Health care–associated infections in the NICU result in increased morbidity and mortality, prolonged lengths of stay, and increased medical costs. Neonates are at high risk of acquiring 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 their skin, use of invasive procedures and devices, and frequent exposure to broad-spectrum antibiotic agents. This clinical report reviews management and prevention of health care–associated infections in newborn infants. Pediatrics 2012;129:e1085–e1093

INTRODUCTION
Health care–associated infections in the NICU are infections acquired in the hospital while receiving treatment of other conditions. Although they are less likely to cause mortality than early-onset infections, they have considerable health and economic consequences. Most health care–associated infections in the NICU result from the instrumentation and procedures required to preserve an infant’s life. Thus, it is not possible to lower the rate of health care–associated infections merely by limiting the use of procedures. Furthermore, it is no longer acceptable to consider health care–associated infections as a consequence of neonatal intensive care. Rather, it is incumbent on clinicians to minimize risks of infection by performing invasive procedures only when needed and in the safest manner possible. There is evidence to support the concept that proactive strategies to prevent health care–associated infections in the NICU are possible,1–5 although data supporting specific infection-control interventions in neonates are lacking. Although neonates clearly have unique vulnerabilities, there is no reason to believe that interventions shown to be effective in the pediatric ICU or adult ICU would not be equally effective in the NICU. Because of unique issues confronting the vulnerable neonate, however, these interventions may require some accommodations and further study.

STRATEGIES FOR THE PREVENTION OF HEALTH CARE–ASSOCIATED INFECTIONS

Hand Hygiene
Hand hygiene remains the most effective method for reducing health care–associated infections.6 Hospitals with higher rates of hand hygiene
compliance have lower rates of central line bloodstream infection; however, compliance with hand hygiene practices is less than optimal. A recent meta-analysis concluded that educational programs and multidisciplinary quality-improvement teams can be effective in increasing compliance with hand hygiene procedures; however, each of the 33 studies included more than 1 intervention, and it was difficult to determine which was most efficacious. The Centers for Disease Control and Prevention (CDC) published guidelines for hand hygiene in health care settings in 2002. Although the guidelines were widely accepted and disseminated by members of the National Nosocomial Infection Surveillance System, a recent analysis demonstrated that implementation of these guidelines had no effect on hand hygiene compliance rates (mean, 56.8%).

The sixth edition of the Guidelines for Perinatal Care recommends use of an antiseptic soap or an alcohol-based gel or foam for routine hand sanitizing if hands are not visibly soiled. When hands are visibly contaminated, they should first be washed with soap and water. Larson et al compared the effectiveness of a traditional antiseptic hand wash with an alcohol handitizer in reducing bacterial colonization. There were no differences in mean microbial counts on nurses’ hands or infection rates among patients in the NICU; however, nurses’ skin condition improved during the alcohol phase. Other studies have demonstrated the effectiveness of alcohol-based products, but there are no data to suggest they are superior. Compliance with hand hygiene may be enhanced if alcohol-based products are available at each infant’s bedside.

In May 2009, the World Health Organization published new consensus recommendations for hand hygiene. The guidelines provide a comprehensive overview of hand hygiene in health care and evidence- and consensus-based recommendations for successful implementation. Consensus recommendations were categorized according to the CDC/Healthcare Infection Control Practice Advisory Committee grading system (Tables 1 and 2). A partial list of recommendations relevant to the NICU is shown in Table 3.

**Prevention of Central Line–Associated Bloodstream Infections**

Catheter-related bloodstream infections are the most common hospital-acquired infections in the NICU. Central line–related infections are in large part a result of poor technique at the time of placement and ongoing care of the catheter site. Attempts to reduce the incidence of central line–associated bloodstream infections primarily fall into 1 of 5 categories: (1) clinical practice guidelines for the insertion and maintenance of indwelling lines; (2) prophylactic administration of antibiotic agents (including antibiotic lock therapy); (3) topical emollients to reduce skin penetration of bacteria; (4) promotion of breastfeeding; and (5) gowning for visitors and attendants. The goal of all infection-control programs should be to reduce the rate of central line–associated bloodstream infections to zero.

Both chlorhexidine (2%) and povidone-iodine are recommended for skin antisepsis in infants 2 months or older; however, chlorhexidine is not approved by the US Food and Drug Administration for infants younger than 2 months. In a randomized trial, use of a chlorhexidine-impregnated gauze dressing (0.5% chlorhexidine gluconate in a 70% alcohol solution) in infants of very low birth weight reduced central venous catheter colonization when compared with use of a 10% povidone-iodine scrub but did not reduce the incidence of central line–associated bloodstream infections. Notably, in the chlorhexidine group, contact dermatitis occurred in...
15% of neonates weighing less than 1000 g. In a meta-analysis of studies comparing chlorhexidine gluconate solution with a povidone-iodine solution, the overall risk reduction (for central line–associated bloodstream infections) with chlorhexidine gluconate compared with a povidone-iodine solution was approximately 50%.18

Extraluminal contamination of the intra-cutaneous tract is believed to be responsible for catheter-related infections that happen in the week after placement.19 Catheters are more mobile during the first week after insertion and can slide in and out of the insertion site, drawing organisms down into the catheter tract. Techniques to reduce the likelihood of extraluminal contamination include proper hand hygiene, aseptic catheter insertion (including use of a maximal sterile barrier for catheter insertion and care [IA]), use of a topical antiseptic [IA], and use of sterile dressing [IA]. Although transparent dressings permit easier inspection of the catheter site, they have no proven benefit in reducing infection.20 Catheter sites must be monitored visually or by palpation on a daily basis (IB) and should be redressed and cleaned on a weekly basis (IA). In neonates, there are no data indicating that tunneled catheters have a lower risk of infection than nontunneled catheters.21 After the first week of placement, intraluminal colonization after hub manipulation and contamination is responsible for most central line–associated bloodstream infections.18 Mahieu et al demonstrated that the frequency of catheter manipulations was directly related to the frequency of central line–associated bloodstream infections. Tubing used to administer blood products or lipid emulsions should be changed daily (IB). Tubing used to infuse dextrose and amino acids should be replaced every 4 to 7 days. It is important to remove all central venous catheters when they are no longer essential (1A). Many NICUs remove central catheters when the volume of enteral feedings reaches 80 to 100 mL/kg per day. Topical antibiotic agents or creams should not be used at the insertion site for catheters (IB).
Guidelines for the prevention of intravascular catheter-related infections have been published.23 These guidelines make specific recommendations for umbilical catheters. Levels of evidence are indicated in parentheses (Table 4).

Recently, there has been a focus on implementing “NICU care bundles” to reduce the incidence of hospital-acquired infections. Care bundles are groups of interventions (extrapolated from studies in adults or recommendations from professional organizations) that are likely to be effective. This multifaceted approach has reduced the incidence of health care–associated sepsis in each center or groups of centers where it has been implemented.24–27

Coagulase-negative staphylococci are the most common cause of central line–associated bloodstream infections in the United States. Therefore, the use of low-dose vancomycin in parenteral alimentation solutions (at concentrations above the minimal inhibitory concentration) has been suggested as a way to decrease the incidence of bacteremia attributable to coagulase-negative staphylococci. Five randomized clinical trials of low-dose vancomycin in preterm neonates have been conducted, all of which date from the late 1990s. In 4 of the studies, there was a statistically significant reduction in the incidence of coagulase-negative staphylococcal sepsis (relative risk [RR], 0.11; 95% confidence interval [CI], 0.05–0.24)28; however, there were no significant differences in mortality or length of stay. The use of antibiotic lock therapy has also been investigated. Lock solutions containing vancomycin are installed into the catheter lumen to reduce intraluminal colonization. Most randomized clinical trials of antibiotic lock therapy have been completed in adults and older children.29 A meta-analysis of these trials demonstrated a significant reduction in bloodstream infections (RR, 0.49; 95% CI, 0.26–0.95).

Use of vancomycin as a true lock solution (instilling it for a defined period rather than flushing it through the catheter) conferred greater benefit. The single study of antibiotic lock therapy in the neonatal population50 demonstrated a statistically significant reduction in central line–associated bloodstream infections (RR, 0.13; 95% CI, 0.01–0.57). No increase in vancomycin resistance occurred in this study; however, the study was not sufficiently powered to address that question. Because of the concern for development of vancomycin-resistant organisms and the lack of long-term efficacy data, neither continuous infusions of vancomycin nor antibiotic lock therapy can be recommended.

Invasive fungal infections are responsible for 9% to 12% of health care–associated infections in infants weighing less than 1500 g.31 In a prospective study from the National Institute for Child Health and Human Development research network, 9% of infants weighing less than 1000 g developed candidiasis.32 Death or neurodevelopmental impairment occurred in 73% of these infants. Prophylactic fluconazole has been suggested as a way to decrease the incidence of invasive fungal disease. The rationale is that prevention of fungal colonization in high-risk infants will lower the risk of invasive disease. A meta-analysis of 5 trials comparing systemic fluconazole with placebo, demonstrated a statistically significant reduction in the incidence of invasive fungal infections (RR, 0.48; 95% CI, 0.31–0.73)33; however, there was no significant difference in the incidence of death before discharge from the hospital and insufficient data to assess neurodevelopmental outcomes. There is a concern that the use of azoles to prevent fungal infections will lead to an increase in fluconazole resistance or will result in toxicity, especially among the most immature infants for whom there are limited pharmacokinetic data.

In many NICUs, it is policy that care providers and visitors wear gowns on entering the nursery. Eight trials have evaluated the benefit of gowning.34 A meta-analysis demonstrated that there was no significant effect of a gowning policy on reducing the incidence of systemic nosocomial infection (RR, 1.24; 95% CI, 0.90–1.71). For that reason,

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**TABLE 4. Guidelines for the Prevention of Intravascular Catheter-related Infections**

1. Remove and do not replace umbilical artery catheters if any signs of central line–associated bloodstream infection, vascular insufficiency in the lower extremities, or thrombosis are present (Category II).
2. Remove and do not replace umbilical venous catheters if any signs of central line–associated bloodstream infection or thrombosis are present (Category II).
3. Cleanse the umbilical insertion site with an antiseptic before catheter insertion. Avoid tincture of iodine because of the potential effect on the neonatal thyroid.
4. Do not use topical antibiotic ointment or creams on catheter insertion sites because of the potential to promote fungal infections and antimicrobial resistance (Category IA).
5. Add low doses of heparin (0.25–1.0 U/mL) to the fluid infused through umbilical arterial catheter (Category IB).
6. Remove umbilical catheters as soon as possible when no longer needed or when any sign of vascular insufficiency to the lower extremities is observed. Optimally, umbilical artery catheters should not be left in place for more than 5 d (Category II).
7. Umbilical venous catheters should be removed as soon as possible when no longer needed but can be used up to 14 d if managed aseptically (Category II).
8. An umbilical catheter may be replaced if it is malfunctioning and there is no other indication for catheter removal and the total duration of catheterization has not exceeded 5 d for an umbilical artery catheter or 14 d for an umbilical vein catheter (Category II).
gowns should not be required for routine admission to the NICU by health care workers or visitors. Despite the lack of overall benefit, gowns and gloves should be worn when an infant is colonized with a resistant or invasive pathogen, consistent with appropriate isolation requirements. Additional personal protective equipment may be required on the basis of isolation requirements of the specific pathogen or clinical condition and the activity or procedure to be performed.

Prevention of Health Care–Associated Pneumonia

The CDC published guidelines for preventing health care–associated pneumonia in 2003.35 These guidelines were not specifically designed to address the unique issues facing the mechanically ventilated patient in the NICU; however, many of the recommendations are relevant to all patient populations. General concepts discussed in the CDC document include the following:

1. Staff Education and Involvement in Infection Prevention. All providers should receive appropriate information relating to the epidemiology of and infection control procedures for preventing health care–associated pneumonia. There should be procedures in place to ensure worker competency, including performance of appropriate infection-control activities. Staff should be involved with implementation of interventions to prevent health care–associated pneumonia using performance-improvement tools and techniques (IA).

2. Infection and Microbiologic Surveillance. Surveillance for health care–associated pneumonia in patients in the NICU should be performed to determine trends and help identify outbreaks or other problems (IB). Routine surveillance cultures of patients or equipment should not be performed (II).

3. Prevention of Transmission of Microorganisms. Within the NICU, risks for acquisition of microorganisms that could result in health care–associated pneumonia can be reduced by (1) proper sterilization or disinfection and maintenance of equipment and devices (IA), and (2) prevention of person-to-person transmission of bacteria by use of Standard Precautions as well as other isolation practices when appropriate (IA).

4. Modifying Host Risk for Infection. Aspiration is a major risk for the development of health care–associated pneumonia. Devices such as endotracheal tubes, tracheostomy tubes, or enteral tubes should be removed from patients as soon as appropriate and clinically indicated (IB). In the absence of medical contraindication(s), the head of the bed should be elevated at an angle of 30 to 45 degrees for mechanically ventilated patients (II). A comprehensive oral-hygiene program should be followed for the infant (II).

Suctioning practices and position of the infant in the bed may influence tracheal colonization. The use of closed-suctioning systems allows endotracheal suctioning without disconnecting patients from the ventilator. Closed-suctioning methods reduce physiologic disruptions (hypoxia and decrease in heart rate), and NICU nurses judged them to be easier to use than an open system.35,37 Closed-suctioning systems provide an opportunity for bacterial contamination when pooled secretions in the lumen are reintroduced into the lower respiratory tract with repeat suctioning. On the other hand, closed-suctioning systems could potentially reduce environmental contamination of the endotracheal tube. In studies evaluating mechanically ventilated adults, airway colonization was more common when closed-suctioning systems were used,38,39 but ventilator-associated pneumonia rates were equal to or slightly less than the rates among patients managed with open systems.38–40 CDC recommendations do not endorse one system over the other, and there is no recommendation addressing the frequency at which closed-suctioning systems should be changed.

Tracheal colonization from oropharyngeal contamination is less common among neonates on mechanical ventilation when the neonates are placed in a lateral position on the bed as compared with the supine position (30% for lateral versus 87% for supine; P < .01).41 Keeping the endotracheal tube and the ventilator circuit in a horizontal position might reduce tracking of oropharyngeal sections down into the lower respiratory tract.42 The lateral position also is associated with reduced aspiration of gastric secretions into the trachea.41 Using a nonsupine position may reduce the risk of ventilator-associated pneumonia.43

Other Strategies to Reduce Health Care–Associated Infections in the NICU

The skin of the preterm newborn infant has compromised barrier and immune function. In addition, the skin of the extremely preterm infant can be easily damaged and serve as a portal for the entry of organisms into the bloodstream. Topical emollients have been used to decrease transepidermal water losses and have been suggested as a method to decrease health care–associated infections. In a meta-analysis of 4 trials completed in industrialized countries, a significantly increased risk of coagulase-negative staphylococcal infection was found in infants treated with prophylactic topical ointment.44 In contrast, infants born at <35 weeks’ gestation in Bangladesh treated topically with sunflower oil were 41% less likely to
develop health care–associated infections than were control infants. The lack of effectiveness of topical emollients in industrialized countries may be attributable to different mechanisms of transcutaneous sepsis. In industrialized countries, instrumentation is used more commonly, and sites of insertion can serve as a portal for bacterial invasion. In developing countries, environmental contamination and malnutrition play a greater role, and invasive devices are used less frequently. Therefore, bacterial invasion is likely attributable to microscopic sites of skin barrier compromise, which might be protected by the use of an emollient.

The use of human milk feedings has been associated with a lower risk of sepsis and necrotizing enterocolitis in preterm infants. Human milk contains a large number of immunoprotective substances, prebiotics, and probiotics and has been shown to decrease the incidence of gastrointestinal and respiratory infections in infancy. Although a number of randomized clinical trials and cohort studies have concluded that human milk feedings had a protective effect on infection in preterm infants, a meta-analysis of 9 studies (6 cohort and 3 randomized clinical trials from India) failed to show an advantage of human milk feedings. The authors believed there were serious methodologic flaws in all of the cohort studies, "including poor study design, inadequate sample sizes, neglecting to account for some confounders, failure to eliminate the effects associated with maternal choice of feeding method and other sociodemographic variables." In addition, the definition of human milk feedings was not consistent among studies. It is important to note that necrotizing enterocolitis was excluded from this systematic review.

A number of other practices may provide opportunities to reduce colonization of the critically ill neonate with health care–associated pathogens or to modify the risk of developing disease if colonized. Specific practices that may provide benefit include (1) appropriate vaccination of health care workers (eg, influenza vaccine and tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis, adsorbed); (2) cohorting in selected outbreak situations; and (3) visitation guidelines to identify ill/infected visitors.

**Antibiotic Use and Misuse**

The use and misuse of antibiotics can be associated with alteration in neonates’ microflora and the development of antibiotic resistance. This is a particular concern within the confines of a NICU, where there is a population of vulnerable children who have medical conditions that may require frequent and/or prolonged antibiotic use, long hospitalizations, crowded conditions, and frequent contact and interventions. Antimicrobial resistance can be intrinsic (ie, present without exposure to antimicrobial agents) or acquired. An example of intrinsic resistance is the resistance of Gram-negative organisms to vancomycin. Acquired antimicrobial resistance is driven by antimicrobial exposure, as is seen in methicillin-resistant *Staphylococcus aureus* and the extended-spectrum β-lactamase (ESBL)-producing organisms. These patterns of resistance represent adaptations of bacteria to antibiotic exposure.

Judicious use of antibiotic agents is commonly recommended as appropriate in the NICU, but it is not commonly practiced. The critically ill nature of patients in the NICU prompts frequent and prolonged use of antimicrobial agents. Judicious use of antibiotic agents in the NICU would include limiting use to only those situations in which a bacterial infection is likely, discontinuing empirical treatment when a bacterial infection has not been identified, changing the antibiotic agents administered to those with the narrowest spectrum on the basis of susceptibility testing, and treating for the appropriate duration. Although clinical situations will vary, these principles remain consistent. It is also relevant to consider the potential for different antibiotic agents to drive the development of resistance. ESBL-producing organisms (primarily Gram-negative enteric agents) are present in many NICUs because of the frequent use of third-generation cephalosporins and other broad-spectrum β-lactam antibiotic agents. Curtailing the use of third-generation cephalosporins and using other antibiotic agents, such as aminoglycosides for empirical therapy, has been associated with less antibiotic resistance, including ESBL-producing organisms. Good infection-control practices also play a significant role in reducing horizontal transmission of antibiotic-resistant bacteria.

The Infectious Diseases Society of America and the Society for Healthcare Epidemiology of America have developed guidelines for “Antimicrobial Stewardship” to reduce antimicrobial resistance. These guidelines are designed to address programmatic changes that improve control of antibiotic resistance (see Table 1 for levels of evidence). Strategies that might be helpful in the NICU setting include the following: (1) auditing antimicrobial use of practitioners and providing feedback (IA); (2) formulary restriction and preauthorization requirements for selected antimicrobial agents (IB); (3) education of prescribers and nurses concerning the role of antimicrobial use and the development of resistance (IB); (4) development of clinical guidelines/pathways for selected conditions (IA); (5) antimicrobial order forms (IB); (6) specific plans for streamlining (broad- to narrow-spectrum antibiotic agents) or deescalating (elimination of redundant or unnecessary) antimicrobial
agents (IB); (7) dose optimization on the basis of individual characteristics (eg, weight, renal status, drug-drug interactions) (IB); and (8) switching from parenteral to oral antibiotic agents when appropriate and feasible (IB). Data are not sufficient to recommend antimicrobial cycling or routine use of combination therapy merely to prevent the development of resistance; however, antimicrobial combinations may be valuable for preventing development of resistance in specific circumstances.

CONCLUSIONS
Health care–associated infections are an important medical morbidity facing an already vulnerable group of infants. The epidemiology and strategies that can reduce these infections are well known; however, implementation of strategies that can influence the occurrence of health care–associated infections within the NICU requires a concerted team effort by all individuals who participate in the care of these infants. Each care provider must understand his or her role in preventing health care–associated infections and have a willingness to modify behaviors such that they comply with recognized infection-control practices. All too frequently, the health of a tiny infant whose life is being saved through the use of the best in 21st-century technology is jeopardized by the smallest of acts—such as a care provider neglecting to wash his or her hands. Recognition of the importance of even the most basic care practices can result in behavior modification within the NICU and improve compliance with established infection-control practices.

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