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96 Hospital-Associated Infections in the Neonate

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As progressively smaller premature infants survive beyond the first few days of life, hospital- (or healthcare-) associated infections (HAI) have emerged as a major cause of morbidity and late mortality in the neonatal intensive care unit (NICU). Effective prevention and treatment of HAI in the NICU require understanding of the distribution of pathogens and 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 HAI in the NICU, and they can occur in isolation or in association with urinary tract infections[1] and meningitis.[2] Endocarditis, osteomyelitis, septic arthritis, ventilator associated pneumonia, peritonitis, conjunctivitis, and skin abscesses are important, less common HAIs (Table 96-1).

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 on or after 72 hours of age in neonates. Late-onset sepsis is most common in very-low-birthweight (VLBW, birthweight <1500 g) infants, in 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 for the Neonatal Networks in Canada (24%)[4] and Israel (30%).[5]

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 NRN[3] and 7% to 74% in the NICUs participating in the Canadian Neonatal Network.[4] Recent data from NICHD NRN confirm 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 was strongly and inversely associated with birthweight and gestational age, decreasing from ~60% in neonates with gestational age <25 weeks to 20% in infants born at 28 weeks' gestation.[6] Consequently, institutions caring for more extremely-low-birthweight (ELBW) infants have higher rates. Management practices, particularly those concerning utilization 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 central catheters (CVCs or PICCs),[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: (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) that are not related to an infection at another site; and (3) presence of a CVC at the time the blood culture is obtained or within 48 hours before the development of the infection. A rate of HAI that is linked to device utilization, such as a CLABSI, helps control for variability in management practices from institution to institution, and the preferred unit of measure is infections per 1000 catheter-days. The NHSN continues to recommend that CLABSI be a major focus of surveillance and prevention efforts in NICUs, and to that end, provide summary data on CLABSI rates for different birthweight groups. The NHSN data help individual NICUs assess their CLABSI rate relative to other NICUs. 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 2009, data on CLABSI rates from NHSN participating Level III NICUs for the years 2006 to 2008 showed a median number BSI per 1000 catheter-days of 3.2 for infants weighing <750 g, 2.5 for those weighing 751 to 1000 g, and 1.4 for those weighing 1001 to 1500 g at birth.[9] These values represent continuing decline in both CLABSI and device utilization. In addition, data were obtained regarding umbilical catheter-associated BSI for the same time period, which revealed low rates of infection in all weight categories.[9]

Coexistence of endocarditis, osteomyelitis, or pyogenic arthritis should be considered whenever BSIs persist in neonates. *Staphylococcus aureus* is the most common cause of both 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 variability 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 >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% versus 2%), and were more likely to die (23% versus 2%).[2] Importantly, one-third (45 of 134) of the infants with meningitis had simultaneously drawn blood cultures that were negative. Because meningitis can alter duration of antibiotic therapy and long-term prognosis, 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

TABLE 96-1. 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; CoNS, coagulase-negative staphylococci; S. aureus, Staphylococcus aureus; *CLABSI, central line-associated 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.*

procedure. In the latter case, lumbar puncture should be performed when clinical stabilization is achieved.

Urinary Tract Infection

Urinary tract infection (UTI) is the one of the most common HAIs in adults.[9] The high rate of UTI in hospitalized adults is associated with frequent use of indwelling urinary catheters, which are seldom used in VLBW infants. 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.[14] Urine specimens obtained by bag collection from infants have notoriously high rates of contamination – up to 63%[15] – and are not recommended. Clinicians have tended to avoid suprapubic bladder aspiration in neonates because of the risk of serious, albeit rare, complications such as bowel perforation[16] and increased pain.[17] Fortunately, 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 there have not been prospective studies of UTI, it may be the second most common HAI in the NICU. The reported prevalence in 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 in 762 VLBW infants in one NICU over an 11-year period.[20] UTI was more common in ELBW infants (12%) than in infants with birthweight 1001 to 1500 g (6%). In a prospective study in one NICU over a one-year period, rate of HAIs was 17.5%, with only 0.7% UTIs.[21] When intervention-associated infections were examined, urinary catheter-associated UTIs (CAUTIs) were up to 17.3%. Again, the highest risk of HAIs was in patients with a birthweight <1000 g (relative risk, 11.8).[21]

Examining paired blood and urine cultures in 189 VLBW infants suspected of having late-onset sepsis, Tamim et al. detected UTIs in 25%.[14] Among the VLBW infants with UTIs, 62% (30 of 48) had negative blood cultures. Phillips and Karlowicz[1] reported a case series of 60 UTIs in NICU patients, 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. As most VLBW infants with UTI do not have BSIs, it is our practice to obtain urine for culture (by sterile urethral catheterization or by suprapubic aspiration), whenever late-onset sepsis is suspected.

Ventilator-Associated Pneumonia

It is difficult to diagnosis healthcare-associated pneumonia in any patient population and even more difficult in the NICU population. New definitions from the CDC/NHSN in 2008 attempt to provide reproducible criteria for surveillance, classifying pneumonia into 3 specific types: clinically defined (PNU1), pneumonia with laboratory finding (PNU2), and pneumonia in immunocompromised patients (PNU3).[8] In general, infants and children fall into category 1. 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 <1 year, but these are not specific to the premature infant. New benchmark data are becoming available through the NHSN. The highest incidence of VAP occurs in infants with a median birthweight of 1.3 per 1000 ventilator days ≤750 grams.[9]

A few investigators have attempted to establish reproducible criteria for VAP specific to the neonatal population. Cordero et al.[22] showed that finding purulent tracheal aspirate with 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 et al.[23] performed a prospective cohort study addressing the risk factors, 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 treatment with antibiotics for >7 days for presumed VAP. By this definition, 19 of 67 (28%) 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 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.[23]

Intestinal Perforation and Peritonitis

Peritonitis associated with intestinal perforation is another serious HAI infection in the NICU. Coates et al.[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 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. Peritoneal fluid cultures were positive and helped direct antimicrobial therapy in 40% (46 of 116) of cases.[24] Peritoneal fluid culture should be obtained in all neonates with intestinal perforation, regardless of cause.

Other Infections

Conjunctivitis is common in healthy full-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 et al.[26] reporting 5% in a prospective study and Couto et al.[27] reporting 12% (although all birthweights were included). The most common pathogens are enteric gram-negative bacilli, but non-enteric flora such as *Pseudomonas aeruginosa* also can occur.[28]

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.[29] Methicillin-resistant and methicillin-susceptible *S. aureus* (MRSA and MSSA) cause similar infections. Carey et al. reported incidence of 4.8% for MSSA and 1.8% of MRSA in ELBW 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 (57% 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] Across many reports the same pathogens cause most episodes: CoNS, *Candida* species, *S. aureus,* and Enterobacteriaceae (Table 96-2).

Usual Pathogens

Frequency of pathogens causing late-onset sepsis but also the likelihood that certain pathogens cause rapid progression to severe complications and death (fulminant sepsis) must be considered in choosing empiric therapy. Karlowicz et al.[33] reported that although gram-negative organisms caused only 25% of BSIs in their series, they caused 69% of *fulminant* late-onset BSIs. 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 CLABSI
Staphylococcus aureus	++	Highest rate of focal complications; MRSA is a problem in some NICUs
Candida species	++	*Candida albicans* and *Candida 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.

+++, most frequent; ++, common; +, occasional.

gram-negative bacilli, *P. aeruginosa* was the most prominent pathogen (42% of fulminant cases) and overall had a case-fatality rate of 56% – in contrast to a case-fatality rate of <1% for CoNS.[33] Similar findings have been reported by others.[3,34]

CoNS are the most common pathogens causing late-onset sepsis, accounting for 35%[29] and 48%[3] of cases. Distinguishing between true BSI and pseudobacteremia can be difficult. The CDC/NHSN defines 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 et al.[3] of late-onset sepsis, a rate of 48% CoNS would fall to 29% if only LCBSIs were included, a rate similar to the 35% reported by Karlowicz et al.[33]

Emerging Pathogens

Prevalence of pathogens in the community and the healthcare and NICU environment, as well as the selective pressure of antibiotic use, contribute to antibiotic-resistant infections in NICUs.[35] Gram-positive bacteria, including both hospital- and community-associated MRSA[30,36–39] and vancomycin-resistant *Enterococcus faecium*,[40] are serious problems in NICUs. Both gram-negative enteric organisms (extended-spectrum β-lactamase-carrying *E. coli* and *Klebsiella* spp.,[41–43] *AmpC* β-lactamase-carrying *Enterobacter* spp.,[44] metallo-β-lactamase-carrying enterics,[45] multidrug-resistant *Serratia marcescens*[46,47]) and nonenteric organisms (*P. aeruginosa*,[48,49] *Burkholderia cepacia*,[50] *Chryseobacterium meningosepticum*[51]) and most recently, highly resistant *Acinetobacter* spp. have emerged in NICU environments.[52,53]

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 caretakers. The former often results from breakdowns in the cleaning procedures used in the NICU or hospital environment[38,45,47,54] and the latter from ineffective use of hand hygiene by healthcare personnel (HCP).[48,55] Molecular fingerprinting of organisms has been useful for characterizing and controlling some outbreaks.[36,41,45,47,51] Control of NICU outbreaks of antibiotic-resistant organisms frequently requires vigorous application of infection control procedures (surveillance cultures, patient and staff cohorting, hand hygiene education interventions[56,57]) 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; these valuable methodologies can be applied successfully to the NICU.[58]

Viral Infections

HAIs caused by viruses are infrequent in the NICU, with an incidence <1%,[59] but because of patient vulnerability and propensity of viruses to spread patient to patient, impact can be substantial. Respiratory syncytial virus (RSV),[60,61] influenza virus,[62] enteroviruses,[63,64] rotavirus,[65,66] adenovirus,[67] coronavirus,[68] parainfluenza,[69] and norovirus[70,71] have been described in NICU outbreaks, sometimes concurrently.[72] Attack rates can be as high as 33%.[62,64,67] Patients can be asymptomatic or have disease that is lethal,[66] and the attributable costs can be high.[60] Viruses can be introduced into the NICU both by family members and by ill HCPs.

RSV infections can manifest as cough, congestion, apnea, increasing oxygen requirement, or respiratory failure.[59,60] Parainfluenza can present similarly, as can adenovirus, in addition to causing epidemic conjunctivitis.[67] Of note, ophthalmologic procedures can contribute to spread of adenovirus.[67] Coronavirus infection can be associated with respiratory decompensation or abdominal distention and fever.[68] Enteroviruses can be associated with clinical manifestations suggestive of NEC, overwhelming septicemia, rash, or aseptic meningitis.[63] 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.[65]

CLINICAL MANIFESTATIONS

The clinical features of sepsis in neonates are nonspecific, with most common clinical features being increased apnea/bradycardia (55%), increased gastrointestinal problems (46%) (feeding intolerance, abdominal distention, or bloody stools), increased respiratory support (29%), and lethargy/hypotonia (23%).[73] Predominant laboratory indicators are 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 of features is low, with the best positive predictive value being 31%, for hypotension.[73]

Abnormal heart rate characteristics (reduced variability and transient decelerations) occur early in the course of neonatal sepsis.[74] Although technology has been developed to calculate a heart rate characteristic index (HRCi),[75] Griffin et al. found that HRCi performed similarly to a clinical scoring system in predicting sepsis.[76]

The most common signs of CLABSI in neonates are fever (49%) and respiratory distress (30%),[77] with only 20% of cases showing 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 (such as from any indwelling catheter along with peripheral sites), cerebrospinal fluid (CSF) culture, and urine culture. The isolation of CoNS from a single blood culture generally 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.[32,78]

When viral infection is suspected, a presumptive diagnosis can be made by rapid diagnostic testing (e.g., a positive direct fluorescent antibody (DFA) test for adenovirus, herpes simplex virus or enzyme immunoassay (EIA) for influenza, respiratory syncytial virus, or rotavirus) and a definitive diagnosis by isolation or polymerase chain reaction testing of nasal wash, tracheal secretions, bronchoalveolar lavage fluid, or stool, as appropriate.

Attempts to identify dependable serum markers for diagnosis, severity, or prognosis have been variably successful, including the use of C-reactive protein (CRP), various proinflammatory cytokines, and/or procalcitonin (PCT) levels. Two recent meta-analysis of PCT showed potential for its use in diagnosis of late-onset sepsis.[79,80] One study found PCT more accurate than CRP,[80] but studies have not had consistent results[81] and it is unlikely that a single test taken out of context and cadence of clinical findings and likely pathogen(s) will have pivotal importance.

TABLE 96-3. 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/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; CLABSI, central line-associated bloodstream infection; CVC, central venous catheter; UTI, urinary tract infection; VAP, ventilator-associated pneumonia.

[a]*After first negative blood culture.*

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 the local susceptibility patterns of likely pathogens. An empiric antibiotic regimen should effectively treat gram-negative pathogens, particularly *P. aeruginosa*. 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 have activity against most *P. aeruginosa* and some Enterobacteriaceae; (2) routine use in NICUs has been associated with emergence of cephalosporin-resistant gram-negative bacilli;[82,83] and (3) use has been associated with increased risk of candidemia in VLBW neonates.[84]

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.[85] If no MRSA is identified, vancomycin should be discontinued. If MSSA is identified, nafcillin is therapeutically superior to vancomycin.

Because CoNS sepsis is common, some advocate broad empiric usage of vancomycin.[86] This creates additional problems. Stoll et al.[3] found it alarming that 44% of all VLBW infants in the Neonatal Research Network were treated with vancomycin whether or not they had CoNS BSI. 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.[87] Karlowicz et al.[33] showed that avoidance of empiric use of vancomycin had no impact on the very low rate of fulminant CoNS sepsis in neonates 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 inappropriately used 32% of the time.[58] It is possible to reduce the empiric use of vancomycin in units that have low levels of MRSA infection without compromising patient care or safety. Chiu et al. demonstrated that the 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 separate NICUs with no change in causes of infection, duration of BSI, or incidence of complications or attributable deaths.[88] Antibiotic stewardship, specific to each NICU, remains critical to prevention of spread of resistant bacteria and avoidance of use of unnecessary medications.

The use of empiric antifungal therapy for VLBW infants at high risk of candidemia is not as standardized as it is in other patient populations. Some studies suggest that empiric therapy may reduce mortality and improve outcomes in this VLBW infants.[89] In a 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 and/or third-generation cephalosporin for 7 days and had ≥1 of the following risks: receipt of total parenteral nutrition, mechanical ventilation, postnatal corticosteroid therapy, or H_2-blocking agent, or mucocutaneous *Candida* infection.[90] No *Candida*-related mortality occurred in patients who received empiric amphotericin B (0 of 6) compared with historical controls (11 of 18).[90] Decision to use an empiric antifungal agent for late-onset sepsis should be made on an individual basis.[91,92]

The suggested duration of therapy for HAIs 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, time to negative blood culture, 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 immune globulin intravenous (IGIV), hematopoietic growth factors (granulocyte colony-stimulating factor (G-CSF) and granulocyte-macrophage colony-stimulating factor (GM-CSF)), granulocyte transfusions, and pentoxifylline. IGIV,[93] G-CSF and GM-CSF,[94] and granulocyte transfusions[95] have been evaluated by the Cochrane Database of Systematic Reviews, with the conclusion that there is insufficient evidence currently to support routine use in the treatment of neonates with sepsis. Pentoxifylline also has been reviewed by the Cochrane Database as an adjunct to antibiotics for treatment of suspected or confirmed sepsis or NEC, with results, suggesting a decrease in all-cause mortality, but the studies evaluated were small.[96] More research is needed to determine the usefulness of this adjunctive agent. A larger, multicenter trial used GM-CSF for prophylaxis of late-onset sepsis in neonates <31 weeks' gestation and small for

gestational age but did not show significant difference in sepsis-free survival.[97] 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, including fluid overload, worsening hypoxia and respiratory distress from leukocyte sequestration in the lung, graft-versus-host disease, and risk of transmission of viral infections.[95] Careful assessment of the risks versus the benefits of leukocyte administration is required, as is the use of any of the other adjunctive therapies.[98]

MANAGEMENT OF CENTRAL LINE ASSOCIATED 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 CLABSI has become more common.[99] BSIs can occur without being a CLABSI; differentiation of these two conditions can be difficult. There have been no randomized trials to guide management of CLABSI in the NICU; however, several large observational cohort 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 contaminated catheter. The algorithm shown in Figure 96-1 provides a framework for management of CLABSI in neonates until evidence becomes available from randomized trials.

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 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).[100] These findings were confirmed in a retrospective multicenter study of ELBW infants with systemic candidiasis.[89] The Infectious Diseases Society of America (IDSA) guidelines for treatment of catheter-related infections[99] strongly recommend that CVCs be removed as soon as *Candida* sepsis if feasible. Unfortunately, in some neonates, the CVCs are vital lifelines and cannot be removed because of severe generalized skin breakdown or unstable critical condition.

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, thus allowing many cases of pseudobacteremia. In a series of 119 cases[101] of CoNS CLABSI, investigators concluded that in situ treatment often could be successful, but observed it was unclear how long clinicians should wait before abandoning sterilizing attempts and removing the CVC. Karlowicz et al. reported that in situ treatment with vancomycin was successful in 46% of cases with CoNS CLABSI;[100] none of 19 patients with CoNS BSI for >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 were successfully treated without CVC removal; successful treatment decreased to 44% when BSI persisted for 3 to 4 days.[100] Therefore, 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, perhaps as long as 3 to 4 days in special circumstances, but never beyond 4 days of persistent bacteremia, before removing a CVC.

The use of antibiotic lock therapy for treatment of CoNS CLABSI is part of the IDSA treatment guidelines for both short- and long-term CVC, using 10- to 14-day lock therapy in combination with systemic antibiotic treatment.[99] The role of vancomycin lock therapy in the NICU for treatment is unclear, with more research involving its preventive use.[102]

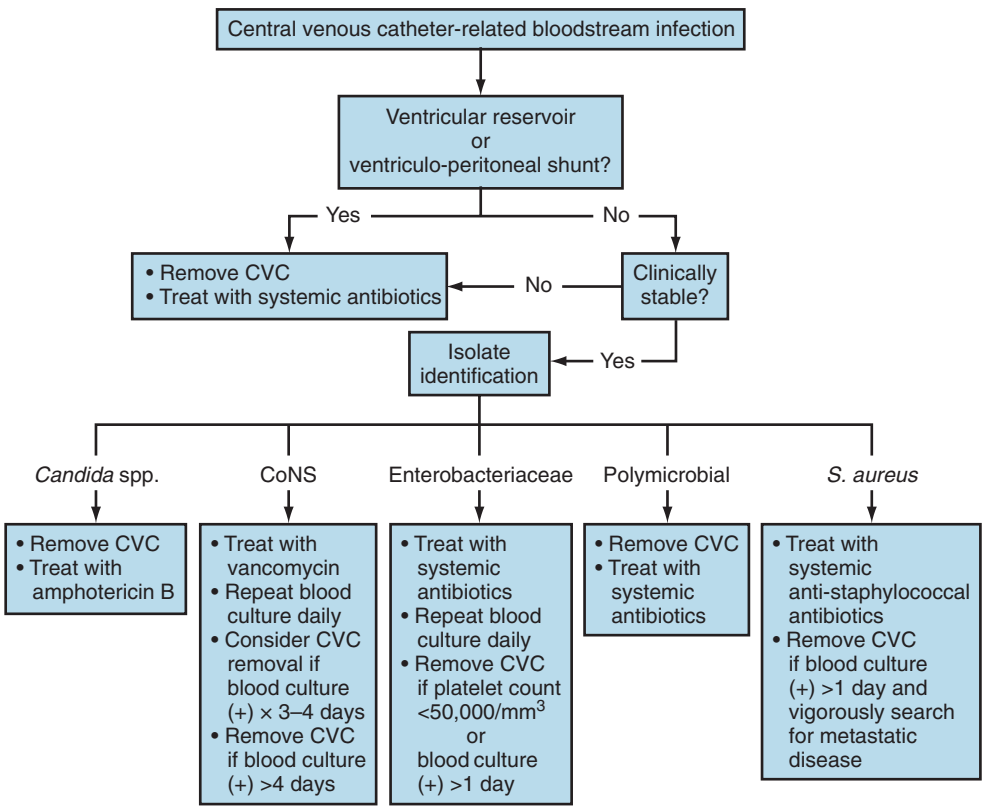

Figure 96-1. Suggested management of central line associated bloodstream infection (CLABSI) in neonates. CoNS, coagulase-negative staphylococci. [a]After commencement of appropriate antibiotic therapy.

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, Karlowicz et al. reported resolution of infection in 45% of cases with use of gentamicin or tobramycin without removal of CVCs.[103] In contrast to successful in situ treatment despite several days of CoNS BSI, successful treatment of Enterobacteriaceae with BSIs of >1 day duration was uncommon without removal of CVC. Attempting to treat Enterobacteriaceae BSI with CVC in situ was not associated with 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 CVCs were removed in 82% of cases.[103] It is our practice to remove CVC in cases associated with severe thrombocytopenia or if Enterobacteriaceae BSI persists >1 day after commencing appropriate antibiotic treatment.

Staphylococcus aureus

In adults, removal of CVC is advised in cases of *S. aureus* BSI, unless there is a *compelling* reason to conserve the catheter.[99] 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 (12 premature neonates),[14] patients had complications related to infection (excluding prolonged bacteremia) with recurrence being most common. The rate of complications was lower in the patients whose catheter was removed <4 days after onset of infection compared with those whose catheter was not removed or was removed >4 days after onset of infection.[104] Data on treating *S. aureus* CLABSI in situ are conflicting, with some showing poor success.[105] Most cases that were treated successfully despite CVC in situ showed resolution of MSSA BSI within 24 hours of starting a penicillinase-resistant penicillin. Focal complications, like soft-tissue abscesses, endocarditis, and osteomyelitis, may be more important risk factors for persistent *S. aureus* BSI than retention of CVC. It is our practice to use a cautious approach, removing CVC immediately if infection persists >1 day after initiation of appropriate antibiotic treatment.

Polymicrobial Infections

Polymicrobial BSI in neonates accounts for about 10% of cases of late-onset sepsis.[106] It occurs generally 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 is seen in combination with other gram-positive and gram-negative organisms.[106] It would seem 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. In addition, when BSI persists, clinicians must make management decisions concerning timing of CVC removal and changes in antimicrobial therapy. Several cases have been reported of successful treatment of persistent CoNS CLABSIs with CVC in situ, without adverse consequences, by adding rifampin to standard antistaphylococcal antimicrobial therapy.[107,108]

Some pathogens, especially *Candida* species, may continue to be isolated from blood cultures despite prompt removal of CVC and administration of antifungal therapy. In one such series of 96 neonatal cases, candidiasis lasted >7 days in 30% of cases.[109] The risk of focal complications of invasive candidiasis was significantly increased in cases with persistent compared with nonpersistent BSI (48% versus 13%). The most common focal complications were "fungus ball" uropathy (29%), renal infiltration (20%), abscess (19%), and endocarditis (9%).[109] Since more than half of neonates with persistent candidiasis do not have focal complications, Chapman and Faix[109] 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 complication. On the other hand, Noyola et al.[110] documented focal complications in 23% of 86 neonates with candidemia, including some with only one positive blood culture, and the authors 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 BSI was reported to be 22% in a series of 335 cases of bacteremia in one NICU.[111] 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 duration of BSI and with persistent non-CoNS BSI compared with persistent CoNS BSI (28% versus 3%).[111] *S. aureus* caused 50% of persistent non-CoNS BSIs and 67% of the cases with focal complications. The authors recommended that all neonates with persistent BSI undergo extensive evaluation for focal complications, especially 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 (sometimes suppurative phlebitis) or bone or joint infections are drained, or the intravascular clot dissolves.

PREVENTION OF HEALTHCARE-ASSOCIATED INFECTIONS

Risk factors for CLABSI have been extensively examined and include use of total parenteral nutrition,[3] mechanical ventilation,[3] previous BSIs,[90] and previous exposure to third-generation cephalosporins.[83] A recent cohort study of monozygotic and dizygotic premature infants concluded that 49% of variance in occurrence of late-onset sepsis may be due to genetic factors and 51% to environmental factors.[112] Manipulation of the central line increases the risk of CLABSI, including the placement of the lines, maintenance of the dressing, and repeated entry into the CVC system. Thus, approaches that minimize these interventions will decrease the rate of CLABSI, with successful programs addressing both technical and contextual factors, often with the use of "bundles" and guidelines.[113] Bizzarro et al. 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,[114] but often is overlooked or performed poorly in the NICU environment.[57,115] Activities such as skin contact, respiratory care, and diaper changes are independently associated with increased hand contamination.[114] The CDC recommends that HCP use alcohol-based hand rubs over antimicrobial soaps.[114] Alcohol-based hand rubs have excellent antimicrobial spectrum against bacteria, fungi, and viruses. In addition, alcohol-based hand rubs have rapid speed of action and are the least likely to cause hand dermatitis in HCP.[114] The institution of a "hand hygiene" taskforce that includes problem-based and task-oriented education programs can help with hand hygiene compliance and concurrent decrease in the infection rate. It is important to have continuous staff involvement to ensure success.[57,116]

The use of chlorhexidine gluconate (CHG) in the NICU for CVC care is increasing, with a recent survey showing 62% of respondents using CHG as off-label use, since it is not approved by the FDA for use in children <2 months of age.[117] At this time, there are no data to support the use of CHG for patient bathing in the neonatal or pediatric population.

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 in VLBW infants is associated with increased risk of late-onset sepsis.[89] Use of H_2-blocking agents in VLBW infants is associated with higher rates of NEC,[118] BSIs,[89] and candidemia.[89,119] Avoiding the use of dexamethasone and H_2-blocking agents should reduce rates of late-onset sepsis.[120]

Human milk contains a number of 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.[121] Human milk also has been found to reduce the development of NEC by 6-fold in a study of 202 VLBW infants who either received >50% compared with <50% human milk in the first 14 days of life.[122] The use of bovine lactoferrin (bLF) also is being studied for prevention of sepsis. The Italian Study Group for Neonatal Infections studied the effect of lactoferrin with and without probiotics (*Lactobacillus* GG) and found a decrease in rate of infection in the infants who were given bLF (5% to 6%) compared with the placebo group (18%).[123] The use of oral lactoferrin was reviewed in a Cochrane Database but only the previously mentioned study was eligible for review. It was shown to be beneficial in infants <1000 g, but more trials are needed.[124]

The American Academy of Pediatrics Red Book 2009 Committee on Infectious Diseases state that the use of fluconazole prophylaxis to prevent invasive candidiasis (IC) in ELBW infants should be considered in nurseries with moderate to high risk of IC after infection control practices are optimized.[125] Kaufman et al. demonstrated a significant reduction in invasive fungal disease in 100 ELBW infants given either fluconazole prophylaxis or placebo, 0% versus 20% respectively, but the level of IC was higher in their NICU than in centers in the Neonatal Research Network at that time.[126] The strongest effect appears to be when prophylaxis is targeted to high-risk patients with birthweight of <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.[120] Nystatin prophylaxis also has been studied (but not as extensively) and it also shows potential effectiveness in the same high-risk population but may have increased gastrointestinal side effects compared with fluconazole.[120]

The use of probiotics in the NICU is controversial since probiotics used in studies have varied and not all probiotics can be considered the same. A recent review acknowledges that different strains may have common characteristics and action but also may have unique properties and actions towards specific targets; generalization is difficult.[127] 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 since the benefits of the reduction of death and NEC disease were clear to the authors.[128] A recent clinical trial using *Bifidobacterium breve* and *Lactobacillus casei* supplementation in human milk fed infants showed reduction of NEC stage >2 in those infants 750 to 1499 g who received the probiotic versus placebo (0 versus 4 cases, respectively).[129] Despite some studies showing benefit, evidence of infection prevention requires further elucidation prior to the universal recommendation of probiotic supplementation, especially with regard to strains used.

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