staphylococci), *Enterococcus*, and *Candida* species.

The stratum cornium of the fetus develops poorly before 26-weeks gestation. In the significantly premature infant (24 weeks through 30 weeks), the skin is

less thick (only a few cell layers) and poorly keratinized.[11] Skin and mucous membranes in premature neonates are more permeable to exogenous antigens. The inherent immaturity of the neonate's skin enhances susceptibility to microorganisms exposed to the infant's skin. This increases the risk for development of dermatitis and cellulitis and is a portal for invasive bacteria to enter deeper tissues or even the vascular space. Regardless of gestational age, the skin matures, and the stratum cornium develops to more mature levels by 2 weeks of age.[11]

EPIDEMIOLOGY AND TRANSMISSION

Infants hospitalized within the NICU can be exposed and acquire health care-associated infections from both human and inanimate sources. A mode of nosocomial transmission that is unique to neonates is natal or intrapartum transmission of microorganisms from mother to infant derived from the maternal birth canal. Any microorganism found in the maternal birth canal can result in infection of the newborn based on the pathogenicity of the microorganism and the susceptibility of the infant (Table 2). NICU residents can also become infected with health care-associated infections through horizontal transmission of microorganisms spread by aerosol or contact (direct or indirect) transmission. Despite the enhanced safety of blood products administered in hospitals at the present time, the frequent utilization of blood products in the stabilization of critically ill newborns allows for the potential transmission of bloodborne pathogens, currently identified and those yet to be identified.[12-15]

Administration of breast milk from either the infant's mother or donor-bank breast milk provides an opportunity for the transmission of agents found in breast milk and skin of the breast milk donor[15-17] (Table 3). However, donor screening and pasteurization of donor breast milk has made this product very safe for use in even the most critically ill neonate.

The rates of health care-associated infections in the NICU are considerably higher than what would be noted in a normal newborn nursery. Rates have varied from 6 to 40 per 100 admissions in the NICU,[18-21] and this compares with a rate of approximately 0.3 to 1.7 per 100 admissions in normal newborn nursery.[20,22] Rates of health care-associated infections in the NICU are higher in lower birth weight infants, with the rates being nearly 3 times higher in infants whose birth weights are <1500 grams compared with those with a birth weight of >1500 grams. In addition, health care-associated infection rates are higher in units that include neonatal surgical patients and in units that include nosocomial viral infections[20] in their surveillance data. Duration of hospitalization, exposure to

Table 1. Quantitative and qualitative immune deficiencies noted in newborn infants[5-7]

Component of the immune system	Defect
Phagocytic cells (PMNs and monocytes)	Decreased migration/chemotaxis
	Decreased phagocytic activity
	Decreased bone marrow storage pool of PMNs
B-cells/immunoglobulins	IgM synthesis delayed until 30 weeks gestation
	Dependence on maternally derived IgG
	Poor response to polysaccharide antigens
T lymphocytes	Diminished T-cell-mediated cytotoxicity
	Diminished participation in delayed-type hypersensitivity
	Diminished potentiation of B-cell differentiation
Complement/opsonization	Decreases in both classic and alternate pathways
	Decreased fibronectin (50% of adult levels)
Natural killer cells	Decreased number
	Decreased cytotoxicity
Reticuloendothelium	Decreased antigen removal

Table 2. Common vertically/natally acquired infections

Bacteria	Viruses	Other
Group B *Streptococcus*	Herpes simplex	*Candida* species
Listeria monocytogenes	Cytomegalovirus	*Chlamydia trachomatis*
Gram-negative enteric rods	HIV	*Ureaplasma urealyticum*
Neisseria gonorrhoeae	Hepatitis B	*Mycoplasma hominis*
Staphylococcus aureus		

broad-spectrum antibiotics, and over crowding and poor staffing ratios[23-25] are risk factors that have been associated with increased rates of health care-associated infections in the NICU. However, the best markers for the risk of nosocomial infection are birth weight, exposure to invasive devices, and acuity of underlying illness. In any effort to compare infection rates in NICUs, the data need to be stratified by birth weight, device days, and acuity of illness.

SELECTED HEALTH CARE-ASSOCIATED INFECTIONS IN THE NICU

Bacteremias or bloodstream infections (BSI) are the single most important infections within the NICU

Table 3. Microorganisms that may be transmitted through breast milk[16,17]

Microorganism contraindicated	Breastfeeding
Cytomegalovirus	No
Hepatitis B	No*
Hepatitis C	No
Human immunodeficiency virus (HIV)	Yes†
Human T-lymphotrophic virus type I (HTLV-I)	Yes
Human T-lymphotrophic virus type II (HTLV-II)	Yes
Herpes simplex	No‡
Rubella	No

*Mothers who are hepatitis B surface antigen positive (newly acquired infection or chronic carriers) may breastfeed after their infant receives hepatitis B immune globulin (HBIG) within 12 hours of birth and initiates the hepatitis B vaccine series.
†Breastfeeding by HIV-infected mothers should be prohibited, unless a safe alternative is not available.
‡Mothers who have after herpetic lesions on their breasts should refrain from breastfeeding until the lesion has resolved.

Table 4. National Nosocomial Infection Surveillance (NNIS) bacteremia and pneumonia rates in NICU patients by birth weight[3,32]

Birth weight category	1990-1995	1995-2003
NNIS bacteremia rate*		
≤1000 grams	12.1	10.6
1001-1500 grams	5.7	6.4
1501-2500 grams	5.0	4.1
>2500 grams	4.1	3.7
NNIS pneumonia rate†		
≤1000 grams	3.4	3.3
1001-1500 grams	2.2	2.5
1501-2500 grams	1.9	2.1
>2500 grams	1.0	1.4

*Rates are the number of bacteremias per 1000 catheter days.
†Rates are the number of pneumonias per 1000 ventilator days.

because of their frequency and their potential for life-threatening consequences. Infants who develop bacteremia in the first few days of life (early onset sepsis) typically acquire their organism from their mother during the intrapartum period. The microorganisms responsible are found in the maternal birth canal and are transmitted to the infant either through an ascending route immediately prior to labor and delivery (especially in the presence of ruptured amniotic membranes) or through exposure as the infant is delivered. The illness is characterized by a fulminant multisystem disease, with a high mortality rate. Premature birth, low birth weight, maternal fever, premature rupture of membranes, maternal chorioamnionitis, and maternal colonization with group B *Streptococcus* are specific risk factors for early onset bacteremia and sepsis. Utilization of antimicrobial chemoprophylaxis to prevent early onset group B *Streptococcus* sepsis has successfully reduced the incidence of early onset group B *Streptococcus* infections[26] but has been associated with an increase in early onset *Escherichia coli* infections in very low-birth-weight infants.[27] Late onset bacteremia occurs after 5 to 7 days of age. This may be due to maternally derived microorganisms that colonize the infant in the intrapartum period or can represent infection acquired nosocomially (horizontal transmission). Most episodes of nosocomial bacteremia in the NICU are associated with indwelling vascular catheters.[27,28] Administration of lipids, low birth weight, respiratory tract disease on admission, catheter hub colonization, blood sampling through the central catheter, and treatment with H2 blockers also are independently associated with bloodstream infections.[29,30] If the infection occurs in the first 30 days of life, microorganisms most commonly identified are coagulase-negative *Staphylococcus* (CONS), *Staphylococcus aureus*, *Enterococcus*, and gram-negative enteric rods. After 30

days of age, coagulase-negative *Staphylococcus* is still the most common organism causing nosocomial bacteremia. However, fungi, particularly *Candida*[31] species, and *Malassezia furfur* become more prominent. Infants whose birth weights are <1000 gram are at greatest risks for nosocomial bacteremia. Despite the recognition of the importance of nosocomial bacteremia in the NICU, the rate of bacteremia in NICU patients identified by the National Nosocomial Infections Surveillance (NNIS) System has not changed considerably over the last decade[3,32] (Table 4).

Critically ill neonates frequently have underlying respiratory tract conditions (hyaline membrane disease, bronchopulmonary dysplasia, meconium aspiration syndrome, and others). The respiratory status of the neonate may be further compromised by the development of pneumonia or tracheitis (Table 4). Similar to bacteremia, respiratory tract infections can be divided into groups by time of onset: early onset pneumonia versus late onset pneumonia/tracheitis. In the first few days of life, neonates who develop pneumonia usually have infections with microorganisms acquired natally. Group B *Streptococcus*, *Listeria monocytogenes*, and gram-negative enteric rods may result in an overwhelming respiratory tract infection that may be present very shortly after birth.[33] Late onset pneumonia and tracheitis are more commonly because of infection with gram-negative enteric bacilli and *Staphylococcus aureus*. Endotracheal intubation is the major risk factor.[33,34] As with other invasive device-related infections, health care-associated pneumonia and tracheitis can be reduced by minimizing intubation days and proper care and maintenance of the ventilator-endotracheal tube circuit. Colonization of the endotracheal tube is virtually inevitable. Lower respiratory tract disease is not established by the mere presence of bacteria isolated from samples of the respiratory tract. Rather, lower respiratory tract disease is diagnosed by

changes in respiratory tract signs and symptoms (eg, changes in oxygen requirements, new or changing infiltrates on the chest x-ray, increased volume or change in consistency of secretions suctioned from the endotracheal tube) combined with evidence of an acute inflammatory response, such as fever or polymorphonuclear leukocytes and a predominant bacteria on gram stain of tracheal secretions. Infants in the NICU are particularly vulnerable to community-acquired viruses. Respiratory syncytial virus (RSV), adenovirus, parainfluenza, and influenza can be devastating to the critically ill neonate and may be responsible for nursery-wide outbreaks.[35-37]

Immature gastrointestinal immunity, diminished interfering normal microbial flora, higher gastric pH, shorter gastric emptying time, increased permeability of gastrointestinal mucosa, and use of nasogastric tubes place the critically ill neonates at particular risk for acquiring gastrointestinal infections while in the NICU. Specific agents responsible for gastrointestinal disease may vary, based on the geographic location of the nursery, but viruses such as rotavirus,[38] and enteric adenovirus and coronavirus, as well as *Escherichia coli* species and other gram-negative enteric rods are most commonly implicated.[39,40] *Clostridium difficile* presents a unique problem. Asymptomatic colonization of the neonate has been identified.[41,42] Neonates have reduced receptors for the *Clostridium difficile* toxin and therefore are less susceptible to development of disease following colonization with *C difficile*.[43] However, although asymptomatic colonization may occur, neonates can develop disease because of *Clostridium difficile*. Identification of *C difficile* toxin in a symptomatic newborn without evidence of another pathogen, and particularly in the presence of colitis (stools with leukocytes and/or red blood cells), warrants therapy and isolation for *C difficile*. Necrotizing enterocolitis is a unique medical condition seen primarily in critically ill newborns. This condition is multifactorial in origin (immature gastrointestinal tract, ischemia; overgrowth of bacteria). Outbreaks of necrotizing enterocolitis have been temporally associated with nursery outbreaks with *Klebsiella, E coli, Entrobacter cloacae, Serratia, Pseudomonas, Staphylococcus aureus,* coagulase-negative *Staphylococcus,* rotavirus, enteric Coronavirus, and *Clostridium difficile*.[44-50]

Superficial and deep skin and subcutaneous infections are common in newborns in the NICU. Neonates have extremely fragile skin, which is frequently traumatized. Cellulitis, abscesses, and dermatitis are common and are frequently noted at sites of percutaneous puncture (lancets, scalp electrodes, and others) and surgical procedures or the sites of diapers or electrodes. Omphalitis is relatively uncommon but occurs more frequently in the preterm infant than in the term infant. *Staphylococcus aureus* is by far the most common microorganism responsible for all skin and subcutaneous infections in NICU patients. Recent increases of methicillin-resistant *Staphylococcus aureus* (MRSA), both endemic health care associated and community acquired, have made management of these infections more complicated. Vancomycin utilization has increased because many of the alternate antibiotics for MRSA have little experience or are not appropriate in neonates (eg, trimethoprim-sulfamethoxazole, linezolid, daptomycin). Gram-negative enteric rods and yeasts are less commonly associated with skin and soft tissue infections than *Staphylococcus aureus*. However, these microorganisms are becoming more prevalent and are particularly associated with surgical procedures affecting the gastrointestinal tract.

INFECTION CONTROL MEASURES

Because of the potential severity associated with health care-associated infections in the NICU in this extremely vulnerable population, it is incumbent on health care providers in the NICU to utilize all opportunities to provide the safest environment possible for NICU patients. As has been established in all areas of the hospital, hand hygiene is the single most important infection control activity in the NICU.[51,52] Hand hygiene should be sufficient to thoroughly wash and rinse the hands. A thorough handwashing of approximately 3 minutes on entry and then at least 10 seconds between patients is usually sufficient.[51,53] Hands should be dried with paper towels. Antimicrobial soaps or alcohol-based waterless antiseptic agents should be utilized, along with alcohol-based waterless products at each patient bedside. In the very low-birth-weight infants, gloves may complement hand hygiene for reducing nosocomial infections within the NICU.[54] Artificial nails may harbor potential pathogens.[55] Short, well-groomed, natural nails should be required for health care providers with direct patient contact within the NICU.

Because many of the most serious nosocomial infections in the NICU are acquired following the use of invasive devices, special attention should be placed on minimizing the use of invasive devices, as well as proper care of the devices once they are in place.[56-58] Proper utilization and maintenance of invasive devices can be enhanced by developing criteria for insertion and removal, with auditing to determine compliance. Because duration of device utilization is correlated with the risk for nosocomial infection, specific attention should be placed on removal of devices when they are no longer necessary. Because small newborns have difficult vascular access, indwelling central catheters may be allowed to remain in place at times when

peripheral catheters would be sufficient. The risks and benefits of continuing the use of indwelling invasive devices need to be determined on at least a daily basis.

Nursery design can have an impact on the risk and rates of infections within the NICU. Unfortunately, NICUs may be located in facilities that do not have significant opportunities to create the optimal environment. When possible, it is optimal for the infant space to be approximately 150 square feet.[59] Incubators or warming beds should have spacing of 6 feet between them.[59] Sinks should be accessible, and, optimally, there should be 1 sink for every 2 patients. Positive-pressure ventilation that goes from the ceiling to the floor, with 6 to 15 air exchanges per hours is optimal.[59] Filters should be at least 90% efficient.[59] NICUs should have access to isolation rooms, particularly those offering negative pressure. Special precautions are needed to protect the infant when construction or renovation is occurring within the NICU.

Employees within the NICU provide valuable service to their patients, but, at times, they also represent a vehicle for transmission of infectious agents. To protect the health of their patients and their self, employees in the NICU should be immune to rubella, measles, polio, hepatitis B, and influenza.[60] Vaccines are available for those who do not have adequate immunity through natural disease. Employees who have herpetic whitlow, varicella, measles, and rubella should be excluded from work in the NICU. More problematic are some of the community-acquired infections. RSV, adenovirus, parainfluenza, and influenza are known to cause significant illness in the vulnerable NICU patients. Potentially, other respiratory viruses may also cause illness in these patients. It may be difficult to determine the optimal management of NICU employees with community-acquired respiratory virus infections. Clearly, when the employee is too sick to provide adequate care to their patients, they should not be at work. However, in many adults, these community-acquired respiratory virus infections result in only minor illness. If all employees with community-acquired respiratory virus illnesses were excluded from work, this might have a significant impact on staffing levels, which could also result in an increased risk for nosocomial infections by the infants. Good infection control practices, when followed strictly, should diminish the risk of transmission from the ill health care worker. However, the introduction of RSV, adenovirus, parainfluenza, or influenza into the nursery by an ill NICU employee could result in serious infection in an NICU patient and potentially the development of an outbreak.

It is optimal to avoid admission of infants with contagious diseases to the NICU. However, there may be times when this is not always possible. Standard Precautions are as essential in the NICU as they are in any other area of the hospital. In addition, CDC Category Specific Isolation Precautions or some similar isolation precautions may be necessary to restrict spread of contagious diseases within the NICU. Availability and appropriate use of gloves, masks, gowns, and goggles is required. When possible, contagious infants should be placed in isolation rooms. However, nurseries are frequently set up in a ward setting and have fewer private or isolation rooms in other areas of the hospital. If and when isolation rooms are not available, cohorting of patients with similar contagious diseases may be necessary. The routine use of gowns is not indicated for staff and visitors.[51] The routine use (not for isolation purposes) of gowns has not been shown to reduce health care-associated infections, increase handwashing, or decrease nursery traffic.[61-65] However, gowns should be used if required for isolation, and soiling is possible. Also, long-armed gowns should be used for handling infants outside of the incubator or bassinet. Caps, masks, and hair nets are not indicated for routine use but may be required for isolation or surgical procedures. The wearing of employee scrubs is of no proven infection control benefit.[51] However, this traditional practice may have some additional benefits for the staff morale.

Visitation policies should be flexible and liberal but safe. Parents and other immediate family members should always be encouraged to visit as often as possible. Allowing other visitors to see the patient should be based on a weighing of the benefits and the risks of these exposures. In addition, there are some security issues that may be important. The NICU should have policies that will identify visitors with contagious diseases. A trained health care professional should interview parents at a site outside of the nursery to assess the health of parents and each sibling visitor. No child with symptoms consistent with an acute contagious illness should be allowed to visit. Fever, rhinorrhea, cough, diarrhea, vomiting, and dermatitis should exclude visitors from entering the NICU. Visitors should perform appropriate hand hygiene on entering the NICU. Visitors should not contact patients other than the one they are visiting. Visitors should not handle patient care equipment. Visitor restrictions may be necessary during community outbreaks, particularly respiratory tract infections such as influenza or RSV.

The nursery and all of the equipment within it should be cleaned. Iodophors chlorine and quaternary ammonium compounds (low-level disinfectants) may be utilized. However, phenolics should be used with extreme caution because absorption through the skin can cause hyperbilirubinemia.[66] Linens should be cleaned, but autoclaving is not necessary. Appropriate high-level disinfection or sterilization of equipment

is required for equipment that has contact with patients.[66]

Surveillance for health care-associated infections within the NICU is an important key to maintenance of a safe environment through quality assurance.[32] Monitoring of infection rates can lead to the identification of any trends or clusters and the impact of any interventions and allow comparison with benchmarks. If resources are limited, it may not be possible to monitor rates of all infections. Efforts should concentrate on those infections that have higher morbidity or those that are more common within the nursery. Surveillance needs to be done in real time so that the information obtained can have an impact in a timely manner. Routine surveillance cultures are generally not recommended.[67-69] However, surveillance cultures may be valuable when trying to identify a point source during an outbreak.

Certain antimicrobial or immune-based prophylaxes are available and appropriate for preventing infections in neonates (Table 5). However, judicious use of antibiotics may represent one of the more important measures for reducing the impact of infections within the NICU. Whenever possible, the narrowest spectrum antibiotics should be used to treat an identified infection or condition. Broad-spectrum antibiotics, particularly those that can impact the endogenous microbial flora of the gastrointestinal tract or skin, have the potential to eradicate many of the helpful bacteria and replace them with more virulent and antibiotic-resistant bacteria. Use of third-generation cephalosporins and vancomycin should be minimized, and possibly restricted, so that they only are prescribed for serious or life-threatening infections for which alternate narrower spectrum antibiotics are not adequate or appropriate. Antibiotics should only be used to treat proven or suspected bacterial infections. The entire antibiotic treatment course should be completed. However, antibiotics should be discontinued when the infection is cured or when it is likely that the condition is not due to a bacterial infection. H2 blockers should be avoided when possible. H2 blockers raise the gastric pH, which might play a role in promoting overgrowth of pathogenic bacteria or fungi. This increase in bacterial and fungal colonization might play a role in increasing respiratory tract and gastrointestinal tract infections in the ill neonate.

Advances in medical therapy of the critically ill newborn have resulted in significant improvements in survival and quality of life. However, some of the same technologic advances (indwelling vascular catheters, mechanical ventilation, broad-spectrum antibiotics, hyperalimentation, and others) that have provided this improvement can also place the infant at significant risk for health care-associated infections. Understanding the risks and utilizing these technologies in the most judicious manner can provide the safest environment for the NICU resident.

Table 5. Exposure prophylaxis for natally acquired infections

Microorganism agent	Chemoprophylaxis/immunoprophylaxis
Neisseria gonorrhoeae	Erythromycin or silver nitrate eye drops
Group B *Streptococcus*	Intrapartum ampicillin
Hepatitis B	HBIG/hepatitis B vaccine
Hepatitis A	Immune serum globulin
Varicella Zoster	Varicella Zoster immunoglobulin (VZIG)
Human immunodeficiency virus	Antiretroviral therapy for the mother and zidovudine and/or nevirapine for the infant
Chlamydia trachomatis	Equivocal benefit for erythromycin[11,70]
Respiratory syncytial virus	Palivizumab[12,71-73]

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