Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

and immunologically mediated thrombocytopenia, can be confused with congenital infection.

The fetus can be adversely affected by maternal medication or illicit drug use. Fetal exposure to alcohol, anticonvulsants, or cocaine can impair brain growth, leading to microcephaly and neonatal encephalopathy similar to those observed in congenital infection. The prolonged use of intravenous vitamin E in premature infants has been associated with thrombocytopenia, encephalopathy, and cholestatic jaundice that could be confused with signs of congenital or neonatal viral infection. Congenital leukemia and neuroblastoma can manifest as anemia, thrombocytopenia, and organomegaly. Finally, some infants with chromosomal defects have microcephaly, encephalopathy, jaundice, anemia, and thrombocytopenia.

Laboratory Diagnosis

Laboratory testing should be targeted and should focus on identification of virus by culture or detection of viral nucleic acid or proteins in the appropriate specimen. The most likely etiologies should be selected on the basis of clinical findings. The specimens required and the approach used depend on the specific viral infection being considered, and are discussed in the chapters dealing with each virus.

Measurement of maternal or neonatal antibody responses is of limited value but can contribute useful information in certain circumstances. Negative immunoglobulin (Ig) G antibody results for specific agents indicate that maternal infection is not present or is very recent, virtually eliminating the possibility of congenital infection. Newborn IgM antibody response has been used to diagnose congenital infections due to CMV, rubella, VZV, and parvovirus B19 as well as nonviral infections, such as syphilis and toxoplasmosis. However, the accuracy of IgM antibody testing of neonatal serum for viral diagnosis is highly variable, depending on the agent, assay used, and laboratory. Most commercial assays are not reliable.

When clinical evidence suggests congenital infection, virus culture or polymerase chain reaction testing should be used to confirm positive or negative IgM antibody test results. For viruses that produce chronic viremic infection, such as HTLV-I, HIV, HBV, and HCV, it is useful to know whether the mother has been infected in order to gauge the risk to the neonate. Tests for IgG antibody can provide this information. Results of test panels for IgG or IgM antibody to multiple possible causes of infection ("TORCH titers") usually fail to establish an etiologic diagnosis or are not relevant; they should not be used as the sole laboratory diagnostic assay.[81]

Treatment

Antiviral treatment is playing an increasingly important role in the management of congenital and neonatal viral infections. Acyclovir treatment of neonates with HSV infection can be life-saving and may improve the quality of life for survivors.[82] When HSV infection is suspected, initiation of empiric antiviral treatment is usually indicated. Acyclovir is also used for perinatal VZV infection.[9] Antiviral treatment for severe symptomatic, congenital CMV infection with 6 weeks of intravenous ganciclovir decreases the risk for progressive or late-onset hearing loss.[83] Pleconaril was studied for the treatment of severe enterovirus infection in newborns; results under compassionate use were encouraging but production of drug by Vira Pharma was halted; Schering-Plough has taken up development.[84] Perinatal HIV infection can be diagnosed within the first month of life, and antiretroviral treatment should be initiated as soon as the diagnosis is made (and *Pneumocystis carinii* prophylaxis is initiated when HIV exposure is confirmed). Among other bloodborne, vertically transmitted agents, HBV and HCV may require treatment during childhood if chronic liver disease occurs. Management of infants with congenital or neonatal viral infection involves provision of supportive care and anticipation of complications, such as hearing loss, mental retardation, cerebral palsy, and chronic liver disease. Anticipatory follow-up should be planned, with focused examinations for possible sequelae and intervention as needed.

CHAPTER 96

Nosocomial Infections in the Neonate

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As progressively smaller premature infants survive beyond the first few days of life, nosocomial infections have emerged as a major cause of morbidity and late mortality in the neonatal intensive care unit (NICU). Effective prevention and treatment of nosocomial infections in the NICU require understanding of the distribution of pathogens that cause these infections, the various patient-related risk factors for these infections, and the roles of medications and invasive procedures in predisposing to their occurrence.

EPIDEMIOLOGY AND ANATOMIC SITES OF INFECTION

Bloodstream infections (BSIs) are the most common nosocomial infections in the NICU, and they can occur in isolation or in association with organ infections, including endocarditis, osteomyelitis, and septic arthritis. Less commonly, nosocomial infections in neonates can involve the lungs, meninges, urinary tract, peritoneum, bowel, conjunctivae, or skin (Table 96-1).

Late-Onset Sepsis

Late-onset sepsis is usually defined as BSIs occurring on or after 7 days of age in neonates. It accounts for the majority of nosocomial infections in all birthweight groups in NICUs. Late-onset sepsis is especially important in very-low-birthweight (VLBW, birth weight < 1500 g) infants, in whom its occurrence increases hospital length of stay by 19 days and causes 45% of deaths beyond 2 weeks of age.[1] Stoll et al.[1] reported that late-onset sepsis occurred in 21% of VLBW infants who survived beyond 3 days of age in the National Institute for Child Health and Human Development (NICHD) Neonatal Research Network, and similar rates have been reported for the Neonatal Networks in Canada[2] (24%) and Israel[3] (30%).

At the institutional level, the prevalence of late-onset sepsis in VLBW infants is more variable: 11% to 32% in the NICUs of the NICHD Neonatal Research Network,[1] and 7% to 74% in the NICUs participating in the Canadian Neonatal Network.[2] The rate of late-onset sepsis was strongly and inversely associated with birthweight and gestational age,[1] decreasing from 43% for infants with birthweights 401 to 750 g, down to 7% for those 1251 to 1500 g; and decreasing from 46% for neonates with gestational age < 25 weeks, down to 10% for 29 to 32 weeks. Consequently, institutions caring for more extremely premature infants have higher apparent rates, and management practices, particularly those concerning utilization of central venous catheters (CVCs) or peripherally inserted central catheters (PICCs), can further impact these figures.

Most cases of late-onset sepsis in neonates are associated with CVCs or PICCs,[4] and are referred to as CVC-BSIs. The Centers for Disease Control and Prevention (CDC) definition[5] for a CVC-BSI includes: (1) isolation of a pathogen from one blood culture or of a skin commensal from two blood cultures; (2) one or more clinical signs of infection (e.g., apnea, bradycardia, or temperature instability); and (3) presence of a CVC at the time the blood culture is obtained. A

TABLE 96-1. Common Sites and Causes of Nosocomial Infections in the Neonatal Intensive Care Unit

	Anticipated Causal Organisms					
Site of Infection	**CONS**	***S. aureus***	**Enterococci**	**GNR**	***Candida***	**Viruses**
BSI	+++	++	++	++	+	–
CVC-BSI	+++	++	+	++	++	–
Osteomyelitis/septic arthritis	–	+++	–	+	+	–
Endocarditis	+	+++	+	+	+	–
Meningitis	+++	+	+	++	++	+
VAP	–	+	–	+++	+	+[a]
Peritonitis	+	–	+	+++	+	–
UTI	–	–	+	+++	++	–
Conjunctivitis	+	+	–	+	–	–
Skin or subcutaneous tissue	+	+++	–	+	+	+

BSI, bloodstream infection; CONS, coagulase-negative staphylococci; *S. aureus*, *Staphylococcus aureus*; CVC-BSI, central venous catheter-related bloodstream infection; GNR, gram-negative rods; UTI, urinary tract infection; VAP, ventilator-associated pneumonia.
+++, most common isolate; ++, frequently; +, occasionally; –, rarely or not.
[a]Includes respiratory syncytial virus, influenza virus, parainfluenza viruses, and enterovirus.

nosocomial infection rate that is linked with device utilization, like the CVC-BSI, helps control for variability in management practices from institution to institution, and the preferred unit of measure is infections per 1000 catheter-days. The National Nosocomial Infection Surveillance System (NNIS) currently recommends that CVC-BSI be the major focus of surveillance and prevention efforts in NICUs, and to that end, provide summary data on CVC-BSI dates for different birthweight groups in the NICU.

In 2004, these data on CVC-BSI rates from 104 NICUs reported a median of 8.5 BSIs per 1000 catheter-days for infants with birthweights ≤ 1000 g (extremely-low-birthweight or ELBW) and a median of 4.0 BSI per 1000 catheter-days for those weighing 1001 to 1500 g.[6] These values represent a 30% to 38% decrease in birthweight-specific CVC-BSI in NICUs since 1998, when the NNIS-reported median CVC-BSI rates for ELBW infants and infants weighing 1001 to 1500 g were 12.1/1000 days and 6.4/1000 days, respectively.[7] The NNIS data help individual NICUs determine where their CVC-BSI rate is relative to other NICUs. Values at the extremes of the NNIS data may indicate problems with effective infection control (outlying above 90 percentile) or underreporting of CVC-BSI events (outlying below the 10 percentile).[6] Individual NICUs are encouraged to monitor and compare their CVC-BSI rates with NNIS data, which are updated annually and usually published in December.[6]

Coexistence of endocarditis, osteomyelitis, or pyogenic arthritis should be considered whenever BSIs persist in neonates. Although *Staphylococcus aureus* is the most common cause of both endocarditis[8–10] and osteomyelitis[11] in neonates, these complications are uncommon, with one series reporting a prevalence of 0.07% for bacterial endocarditis in the NICU.[10]

Ventilator-Associated Pneumonia

According to the NNIS, ventilator-associated pneumonia (VAP) is the second most common nosocomial infection in neonates. Unfortunately, even the 2004 NNIS report considered its VAP data as provisional[6] due to the vagaries in the definition of VAP when applied to the neonatal population. Diagnosis of VAP in neonates is more difficult because noninfectious conditions such as respiratory distress syndrome and bronchopulmonary dysplasia are common and frequently cause radiologic abnormalities. Consequently, the data concerning the incidence, risk factors, microbiology, and outcomes of VAP in critically ill newborns are limited.

A few investigators have attempted to establish reproducible criteria for VAP specific to the neonatal population. Cordero et al.[12] showed that isolated purulent tracheal aspirates with positive tracheal cultures in mechanically ventilated neonates, in the absence of worsening clinical or radiologic findings, are more consistent with clinically insignificant tracheal colonization than with VAP. Apisarnthanarak et al.[13] performed a prospective cohort study addressing the risk factors, the microbiology, and outcomes of VAP in neonates. Their definition of VAP required new and persistent radiologic evidence of focal infiltrates > 48 hours after initiating mechanical ventilation and that the neonate received antibiotics for > 7 days to treat VAP. By this definition, the prevalence of VAP was 28% (19 of 67) in mechanically ventilated VLBW infants and the VAP rate was 6.5 per 1000 ventilator-days,[13] which places their results at the 75th to 90th percentile of the NNIS VAP rates. Gram-negative bacteria were isolated from tracheal aspirates in 94% of VAP episodes and most cases were polymicrobial. VAP developed in neonates on a median of day 30 and the risk of VAP increased by 11% for every additional week an infant was mechanically ventilated. VAP was strongly associated with mortality in neonates who required NICU care > 30 days.[13] A large multicenter study is needed to validate this definition of VAP and their findings.

Late-Onset Meningitis

Until recently, there were few surveillance data on the incidence of late-onset meningitis in the NICU. Consequently, considerable variability has existed in clinical practice concerning lumbar puncture in neonates with suspected late-onset sepsis. Stoll et al.[14] prospectively studied late-onset meningitis in 9641 VLBW infants who survived > 3 days, finding that it occurred in 134 infants. This represented 1.4% of all infants and 5% of those who had a lumbar puncture performed. Compared with nonseptic infants, VLBW infants with meningitis were more likely to have seizures (25% versus 2%), and were more likely to die (23% versus 2%).[14] One-third (45 of 134) of the infants with meningitis had simultaneous negative blood cultures. Because many neonatologists do not perform lumbar punctures when late-onset sepsis is suspected, it is likely that late-onset meningitis has been underdiagnosed in VLBW infants. Because meningitis can alter long-term prognosis and duration of antibiotic therapy, all VLBW infants with suspected late-onset sepsis should have a lumbar puncture as part of the initial diagnostic evaluation, unless they are too critically ill to tolerate the procedure. In the latter case, it should be performed when clinical stabilization is achieved.

Urinary Tract Infection

Urinary tract infection (UTI) is the most common nosocomial infection in adults.[6] The high rate of UTI in hospitalized adults is associated with frequent use of indwelling urinary catheters, which

are seldom used in VLBW infants. But, as with lumbar puncture, there is considerable practice variability in performing urine culture and analysis by either suprapubic bladder aspiration or urethral catheterization when late-onset sepsis is suspected.[15] Urine specimens obtained by bag collection from infants have notoriously high rates of contamination – up to 63%[16] – and are not recommended. Clinicians have tended to avoid suprapubic bladder aspiration in neonates because of the risk of serious, albeit rare, complications like bowel perforation.[17] Fortunately, sterile urethral catheterization can easily be performed by experienced nurses, even in ELBW infants, and has a significantly higher rate of success in obtaining urine than suprapubic bladder aspiration – 100% versus 46% in one report.[18]

The prevalence of late-onset UTI in NICUs is uncertain: there has not been a prospective study of UTI, as there has been for late-onset sepsis[1] and meningitis.[14] The reported prevalence of UTI in premature infants ranges from 4% to 25%, but these reports are from the 1960s, and consequently not based on the typical population of infants in today's NICUs. A recent retrospective study has reported an 8% prevalence of late-onset UTI in 762 VLBW infants in one NICU over an 11-year period.[19] UTI was more common in ELBW infants (12%) than in infants with birthweight 1001 to 1500 g (6%). These findings suggest that UTI may be the second most common cause of nosocomial infections in the NICU, but a large multicenter prospective study is needed.

Tamim et al.[15] examined paired blood and urine cultures in a group of 189 VLBW infants suspected of having late-onset sepsis. UTIs were detected in 25%. Among the VLBW infants with UTIs, 62% (30 of 48) had negative blood cultures. Phillips & Karlowicz[20] reported a case series of 60 UTIs in an NICU, primarily documented through specimens obtained by urethral catheterization when late-onset sepsis was suspected. Simultaneous BSIs with the same pathogen were present in 52% of cases of *Candida* UTI and 8% of cases of bacterial UTI. Since many neonatologists do not obtain a urine culture when late-onset sepsis is suspected, it is likely that UTIs are under-diagnosed. As most VLBW infants with UTI do not have BSIs, we recommend obtaining urine for culture, either by sterile urethral catheterization or by suprapubic aspiration, whenever late-onset sepsis is suspected in neonates.

Intestinal Perforation and Peritonitis

Peritonitis in NICUs is associated with intestinal perforation. Coates et al.[21] reported striking differences in the distribution of pathogens associated with peritonitis in 36 infants with focal intestinal perforation (FIP) compared with 80 infants with necrotizing enterocolitis (NEC). Enterobacteriaceae were present in 75% of NEC cases compared with 25% of FIP cases. In contrast, *Candida* species were found in 44% of FIP cases compared with 15% of NEC cases, and coagulase-negative staphylococci (CONS) were present in 50% of FIP cases versus 14% of NEC cases. Most importantly, results from peritoneal fluid cultures resulted in changes in antimicrobial therapy in 40% (46 of 116) of cases.[21] These findings suggest that a peritoneal fluid culture should be obtained in all neonates with intestinal perforation, regardless of cause, since it helps direct the choice of the most effective antimicrobial treatment.

Other Infections

Although conjunctivitis is common in neonates, there are few studies addressing its occurrence in the NICU. Diagnosis can be complicated because conjunctival colonization, especially with CONS, is common among infants in the NICU.[22] Haas et al.[23] reported the results of a prospective study of conjunctivitis in the NICU and found a prevalence of 5%.

Most neonatal skin infections are caused by *Staphylococcus aureus*. Clinical manifestations include impetigo, cellulitis, soft-tissue abscesses, and toxin-mediated diseases such as staphylococcal scaled-skin syndrome and toxic shock syndrome.[24] *Pseudomonas aeruginosa* can cause ecthyma gangrenosum lesions in the premature infant,[25] and Enterobacteriaceae can cause purpura fulminans.[26] *Zygomycetes* can cause progressive necrotizing skin lesions in neonates.[27] Vesicular lesions in neonates are usually associated with herpes simplex and enteroviral infections.

DISTRIBUTION OF PATHOGENS CAUSING LATE-ONSET SEPSIS AND CASE-FATALITY RATES

Multiple organisms cause late-onset sepsis in the NICU. Gram-positive organisms are predominant (57% to 70% of cases), but gram-negative organisms (19% to 25% of cases) and fungi (12% to 18% of cases) also cause disease.[1,28] It is noteworthy that many studies have the same organisms causing most of the episodes: CONS, *Candida* species, *S. aureus*, and Enterobacteriaceae (Table 96-2).

Usual Pathogens

Frequency of pathogens causing late-onset sepsis in a NICU is a consideration when empiric antibiotics are selected; it should not be the only consideration. All pathogens do not have equal likelihood of causing severe complications and death; clinicians should be concerned especially about late-onset sepsis in which infants die in less than 48 hours of onset of illness (fulminant sepsis), often before pathogens are identified or their antibiotic susceptibilities known. Karlowicz et al.[28] reported that, although gram-negative organisms caused only 25% of

TABLE 96-2. Pathogens Commonly Causing Late-Onset Sepsis in the Neonatal Intensive Care Unit (NICU)

Pathogen	Relative Frequency of Isolation	Comment
CONS	+++	Most common cause of CVC-BSI
Staphylococcus aureus	++	Highest rate of focal complications; MRSA is a problem in some NICUs
Fungi	++	*Candida albicans* and *Candida parapsilosis* are the most common species
GNR	++	GNR are most common cause of fulminant sepsis; *Klebsiella* species is the most common GNR
Pseudomonas aeruginosa	+	GNR with highest case-fatality rate
Enterococcus species	+	Increased in importance as a nosocomial pathogen since the 1990s
Group B streptococci	+	Rate of late-onset cases unchanged, in contrast to dramatic decrease in early-onset cases with intrapartum antibiotics

CONS, coagulase-negative staphylococci; CVC-BSI, central venous catheter-related bloodstream infection; GNR, gram-negative rods; MRSA, methicillin-resistant *Staphylococcus aureus.*
+++, most frequent; ++, common; +, occasional

sepsis cases in their series, these agents caused 69% of *fulminant* late-onset sepsis. Of gram-negative bacilli, *Pseudomonas aeruginosa* was the most prominent pathogen (42% of fulminant sepsis cases) and overall had a case-fatality rate of 56% – in contrast to a case-fatality rate of < 1% for CONS.[28] Similar findings have been reported by others.[1,29] VLBW infants infected with gram-negative organisms or fungi had the greatest risk of death, infants infected with gram-positive organisms were not more likely to die than infants who were not infected, and infants infected with gram-negative organisms were more likely to succumb to acute mortality, with *Pseudomonas aeruginosa* having the highest fulminant case-fatality rate.

CONS are the most common pathogens causing late-onset sepsis in neonates, with a prevalence between 35%[28] and 48%[1] of cases. Identification of definite CONS sepsis is problematic because pseudobacteremia is common.[30] Some of the reported variation in the prevalence of CONS infection depends upon how it was defined. Karlowicz et al.[28] required at least two positive blood cultures. Stoll et al.[1] distinguished between: (1) definite CONS infection, defined as either two positive blood cultures drawn within 2 days of each other or one positive blood culture and an elevated C-reactive protein within 2 days of blood culture; (2) possible infection, defined as one positive blood culture in a patient treated with vancomycin or a semisynthetic antistaphylococcal antibiotic for > 5 days; and (3) probable contaminant, defined as one positive blood culture without an elevated C-reactive protein or antibiotic therapy as described above. Both definite CONS infections and possible CONS infections were combined by Stoll et al.[1] to make CONS responsible for 48% of cases of late-onset sepsis. If the 353 possible CONS cases are excluded, then the prevalence of CONS sepsis in their series was 29% (276/960),[1] similar to the rate of 35% reported by Karlowicz et al.,[28] which still makes CONS the single most common pathogen causing late-onset sepsis in neonates.

Emerging Pathogens

Frequent antibiotic use in the NICU results in heavy antibiotic pressure on the organisms within this environment, and often, emergence of antibiotic-resistant strains. The placement of NICUs within larger healthcare facilities provides an additional opportunity for the introduction of antibiotic-resistant organisms. Antibiotic use increases the rates of infant colonization with antibiotic-resistant organisms.[31] Gram-positive bacteria, including methicillin-resistant *Staphylococcus aureus* – both hospital- and community-acquired[32–34] – and vancomycin-resistant *Enterococcus faecium*[35] have been clearly identified as serious problems in some NICUs. Both gram-negative enteric organisms (extended-spectrum β-lactamase-carrying *Escherichia coli* and *Klebsiella* spp.,[36] *AmpC* β-lactamase-carrying *Enterobacter* spp.,[37] multidrug-resistant *Serratia marcescens*[38]) and nonenteric organisms (*Pseudomonas aeruginosa*,[39] *Burkholderia cepacia*[40]) have emerged in NICU environments. In many instances, reservoirs containing the organism are present within the healthcare environment; patients are exposed either through the use of contaminated medical equipment or via the hands of their caretakers. The former often results from breakdowns in the cleaning procedures used in the NICU or hospital environment[35,37,38,40,41] and the latter from ineffective use of hand hygiene by healthcare workers.[42] Control of NICU outbreaks of antibiotic-resistant organisms frequently requires vigorous application of infection control procedures (surveillance cultures, patient and staff cohorting) and active education about the factors that predispose to infection. Molecular fingerprinting of organisms has been useful for characterizing and controlling some outbreaks.[31,39–41]

Nosocomial Viral Infections

Nosocomial infections caused by viruses are infrequent in the NICU, with an incidence < 1%,[43] but because of their propensity to spread from patient to patient, they can cause significant clinical problems. Respiratory syncytial virus,[44,45] influenza virus,[46] enteroviruses,[47,48] rotavirus,[49] adenovirus,[50] and coronavirus[51] have been described in NICU outbreaks, sometimes concurrently.[52] Attack rates can be as high as 33%.[47,49,51] Patients can be asymptomatic or have disease that is lethal,[50] and the attributable costs can be high.[45] Respiratory syncytial virus infections can present as cough, congestion, apnea, increasing oxygen requirement, or respiratory failure.[44,45] Adenovirus can have the same clinical presentation, in addition to causing epidemic conjunctivitis.[50] Of note, ophthalmologic procedures can contribute to adenovirus spread.[50] Coronavirus infection can be associated with respiratory decompensation or abdominal distention and fever.[51] Enteroviruses can be associated with a clinical picture suggestive of NEC,[48] overwhelming septicemia, rash, or aseptic meningitis.[47] Rotavirus infection is associated with diarrhea that is frequent and watery in term infants, whereas in preterm infants it is more frequently bloody and associated with abdominal distention and intestinal dilatation.[49]

CLINICAL MANIFESTATIONS

The clinical features of nosocomial sepsis in neonates are nonspecific. There are no clinical features that are characteristic exclusively of infections caused by nosocomial pathogens. Fanaroff et al.[53] reviewed data from the Neonatal Research Network Intravenous Immunoglobulin trial in order to identify the predominant clinical features of late-onset sepsis in neonates. The most common clinical features were increased apnea/bradycardia (55%), increased gastrointestinal problems (46%) (such as feeding intolerance, abdominal distention, or bloody stools), increased respiratory support (29%), and lethargy/hypotonia (23%). The predominant laboratory indicators were an abnormal white blood cell count (46%), (e.g., leukocytosis, increased immature white blood cells, or neutropenia), unexplained metabolic acidosis (11%), and hyperglycemia (10%). Unfortunately, the predictive value was low for any of these clinical or laboratory features, with the best positive predictive value only 31%, for hypotension.[53] None of the clinical features was pathogen-specific. In addition, sepsis caused by CONS or *Candida* species can be more indolent in clinical presentation.[54]

Abnormal heart rate characteristics (reduced variability and transient decelerations) occur early in the course of neonatal sepsis.[55] Technology has been developed to monitor changes in heart rate characteristics continuously and noninvasively in an attempt to provide a clinical tool with the potential for alerting medical personnel in advance of overt clinical illness from late-onset sepsis.[56]

The most common signs of CVC-BSI in neonates are fever (49%) and pulmonary dysfunction (30%).[57] Erythema or purulent discharge at the insertion site was present in only 20% of cases of CVC-BSI in neonates.

LABORATORY DIAGNOSIS

Whenever a nosocomial infection is suspected enough to begin antibiotics, the pretreatment diagnostic evaluation should include blood cultures, cerebrospinal fluid (CSF) culture, and urine culture. Late-onset meningitis and UTIs commonly occur in neonates with negative blood cultures[14,15] and will be missed if CSF or urine cultures are not obtained. The Pediatric Prevention Network recommends routinely obtaining two blood cultures from neonates with suspected sepsis because isolation of CONS from a single blood culture, especially without an elevated C-reactive protein within 2 days,[1] should generally be interpreted as a contaminant in order to reduce vancomycin use in neonates.[58]

A definitive diagnosis of nosocomial infection due to bacterial or fungal species requires isolation of the organism from blood or another normally sterile body site or fluid. Exceptions are fungi such as *Aspergillus* and those that cause zygomycosis, as they can cause

disseminated multiorgan infection but are rarely isolated from blood.[27] Skin biopsy is the sole means of establishing the diagnosis of zygomycosis in premature infants with progressive necrotizing skin lesions.[27]

When viral infections are suspected, clinicians can make a presumptive diagnosis by rapid diagnostic testing (e.g., a positive direct fluorescent antibody test or enzyme immunoassay (EIA) for influenza A, respiratory syncytial virus, adenovirus, or EIA for rotavirus) and a definitive diagnosis by identification of a viral pathogen from nasal wash, tracheal secretions, bronchoalveolar lavage fluid, or stool, as appropriate.

Other laboratory studies provide clinicians with an index of the severity of infection, help guide therapy, and monitor response to treatment. As with infections in older children, laboratory evidence of organ dysfunction(s), particularly renal failure, consumption coagulopathy, neutropenia, thrombocytopenia, or hypoperfusion, usually indicate severe illness and a more guarded prognosis. Attempts to identify dependable serum markers for diagnosis, severity, or prognosis have been variably successful. The utilities of C-reactive protein,[59] various proinflammatory cytokines,[60] and/or procalcitonin[61] levels as useful markers for diagnosis and severity of neonatal sepsis continue to be debated.

TREATMENT

Empiric Therapy

Empiric antimicrobial therapy for suspected nosocomial infections without a clinical focus in neonates should be guided by knowledge of the distribution and case-fatality rates of pathogens and the susceptibility patterns of likely pathogens in a particular NICU. Empiric antibiotic regimen should effectively treat gram-negative pathogens, particularly *Pseudomonas aeruginosa*, because these organisms account for the majority of cases of fulminant late-onset sepsis in neonates.[28] An aminoglycoside should be used for empiric treatment of possible gram-negative sepsis, the choice of which is determined by the antimicrobial susceptibility patterns of isolates from the NICU. During an outbreak of gentamicin-resistant gram-negative septicemia, amikacin may be the preferred aminoglycoside. Third-generation cephalosporins are not recommended for routine empiric therapy in neonates (unless knowledge of the patient's flora or the NICU pattern of infections specifically dictates) because: (1) they do not effectively treat most *Pseudomonas aeruginosa* and some Enterobacteriaceae; (2) routine use in NICUs has been associated with emergence of cephalosporin-resistant gram-negative bacilli[62,63]; and (3) they have been associated with increased risk of candidemia in VLBW neonates.[54]

Ampicillin may be considered for empiric treatment of possible gram-positive septicemia, especially if *Enterococcus* and *Streptococcus agalactiae* are common pathogens causing late-onset sepsis in the NICU. In the past, a semisynthetic penicillin, such as oxacillin, was considered for empiric treatment of possible gram-positive late-onset septicemia in neonates, because methicillin-susceptible *Staphylococcus aureus* (MSSA) was prevalent.[1,28] The recent emergence of community-acquired methicillin-resistant *S. aureus* (CA-MRSA) as a neonatal pathogen may require modification of this approach in the future.[33,34]

Broad empiric usage of vancomycin, as recommended by some,[64] because CONS sepsis is common and MRSA sepsis is possible in VLBW infants, creates additional problems. Stoll et al.[1] found it alarming that 44% of all VLBW infants in the NICHD Neonatal Research Network were treated with vancomycin whether or not they had CONS sepsis. The Hospital Infection Control and Practices Advisory Committee of the CDC recommends avoiding empiric vancomycin therapy in patients with suspected sepsis to prevent the emergence and spread of vancomycin-resistant enterococci.[65] Karlowicz et al.[28] showed that avoidance of vancomycin as an empiric antibiotic had no impact on the very low rate of fulminant sepsis for CONS sepsis in neonates and that the practice of starting vancomycin only after CONS were identified in blood cultures did not prolong the duration of sepsis caused by CONS. Sanchez et al.[66] reported their experience with restricted use of vancomycin in neonates, even though CONS was the predominant pathogen, and found no change in the number of deaths as a result of CONS sepsis despite a 53% reduction in vancomycin use. Consequently, the Pediatric Prevention Network has recommended restricting the use of vancomycin for empiric therapy of neonates with suspected late-onset sepsis.[58] Because, in the past, MRSA has been rare in most NICUs,[58] it is recommended that empiric use of vancomycin be reserved for neonates in NICUs with persisting MRSA colonization and infections that do not resolve with cohorting and standard infection control measures. How CA-MRSA will modify this recommendation remains to be seen.[33,34]

Some investigators have suggested empiric antifungal therapy for VLBW infants at high risk of candidemia,[67] hoping to reduce morbidity and mortality in an approach analogous to the algorithm for persistent fever and neutropenia in patients with cancer.[68] A predictive model for empiric antifungal therapy in neonates has been developed,[67] but it has not been validated in prospective trials. Consequently, empiric antifungal therapy cannot be recommended in neonates with suspected late-onset sepsis.

The suggested duration of therapy for nosocomial infections by anatomic site is summarized in Table 96-3. The duration of treatment for individual patients should be determined by virulence of the pathogen, time it takes for follow-up cultures to become negative, rapidity of clinical response, removal or retention of CVC, and adequate drainage of purulent foci, if present.

Adjunctive Therapy

Several adjunctive therapies have been investigated in late-onset sepsis, including immunoglobulin intravenous (IGIV), hematopoietic growth factors (granulocyte colony-stimulating factor (G-CSF) and granulocyte–macrophage colony-stimulating factor (GM-CSF)), and granulocyte transfusions. IGIV,[69] G-CSF and GM-CSF[70] have been evaluated by the Cochrane Database of Systematic Reviews, with the conclusion that there is currently insufficient evidence to support routine use in the treatment of neonates with sepsis, even though mortality was decreased. Zipursky[71] advised against the use of G-CSF or GM-CSF in newborns because of considerable potential for harm due to formation of antibodies against these factors.[72] A review of the data from studies of granulocyte transfusions in septic neonates demonstrated improved outcome in the situation of neutropenia depletion of the marrow storage pool, but associated morbidities, including fluid overload, worsening hypoxia and respiratory distress from leukocyte sequestration in the lung, graft-versus-host disease,

TABLE 96-3. Suggested Duration of Therapy for Selected Nosocomial Infections

Site or Manifestation of Infection	Duration of Therapy (days)
BSI	10–14
Meningitis	14–21
CVC-BSI without removal of CVC	14[a]
Osteomyelitis/septic arthritis	4–6 weeks
VAP	10–14
UTI	10–14
Endocarditis	4–6 weeks
Candidemia, catheter removed, rapidly resolving	10–14
Fungemia, disseminated	~4 weeks
Skin or subcutaneous lesion	7–10

BSI, bloodstream infection; CVC-BSI, central venous catheter-related bloodstream infection; CVC, central venous catheter; UTI, urinary tract infection; VAP, ventilator-associated pneumonia.
[a]After first negative blood culture.

and risk of transmission of viral infections.[73] Careful assessment of the risks versus the benefits of leukocyte administration is required.

MANAGEMENT OF CENTRAL VENOUS CATHETER-RELATED BLOODSTREAM INFECTIONS

Catheters are intravascular foreign bodies; removal is the optimal management when a BSI occurs. Nevertheless, the vital importance of CVCs in critically ill neonates must be acknowledged, especially since successful in situ treatment of CVC-BSI has become more common.[74,75] It is clear that BSI can occur with or without CVC involvement. Differentiation of these two conditions is difficult, however. No data derived from large randomized trials are available as guidelines for the management of CVC-BSI. However, several large observational studies have compared outcomes of late-onset sepsis in neonates with CVCs treated with and without CVC removal. Data suggest that management strategies can be different, depending on the pathogen and clinical condition of the infant. If treatment with the CVC in situ is attempted, antimicrobial agents should be administered through the infected catheter. The algorithm shown in Figure 96-1 may help clinicians manage CVC-BSI in neonates until better evidence becomes available from randomized trials.

Candida Species

Until recently, the attitude towards removal of CVCs at time of diagnosis of *Candida* sepsis varied among pediatric specialists. A 1998 survey reported that only 35% of neonatologists and 53% of infectious disease specialists would immediately remove a CVC from a neonate with the first positive blood culture for *Candida* species.[76] A single-center retrospective study of 104 cases reported that failure to remove CVCs as soon as *Candida* sepsis was detected in neonates was associated with significantly increased mortality in *C. albicans* sepsis (case-fatality risk increase of 39%, number needed to harm of 2.6) and significantly prolonged duration of *Candida* sepsis regardless of *Candida* species (median of 6 days versus 3 days).[77] These findings were confirmed in a retrospective multicenter study of ELBW infants with candidiasis.[78] Consequently, the Infectious Diseases Society of America guidelines for treatment of candidiasis[79] strongly recommend that CVCs be removed as soon as *Candida* sepsis is detected in neonates, if feasible. Unfortunately, in some neonates, CVCs cannot be removed because of severe generalized skin breakdown or unstable critical condition, but these conditions should be present in less than 15% of cases.[80]

Coagulase-Negative Staphylococci

In contrast to cases of *Candida* sepsis, CVC-BSI in neonates associated with bacterial pathogens have a reasonable chance of success with in situ treatment. CONS bacteremia is the most common cause of CVC-BSI in neonates.[4] It has been difficult to interpret clinical studies of CONS CVC-BSI in neonates because many studies required only a single positive blood culture to diagnose CONS bacteremia,[81–83] allowing inclusion of many cases of pseudobacteremia.[30] A series of 119 cases[84] in which two positive blood cultures yielding CONS within 3 days of each other were required for entry consideration (definition of CONS bacteremia consistent with CDC guidelines)[65] concluded that in situ treatment could be successful in many neonates with CONS CVC-BSI, but observed it was unclear how long clinicians should wait before abandoning sterilizing attempts and removing the CVC.[85] Karlowicz et al. reported that in situ treatment with vancomycin was successful in 46% of cases with CONS CVC-BSI.[84] In their report, none of 19 patients with CONS bacteremia > 4 days' duration after institution of antibiotic therapy showed resolution of bacteremia until CVC were removed. In contrast, 79% of cases with CONS bacteremia for 1 or 2 days were successfully treated without CVC removal, but successful treatment decreased to 44% when bacteremia persisted for 3 to 4 days.[84] Therefore, when CONS bacteremia persists in neonates who have CVCs that are vital

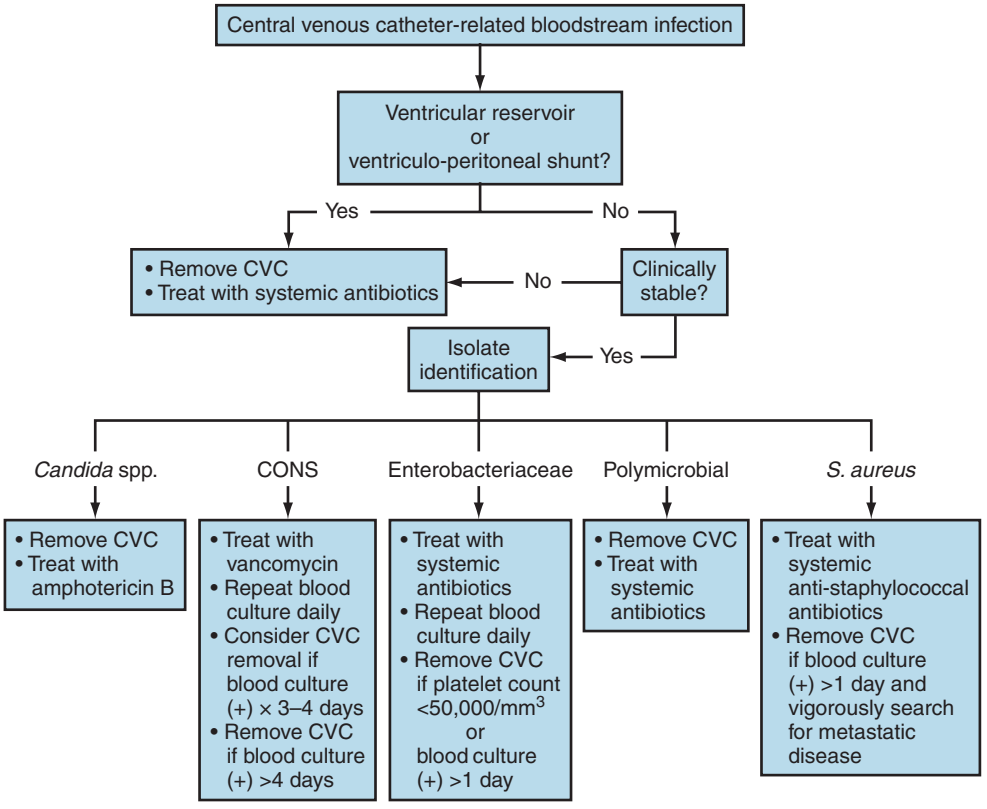

Figure 96-1. Suggested management of central venous catheter (CVC)-related bloodstream infections in neonates. CONS, coagulase-negative staphylococci; MSSA, methicillin-susceptible *Staphylococcus aureus*. [a]After commencement of appropriate antibiotic therapy.

to clinical care, we recommend that clinicians give antibiotic treatment for 2 days, perhaps as long as 3 to 4 days in special circumstances, but never beyond 4 days of persistent bacteremia, before removing CVCs.

Enterobacteriaceae

Enterobacteriaceae are a common cause of late-onset sepsis in neonates,[86] but, until recently, data were limited concerning Enterobacteriaceae CVC-BSI. In a report of 53 cases of Enterobacteriaceae CVC-BSI in neonates, Enterobacteriaceae bacteremia resolved with use of gentamicin or tobramycin without removal of CVCs in 45% of cases in which it was attempted.[87] In contrast to successful in situ treatment despite several days of CONS bacteremia, successful treatment of Enterobacteriaceae bacteremia of greater than 1 day's duration was unlikely without removal of CVCs, decreasing from 85% to 24% successful in situ treatment. Attempting to treat Enterobacteriaceae bacteremia with CVC in situ was not associated with increased mortality, increased morbidity, or increased recurrence. In addition, Enterobacteriaceae cases with severe thrombocytopenia (platelet count < 50,000/mm^3) on the first day of bacteremia did not resolve until CVCs were removed in 82% of cases, compared with 32% of cases without severe thrombocytopenia.[87] Therefore, we recommend that CVCs be removed in cases associated with severe thrombocytopenia or if Enterobacteriaceae bacteremia persists > 1 day after commencing appropriate antibiotic treatment.

Polymicrobial Agents

Polymicrobial sepsis in neonates now accounts for about 14% of cases of late-onset sepsis.[88] In a preliminary report of 70 cases of polymicrobial CVC-BSI in neonates,[89] successful in situ treatment of polymicrobial sepsis was uncommon, occurring in only 20% of cases, even when one of the pathogens was CONS. The risk of case fatality was significantly increased by 20% when in situ treatment was attempted. On the basis of this experience, our recommendation is for removal of CVCs, as soon as possible, in cases of polymicrobial sepsis.

Staphylococcus aureus

Finally, *S. aureus* is one of the most common and most serious causes of late-onset sepsis in the NICU.[90] In adults, removal of CVC is advised in cases of *S. aureus* bacteremia, unless there is a *compelling* reason to conserve the catheter.[74] There are few published reports concerning *S. aureus* CVC-BSI in neonates. In a case series of 11 infants, many developed end-organ damage, and only 1 case was successfully treated with CVC in situ.[83] Another case series concerning invasive staphylococcal disease in neonates included 25 cases of *S. aureus* bacteremia, and found no difference in occurrence of complications or outcome in cases treated with or without CVC removal.[64] Recently, there was a preliminary report that MSSA CVC-BSIs were successfully treated with CVCs in situ in 13 (62%) of 21 cases.[91] Most cases that were successfully treated with CVC in situ showed resolution of the *S. aureus* bacteremia within 24 hours of starting a penicillinase-resistant penicillin. Focal complications occurred in 34% of 47 cases of MSSA bacteremia, but, unlike a previous report,[83] at least 75% of focal complications were already present when the first blood culture was obtained.[91] The duration of bacteremia was significantly longer in cases with focal complications compared with those without complications – a median of 6 days versus 1 day, respectively. Focal complications, like soft-tissue abscesses, endocarditis, and osteomyelitis, may be more important risk factors for persistent *S. aureus* bacteremia than retention of CVCs. Similar to that for Enterobacteriaceae CVC-BSI, and we advise a cautious approach and recommend that CVCs be removed immediately if MSSA CVC-BSI persists > 1 day with appropriate antibiotic treatment.

Other Considerations

Another clinical feature to consider when deciding whether to treat CVC-BSI without CVC removal is the presence of other foreign bodies. We reported an infant with a ventricular reservoir who developed CONS meningitis on day 7 of 9 days of persistent CONS bacteremia despite vancomycin therapy with the CVC in situ.[84] The long-term consequences of meningitis and shunt revision are so potentially devastating that we consider the presence of a ventricular reservoir or ventriculoperitoneal shunt to be a contraindication to attempting to treat CVC-BSI with CVC in situ.

MANAGEMENT OF PERSISTENT BLOODSTREAM INFECTIONS

The likelihood of adverse outcomes, such as focal complications, increases when BSIs persist in neonates. Although it is uncertain whether focal complications are the cause or the consequence of persistent BSIs, it is imperative that clinicians obtain serial blood cultures to document resolution of BSIs and perform thorough diagnostic evaluations searching for focal complications if BSIs persist. In addition, when BSIs persist, clinicians must make management decisions concerning timing of CVC removal and changes in antimicrobial therapy.

Removal of CVC in cases of persistent bacterial BSI, defined as > 1 day of appropriate antibiotic therapy for Enterobacteriaceae and MSSA and > 2 to 4 days for CONS, should be done promptly. Of note, two case series reported success treating persistent staphylococcal bacteremia in neonates with CVC in situ, without adverse consequences, by adding rifampin to standard antistaphylococcal antimicrobial therapy.[92,93]

Some pathogens, especially *Candida* species, may continue to grow from blood cultures even when CVCs are removed promptly, and the neonate is given antibiotic therapy to which the organism is susceptible. In one report of 96 cases, candidiasis lasted > 7 days in 30% of cases, even when CVCs were removed on the day the first positive culture report was received, and the infants were promptly given systemically therapeutic doses antifungal therapy.[94] The risk of focal complications was significantly increased in cases with persistent invasive candidiasis compared with nonpersistent cases (48% versus 13%). The most common focal complications in neonates with persistent candidiasis are "fungus ball" uropathy (29%), renal infiltration (20%), abscess (19%), and endocarditis (9%).[94] Since more than half of neonates with persistent candidiasis do not have focal complications, Chapman & Faix[94] suggested that aggressive imaging for focal complications be reserved for cases in which blood cultures remain positive after several days of antifungal therapy, or if there are clinical signs suggesting focal complication. On the other hand, Noyola et al.[95] documented focal complications in 23% of 86 neonates with candidemia, including some with only one positive blood culture, and they recommended renal, cardiac, and ophthalmologic diagnostic evaluations in all neonates with candidemia because the presence of focal complications may affect the duration of therapy and outcome.

The prevalence of persistent bacteremia, defined as recovery of the same pathogen > 24 hours after initiation of antibiotic therapy to which the organism is susceptible, was reported to be 22% in a series of 335 cases of bacteremia in one NICU.[93] In this case series, the frequent decision to treat bacterial BSI with CVC in situ contributed to the high prevalence of persistent cases. The prevalence of focal suppurative complications (osteomyelitis, septic arthritis, abscess, infected thrombus, or endocarditis) was significantly increased in infants with persistent non-CONS BSI compared with persistent CONS BSI (28% versus 3%).[93] *S. aureus* caused 50% of persistent non-CONS BSIs and 67% of the cases with focal complications. The duration of persistence of bacteremia significantly correlated with the presence of focal complications in non-CONS cases. Consequently, Chapman & Faix[93] recommended that all neonates with persistent bacteremia undergo extensive evaluation for focal complications,

especially looking for endocarditis, osteomyelitis, and soft-tissue abscesses. This evaluation is especially important in cases of persistent BSI caused by *S. aureus* or Enterobacteriaceae, because the bacteremia will not resolve until the soft-tissue abscesses or bone or joint infections are surgically drained, or the intravascular clot dissolves.

PREVENTION OF NOSOCOMIAL INFECTIONS

The largest proportion of healthcare-associated infections in the NICU result from patient requirements for technological support and hands-on care by healthcare workers. The most commonly utilized devices in the NICU are mechanical ventilation and intravascular access. Risk factors for CVC-BSI have been extensively examined and include blood and blood component transfusion,[96] blood drawing and manipulation (including disinfection) of the catheter hub,[97] catheter hub colonization, exit site colonization, and duration of parenteral nutrition.[98] Thus, approaches that minimize catheter manipulation, blood drawing, and blood product administration via the catheter prevent colonization of the skin entry site and prevent infections.[99]

Hand decontamination by healthcare workers is the most effective means of preventing healthcare-associated infection in the NICU, but is often overlooked or performed poorly in the NICU environment.[100] A remote video camera study on random nursing shifts reported handwashing only 24% of the time before infant contact by healthcare workers in a regional referral NICU.[101] Activities such as skin contact, respiratory care, and diaper changes are independently associated with increased hand contamination.[42]

Recently, the CDC Guideline for Hand Hygiene in Health Care Settings recommended that healthcare workers use alcohol-based hand rubs over antimicrobial soaps.[102] Alcohol-based hand rubs have excellent antimicrobial spectrum against bacteria, fungi, and viruses. In addition, alcohol-based hand rubs have fast speed of action and are the least likely to cause dermatitis on the hands of healthcare workers.[103] Use of alcohol-based hand rubs in a NICU has been associated with significantly improved hand hygiene by healthcare workers compared with use of antimicrobial soap.[104] Unfortunately, compliance was still unacceptably low (23%).

Support of respiratory and enteral function figure prominently in the care of the premature infant. Systemic corticosteroid and H_2-blocking agents have been used to prevent chronic lung disease and enhance gastrointestinal function, respectively. Dexamethasone therapy in VLBW infants is associated with increased risk of late-onset sepsis.[105] Use of H_2-blocking agents in VLBW infants is associated with higher rates of NEC,[106] BSIs,[105] and candidemia.[107] Avoiding the use of dexamethasone and H_2-blocking agents should reduce rates of late-onset sepsis. Establishing full enteral feeds with human milk is associated with lower risks of late-onset sepsis in ELBW infants.[108]

Prophylactic administration of IGIV has been associated with decrease in infection rates by 3% to 4% in premature infants without improving mortality rates[109]; it is not recommended.

Several clinical trials have examined prophylactic administration of fluconazole for prevention of *Candida* colonization and BSI in ELBW infants, observing that daily or twice-weekly administration can decrease *Candida* BSI and attendant mortality.[110,111] However, it is unclear whether prophylaxis significantly alters morbidity or how great is the risk of emergence of fluconazole resistance. Use of fluconazole prophylaxis to prevent *Candida* BSI in ELBW infants remains controversial, especially because the rates of *Candida* BSIs vary greatly among NICUs.[112] In their editorial review of fluconazole prophylaxis studies in NICUs, Long & Stevenson concluded that fluconazole prophylaxis for ELBW infants should not be implemented in NICUs.[113] They identified the need for a multicenter study to answer the questions of benefit and risk in ELBW infants of fluconazole prophylaxis which is adequately powered to investigate all BSIs, all-cause mortality, and weighing potential unintended consequences (such as prolongation of use of catheter, antibiotics, corticosteroids) and the long-term expectation of emergence of resistant pathogens.

Rates of infection among regional NICUs vary by as much as fivefold.[113] Lower rates are attributable to more restrictive use of CVCs and parenteral nutrition, but other, undefined practices also influence rates. Systematic investigation of clinical practices in NICUs with low rates of nosocomial infection may lead to strategies for prevention of infection that can be applied to other NICUs.[114] Schelonka et al.[115] reported that comprehensive infection control practices resulted in a sustained reduction in both bacterial and fungal nosocomial infection rates in a single regional NICU. The comprehensive infection control intervention[115] included: (1) improving hand hygiene and reducing microbial contamination of patient care space; (2) limiting duration of umbilical catheters and developing a highly trained core of nurses to insert and maintain peripherally inserted CVCs; (3) increasing rates of breastfeeding and shortening the interval to full enteral feeding; (4) reducing the duration of empiric antibiotic therapy with negative culture results; and (5) educating and empowering the entire NICU staff to encourage maximal adherence to comprehensive infection control practices. A similar program using evidence-based infection control practices virtually eliminated CVC-BSIs in an adult surgical intensive care unit.[116] The best hope for sustained prevention of nosocomial infections in NICUs appears to be changing the NICU culture to one of collaborative continuous quality improvement and more pervasive use of human milk feeding.