The Epidemiology and Diagnosis of Invasive Candidiasis Among Premature Infants

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KEYWORDS

• Neonatal candidiasis • *Candida* • Premature infants • Risk factors

KEY POINTS

- Invasive candidiasis occurs primarily in extremely premature infants and is associated with substantial morbidity and mortality.
- The incidence of invasive candidiasis is strongly related to gestational age and birth weight, but most cases are preventable.
- The diagnosis of invasive candidiasis relies on clinical suspicion and detection of *Candida* in blood culture or cultures from other normally sterile sites.
- Several methods were recently developed that can shorten the time needed for the identification of yeast from a positive culture, but improved diagnostics are still needed.

BACKGROUND

Invasive candidiasis is a leading infectious cause of morbidity and mortality in extremely premature infants. It affects 4% to 8% of extremely low-birth-weight (ELBW; birth weight <1000 g) infants and is associated with 30% mortality.[1–8] Infants with invasive candidiasis who survive frequently have long-term neurological impairment, including cerebral palsy, blindness, hearing impairment, cognitive deficits, and periventricular leukomalacia.[2,5,9–11]

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The incidence of neonatal candidiasis rose rapidly in the 1980s and 1990s with the improved survival of ELBW infants and the increased use of central venous catheters.[12] However, this trend has reversed, with the incidence of invasive candidiasis among premature infants declining substantially over the past 15 years.[13–15] In one study that included data from 322 neonatal intensive care units (NICUs), the incidence of invasive candidiasis decreased from 3.6 episodes per 1000 infants in 1997 to 1.4 episodes per 1000 infants in 2010.[15] Fluconazole prophylaxis, reduced use of broad-spectrum antibacterial antibiotics, empirical antifungal therapy, and improved care of central venous catheters have contributed to the declining incidence of invasive candidiasis.[13,15]

PATHOGENESIS

Candida species are yeast that frequently colonize skin, the gastrointestinal (GI) tract, and the female genitourinary tract.[16] Infants admitted to the NICU are colonized by *Candida* rapidly after birth, with the GI and respiratory tracts being the most frequent sites during the first 2 weeks of life.[17–21] Colonization during this age period may be related to the birthing process; infants delivered vaginally have higher rates of colonization than infants born by Caesarean section, and the colonizing *Candida* species are identical to those isolated from the maternal genitourinary tract in most cases.[17,20–22] Colonization of infants greater than 2 weeks of age frequently occurs on the skin and may be related to contact with maternal skin or the hands of health care providers.[20] In particular, health care workers may be the primary source of *Candida parapsilosis* colonization in the NICU environment.[22,23]

Colonization of infants by *Candida* species is not sufficient for the development of invasive candidiasis (**Fig. 1**), although up to 5% to 10% of very low-birth-weight (VLBW; birth weight <1500 g) infants colonized by *Candida* develop invasive disease.[18,20,24,25] Premature infants are predisposed to invasive candidiasis for several reasons. First, the typical barriers to invasion by *Candida* species are not fully developed in premature infants. The epidermis of the infant born at less than 30 weeks gestational age is thin and poorly formed compared with the skin of term infants.[26] Moreover, immaturity of the barrier and immune functions of the GI tract predispose to translocation by *Candida*.[27] Cellular immunity is also impaired; premature infants have fewer neutrophils and T lymphocytes than term infants, and both groups have altered neutrophil chemotaxis and phagocytosis compared with older children and adults.[28–30] Finally, virulence factors of the colonizing yeast isolate also seem to be important in determining the risk of progression to invasive disease. Bliss and colleagues[31] observed enhanced virulence characteristics among more than half of *Candida* isolates from infants with invasive candidiasis.

Once *Candida* species invade across mucosal surfaces or enter the bloodstream, they have a predilection for tissue invasion in the central nervous system, kidneys, liver, spleen, heart, and retina. Within the central nervous system, *Candida* can cause meningoencephalitis, cerebral abscesses, and ventriculitis with obstructive hydrocephalus.[32,33] *Candida* can also infiltrate with or without abscess formation in the liver, spleen, and (most commonly) the kidneys.[32,34] Finally, endocarditis and endogenous endophthalmitis may result from seeding of the heart valves or eyes during fungemia.

RISK FACTORS

Neonatal candidiasis generally occurs after the first 2 weeks of life in the setting of extreme prematurity or among infants of any gestational age with GI processes.[35]