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94 Healthcare-Associated Infections in the Neonate

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As progressively smaller premature infants survive beyond the first few days of life, healthcare-associated infections (HAIs) have emerged as a major cause of morbidity and late mortality in the neonatal intensive care unit (NICU). Effective prevention and treatment of HAIs in the NICU require an understanding of the distribution of pathogens, 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 HAIs in the NICU. They can occur in isolation or in association with urinary tract infections (UTIs)[1] and meningitis.[2] Endocarditis, osteomyelitis, pyogenic arthritis, ventilator associated pneumonia, peritonitis, conjunctivitis, and skin abscesses are important, less common HAIs (Table 94.1).

Late-Onset Sepsis

Late-onset sepsis is defined by the National Institute for Child Health and Human Development Neonatal Research Network (NICHD NRN) as BSIs occurring in neonates at or after 72 hours of age. Late-onset sepsis is most common in very low birth weight (VLBW) infants (<1500 g), for whom HAIs increase hospital length of stay by 19 days and cause 45% of deaths beyond 2 weeks of age.[3] Late-onset sepsis occurred in 21% of VLBW infants who survived beyond 3 days of age in the NICHD NRN study,[3] and similar rates have been reported from the Neonatal Networks in Canada (24%)[4] and Israel (30%).[5]

At the institutional level, the prevalence of late-onset sepsis in VLBW infants varies more: 11% to 32% in the NICUs of the NICHD NRN[3] and 7% to 74% in the NICUs participating in the Canadian Neonatal Network.[4] Data from the NICHD NRN confirm the risk of late-onset sepsis despite advances in medical care for the extremely premature infant, with 36% of infants born between 22 and 28 weeks' gestation having late-onset sepsis. The rate of late-onset sepsis is strongly and inversely associated with birth weight and gestational age, decreasing from about 60% among neonates with a gestational age of less than 25 weeks to 20% among infants born at 28 weeks' gestation.[6] Consequently, institutions caring for more extremely low birth weight (ELBW) infants have higher rates. Management practices, particularly those concerning the use and maintenance care of central venous catheters (CVCs) or peripherally inserted central catheters (PICCs), can further impact these rates of infection.[7]

Most cases of late-onset sepsis in neonates are associated with a central catheter (i.e., CVC or PICC)[3] and are referred to as central line–associated bloodstream infections (CLABSIs). The Centers for Disease Control and Prevention (CDC) and National Healthcare Safety Network (NHSN) definition[8] for a CLABSI includes isolation of a pathogen from one blood culture or of a skin commensal from two blood cultures, one or more clinical signs of infection (e.g., apnea, bradycardia, temperature instability) that are not related to an infection at another site, and presence of a CVC at the time the blood culture is obtained or within 48 hours before the development of the infection.

TABLE 94.1 Common Sites and Causes of Healthcare-Associated Infections in the Neonatal Intensive Care Unit

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

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

A rate of HAI that is linked to device use, such as for a CLABSI, helps control for variation in management practices from institution to institution. The preferred unit of measure is infections per 1000 catheter-days. The NHSN continues to recommend that CLABSI should be a major focus of surveillance and prevention efforts in NICUs and that institutions provide summary data on CLABSI rates for different birth weight groups. Values at the extremes of the NHSN data indicate problems with effective infection control or underreporting of CLABSI events, respectively. Individual NICUs are encouraged to monitor and compare their CLABSI rates with NHSN data, which are updated annually and usually published in December.[9]

In 2015, data on CLABSI rates from NHSN participating level III NICUs for the year 2013 showed a median number BSIs per 1000 catheter-days of 1 for infants weighing 750 g or less, 0 for those weighing 751 to 1000 g, and 0 for those weighing 1001 to 1500 g at birth.[9] The 90th percentile of BSIs per 1000 catheter-days was 6.3 for infants weighing 750 g or less, 4.4 for those weighing 751 to 1000 g, and 3.2 for those weighing 1001 to 1500 g at birth. These values represent a continuing decline in CLABSIs and device use. Data also were obtained for umbilical catheter–associated BSIs for the same period, which revealed low rates of infection in all weight categories.[9]

Coexistence of endocarditis, an infected intravascular thrombus, osteomyelitis, or pyogenic arthritis should be considered when BSIs persist in neonates. *Staphylococcus aureus* is the most common cause of endocarditis[10,11] and osteomyelitis[12,13] in neonates. These complications are uncommon, but the diagnosis should be considered when multiple blood cultures are positive in a neonate with a CVC.

Late-Onset Meningitis

Until recently, there were few surveillance data on the incidence of late-onset meningitis in the NICU. Consequently, considerable variation has existed in clinical practice concerning performance of a lumbar puncture in neonates with suspected late-onset sepsis. In a prospective study of 9641 VLBW infants who survived more than 3 days, late-onset meningitis occurred in 134 infants. This represented 1.4% of all infants and 5% of those who had a lumbar puncture performed. Compared with infants without septicemia, VLBW infants with meningitis were more likely to have seizures (25% vs. 2%), and were more likely to die (23% vs. 2%).[2] One third (45 of 134) of the infants with meningitis had blood cultures drawn simultaneously that were negative.

Because meningitis can alter duration of antibiotic therapy, affect long-term prognosis, and be complicated by parameningeal or brain abscess, 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, lumbar puncture should be performed when clinical stabilization is achieved.

Urinary Tract Infection

UTI is a common HAI in adults and frequently is associated with an indwelling urinary catheter,[9] which seldom is used in VLBW infants. There is considerable variation in performing urine culture and analysis when late-onset sepsis is suspected.[14] Urine specimens obtained by bag collection from infants have notoriously high rates of contamination—up to 63%[15]—and are not recommended. Suprapubic bladder aspiration is performed less commonly because of the risk of serious, albeit rare, complications such as bowel perforation[16] and increased pain.[17] Sterile urethral catheterization can be performed easily by experienced nurses, even in ELBW infants, and has a potentially higher rate of success in obtaining urine compared with suprapubic bladder aspiration.[18,19]

Although prospective studies have not been performed, UTI, may be the second most common HAI in the NICU. The reported prevalence among premature infants ranges from 4% to 25%, but these reports are from the 1960s and do not represent the typical population in NICUs currently. A retrospective study reported an 8% rate of late-onset UTI among 762 VLBW infants in one NICU over an 11-year period.[20] UTI was more common in ELBW infants (12%) than in infants with birth weights between 1001 and 1500 g (6%). In a prospective study of one NICU over a 1-year period, the rate of HAIs was 17.5%, with only a 0.7% rate if UTIs.[21] When intervention-associated infections were examined, urinary catheter–associated UTIs (CAUTIs) accounted for up to 17.3%. The highest risk of HAIs was found for patients with a birth weight of less than 1000 g (relative risk, 11.8).[21]

Examining paired blood and urine cultures for 189 VLBW infants suspected of having late-onset sepsis, Tamim and colleagues detected UTI in 25%.[14] Among VLBW infants with UTIs, 62% (30 of 48) had a negative blood culture. Phillips and Karlowicz[1] reported a case series of 60 UTIs among NICU patients, primarily documented through specimens obtained by urethral catheterization when late-onset sepsis was suspected. Simultaneous BSIs with the same pathogen were detected in 52% of cases of *Candida* UTI and 8% of cases of bacterial UTI. Because most VLBW infants with UTI do not have a BSI, it is our practice to obtain urine for culture by sterile urethral catheterization or by suprapubic aspiration, when late-onset sepsis is suspected.

Ventilator-Associated Pneumonia

It is difficult to diagnosis healthcare-associated pneumonia in any patient population and particularly in the NICU population. New definitions from the CDC and NHSN in 2008 attempted to provide reproducible criteria for surveillance, classifying pneumonia as three specific types: clinically defined (PNU1), pneumonia with laboratory findings (PNU2), and pneumonia in immunocompromised patients (PNU3).[8] Infants and children usually fall into category PNU1. Diagnosis of ventilator-associated pneumonia (VAP) is especially difficult in neonates because noninfectious conditions such as respiratory distress syndrome and bronchopulmonary dysplasia are common and frequently cause radiologic abnormalities.

The NHSN has published specific guidelines adapted to infants younger than 1 year of age, but they are not specific to the premature infant. New benchmark data are becoming available through the NHSN. The highest incidence of VAP (i.e., 1.3 cases per 1000 ventilator days) occurs among infants with a median birth weight of less than 750 grams.[9]

A few investigators have attempted to establish reproducible criteria for VAP specific to the neonatal population. Cordero and coworkers[22] showed that finding purulent tracheal aspirate fluid with a positive tracheal culture in mechanically ventilated neonates in the absence of worsening clinical or radiologic findings is more consistent with clinically insignificant tracheal colonization than with VAP.

Apisarnthanarak and colleagues[23] performed a prospective cohort study addressing risk factors, microbiology, and outcomes of VAP in neonates. Their definition of VAP required new and persistent radiologic evidence of focal infiltrates more than 48 hours after initiating mechanical ventilation and treatment with antibiotics for more than 7 days for presumed VAP. By this definition, 19 (28%) of 67 of mechanically ventilated VLBW infants developed VAP, with a rate of 6.5 per 1000 ventilator-days.[23] Gram-negative bacteria were isolated from tracheal aspirates in 94% of VAP episodes, and most cases were polymicrobial. VAP developed in neonates at a median of ventilation 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 among neonates who required NICU care more than 30 days.[23]

Intestinal Perforation and Peritonitis

Peritonitis associated with intestinal perforation is a serious HAI in the NICU. Coates and associates[24] 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 found in 75% of NEC cases, compared with 25% of FIP cases. *Candida* species were found in 44% of FIP cases and in 15% of NEC cases. Coagulase-negative staphylococci (CoNS) were found in 50% of FIP cases and in 14% of NEC cases.

Peritoneal fluid cultures were positive and helped direct antimicrobial therapy in 40% (46 of 116) of cases.[24] Peritoneal fluid culture should be obtained for all neonates with intestinal perforation, regardless of cause.

Other Infections

Conjunctivitis is common in healthy term newborns. Few studies address its occurrence in the NICU. Diagnosis can be complicated because conjunctival colonization, especially with CoNS, is common in the NICU.[25]

Occurrence rates of conjunctivitis in NICUs vary, with Haas and colleagues[26] reporting 5% in a prospective study and Couto and coworkers[27] reporting 12% (although infants of all birth weights were included). The most common pathogens are enteric gram-negative bacilli, but nonenteric flora such as *Pseudomonas aeruginosa* also can occur.[28]

Most neonatal skin infections are caused by *S. aureus.* Clinical manifestations include impetigo, cellulitis, soft tissue abscesses, and toxin-mediated diseases such as staphylococcal scalded skin and toxic shock syndromes.[29] Methicillin-resistant and methicillin-susceptible *S. aureus* (MRSA and MSSA) cause similar infections. Carey and associates reported an incidence of 4.8% for MSSA and 1.8% for MRSA among ELBW (<1000 g) infants' skin infections, with 53% of all NICU skin infections occurring in the ELBW cohort.[30] *P. aeruginosa* can cause ecthyma gangrenosum lesions even in a VLBW or ELBW infant.[31] Zygomycetes can cause progressive necrotizing skin lesions in neonates, with or without gastrointestinal manifestations.[32]

PATHOGENS OF LATE-ONSET INFECTIONS

Gram-positive organisms are the predominant cause of late-onset sepsis in the NICU (48% to 70% of cases), but gram-negative organisms (19% to 25% of cases) and fungi (12% to 18% of cases) also are important.[3,33–36] Across many reports, the same pathogens cause most episodes: CoNS, *Candida* species, *S. aureus,* and Enterobacteriaceae (Table 94.2).

Very-late-onset sepsis (VLOS) is becoming more common as VLBW infants are living longer with ongoing needs for interventions. VLOS is defined as an infection after 120 days of life. The organisms that cause late-onset sepsis also cause VLOS.[34,37]

Usual Pathogens

The frequency of pathogens and likelihood that certain pathogens cause rapid progression to severe complications and death (i.e., fulminant sepsis) must be considered when choosing empiric therapy. Karlowicz and colleagues[33] reported that although gram-negative organisms caused only 25% of BSIs in their series, they caused 69% of *fulminant* late-onset BSIs. Of the gram-negative bacilli, *P. aeruginosa* caused 42% of fulminant cases and overall had a case-fatality rate of 56%, which contrasts with a case-fatality rate of less than 1% for CoNS.[33] Similar findings have been reported by others.[3,38]

CoNS are the most common pathogens causing late-onset sepsis, accounting for 35%[29] to 48%[3] of cases. Distinguishing between true BSI and pseudobacteremia can be difficult. The CDC and NHSN define a laboratory-confirmed bloodstream infection (LCBI) with common skin contaminant flora as ≥2 positive blood cultures drawn on separate occasions.[8] In the report of Stoll and coworkers[3] of late-onset sepsis, a rate of 48% for CoNS would have fallen to 29% if LCBSIs had been included, a rate similar to the 35% reported by Karlowicz and colleagues.[33] There has been a substantial decline in late-onset CoNS BSIs the past decade due to implementation of several infection prevention initiatives.[39]

Gram-positive organisms are the predominant pathogens in VLOS, although *S. aureus* and *Enterococcus* species can be more common than CoNS. Wynn and associates found that 48% of infections in VLBW infants were caused by gram-positive organisms, followed by gram-negative bacilli and then fungi. *Candida* species produced the highest organism-specific mortality rate in their cohort (33%), followed by gram-positive cocci (28%), but the highest organism-specific mortality rate (44%) was attributed to *S. aureus*, followed by *P. aeruginosa* (38%), similar to late-onset sepsis.[34]

Emerging Pathogens

The prevalence of pathogens in the community, healthcare, and NICU environments and the selective pressure of antibiotic use contribute to antibiotic-resistant infections in NICUs.[40] Gram-positive bacteria, including hospital- and community-associated MRSA (CA-MRSA)[30,41–45] and vancomycin-resistant *Enterococcus faecium,*[46] are serious problems in NICUs. The incidence of CA-MRSA varies widely across NICUs, and mortality rates for MRSA and MSSA infections remain high and frequently are not catheter related.[47] Gram-negative enteric organisms (e.g., extended-spectrum β-lactamase-carrying *E. coli* and *Klebsiella* spp.,[48–50] *AmpC* β-lactamase-carrying *Enterobacter* spp.,[51] metallo-β-lactamase–carrying enteric bacilli,[52] multidrug-resistant *Serratia marcescens,*[53,54] *Leclercia adecarboxylata*[55,56]), nonenteric organisms (e.g., *P. aeruginosa,*[57,58] *Burkholderia cepacia,*[59] *Chryseobacterium meningosepticum*[60]), and recently, highly resistant *Acinetobacter* spp. have emerged in NICU environments.[61,62]

In many instances, reservoirs containing the organism exist within the healthcare environment. Patients are exposed through the use of contaminated medical equipment or by the hands of caretakers, including family members. The former often results from breakdowns in the cleaning procedures used in the NICU or hospital environment,[44,52,54,63] and the latter results from ineffective use of hand hygiene.[57,64,65] Molecular fingerprinting of organisms has been useful for characterizing and controlling some outbreaks.[42,48,52,54,60] Control of NICU outbreaks of antibiotic-resistant organisms frequently requires vigorous application of infection control procedures (e.g., surveillance cultures, patient and staff cohorting, hand hygiene education interventions[66,67]) and active education about the factors that predispose to infection. The CDC began a 12-Step Campaign in 2002 to prevent antimicrobial resistance in various healthcare settings, and these valuable methods can be applied successfully to the NICU.[68]

Viral Infections

HAIs caused by viruses are uncommon in the NICU (incidence <1%),[69] but because of patient vulnerability and the propensity of viruses to spread patient to patient, the impact can be substantial. NICU outbreaks have been caused by respiratory syncytial virus (RSV),[70,71] influenza virus,[72] enteroviruses,[73,74] rotavirus,[75,76] adenovirus,[77] coronavirus,[78] parainfluenza,[79] and norovirus,[80,81] sometimes concurrently.[82] Attack

TABLE 94.2 Pathogens That Commonly Cause Late-Onset Sepsis in the Neonatal Intensive Care Unit

Pathogen	Relative Frequency of Isolation	Comment
CoNS	+++	Most common cause of CLABSI but decreasing with implementation of multipronged infection prevention
Staphylococcus aureus	++	Highest rate of focal complications; MRSA is a problem in some NICUs
Candida species	++	*Candida albicans* and *C. parapsilosis* are the most common species
Enteric GNR	++	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; CLABSI, central line–associated bloodstream infection; GNR, gram-negative rods; MRSA, methicillin-resistant *Staphylococcus aureus*; NICU, neonatal intensive care unit; +++, most frequently isolated; ++, commonly isolated; +, occasionally isolated.

rates can be as high as 33%.[72,74,77] Patients can be asymptomatic or have disease that is lethal,[76] and attributable costs can be high.[70] Viruses can be introduced into the NICU by family members and by ill healthcare personnel (HCP).

RSV, adenovirus and parainfluenza infections manifest with cough, congestion, apnea, increasing oxygen requirement, or respiratory failure.[69,70] Parainfluenza and adenovirus infections manifest with epidemic conjunctivitis (in which ophthalmologic procedures can contribute to spread).[77] Coronavirus infection manifests with respiratory decompensation or abdominal distention and fever.[78] Infections with enteroviruses manifest with NEC-like signs, overwhelming septicemia, rash, or aseptic meningitis.[73] Rotavirus infection manifests with diarrhea that is frequent and watery in term infants, whereas in preterm infants, it more often is bloody and associated with abdominal distention and intestinal dilatation.[75]

CLINICAL MANIFESTATIONS

The clinical features of sepsis in neonates are nonspecific. The most common clinical features are an increase in apnea or bradycardia (55%), gastrointestinal problems (46%) (i.e., feeding intolerance, abdominal distention, or bloody stools), need for respiratory support (29%), and lethargy or hypotonia (23%).[83] Predominant laboratory indicators are 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 values of these features are low; the best positive predictive value is for hypotension (31%).[83]

Abnormal heart rate characteristics (i.e., reduced variability and transient decelerations) occur early in the course of neonatal sepsis.[84] Although technology has been developed to calculate a heart rate characteristic index (HRCi),[85] Griffin and colleagues found that the HRCi performed similar to a clinical scoring system in predicting sepsis.[86]

The most common signs of CLABSI in neonates are fever (49%) and respiratory distress (30%).[87] Only 20% of patients had erythema or purulent discharge at the catheter insertion site.

LABORATORY DIAGNOSIS

The pretreatment diagnostic evaluation of suspected HAI should include at least two blood cultures (e.g., from any indwelling catheter along with peripheral sites), cerebrospinal fluid (CSF) culture, and urine culture. The isolation of CoNS from a single blood culture usually should be interpreted as a contaminant. A definitive diagnosis of a HAI 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 Zygomycetes, which can cause potentially fatal disseminated multiorgan infection but rarely are isolated from blood.[32,88] The use of serum biomarkers for fungal disease such as the 1,3-β-D-glucan assay in neonates requires more study.[89]

When viral infection is suspected, a presumptive diagnosis can be made by rapid diagnostic testing (e.g., positive direct fluorescent antibody [DFA] test for adenovirus, herpes simplex virus; enzyme immunoassay [EIA] for influenza, respiratory syncytial virus, or rotavirus; polymerase chain reaction tests) and a definitive diagnosis by isolation in viral culture. As they become available and validated for testing of body fluids such as blood, CSF, nasal washings, tracheal secretions, bronchoalveolar lavage fluid, or stool, they permit rapid viral diagnosis.

Attempts to identify dependable serum markers for diagnosis, severity, or prognosis have been somewhat successful, including use of the complete blood cell count,[90] C-reactive protein (CRP), various proinflammatory cytokines, serum hepcidin,[91] and procalcitonin (PCT) levels. Two meta-analysis of PCT showed potential for its use in the diagnosis of late-onset sepsis.[92,93] One study found PCT more accurate than the CRP level,[93] but studies have not had consistent results.[94]

TREATMENT

Empiric Therapy

Empiric antimicrobial therapy for suspected HAIs without a clinical focus in neonates should be guided by knowledge of the distribution, case-fatality rates of pathogens, and local susceptibility patterns of likely pathogens. An empiric antibiotic regimen should effectively treat gram-negative pathogens, particularly *P. aeruginosa* and other nonenteric flora. An aminoglycoside should be used for empiric treatment of possible gram-negative septicemia, the choice of which is determined by the antimicrobial susceptibility patterns of isolates from the NICU. 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: they do not have activity against most *P. aeruginosa* and some Enterobacteriaceae, routine use in NICUs has been associated with emergence of cephalosporin-resistant gram-negative bacilli,[95,96] and use has been associated with increased risk of candidemia in VLBW neonates.[97]

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. If MRSA is prevalent in the community or NICU, vancomycin should be used as first-line therapy.[98] If MRSA is not identified, vancomycin should be discontinued promptly. If MSSA is identified, nafcillin is therapeutically superior to vancomycin.

Because CoNS sepsis is common, some physicians advocate broad empiric use of vancomycin.[99] This creates additional problems. Stoll and associates[3] found it alarming that 44% of all VLBW infants in the NICHD NRN were treated with vancomycin whether they had CoNS BSI or not. The Hospital Infection Control and Practices Advisory Committee of the CDC recommend avoiding empiric vancomycin therapy in patients with suspected sepsis to prevent the emergence and spread of vancomycin-resistant enterococci.[100] Karlowicz and coworkers[33] showed that avoidance of empiric use of vancomycin had no impact on the very low rate of fulminant CoNS sepsis and that the practice of beginning vancomycin only after CoNS was identified in blood culture did not prolong the duration of BSI.

Despite ongoing education, vancomycin continues to be the most commonly used drug in NICUs surveyed and was used inappropriately in 32% of instances.[68] In one study, application of guidelines for vancomycin use decreased neonatal vancomycin exposure from 5.2 to 3.1 per 1000 patient-days (40% reduction) and 10.8 to 5.5 per 1000 patient-days (49% reduction) in two NICUs with no change in causes of infection, duration of BSI, or incidence of complications or attributable deaths.[101] In a retrospective study of 4364 infants with CoNS BSIs across 348 NICUs, there was no 30-day survival benefit of empiric therapy with vancomycin versus therapy delayed 1 to 3 days after a first positive blood culture.[102]

In a retrospective review of 126 VLBW infants with CoNS sepsis (≥2 positive blood cultures), there was no difference in outcomes when infants were treated with vancomycin for 5 days after the last positive blood culture compared with a longer course (infants with endocarditis or infected thrombi were excluded).[103] This approach requires prospective study but is promising for reducing vancomycin use. Antibiotic stewardship specific to each NICU remains critical to the prevention of spread of resistant bacteria and avoidance of use of medications unnecessarily.

The use of empiric antifungal therapy for VLBW infants at high risk for candidemia is not standardized. Some studies suggest that empiric therapy may reduce mortality rates and improve outcomes for VLBW infants.[104] In a small, retrospective study, empiric antifungal treatment was given to critically ill neonates (<1500 g) with additional risk factors for invasive *Candida* infection who had received vancomycin or a third-generation cephalosporin, or both, for 7 days and had one or more of the following risks: receipt of total parenteral nutrition, mechanical ventilation, postnatal corticosteroid therapy, or an H_2-blocking agent or had a mucocutaneous *Candida* infection.[105] No *Candida*-related mortality occurred for patients who received empiric amphotericin B (0 of 6) compared with historical controls (11 of 18).[105] The decision to use an empiric antifungal agent for late-onset sepsis should be made on an individual basis.[106,107]

The suggested duration of therapy for HAIs by anatomic site is summarized in Table 94.3. 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, time to negative blood culture, removal or retention of a CVC, and adequate drainage of any purulent foci.

Adjunctive Therapy

Several adjunctive therapies have been investigated for late-onset sepsis, including immune globulin intravenous (IGIV), hematopoietic growth factors (i.e., granulocyte colony-stimulating factor [G-CSF] and granulocyte-macrophage colony-stimulating factor [GM-CSF]), granulocyte transfusions, and pentoxifylline. IGIV,[108] G-CSF and GM-CSF administration[109] and granulocyte transfusions[110] have been evaluated in the Cochrane Database of Systematic Reviews, with the conclusion that there is insufficient evidence to support routine use in the treatment of neonates with sepsis. Pentoxifylline also has been reviewed in the Cochrane Database as an adjunct to antibiotics for treatment of suspected or confirmed sepsis or NEC, with results showing a decrease in all-cause mortality and decrease in length of stay, but the studies evaluated were small.[111,112] Larger clinical trials are needed to determine the usefulness of this adjunctive agent, but it may be promising.

A larger, multicenter trial used GM-CSF for prophylaxis of late-onset sepsis in neonates younger than 31 weeks' gestation and small for gestational age but did not show significant difference in sepsis-free survival.[113] A review of the data from studies of granulocyte transfusions in septic neonates demonstrated improved outcome in the situation of neutropenic depletion of the marrow storage pool, but associated morbidities included fluid overload, worsening hypoxia, respiratory distress from leukocyte sequestration in the lung, graft-versus-host disease, and risk of transmission of viral infections.[110] Careful assessment of the risks and benefits of leukocyte administration is required, as is the use of any of the other adjunctive therapy.[114]

TABLE 94.3 Suggested Duration of Therapy for Selected Healthcare Infections

Site or Manifestation of Infection	Duration of Therapy (Days)
BSI	10–14
Meningitis	14–21
CLABSI without removal of CVC	14[a]
Osteomyelitis or pyogenic arthritis	4–6 wk
VAP	10–14
UTI	10–14
Endocarditis	4–6 wk
Candidemia, catheter removed, rapidly resolving	10–14
Fungemia, disseminated	≈4 wk
Skin or subcutaneous lesion	7–10

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

MANAGEMENT OF CENTRAL LINE–ASSOCIATED BLOODSTREAM INFECTIONS

Removal of an intravascular catheter constitutes optimal management when a BSI occurs. Nevertheless, the vital importance of CVCs in critically ill neonates must be acknowledged, especially because successful treatment of CLABSI in situ has become more common.[115] BSIs can occur without being CLABSIs; differentiation of these two conditions can be difficult.

There have been no randomized trials to guide management of CLABSIs in the NICU, but several large, observational cohort studies have compared outcomes of late-onset sepsis in neonates with CVCs treated with or without CVC removal. Data suggest that management strategies depend 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 contaminated catheter. The algorithm shown in Fig. 94.1 provides a framework for the management of CLABSIs in neonates until evidence becomes available from randomized trials.

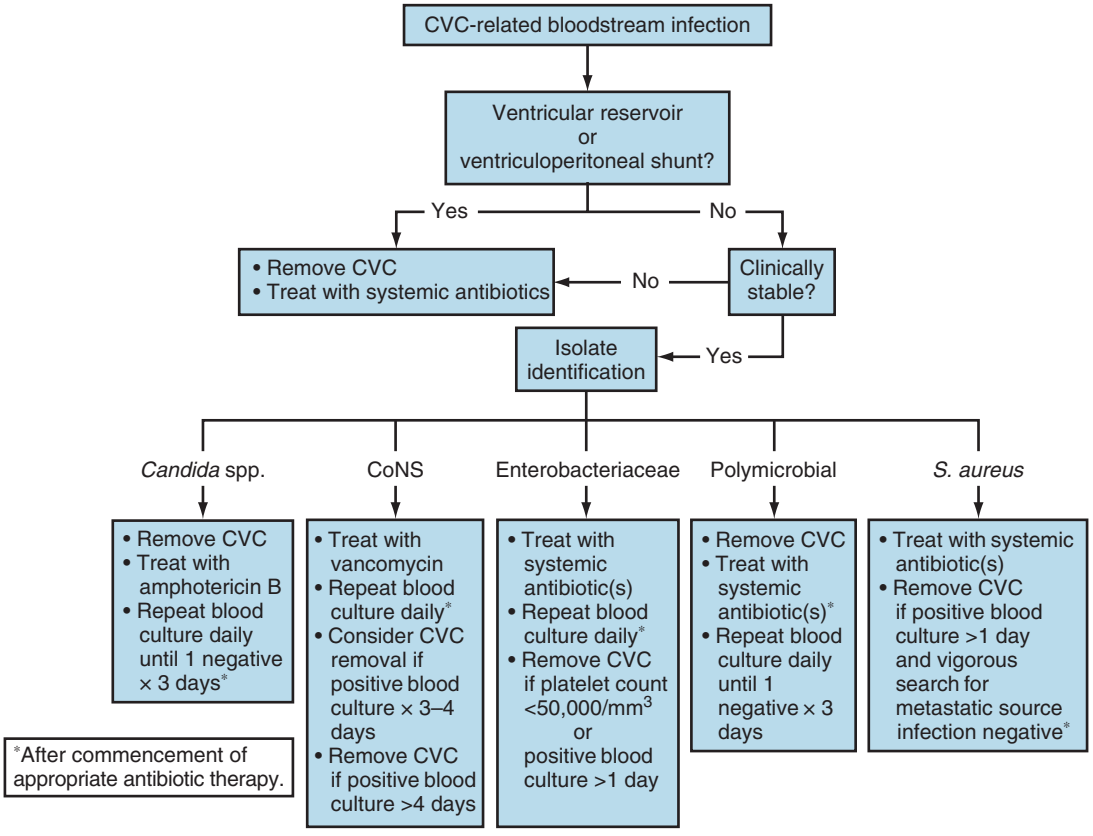

FIGURE 94.1 Suggested management of central line–associated bloodstream infection (CLABSI) in neonates. CoNS, coagulase-negative staphylococci; CVC, central venous catheter.

***Candida* Species.** 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 rates for *C. albicans* sepsis (i.e., case-fatality risk increase of 39%; number needed to harm of 2.6) and significantly prolonged duration of *Candida* sepsis regardless of the *Candida* species (i.e., median of 6 days vs. 3 days).[116] These findings were confirmed in a retrospective, multicenter study of ELBW infants with systemic candidiasis.[104]

The Infectious Diseases Society of America (IDSA) guidelines for treatment of catheter-related infections[115] and guidelines for management of candidiasis in NICU patients[117] strongly recommend that CVCs be removed as soon as *Candida* sepsis is detected (if feasible) and that a lumbar puncture and dilated retinal examination be performed.

Coagulase-Negative Staphylococci. It has been difficult to interpret clinical studies of CoNS CLABSI in neonates because many studies required only a single positive blood culture for inclusion, including many cases of pseudobacteremia. In a series of 119 cases[118] of CoNS CLABSI with at least two positive blood cultures, investigators concluded that treatment in situ often could be successful, but they observed it was unclear how long clinicians should wait before abandoning sterilizing attempts and removing the CVC.

Karlowicz and colleagues reported that treatment in situ with vancomycin was successful in 46% of cases with CoNS CLABSI,[118] but none of 19 patients with CoNS BSI for more than 4 days after institution of antibiotic therapy had resolution until the CVC was removed. In contrast, 79% of cases with CoNS BSI for 2 days or less were successfully treated without CVC removal; the successful treatment rate decreased to 44% when BSI persisted for 3 to 4 days.[118] When CoNS CLABSI persists in neonates whose catheter is vital to clinical care, it is our practice to administer antibiotic treatment through the CVC for 2 days and perhaps as long as 3 to 4 days in special circumstances but never beyond 4 days of persistent bacteremia before removing a CVC.

Although the use of antibiotic lock therapy for 10 to 14 days in combination with systemic antibiotic treatment for the treatment of CoNS CLABSI is part of the 2009 IDSA treatment guidelines for short- and long-term CVC,[115] the role of a vancomycin lock for therapy or prevention in the NICU requires further study.[119]

Enterobacteriaceae. Although Enterobacteriaceae are a common cause of late-onset sepsis, data are limited concerning CLABSI. In a report of 53 cases of Enterobacteriaceae CLABSI in neonates, resolution of infection was reported in 45% of cases with the use of gentamicin or tobramycin without CVC removal.[120] Successful treatment of Enterobacteriaceae with a BSI of more than 1 day's duration was uncommon without removal of the CVC.

Attempting to treat Enterobacteriaceae BSI with CVC in situ was not associated with an observable increase in mortality, morbidity, or recurrence. Severe thrombocytopenia (platelet count <50,000/mm^3) on the first day of Enterobacteriaceae BSI did not resolve until the CVC was removed in 82% of cases.[120] It is our practice to remove the CVC in cases associated with severe thrombocytopenia or if Enterobacteriaceae BSI persists for more than 1 day after commencing appropriate antibiotic treatment.

Staphylococcus aureus. For adults, removal of the CVC is advised in cases of *S. aureus* BSI, unless there is a compelling reason to conserve the catheter.[115] There are few published reports concerning *S. aureus* CLABSI in neonates or children. In a review of 154 cases of *S. aureus* CLABSI in 112 patients in one institution (including 12 premature neonates),[14] patients had complications related to infection (excluding prolonged bacteremia), with recurrence being most common. The rate of complications was lower among the patients whose catheter was removed less than 4 days after onset of infection compared with those whose catheter was not removed or was removed more than 4 days after onset.[121]

Data on treating *S. aureus* CLABSI in situ are conflicting, with some showing poor success.[122] Most cases that were treated successfully with a CVC in situ showed resolution of MSSA BSI within 24 hours of starting a penicillinase-resistant penicillin. Focal complications (e.g., soft tissue abscesses, endocarditis, osteomyelitis) may be more important risk factors for persistent *S. aureus* BSI than retention of the CVC. It is our practice to use a cautious approach, removing the CVC immediately if infection persists more than 1 day after initiation of appropriate antibiotic treatment, especially if no other source of *S. aureus* infection is identified.

Polymicrobial Infections. Polymicrobial BSI in neonates accounts for about 10% of cases of late-onset sepsis.[123] It usually occurs later than monomicrobial sepsis in neonates with a severe underlying condition and among those with longer-indwelling CVCs.

CoNS is the most common organism recovered from culture, and it is seen in combination with other gram-positive and gram-negative organisms.[123] It is prudent to remove CVCs as soon as possible in cases of polymicrobial sepsis.

MANAGEMENT OF PERSISTENT BLOODSTREAM INFECTIONS

The likelihood of adverse outcomes, such as focal complications, increases when BSI persists in neonates. Although it is uncertain whether focal complications are the cause or the consequence of persistent BSI, it is imperative that clinicians obtain serial blood cultures to document resolution of BSI and perform thorough diagnostic evaluations searching for focal complications if BSI persists. When BSI persists, clinicians must make management decisions concerning the timing of CVC removal and changes in antimicrobial therapy. Several cases have been reported of successful treatment of persistent CoNS CLABSIs with CVCs in situ without adverse consequences by adding rifampin to standard anti-staphylococcal antimicrobial therapy.[124,125]

Some pathogens, especially *Candida* species, may continue to be isolated from blood cultures despite prompt removal of the CVC and administration of antifungal therapy. In one series of 96 neonatal cases, candidiasis lasted more than 7 days in 30% of cases.[126] The risk of focal complications of invasive candidiasis was significantly increased in cases with persistent compared with nonpersistent BSI (48% vs. 13%). The most common focal complications were "fungus ball" uropathy (29%), renal infiltration (20%), abscess (19%), and endocarditis (9%).[126]

Because more than one half of neonates with persistent candidiasis do not have focal complications, Chapman and Faix[126] suggested that aggressive imaging for focal complications be reserved for cases in which blood cultures remain positive despite several days of antifungal therapy or if there are clinical signs suggesting focal complications. Noyola and associates[127] documented focal complications in 23% of 86 neonates with candidemia, including some with only one positive blood culture, and the investigators recommended renal, cardiac, and ophthalmologic diagnostic evaluations for all neonates with candidemia because the existence of focal complications may affect the duration of therapy and outcome.

The prevalence of persistent BSI was 22% in a series of 335 cases of bacteremia in one NICU.[128] In this case series, the frequent decision to treat bacterial BSI with a CVC in situ contributed to the high prevalence of persistent cases. The prevalence of focal suppurative complications (i.e., osteomyelitis, septic arthritis, abscess, infected thrombus, or endocarditis) was significantly increased with the duration of BSI and was greater with persistent non-CoNS BSI compared with persistent CoNS BSI (28% vs. 3%).[128] *S. aureus* caused 50% of persistent non-CoNS BSIs and 67% of the cases with focal complications.

The study authors recommended that all neonates with persistent BSI undergo extensive evaluation for focal complications, especially for endocarditis, osteomyelitis, and soft tissue abscesses.[128] This evaluation is especially important in cases of persistent BSI caused by *S. aureus* or Enterobacteriaceae because the bacteremia does not resolve until the soft tissue abscesses (sometimes suppurative phlebitis) or bone or joint infections are drained or until the intravascular clot dissolves.

PREVENTION OF HEALTHCARE-ASSOCIATED INFECTIONS

Risk factors for CLABSI have been extensively examined and include the use of total parenteral nutrition,[3] mechanical ventilation,[3] previous BSIs,[105] and previous exposure to third-generation cephalosporins.[96] A cohort study of monozygotic and dizygotic premature infants concluded that 49% of variance in the occurrence of late-onset sepsis might result from genetic factors and 51% from environmental factors.[129]

Manipulation of the central line increases the risk of CLABSI, including placement of the lines, maintenance of the dressing, and repeated entry into the CVC system. Approaches that minimize these interventions decrease the rate of CLABSI. Successful programs address technical and contextual factors, often with the use of care bundles and guidelines.[130] Bizzarro and coworkers performed a quality improvement initiative designed to reduce their NICU infection rate by implementing several interventions using a multidisciplinary approach and using guidelines for CVC care.[7] Interventions were associated with a decrease in the rates of CLABSI from 8.40 to 1.28 cases per 1000 central line–days and late-onset sepsis from 5.84 to 1.42 cases per 1000 patient-days.[7]

Hand decontamination by HCP is the most effective means of preventing HAIs,[131] but it often is overlooked or performed poorly in the NICU environment.[67,132] Activities such as skin contact, respiratory care, and diaper changes are independently associated with increased hand contamination.[131] The CDC recommends that HCP use alcohol-based hand rubs rather than antimicrobial soaps.[131] Alcohol-based hand rubs have excellent antimicrobial spectrum against bacteria, fungi, and viruses. The alcohol-based hand rubs also have a rapid speed of action and are the least likely to cause hand dermatitis in HCP.[131] The institution of a hand hygiene taskforce that includes problem-based and task-oriented education programs can help with hand hygiene compliance and a concurrent decrease in the infection rate. It is important to have continuous staff involvement to ensure success.[67,133]

The use of chlorhexidine gluconate (CHG) in the NICU for CVC care is increasing, with one survey showing 62% of respondents using CHG as off-label use because it is not approved by the US Food and Drug Administration for use in children younger than 2 months of age.[134] There are no data to support the use of CHG for patient bathing in the neonatal or pediatric population.

CHG antisepsis has been part of the Central Venous Catheter Guidelines in the United Kingdom since 2007,[135] but evidence from clinical trials has been lacking. In 2009, Soothill and colleagues at Great Ormond Street Hospital (GOSH) for Children reported a "profound, sustained fall" in CLABSIs from 12 to 3 per 1000 line-days in their hematopoietic stem cell transplantation pediatric patients.[136] This profound, sustained fall in CLABSIs occurred after changing from 30-second CVC hub antisepsis with 70% isopropyl alcohol to a 30-second CVC hub antisepsis with 2% CHG. Because the 30-second hub scrub was identical in the CHG and the 70% isopropyl alcohol groups, the significant reduction in the CLABSI rate was more likely associated with the introduction of CHG CVC hub antisepsis and not the friction of the 30-second hub scrub.

Soothill and colleagues[136] also reported that CVC hub antisepsis with 2% CHG was associated with a "marked fall" in the CLABSI rate throughout GOSH. The advantage of 3.15% CHG CVC hub antisepsis over 2% CHG CVC hub antisepsis, as used by Soothill and colleagues at GOSH,[136] is that 3.15 % CHG has similar effectiveness but requires only one half of the time. The 3.15% CHG CVC hub antisepsis takes 30 seconds (i.e., 15-second hub scrub followed by a 15-second drying time) compared with 60 seconds for the 2% CHG CVC hub antisepsis (i.e., 30-second hub scrub followed by a 30-second drying time), as described in the 3.15% and 2% CHG package inserts.

Premature infants require respiratory and enteral support. Systemic corticosteroid and H_2-blocking agents have been used to prevent chronic lung disease and enhance gastrointestinal function, respectively. Dexamethasone therapy for VLBW infants is associated with increased risk of late-onset sepsis.[104] Use of H_2-blocking agents in VLBW infants is associated with higher rates of NEC,[137] BSIs,[104] and candidemia.[104,138] Avoiding the use of dexamethasone and H_2-blocking agents should reduce rates of late-onset sepsis.[139]

Human milk contains several substances that provide a beneficial effect to the premature infant, including enhancement of innate immunity and enhancement of mucosal barriers. Establishing full enteral feedings with human milk is associated with lower risks of late-onset sepsis in ELBW infants.[140] Human milk was found to reduce the development of NEC by sixfold in a study of 202 VLBW infants who received more than 50% compared with those who received less than 50% human milk in the first 14 days of life.[141]

The use of bovine lactoferrin (bLF) also is being studied for the prevention of sepsis. The Italian Study Group for Neonatal Infections studied the effect of lactoferrin with or without probiotics (*Lactobacillus* GG) and found a decrease in the rate of infection in infants who were given bLF (6%) compared with the placebo group (18%).[142] The use of oral lactoferrin was reviewed in a 2015 Cochrane Database, which concluded that evidence of low to moderate quality suggests that oral lactoferrin prophylaxis decreases late-onset sepsis in preterm infants. Completion of several ongoing trials may improve the quality of the evidence.[143]

The American Academy of Pediatrics Red Book 2015 Committee on Infectious Diseases said that the use of fluconazole prophylaxis to prevent invasive candidiasis in ELBW infants should be considered in nurseries with moderate (5%–10%) to high (>10%) rates of invasive candidiasis after infection control practices are optimized.[144] Kaufman and colleagues demonstrated a significant reduction in invasive fungal disease in 100 ELBW infants given fluconazole prophylaxis or placebo (0% vs. 20%, respectively), but the level of invasive candidiasis was higher in their NICU than in centers in the NICHD NRN at that time.[145]

The strongest effect appears to occur when prophylaxis is targeted to high-risk patients with birth weights of less than 1000 g and with use of CVCs. It may be reasonable to use fluconazole with dosing of 3 mg/kg twice per week until intravenous (central or peripheral) access is no longer needed in the high-risk populations, starting in the first 2 days of life.[139] Nystatin prophylaxis also has been studied, although not as extensively, and it shows potential effectiveness in the same high-risk population but may have increased gastrointestinal side effects compared with fluconazole.[139]

The use of probiotics in the NICU is controversial because probiotics used in studies have varied and not all probiotics can be considered the same. Different strains of probiotic may have common characteristics and action but also may have unique properties and actions toward specific targets; generalization is difficult.[146] A meta-analysis of 15 randomized, controlled trials of enteral probiotic supplementation recommended the use of probiotics in preterm infants if a suitable product is available because the benefits of the reduction of death and NEC disease were clear to the inestigators.[147]

One multicenter, randomized, controlled trial showed a higher prevalence of sepsis and periventricular leukomalacia among infants weighing 500 to750 g in the probiotic group.[148] Another randomized, controlled trial showed an increased association of vancomycin-resistant enterococcus colonization in VLBW infants given probiotics.[149] Despite some studies showing benefit, evidence of infection prevention and product safety require further elucidation before a universal recommendation of probiotic supplementation, especially with regard to the strains used.

All references are available online at www.expertconsult.com.

KEY REFERENCES

9. Dudeck MA, Edwards JR, Allen-Bridson K, et al. National Health Safety Network report—, data summary for 2013: device-associated module. Am J Infect Control 2015;43:206–221.
34. Wynn JL, Benjamin DK Jr, Benjamin DK, et al. Very late onset infections in the neonatal intensive care unit. Early Hum Dev 2012;88:217–225.
35. Didier C, Streicher MP, Chognot D, et al. Late-onset infections: incidences and pathogens in the era of antenatal antibiotics. Eur J Pediatr 2012;171:681–687.
39. Bizzarro MJ, Shabanova V, Baltimore RS, et al. Neonatal sepsis 2004–2013: the rise and fall of coagulase-negative staphylococcus. J Pediatr 2015;166:1193–1199.
46. Iosifidis E, Evdoridou I, Agakidou E, et al. Vancomycin-resistant *Enterococcus* outbreak in a neonatal intensive care unit: epidemiology, molecular analysis and risk factors. Am J Infect Control 2013;41:857–861.
47. Shane AL, Hansen NI, Stoll BJ, et al. Methicillin-resistant and susceptible *Staphylococcus aureus* bacteremia and meningitis in preterm infants. Pediatrics 2012;129:e914–e922.
102. Ericson JE, Thaden J, Cross HR, et al. No survival benefit with empirical vancomycin therapy for coagulase-negative staphylococcal bloodstream infections in infants. Pediatr Infect Dis J 2015;34:371–374.
115. Mermel LA, Allon M, Bouza E, et al. Clinical practice guidelines for the diagnosis and management of intravascular catheter-related infection: 2009 update by the Infectious Disease Society of America. Clin Infect Dis 2009;49:1–45.
117. Pappas PG, Kauffman CA, Andes DR, et al. Clinical practice guideline for the management of candidiasis: 2015 update by the Infectious Diseases Society of America. Clin Infect Dis 2016;62:e1–e50.

REFERENCES

1. Phillips JR, Karlowicz MG. Prevalence of *Candida* species in hospital-acquired urinary tract infections in a neonatal intensive care unit. Pediatr Infect Dis J 1997;16:190–194.
2. Stoll BJ, Hansen N, Fanaroff AA, et al. To tap or not to tap: high likelihood of meningitis without sepsis among very low birth weight infants. Pediatrics 2004;113:1181–1186.
3. Stoll BJ, Hansen N, Fanaroff AA. Late-onset sepsis in very low birth weight neonates: the experience of the NICHD Neonatal Research Network. Pediatrics 2002;110:285–291.
4. Aziz K, McMillan DD, Andrews W, et al. Variations in rates of nosocomial infection among Canadian neonatal intensive care units may be practice-related. BMC Pediatr 2005;5:22.
5. Makhoul IR, Sujov P, Smolkin T, et al. Epidemiological, clinical, and microbiological characteristics of late-onset sepsis among very low birth weight infants in Israel: a national survey. Pediatrics 2002;109:34–39.
6. Stoll BJ, Hansen NI, Bell EF, et al. Neonatal outcomes of extremely preterm infants from the NICHD Neonatal Research Network. Pediatrics 2010;126:443–456.
7. Bizzarro MJ, Sabo B, Noonan RN, et al. A quality improvement initiative to reduce central line-associated bloodstream infections in a neonatal intensive care unit. Infect Control Hosp Epidemiol 2010;31:241–248.
8. Horan TC, Andrus M, Dudeck MA. CDC/NHSN surveillance definition of health care-associated infection and criteria for specific types of infections in the acute care setting. Am J Infect Control 2008;36:309–332.
9. Dudeck MA, Edwards JR, Allen-Bridson K, et al. National Health Safety Network report—, data summary for 2013: device-associated module. Am J Infect Control 2015;43:206–221.
10. Day MD, Gauvreau K, Shulman S, et al. Characterisitics of children hospitalized with infective endocarditis. Circulation 2009;119:865–870.
11. Valente AM, Jain R, Scheurer M, et al. Frequency of infective endocarditis among infants and children with *Staphylococcus aureus* bacteremia. Pediatrics 2005;115:e15–e19.
12. Offiah AC. Acute osteomyelitis, septic arthritis and discitis: differences between neonates and older children. Eur J Radiol 2006;60:221–232.
13. Dessi A, Crisafulli M, Setzu V, et al. Osteo-articular infections in newborns: diagnosis and treatment. J Chemother 2008;20:542–550.
14. Tamin MM, Alesseh H, Aziz H. Analysis of the efficacy of urine culture as part of sepsis evaluation in the premature infant. Pediatr Infect Dis J 2003;22: 805–808.
15. Al-Orifi F, McGillivray D, Tange S, et al. Urine culture from bag specimens in young children: are the risks to high? J Pediatr 2000;137:221–226.
16. Polnay L, Fraser AM, Lawes JM. Complications of suprapubic bladder aspiration. Arch Dis Child 1975;50:80–81.
17. Kozer E, Rosenbloom E, Goldman D, et al. Pain in infants who are younger than 2 months during suprapubic aspiration and transurethral bladder catheterization: a randomized controlled study. Pediatrics 2006;118:e51–e56.
18. Pollack CV Jr, Pollack ES, Andrew ME. Suprapubic bladder aspiration versus urethral catheterization in ill infants: success, efficiency, and complication rates. Ann Emerg Med 1994;23:225–230.
19. Tobiansky R, Evans N. A randomized controlled trial of two methods for collection of sterile urine in neonates. J Paediatr Child Health 1998;34:460–462.
20. Bauer S, Eliakim A, Pomeranz A, et al. Urinary tract infection in very low birth weight preterm infants. Pediatr Infect Dis J 2003;22:426–429.
21. Su BH, Hsieh HY, Chiu HY, et al. Nosocomial infection in a neonatal intensive care unit: a prospective study in Taiwan. Am J Infect Control 2007;35:190–195.
22. Cordero L, Sananes M, Dedhiya P, et al. Purulence and gram-negative bacilli in tracheal aspirates of mechanically ventilated very low birth weight infants. J Perinatol 2001;21:376–381.
23. Apisarnthanarak A, Holzmann-Pazgal G, Hamvas A, et al. Ventilator-associated pneumonia in extremely preterm neonates in a neonatal intensive care unit: characteristics, risk factors, and outcomes. Pediatrics 2003;112:1283–1289.
24. Coates EW, Karlowicz MG, Croitoru DP, Buescher ES. Distinctive distribution of pathogens associated with peritonitis in neonates with focal intestinal perforation compared with necrotizing enterocolitis. Pediatrics 2005;116:e241–e246.
25. Rashkind CH, Sabo BE, Callan DA, et al. Conjunctival colonization of infants hospitalized in a neonatal intensive care unit: a longitudinal analysis. Infect Control Hosp Epidemiol 2004;25:216–220.
26. Haas J, Larson E, Ross B, et al. Epidemiology and diagnosis of hospital-acquired conjunctivitis among neonatal intensive care unit patients. Pediatr Infect Dis J 2005;24:586–589.
27. Couto RC, Carvalho EA, Pedrosa TM, et al. A 10-year prospective surveillance of nosocomial infections in neonatal intensive care units. Am J Infect Control 2007;35:183–189.
28. Chen CJ, Starr CE. Epidemiology of gram-negative conjunctivitis in neonatal intensive care unit patients. Am J Ophthalmol 2008;145:966–970.
29. Graham PL III. Staphylococcal and enterococcal infections in the neonatal intensive care unit. Semin Perinatol 2002;5:322–331.
30. Carey AJ, Duchon J, Della-Latta P, Saiman L. The epidemiology of methicillin-susceptible and methicillin- resistant *Staphylococcus aureus* in a neonatal intensive care unit, 2000–2007. J Perinatol 2010;30:135–139.
31. Freeman AF, Mancini AJ, Yogev R. Is noma neonatorum a presentation of ecthyma gangrenosum in the newborn? Pediatr Infect Dis J 2002;116:e241–e246.
32. Roilides E, Zaoutis TE, Walsh TJ. Invasive zygomycosis in neonates and children. Clin Microbiol Infect 2009;15(suppl 5):50–54.
33. Karolwicz MG, Buescher ES, Surka AE. Fulminant late-onset sepsis in a neonatal intensive care unit, 1988–1997, and the impact of avoiding empiric vancomycin therapy. Pediatrics 2000;106:1387–1390.
34. Wynn JL, Benjamin DK Jr, Benjamin DK, et al. Very late onset infections in the neonatal intensive care unit. Early Hum Dev 2012;88:217–225.
35. Didier C, Streicher MP, Chognot D, et al. Late-onset infections: incidences and pathogens in the era of antenatal antibiotics. Eur J Pediatr 2012;171:681–687.
36. Wojkowska-Mach J, Gulczyriska E, Nowiczewski M, et al. Late-onset bloodstream infections of very-low-birth-weight infants: data from the Polish Neonatalogy Surveillance Network in 2009–2011. BMC Infect Dis 2014;14:339–346.
37. Ozkan H, Cetinkaya M, Koksal N, et al. Culture-proven neonatal sepsis in preterm infants in a neonatal intensive care unit over a 7 year period: coagulase-negative *Staphylococcus* as the predominant pathogen. Pediatr Int 2014;56:60–66.
38. Makhoul IR, Sujov P, Smolkin T, et al. Pathogen-specific early mortality in very low birth weight infants with late-onset sepsis:a national survey. Clin Infect Dis 2005;40:218–224.
39. Bizzarro MJ, Shabanova V, Baltimore RS, et al. Neonatal sepsis 2004–2013: the rise and fall of coagulase-negative staphylococcus. J Pediatr 2015;166:1193–1199.
40. Almuneef MA, Baltimore RS, Farrel PA, et al. Molecular typing demonstrating transmission of gram-negative rods in a neonatal intensive care unit in the absence of a recognized epidemic. Clin Infect Dis 2001;32:220–227.
41. Morioka I, Morikawa S, Miwa A, et al. Culture-proven neonatal sepsis in Japanese neonatal care units in 2006–2008. Neonatology 2012;102:75–80.
42. Nambiar S, Herwaldt LA, Singh N. Outbreak of invasive disease caused by methicillin-resistant *Staphylococcus aureus* in neonates and prevalence in the neonatal intensive care unit. Pediatr Crit Care Med 2003;4:220–226.
43. Regev-Yochay G, Rubinstein E, Barzilai A, et al. Methicillin-resistant *Staphylococcus aureus* in the neonatal intensive care unit. Emerg Infect Dis 2005;11: 453–456.
44. Healy CM, Hulten KG, Palazzi DL, et al. Emergence of new strains of methicillin-resistant *Staphylococcus aureus* in a neonatal intensive care unit. Clin Infect Dis 2004;39:1460–1466.
45. Carey AJ, Della-Latta P, Huard R, et al. Changes in the molecular epidemiological characteristics of methicillin-resistant *Staphylococcus aureus* in a neonatal intensive care unit. Infect Control Hosp Epidemiol 2010;31:613–616.
46. Iosifidis E, Evdoridou I, Agakidou E, et al. Vancomycin-resistant *Enterococcus* outbreak in a neonatal intensive care unit: epidemiology, molecular analysis and risk factors. Am J Infect Control 2013;41:857–861.
47. Shane AL, Hansen NI, Stoll BJ, et al. Methicillin-resistant and susceptible *Staphylococcus aureus* bacteremia and meningitis in preterm infants. Pediatrics 2012;129:e914–e922.
48. Linkin DR, Fishman NO, Patel JB, et al. Risk factors for extended-spectrum beta-lactamase–producing Enterobacteriaceae in a neonatal intensive care unit. Infect Control Hosp Epidemiol 2004;25:781–783.
49. Dashti AA, Jadaon MM, Gomaa HH, et al. Transmission of a *Klebsiella pneumoniae* clone harboring genes for CTX-M-15–like and SHV-112 enzymes in a neonatal intensive care unit of a Kuwaiti hospital. J Med Microbiol 2010;59:687–692.
50. Kristof K, Szabo D, Marsh JW, et al. Extended-spectrum beta-lactamase producing *Klebsiella* spp. in a neonatal intensive care unit: risk factors for the infection and the dynamics of the molecular epidemiology. Eur J Clin Microbiol Infect Dis 2007;26:563–570.
51. Anderson B, Nicholas S, Sprague B, et al. Molecular and descriptive epidemiology of multidrug-resistant Enterobacteriaceae in hospitalized infants. Infect Control Hosp Epidemiol 2008;29:250–255.
52. Mammina C, DiCarlo P, Cipolla D, et al. Surveillance of multidrug-resistant gram-negative bacilli in a neonatal intensive care unit: prominent role of cross transmission. Am J Infect Control 2007;35:222–230.
53. Arslan U, Erayman I, Kirdar S, et al. *Serratia marcescens* sepsis outbreak in a neonatal intensive care unit. Pediatr Int 2010;52:208–212.
54. Maragakis LL, Winkler A, Tucker MG, et al. Outbreak of multidrug-resistant *Serratia marcescens* in a neonatal intensive care unit. Infect Control Hosp Epidemiol 2008;29:418–423.
55. Myers KA, Jeffery RM, Lodha A. Late-onset *Leclerica adecarboxylata* bacteremia in a premature infant in the NICU. Acta Paediatr 2012;101:e37–e39.
56. Nelson MU, Maksimova Y, Schulz V, et al. Late-onset *Leclercia adecarboxylata* sepsis in a premature neonate. J Perinatol 2013;33:740–742.
57. Naze F, Jouen E, Randriamahazo RT, et al. *Pseudomonas aeruginosa* outbreak linked to mineral water bottles in a neonatal intensive care unit: fast typing by use of high resolution melting analysis of a variable-number tandem- repeat locus. J Clin Microbiol 2010;48:3146–3152.
58. Crivaro V, DiPopolo A, Caprio A, et al. *Pseudomonas aeruginosa* in a neonatal intensive care unit: molecular epidemiology and infection control measures. BMC Infect Dis 2009;9:70.
59. Loukil C, Saizou C, Doit C, et al. Epidemiologic investigation of *Burkholderia cepacia* acquisition in two pediatric intensive care units. Infect Control Hosp Epidemiol 2003;24:707–710.
60. Maraki S, Scoulica E, Manoura A, et al. A *Chryseobacterium meningosepticum* colonization outbreak in a neonatal intensive care unit. Eur J Clin Microbiol Infect Dis 2009;28:1415–1419.
61. Touati A, Achour W, Cherif A, et al. Outbreak of *Acinetobacter baumannii* in a neonatal intensive care unit: antimicrobial susceptibility and genotyping analysis. Ann Epidemiol 2009;19:372–378.
62. Giannouli M, Cuccurullo S, Cirvaro V, et al. Molecular epidemiology of multi-drug resistant *Acinetobacter baumannii* in a tertiary care hospital in Naples, Italy, shows the emergence of a novel epidemic clone. J Clin Microbiol 2010;48:1223–1230.

63. Ganeswire R, Thong KL, Putucheary SD. Nosocomial outbreak of *Enterobacter gergoviae* bacteremia in a neonatal intensive care unit. J Hosp Infect 2003;53:292–296.
64. Pessoa-Silva CL, Dharan S, Hugonnet S, et al. Dynamics of bacterial hand contamination during routine neonatal care. Infect Control Hosp Epidemiol 2004;25:192–197.
65. Gray J, Arvelo W, McCracken J, et al. An outbreak of *Klebsiella pneumoniae* late-onset sepsis in a neonatal intensive care unit in Guatemala. Am J Infect Control 2012;40:516–520.
66. Song X, Cheung S, Klontz K, et al. A stepwise approach to control an outbreak and ongoing transmission of methicillin- resistant *Staphylococcus aureus* in a neonatal intensive care unit. Am J Infect Control 2010;38:607–611.
67. Lam BC, Lee J, Lau YL. Hand hygiene practices in a neonatal intensive care unit: a multimodal intervention and impact on nosocomial infection. Pediatrics 2004;114:e565–e571.
68. Patel SJ, Oshodi A, Prasad P, et al. Antibiotic use in neonatal intensive care units and adherence with Centers for Disease Control and Prevention 12 Step Campaign to Prevent Antimicrobial Resistance. Pediatr Infect Dis J 2009;28:1047–1051.
69. Verboon-Maciolek MA, Krediet TG, Gerards LJ, et al. Clinical and epidemiologic characteristics of viral infections in a neonatal intensive care unit during a 12-year period. Pediatr Infect Dis J 2005;24:901–904.
70. Dizdar EA, Aydemir C, Erdeve O, et al. Respiratory syncytial virus outbreak defined by rapid screening in a neonatal intensive care unit. J Hosp Infect 2010;75:292–294.
71. Halasa NB, Williams JV, Wilson GJ, et al. Medical and economic impact of respiratory syncytial virus outbreaks in a neonatal intensive care unit. Pediatr Infect Dis J 2005;24:1040–1044.
72. Sagrera X, Ginovart G, Raspall F, et al. Outbreaks of influenza A virus infection in neonatal intensive care units. Pediatr Infect Dis J 2002;21:196–200.
73. Syriopoulou VP, Hadjichristodoulou C, Daikos GL, et al. Clinical and epidemiological aspects of an enteroviral outbreak in a neonatal unit. J Hosp Infect 2002;51:275–280.
74. Kusuhara K, Saito M, Sasaki Y, et al. An echovirus type 18 outbreak in a neonatal intensive care unit. Eur J Pediatr 2008;167:587–589.
75. Sharma R, Hudak ML, Premachandra BR, et al. Clinical manifestations of rotavirus infection in the neonatal intensive care unit. Pediatr Infect Dis J 2002;21:1099–1105.
76. Sharma R, Garrison RD, Tepas JJ 3rd, et al. Rotavirus- associated necrotizing enterocolitis: an insight into a potentially preventable disease? J Pediatr Surg 2004;39:453–457.
77. Faden H, Wynn RJ, Campagna L, et al. Outbreak of adenovirus type 30 in a neonatal intensive care unit. J Pediatr 2005;146:523–527.
78. Sizun J, Soupre D, Legrand MC, et al. Neonatal respiratory infection with coronavirus: a prospective study in a neonatal intensive care unit. Acta Paediatr 1995;84:617–620.
79. Simmonds A, Munoz J, Montecalvo M, et al. Outbreak of parainfluenza virus type 3 in a neonatal intensive care unit. Am J Perinatol 2009;26:361–364.
80. Stuart RL, Tan K, Mahar JE, et al. An outbreak of necrotizing enterocolitis associated with norovirus genotype G11.3. Pediatr Infect Dis J 2010;29:644–647.
81. Turcios-Ruiz RM, Axelrod P, St John K, et al. Outbreak of necrotizing enterocolitis caused by norovirus in an neonatal intensive care unit. J Pediatr 2008;153:339–343.
82. Wilson CW, Stevenson DK, Arvin AM. A concurrent epidemic of respiratory syncytial virus and echovirus 7 infections in an intensive care unit. Pediatr Infect Dis J 1989;8:24–29.
83. Fanaroff AA, Korones SB, Wright LL, et al. Incidence, presenting features, risk factors and significance of late onset septicemia in very low birth weight infants. Pediatr Infect Dis J 1998;17:593–598.
84. Griffin MP, O'Shea TM, Bissonette EA, et al. Abnormal heart rate characteristics preceding neonatal sepsis and sepsis-like illness. Pediatr Res 2003;53:920–926.
85. Fairchild KD, O'Shea TM. Heart rate characteristics: physiomarkers for detection of late-onset sepsis. Clin Perinatol 2010;37:581–598.
86. Griffin MP, Lake DE, O'Shea TM, et al. Heart rate characteristics and clinical signs in neonatal sepsis. Pediatr Res 2007;61:222–227.
87. Fallet ME, Gallinaro RN, Stover BH, et al. Central venous catheter bloodstream infections in the neonatal intensive care unit. J Pediatr Surg 1998;33:1383–1387.
88. Langan EA, Agarwal RP, Subudhi CP, Judge MR. *Aspergillus fumigatus:* a potentially lethal ubiquitous fungus in extremely low birthweight neonates. Pediatr Dermatol 2010;27:403–404.
89. Mackay CA, Ballot DE, Perovic O. Serum 1,3-βD-glucan assay in the diagnosis of invasive fungal disease in neonates. Pediatr Rep 2011;3(2):e14.
90. Hornik CP, Benjamin DK, Becker KC, et al. Use of the complete blood count in late-onset neonatal sepsis. Pediatr Infect Dis J 2012;31:803–807.
91. Wu TW, Tabangin M, Kusano R, et al. The utility of serum hepcidin as a biomarker for late-onset neonatal sepsis. J Pediatr 2013;162:67–71.
92. Vouloumanou EK, Plessa E, Karageorgopoulos DE, et al. Serum procalcitonin as a diagnostic marker for neonatal sepsis: a systemic review and meta-analysis. Intensive Care Med 2011;37:747–762.
93. Yu Z, Liu J, Sun Q, et al. The accuracy of the procalcitonin test for the diagnosis of neonatal sepsis: a meta-analysis. Scand J Infect Dis 2010;42:723–733.
94. Kordek A. Concentrations of procalcitonin and C-reactive protein, white blood cell count, and the immature-to-total neutrophil ratio in the blood of neonates with nosocomial infections: gram-negative bacilli vs coagulase-negative staphylococci. Eur J Clin Microbiol Infect Dis 2011;30:455–457.
95. de Man P, Verhoeven BA, Verbrugh HA, et al. An antibiotic policy to prevent emergence of resistant bacilli. Lancet 2000;355:973–978.
96. Cotton CM, McDonald S, Stoll B, et al. The association of third-generation cephalosporin use and invasive candidiasis in extremely low birth weight infants. Pediatrics 2006;118:717–722.
97. Benjamin DK Jr, Ross K, McKinney RE Jr, et al. When to suspect fungal infections in neonates: a clinical comparison of *Candida albicans* and *Candida parapsilosis* fungemia with coagulase-negative staphylococcal bacteremia. Pediatrics 2000;106:712–718.
98. Carey AJ, Saiman L, Polin RA. Hospital-acquired infections in the NICU: epidemiology for the new millennium. Clin Perinatol 2008;35:223–249.
99. Healy CM, Palazzi DL, Edwards MS, et al. Features of invasive staphylococcal disease in neonates. Pediatrics 2004;114:953–961.
100. Hospital Infection Control Advisory Committee. Recommendations for preventing the spread of vancomycin resistance. Infect Control Hosp Epidemiol 1995;16:105–133.
101. Chiu CH, Michelow IC, Cronin J, et al. Effectiveness of a guideline to reduce vancomycin use in the neonatal intensive care unit. Pediatr Infect Dis J 2011;30:273–278.
102. Ericson JE, Thaden J, Cross HR, et al. No survival benefit with empirical vancomycin therapy for coagulase-negative staphylococcal bloodstream infections in infants. Pediatr Infect Dis J 2015;34:371–374.
103. Linder N, Lubin D, Hernandez A, et al. Duration of vancomycin treatment for coagulase-negative *Staphylococcus* sepsis in very low birth weight infants. Br J Clin Pharmacol 2013;76:58–64.
104. Benjamin DK, Stoll BJ, Fanaroff AA, et al. Neonatal candidiasis among extremely low birth weight infants: risk factors, mortality rates, and neurodevelopmental outcomes at 18 to 22 months. Pediatrics 2006;117:84–92.
105. Procianoy RS, Eneas MV, Silveira RC. Empiric guidelines for treatment of *Candida* infection in high-risk neonates. Eur J Pediatr 2006;165:422–423.
106. Makhoul IR, Kassis I, Smolkin T, et al. Review of 49 neonates with acquired fungal sepsis: further characterization. Pediatrics 2001;107:61–66.
107. Kaufman DA, Manzoni PM. Strategies to prevent invasive candidal infection in extremely preterm infants. Clin Perinatol 2010;37:611–628.
108. Ohlsson A, Lacy J. Intravenous immunoglobulin for suspected or subsequently proven infection in neonates. Cochrane Database Syst Rev 2010;(3):CD001239.
109. Carr R, Modi N, Dore C. G-CSF and GM-CSF for treating or preventing neonatal infections. Cochrane Database Syst Rev 2003;(3):CD003066.
110. Mohan P, Brocklehurst P. Granulocyte transfusions for neonates with confirmed or suspected sepsis and neutropenia. Cochrane Database Syst Rev 2003;(4):CD003956.
111. Haque KM, Pammi M. Pentoxifylline for treatment of sepsis and necrotizing enterocolitis in neonates. Cochrane Database Syst Rev 2011;(5):CD004205.
112. Shabaa AE, Nasef N, Shouman B, et al. Pentoxifyline therapy for late-onst sepsis in preterm infants: a randominzed control trial. Pediatr Infect Dis J 2015;34:e143–e148.
113. Carr R, Brocklehurst P, Dore CJ, et al. Granulocyte-macrophage colony stimulating factor administered as prophylaxis for reduction of sepsis in extremely preterm, small for gestational age neonates (the PROGRAMS trial): a single-blind, multicentre, randomized controlled trial. Lancet 2009;373:226–233.
114. Tarnow-Mordi W, Isaacs D, Dutta S. Adjunctive immunologic interventions in neonatal sepsis. Clin Perinatol 2010;37:481–499.
115. Mermel LA, Allon M, Bouza E, et al. Clinical practice guidelines for the diagnosis and management of intravascular catheter-related infection: 2009 update by the Infectious Disease Society of America. Clin Infect Dis 2009;49:1–45.
116. Karlowicz MG, Hashimoto LN, Kelly RE Jr, Buescher ES. Should central venous catheters be removed as soon as candidemia is detected in neonates? Pediatrics 2000;106(5):e63.
117. Pappas PG, Kauffman CA, Andes DR, et al. Clinical practice guideline for the management of candidiasis: 2015 update by the Infectious Diseases Society of America. Clin Infect Dis 2016;62:e1–e50.
118. Karlowicz MG, Furigay PJ, Croitoru DP, Buescher ES. Central venous catheter removal versus in situ treatment in neonates with coagulase-negative staphylococcal bacteremia. Pediatr Infect Dis J 2002;21:22–27.
119. Garland JS, Alex CP, Henrickson KJ, et al. A vancomycin-heparin lock solution for prevention of noscomial bloodstream infection in critically ill neonates with peripherially inserted central venous catheters: a prospective, randomized trial. Pediatrics 2005;116:e198–e205.
120. Nazemi KJ, Buescher ES, Kelly RE Jr, Karlowicz MG. Central venous catheter versus in situ treatment in neonates with Enterobacteriaceae bacteremia. Pediatrics 2003;111:e269–e274.
121. Carrillo-Marquez MA, Hulten KG, Mason EO, Kaplan SL. Clinical and molecular epidemiology of *Staphylococcus aureus* catheter-related bacteremia in children. Pediatr Infect Dis J 2010;29:410–414.
122. Benjamin DK Jr, Miller W, Garges H, et al. Bacteremia, central catheters, and neonates: when to pull the line. Pediatrics 2001;107:1272–1276.
123. Bizzarro MJ, Dembry LM, Baltimore RS, Gallagher PG. Matched case-control analysis of polymicrobial bloodstream infection in a neonatal intensive care unit. Infect Control Hosp Epidemiol 2008;29:914–920.
124. Shama A, Patole SK, Whitehall JS. Intravenous rifampicin in neonates with persistent staphylococcal bacteremia. Acta Paediatr 2002;91:670–673.
125. van der Lugt MN, Steggerda SJ, Walther FJ. Use of rifampin in persistent coagulase negative staphylococcal bacteremia in neonates. BMC Pediatr 2010;10:84.
126. Chapman RL, Faix RG. Persistently positive cultures and outcomes in invasive neonatal candidiasis. Pediatr Infect Dis J 2000;19:822–827.
127. Noyola DE, Fernandez M, Moylett EH, Baker CJ. Ophthalmologic, visceral, and cardiac involvement in neonates with candidemia. Clin Infect Dis 2001;32:1018–1023.
128. Chapman RL, Faix RG. Persistent bacteremia and outcome in late-onset infection among infants in a neonatal intensive care unit. Pediatr Infect Dis J 2003;22:17–21.
129. Bizzarro MJ, Jiang Y, Hussain N, et al. The impact of environmental and genetic factors on neonatal late-onset sepsis. J Pediatr 2011;158:234–238.
130. Powers RJ, Wirtschafter DW. Decreasing central line associated bloodstream infection in neonatal intensive care. Clin Perinatol 2010;37:247–272.

131. Boyce JM, Pittet D. Guideline for hand hygiene in healthcare settings: recommendations of the healthcare infection control practices advisory committee and the HICPAC/SHEA/APIC/IDSA hand hygiene task force. MMWR Recomm Rep 2002;51(RR-16):1–45.
132. Chudleigh J, Fletcher M, Gould D. Infection control in neonatal intensive care units. J Hosp Infect 2005;61:123–129.
133. Downey LC, Smith PB, Benjamin DK Jr. Risk factors and prevention of late-onset sepsis in premature infants. Early Hum Dev 2010;86:s7–s12.
134. Bryant KA, Zerr DM, Huskins C, Milstone AM. The past, present, and future of healthcare-associated infection prevention in pediatrics: catheter-associated bloodstream infections. Infect Control Hosp Epidemiol 2010;31(S1):s27–s31.
135. Pratt RJ, Pellowe CM, Wilson JA, et al. epic2: national evidence-based guidelines for preventing healthcare-associated infections in NHS hospitals in England. J Hosp Infect 2007;65(suppl 1):S1–S64.
136. Soothill JS, Bravery K, Ho A, et al. A fall in bloodstream infections followed a change to 2% chlorhexidine in 70% isopropanol for catheter connection antisepsis: a pediatric single center before/after study on a hemopoietic stem cell transplant ward. Am J Infect Control 2009;37:626–630.
137. Guillet R, Stoll BJ, Cotton M, et al. Association of H2-blocker therapy and higher incidence of necrotizing enterocolitis in very low birth weight infants. Pediatrics 2006;117:e137–e142.
138. Saiman L, Ludington E, Pfaller M, et al. Risk factors for candidemia in neonatal intensive care unit patients. Pediatr Infect Dis J 2000;19:319–324.
139. Kaufman DA. Challenging issues in neonatal candidiasis. Curr Med Res Opin 2010;26:1769–1778.
140. Ronnestad A, Abrahamsen TG, Medbo S, et al. Late-onset septicemia in a Norwegian national cohort of extremely premature infants receiving very early human milk feedings. Pediatrics 2005;115:e269–e276.
141. Sisk PM, Lovelady CA, Dillard RG, et al. Early human milk feeding is associated with a lower risk of necrotizing enterocolitis in very low birth weight infants. J Perinatol 2007;27:428–433.
142. Manzoni R, Rinaldi M, Cattani S, et al. Bovine lactoferrin supplementation for prevention of late-onset sepsis in very low-birth-weight neonates: a randomized trial. JAMA 2009;302:1421–1428.
143. Pammi M, Abrams SA. Oral lactoferrin for the prevention of sepsis and necrotizing enterocolitis in preterm infants. Cochrane Database Syst Rev 2015;(2):CD007137.
144. American Academy of Pediatrics. Candidiasis. In: Kimberlin DW, Brady MT, Jackson MA, Long SS (eds) Red Book: 2015 Report of the Committee on Infectious Diseases, 30th ed. Elk Grove Village, IL, American Academy of Pediatrics, 2015, pp 279–280.
145. Kaufman D, Boyle R, Hazen KC, et al. Fluconazole prophylaxis against fungal colonization and infection in preterm infants. N Engl J Med 2001;345:1660–1666.
146. Manzoni P, Rizzollo S. Probiotic use in preterm neonates: what further evidence is needed? Early Hum Dev 2011;87S:s3–s4.
147. Deshpande G, Rao S, Patole S, Bulsara M. Updated meta-analysis of probiotics for preventing necrotizing enterocolitis in preterm infants. Pediatrics 2010;125:921–930.
148. Lin HC, Hsu CH, Chen HL, et al. Oral probiotics prevent necrotizing enterocolitis in very low birth weight preterm infants: a multicenter, randomized, controlled trial. Pediatrics 2008;122:693–700.
149. Topcuoglu S, Gursoy T, Ovali F. A new risk factor for neonatal vancomycin-resistant *Enterococcus* colonization: bacterial probiotics. J Matern Fetal Neonatal Med 2015;28:1491–1494.