Nosocomial Neonatal Candidiasis

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As the survival of our smallest, most immature patients has increased, a concurrent increase in the length of stay on the Neonatal Intensive Care Unit (NICU) and the risk of nosocomial infection has been observed. In a representative cohort of >6000 very low birth weight (VLBW) infants (401–1500 g), 21% had blood culture-proved late onset sepsis (defined as sepsis occurring after 3 days of age).1 Fungal infections accounted for 12% of the episodes of late onset sepsis; Candida albicans, the third most common single organism isolated, was responsible for ~6% of all such infections in this patient population.1 Rates of nosocomial candidemia approached 17% among the subpopulation of extremely low birth weight (ELBW) infants (<1000 g).1 Unique among the NICU population is the distribution of non-C. albicans Candida species isolated from the bloodstream of infected neonates. Candida parapsilosis is the second most common yeast responsible for late onset fungemia, and Candida glabrata ranks third.2 Candida is an important pathogen in this fragile group of immunocompromised patients with high rates of mortality (25–30%) and morbidity (20–50%), including significant adverse neurodevelopmental outcomes.3

TRANSMISSION AND PATHOGENESIS

Candida species are commensal organisms colonizing the skin, gastrointestinal tract and female genitourinary tract. Nearly 75% of infants admitted to the NICU are colonized by 1 month of age.4 The Candida strain colonizing the infant is acquired either by vertical transmission during vaginal delivery or postnatally from contact with maternal skin or the skin of direct care providers.5 The latter appears to be the primary mode of transmission for C. parapsilosis, the most common Candida species recovered from the hands of health care workers.6 Gastrointestinal colonization is associated with systemic infection, presumably by translocation of commensal yeast across the gastrointestinal tract epithelium to the mesenteric lymph nodes and bloodstream.7 Molecular epidemiologic studies support concordance between the colonizing and infecting Candida strain.7,8 Direct transmissions of Candida to neonates from the hands of NICU personnel and from contaminated equipment or intravenous fluids/medications are other documented sources of nosocomial infections.9

The likelihood of nosocomial neonatal candidemia depends on the combination of yeast virulence and host risk factors. Important yeast virulence factors include species (C. albicans is the most pathogenic), filament formation (hyphae are associated with tissue invasion and necrosis), adhesins and biofilm formation. The biofilm microenvironment (a mass of extracellular matrix proteins, yeast cells and hyphae) provides a sequestered area optimal for avoiding host defense mechanisms and antimicrobial drugs.10 These fungal masses, adherent to catheters, tissue epithelium and vascular epithelium, are associated with ongoing fungemia despite appropriate therapy, septic emboli and coinfection by nosocomial bacterial pathogens.10

The 3 primary host risk factors for nosocomial candidiasis are prolonged broad spectrum antibiotic administration, extreme prematurity with gestational age younger than 28 weeks and indwelling catheters.11,12 Catheters of all types (vascular, urinary, endotracheal, peritoneal, ventriculoperitoneal, mediastinal, thoracic) provide a portal of entry for Candida, as well as a perfect inert surface for adhesion, multiplication and biofilm formation by the yeast. Additional host risk factors include VLBW, steroid therapy, hyperglycemia, neutropenia, hypoxia, cardiac or abdominal surgery, necrotizing enterocolitis and spontaneous intestinal perforation.11,12 Limitation of predisposing conditions is optimal in preventing candidal infections, but rarely feasible, especially in the VLBW infant.

CLINICAL FINDINGS

Infants with late onset candidal infections often have nonspecific general features of sepsis, including lethargy, feeding intolerance, cardiovascular instability, apnea, new or worsening respiratory failure or hyperbilirubinemia.11 The preterm infant can rapidly become critically ill, requiring initiation or escalation of cardiorespiratory support. New onset glucose intolerance and thrombocytopenia are extremely common presenting symptoms, with persistence suggesting inadequate antifungal therapy.12 Neutropenia is associated with overwhelming disease.

Although candidemia alone (without distant organ involvement) can occur in the neonate, dissemination is the rule rather than the exception in the NICU.13 Similarly, although isolated catheter-related infections can occur in neonates, associated systemic disease is more common and is particularly true for the infant with persistent candidemia.13 Candida has a strong affinity for specific organs (eg, kidney, eye, heart, central nervous system), and infants might have specific organ involvement such as renal insufficiency, urinary obstruction, endophthalmitis, endocarditis, meningitis or osteomyelitis, which confirms dissemination by hematogenous spread. The diagnosis of candidemia, or of candidal infection involv-
ing any single organ, should prompt a thorough survey for multiorgan involvement. Cultures of the blood, cerebrospinal fluid and urine are always indicated. Specific imaging studies should include renal ultrasonography, echocardiography, ultrasonography of all indwelling catheter tips, cranial imaging and an ophthalmologic examination to evaluate for chorioretinitis.

Two unique clinical presentations of nosocomial candidiasis are specific to ELBW neonates born before 26 weeks of gestation. Invasive fungal dermatitis occurs most often during the second week of life after vaginal delivery, postnatal steroid administration and hyperglycemia. The extremely immature skin is not an efficient barrier to the external invasion of Candida, and affected neonates develop characteristic skin lesions with severe erosion, serous drainage and crusting, which is present primarily on dependent skin surfaces. Invasive disseminated candidiasis is associated with spontaneous intestinal perforation, which occurs during the second or third weeks of life in the ELBW infant. This syndrome is distinct from necrotizing enterocolitis, and up to 33% of affected neonates have blood, peritoneal fluid, cerebrospinal fluid or urine cultures positive for Candida species, as well as histopathologic evidence of fungal invasion at the site of intestinal perforation.

**THERAPY AND MANAGEMENT**

Amphotericin B remains the antifungal of choice for this high risk group of patients. Therapeutic levels are easily achieved, few side effects are noted in neonates and C. albicans, C. parapsilosis and C. glabrata all remain sensitive to amphotericin B. Lipid-associated amphotericin preparations appear to be safe and effective in neonates, but not superior to conventional amphotericin B, especially when treating urinary tract infections, due to poor renal penetration. Fluconazole is well-concentrated in the urine and is an excellent choice for treatment of isolated urinary tract infections, but it is not an optimal choice for empiric therapy because up to 50% of C. glabrata are intrinsically resistant to this azole. Caspofungin, the first licensed echinocandin, is recommended by the Infectious Diseases Society of America as an alternative therapy for candidemia among children and neonates, but pharmacokinetic data in neonates are not available.

Treatment of disseminated candidiasis must include attempts to reduce or eliminate risk factors for ongoing disease. Removal of central vascular catheters is indicated, as well as the avoidance of both hyperglycemia and steroid therapy. Ultimately the reduction or elimination of risk factors as early as possible in the NICU course may prevent nosocomial neonatal candidiasis.

**REFERENCES**