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Neonatal fungal infections: when to treat?

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Abstract

Candida infections are a major cause of morbidity and mortality in neonatal intensive care units. Mortality following *Candida* bloodstream infections is as high as 40%, and neurodevelopmental impairment is common among survivors. Because invasive fungal infections are common and extremely difficult to diagnose, empirical treatment with antifungal therapy should be considered in high-risk, low-birth-weight infants who fail to quickly respond to empirical antibacterial treatment. Risk factors to consider when deciding to administer empirical antifungal therapy include: prior exposure to third-generation cephalosporins, extreme prematurity, and presence of central venous catheters.

Keywords

neonatal intensive care unit; empirical; *Candida*; infection; antifungal therapy

1. Introduction

Candida species are a common cause of neonatal nosocomial bloodstream infections in premature infants and are a leading cause of infectious-related mortality in the neonatal intensive care unit (NICU) [1]. Invasive candidiasis refers to systemic infection with *Candida* of either vital organs or normally sterile body fluid (blood, cerebrospinal fluid [CSF], or urine acquired by sterile catheterization or suprapubic aspiration). In patients at risk for invasive candidiasis, empirical antifungal therapy is the administration of antifungals prior to the availability of culture. In some populations at risk for invasive candidiasis (e.g., febrile neutropenic patients), empirical antifungal therapy is known to improve survival [2].

Although blood cultures are the gold standard for detecting candidemia, blood cultures have low sensitivity for invasive candidiasis. In an adult autopsy study, the sensitivity of the blood culture for invasive candidiasis was only 29% based on multiple large-volume blood samples [3]. Blood culture sensitivity is likely worse in premature infants, where blood culture volumes range from 0.5–1 mL. Relying on blood culture results potentially may lead to under-diagnosis of *Candida* infections and significantly delay initiation of antifungal therapy.

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2. Long-term outcomes

In addition to high mortality (30–40%) [4], invasive candidiasis is associated with poor neurodevelopmental outcomes among survivors [5]. Seventy-three percent of children (130/178) in a study of extremely-low-birth-weight (ELBW, <1000 g) infants died or had neurodevelopmental impairment at 18–22 months adjusted age [5]. ELBW infants with candidemia were more likely to have moderate or severe cerebral palsy (13.6% vs. 5.8%) and were more likely to be blind or deaf (8.1% vs. 1.9%) than uninfected infants. Prompt removal or replacement of central catheters after a diagnosis of candidemia was associated with decreased mortality rates and improved neurodevelopmental outcomes among survivors. In infants with candidemia, mortality was 21% in infants whose central catheters were removed promptly vs. 37% in infants with delayed catheter removal ($p<0.02$). In addition, persistent candidemia was more common among infants whose catheters were not promptly replaced.

3. Risk factors for candidiasis in premature infants

Broad-spectrum antibiotics (e.g., third-generation cephalosporins) enhance fungal colonization by destroying competing bacterial flora [6]. In a multicenter, retrospective cohort of 6172 infants, third-generation cephalosporin or carbapenem use in the 7 days prior to culture was associated with an increased risk for candidiasis [7] (Table 1). Gastric acidity is thought to be protective against *Candida* colonization of the gastrointestinal tract. Use of antacids (e.g., histamine-2 blockers and proton pump inhibitors) raises gastric pH, promoting bacterial and fungal overgrowth in the gastrointestinal tract [9]. Similarly, mechanical ventilation is a likely risk factor for candidemia because the endotracheal tubes bypass normal mucociliary clearance, and the act of suctioning may promote bidirectional colonization of the respiratory and gastrointestinal tract [10].

In a prospective study of 4579 ELBW infants, several early risk factors (present by day of life 3) were identified that increased susceptibility to candidiasis [5]. These included exposure to third-generation cephalosporins, prematurity, lower birth weight, and delayed alimentation (Table 1). Infants with birth weights <750 g had a higher incidence of candidiasis than infants weighing 751–1000 g (11.4% vs. 3.4%, respectively). Infants who received enteral feeding by day of life 3 developed candidiasis less frequently than those with delayed enteral feedings (3.4% vs. 8.7%, respectively).

Both the number of antibiotics administered and the number of days of antibiotic administration were associated with increased risk of candidemia. Of 866 infants who received >2 antibiotics, 3.2% (28) had candidemia compared with 0.4% (7/1981) of infants who received 2 or fewer antibiotics [8]. Of the 2121 infants receiving antibiotics for >5 days, 1.6% (34) had candidemia, as compared with 0.1% (1/726) of patients on ≤5 days of antibiotics. This study also identified histamine-2 receptor blockers, intralipids and parenteral nutrition, intubation, and length of hospital stay >7 days as risk factors for candidemia (Table 1).

Wide variation in center incidence of invasive candidiasis has been well described. A prospective study of 3702 ELBW infants found that the range of center incidence of candidiasis varied from 2.4% to 20.4% [11]. Center incidence of candidiasis was significantly correlated with broad-spectrum antibiotic use after day of life 3, especially with third-generation cephalosporin use. Furthermore, prolonged initial courses of antibiotics >5 days and center demographics (day of life 3 survivors of lower gestational age and birth weight) showed a positive trend toward higher incidence of candidiasis.

The presence and duration of central vascular catheter use is important in the development and management of neonatal candidiasis [9]. *Candida* forms a thrombin sheath around the catheter to promote adhesion to the extracellular matrix. A prospective multicenter cohort study of 2847 infants in the NICU found a significant association between catheter and antibiotic use (especially in relation to invasive procedures and treatments) and the subsequent development of candidemia [8]. A higher percentage of infants with a central catheter (2.8%) had candidemia when compared with those infants without a central catheter (0.3%). In addition, prolonged catheter use was also associated with risk of candidemia: infants with candidemia had a median of 32 days of catheter use compared with only 9 days in infants without candidemia.

4. Predictive models for invasive candidiasis

A prospective cohort study of 1515 ELBW infants compared the accuracy of clinical judgment versus a prediction model of invasive candidiasis [4]. This clinical judgment model included components of the history and clinical presentation at the time of blood culture, which could be used to estimate the probability of candidiasis. Clinicians (including nurse practitioners, residents, fellows, and attendings) were asked to estimate the probability of invasive candidiasis based on their experience and to document whether antifungal therapy was initiated at the time of a sepsis evaluation. The clinical prediction model used factors related to candidiasis from hospitalization of the mother for labor, through birth of the infant, until the time of invasive disease, day of life 120, or discharge. The area under the receiver operating characteristic (ROC) curve was 0.79 (95% CI: 0.75–0.84) for the clinical prediction model and was superior to clinical judgment ($p=0.002$). Furthermore, accuracy of clinician judgment in predicting candidiasis did not differ significantly with level of expertise. The area under the ROC curve for the clinical judgment model was similar regardless of whether an attending physician was involved in the decision to start antifungal therapy on the day of culture (ROC = 0.76 [0.69–0.82] without attending physician input vs. ROC = 0.70 [0.64–0.77] with attending physician input).

Another clinical predictive model for neonatal candidemia was developed from a multicenter, retrospective cohort study of NICU patients <1250 g birth weight ($N = 6172$) [7]. A score was assigned to each of the following variables: thrombocytopenia (2 points), third-generation cephalosporin or carbapenem use (1 point), gestational age of 25–27 weeks (1 point), and gestational age <25 weeks (2 points). A combined score of 2 had a sensitivity of 85% and a specificity of 47% for candidemia. Based on this analysis, the authors suggested a target population for empirical antifungal therapy in the nursery: infants with unexplained thrombocytopenia; infants <25 weeks estimated gestational age; or infants 25–27 weeks gestational age with a history of third-generation cephalosporin or carbapenem exposure in the 7 days prior to evaluation.

5. Evidence for empirical therapy in adults

Empirical antifungal therapy in adults with fever and neutropenia has been shown to be beneficial. A multicenter, randomized trial of 293 high-risk, febrile, neutropenic adults found that empirical antifungal therapy decreased the incidence of invasive fungal infection more than preemptive therapy (defined as treatment in the presence of clinical, imaging, or laboratory evidence of fungal disease) [12]. However, there was no difference in mortality between the groups. In a randomized study of cancer patients with prolonged fever after 7 days of broad-spectrum antibiotics, subjects receiving amphotericin B deoxycholate in addition to the current antibiotic regimen defervesced faster and had fewer infectious complications than subjects who either discontinued the antibiotic regimen or continued the current antibiotic regimen alone [2]. Another randomized study of adult neutropenic cancer

patients with fever of unknown origin showed that antimicrobial agents combined with amphotericin B deoxycholate and 5-flucytosine led to a faster resolution of fever than antibacterial therapy alone [13]. Delay in empirical antifungal therapy may also increase mortality [14].

6. Evidence for empirical therapy in infants

Although the benefits of empirical therapy in premature infants have not been evaluated in the context of a well-powered randomized trial, there are several small studies that suggest benefit. In a retrospective study of infants admitted to the NICU, empirical antifungal therapy in infants with candidemia was associated with decreased incidence of disseminated infection and reduced mortality [15]. This study suggested amphotericin B deoxycholate as a reasonable choice for empirical therapy in an infant with birth weight <1500 g who is deteriorating despite usual empirical antibacterial treatment and who has 6 of the following 9 clinical features: admission to an intensive care unit with a substantial rate of candidemia; significant history of broad-spectrum antibiotic coverage; administration of a third-generation cephalosporin; negative blood culture result; falling platelet count; exposure to systemic steroids; not currently being fed; intubated; and cardiovascular instability.

7. Empirical therapy: duration and type of antifungal therapy

The appropriate duration of empirical antifungal therapy in the presence of negative cultures is unknown. Antifungal options for empirical therapy include amphotericin B deoxycholate, fluconazole, and micafungin. Amphotericin B deoxycholate is a polyene with a very broad spectrum, including most species of *Candida*. Fluconazole is effective against most *Candida* spp., with the exception of *C. glabrata* and *C. krusei* [16]. Fluconazole is well tolerated in both the adult and neonatal populations [17] and distributes well in body tissues including the central nervous system. Echinocandins (caspofungin, micafungin, anidulafungin) are effective against all species of *Candida*.

In contrast with older children and adults, central nervous system (CNS) involvement commonly complicates invasive candidiasis in infants [5]. Candidiasis of the CNS is more accurately described as meningoencephalitis and should be assumed in the context of a positive sterile body fluid culture, including instances when the blood culture is positive and CSF is negative [17]. In a retrospective study of initial lumbar puncture results from 150 infants in the NICU, over half of the infants with *Candida* meningitis had negative blood cultures, underscoring the importance of lumbar puncture in infants at risk for candidiasis [18]. However, negative lumbar puncture findings should not be viewed as proof that the CNS is free of involvement. Because CNS candidiasis often develops as a meningoencephalitis with granulomas, parenchymal abscesses, and vasculitis, unremarkable CSF parameters in the presence of CNS infection are common [19]. In one cohort, only 25% of infants with *Candida* meningoencephalitis had CSF parameter abnormalities [20]. In addition, sensitivity of CSF cultures is often complicated by delay in lumbar puncture until after institution of empirical antifungal therapy [21]. As a result, empirical therapy should include an antifungal dosed appropriately to treat CNS disease.

Once the decision is made to discontinue empirical antifungal therapy in infants with negative cultures, they should be monitored closely for deterioration following cessation of therapy.

8. Treatment of candidemia and candiduria

Before choosing an antifungal as empirical or treatment therapy for *Candida* infections, clinicians should know whether their center routinely uses fluconazole as prophylaxis. In

addition, they should also make sure that the predominant organism isolated in the NICU is not *Candida glabrata*, which is often resistant to fluconazole. In infants with blood cultures positive for *Candida*, cultures from the blood, urine, and/or CSF should be obtained and an appropriate dose of fluconazole, amphotericin product, or micafungin given. If the patient is receiving fluconazole prophylaxis or if *Candida glabrata* is isolated, then an amphotericin product or micafungin should be given. During the first week of infection, microbiologic clearance should be documented in the blood (2 negative cultures 24 hours apart), urine, and CSF. Addition of a second agent is also worth consideration when cultures are consistently positive. If cultures are still positive by the end of week 1, catheter management should be checked and the addition of micafungin should be considered. The total course of therapy should be 21 days after microbiologic clearance is documented, and neurodevelopmental follow-up of survivors should be completed. A proposed timeline for a reasonable treatment strategy is shown in Figure 1.

Candida spp. are common causes of urinary tract infection in the NICU [22]. The Infectious Disease Society of America recommended that certain groups be treated for candiduria, including infants <1500 g birth weight [23]. Positive urine cultures in a premature infant, obtained by either sterile urethral catheterization or suprapubic aspiration, should be viewed as equivalent to positive blood cultures and result in systemic evaluation and treatment of invasive candidiasis [24]. Fluconazole is a reasonable first-line therapy for candiduria given its kinetics: it is primarily excreted unchanged in the urine [25]. Clinicians should generally not use amphotericin lipid products to treat isolated candiduria as they do not penetrate well into the kidney [26].

9. Conclusions and further areas of research

Neonatal candidiasis is associated with significant morbidity and mortality. Blood culture, although not a sensitive test, remains the only reliable method for diagnosis. Although risk factors are known, the incidence of *Candida* varies greatly by center. The most effective type and length of empirical therapy for presumed neonatal candidiasis should be determined by a randomized controlled trial. Current treatment options for the management of neonatal candidiasis include prompt removal and/or replacement of central venous catheters and treatment with amphotericin B deoxycholate, fluconazole, or micafungin.

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Figure 1. Treatment timeline for candidiasis. CSF = cerebral spinal fluid; NICU = neonatal intensive care unit.

Table 1

Risk factors for candidiasis in infants (OR presented from multivariable regressions)

Study years	Cohort	Risk factor	OR (95% CI)
2004–2007 [4]	<1000 g birth weight		
		Mechanical ventilation	1.58 (1.07–2.35)
		Broad-spectrum antibiotics in week before culture	1.98 (1.37–2.86)
1998–2001 [5]	<1000 g birth weight		
		Enteral feeding by day of life 3	0.57 (0.42–0.79)
		Male	1.28 (1.01–1.62)
		Cephalosporin use by day of life 3	1.77 (1.31–2.38)
		Birth weight 400–750 g	3.22 (2.47–4.19)
1996–2001 [7]	1250 g birth weight		
		Broad-spectrum antibiotics in week before culture	1.77 (1.33–2.29)
		Platelet count <150,000/ μ L	3.56 (2.68–4.74)
		Gestational age <25 weeks	4.15 (3.12–6.12)
1993–1995 [8]	NICU patients hospitalized 3 days		
		H2 blockers	2.44 (1.11–5.29)
		Intralipid use >7 days	2.91 (1.22–7.19)
		Parenteral nutrition >5 days	2.93 (1.11–8.39)
		Shock	3.55 (1.61–7.73)
		Apgar <5 at 5 minutes	3.40 (1.32–8.08)
		Gestational age <32 weeks	4.00 (1.20–14.4)
		Central catheter	3.94 (1.48–12.3)
		Use of >2 antibiotics	3.83 (1.44–11.4)
		Length of stay >7 days	5.33 (1.23–48.4)
		Intubation	10.71 (1.66–450)

CI = confidence interval; H2 = histamine-2; OR = odds ratio.