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NEONATAL CANDIDIASIS: DIAGNOSIS, PREVENTION, AND TREATMENT

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Abstract

Infection with *Candida* species is associated with significant morbidity and mortality in infants. The incidence of *Candida* infection varies widely across centers, likely due to differences in practice related to modifiable risk factors such as exposure to empiric antibiotics and length of parenteral nutrition. Early diagnosis of *Candida* and prompt treatment with appropriate antifungal agents, such as fluconazole, amphotericin B deoxycholate, and micafungin, are critical for improved outcomes. This paper reviews the current literature relating to the prevention, diagnosis, and treatment of *Candida* infections in the neonatal intensive care unit.

Keywords

Candida; neonatal intensive care unit; diagnosis; prevention; antifungal therapy

Introduction

Infection with *Candida* species is associated with significant morbidity and mortality in infants. Extremely low birth weight (ELBW; <1000 g) infants carry the highest burden of disease. The incidence of candidiasis in ELBW infants is approximately 10%, although it varies as much as 20-fold between centers.[1,2] Neonatal candidiasis is associated with 20% mortality, and 50% of survivors have severe neurodevelopmental impairment.[3] End-organ damage in the central nervous system, heart, and genitourinary tract is also common.[4] Few clinical signs or laboratory assays have been validated for candidiasis in infants, thus prevention of infection is critical. When infection occurs, treatment with appropriate antimicrobial agents must be prompt.

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Diagnosis

The blood culture is the gold standard for detection of candidiasis, although its sensitivity is poor.[5] Even with multiple organs infected with candidiasis, the sensitivity of blood culture to detect infection in adults is only 50%.[6] The small blood volume used for culture in infants makes isolation of *Candida* species in blood (candidemia) even more difficult. Because four or more vital organs are typically involved prior to documentation of candidemia, a positive blood culture for *Candida* should almost never be considered a contaminant and should generally be regarded as the "tip of the iceberg" for infection. Even when blood culture is able to diagnose *Candida*, the time to detection of the organism can be problematic - median time to detection of *Candida* species from blood culture in infants is 36 hours and increases to 42 hours when the infant is receiving antifungal therapy.[7]

Even more difficult than diagnosing candidemia is diagnosis of central nervous system involvement. Only 37% of infants with proven candidal meningitis also had positive blood cultures for *Candida*.[8] In addition, normal cerebrospinal fluid (CSF) parameters are present in almost half of infants with candidal meningitis.

Given the limitations of culture for the diagnosis of *Candida* infections, laboratory investigators have begun to explore other methods. 1,3-β-D-glucan is a fungal cell wall component that has been used to diagnose a variety of fungal infections, including *Candida*. Levels of this polysaccharide can be detected spectrophotometrically. Although several studies have shown promising results in adult leukemic patients with relatively high specificity for this method, the sensitivity is only 50-60%.[9,10] Polymerase chain reaction (PCR) testing has also been used to detect *Candida* DNA in blood and serum samples. This method has yielded promising results based on several small studies, with sensitivity to detect fungal disease equal to or higher than blood culture.[11,12] Enzyme and PCR assays, however, remain experimental methods. These tests have not been validated in infants, and further studies are needed to evaluate their usefulness.

Prevention

Previous investigators have identified risk factors associated with *Candida* infection in infants.[3,13] Some of these risk factors, such as gestational age and birth weight, cannot be altered. However, multiple modifiable risk factors have been identified; foremost among these is prolonged exposure to empiric antibiotics (greater than 48 hours despite negative blood cultures) and exposure to third-generation cephalosporins and other broadly-acting antibiotics such as carbapenems and beta-lactam/beta-lactamase inhibitor combinations. Differences in practices related to these risk factors likely account for the widely varying incidence of *Candida* infection across centers. For prevention of *Candida* infection, the following steps should be taken: 1) avoid the use of third-generation cephalosporins; 2) avoid the use of unnecessarily prolonged courses of antibiotics; 3) minimize the use of foreign bodies such as central venous or arterial catheters and other hardware; and 4) institute strict hand hygiene policies.

If, despite these measures, *Candida* incidence remains high (greater than 10% within a particular gestational age or birth weight stratum), then antifungal prophylaxis should be

considered for high-risk infants. Fluconazole prophylaxis has been shown to reduce colonization and prevent invasive fungal infection.[14,15] The recommended dose of fluconazole is 6 mg/kg twice weekly.[16]

Treatment

Prompt treatment is critical to improving outcomes for infants with candidiasis. If clinicians await a positive blood culture prior to starting therapy, treatment can be delayed as much as 72 hours. In ELBW infants, empirical antifungal therapy (receipt of therapy on the day of or the day before the first positive blood culture for *Candida*) is associated with increased survival without neurodevelopmental impairment.[17] Thus, empirical antifungal therapy should be considered in high-risk infants once *Candida* infection is suspected. Infants at highest risk for *Candida* who may benefit most from empirical antifungal therapy include those less than 25 weeks gestational age, those with thrombocytopenia at time of blood culture, and those with a history of third-generation cephalosporin or carbapenem exposure in the seven days before blood culture.[18]

Suitable selection of antifungal therapy at adequate dosages is crucial. Antifungal agents act via a variety of mechanisms, including inhibition of cell wall or cell membrane synthesis, disruption of cell membrane integrity, and interference with fungal DNA and RNA synthesis. For many of these agents, the appropriate dosing recommendations in infants have only recently been elucidated.

Polyenes

The polyene class of antifungals includes amphotericin B deoxycholate (AMBD), liposomal amphotericin B (L-AmB), and amphotericin B lipid complex (ABLC). These agents act by binding to ergosterol (a sterol in fungal cell membranes), resulting in the leaking of small organic molecules and eventual cell death. AMBD is the most commonly used agent to treat systemic *Candida* infections in infants,[19] and recommended dosing is 1 mg/kg/day. Studies of AMBD and amphotericin B lipid products in infants have demonstrated efficacy of these agents in the treatment of candidiasis.[20,21] A recent cohort study of infants, however, reported higher mortality in infants treated with amphotericin B lipid products compared to those treated with AMBD.[22] These results potential may be explained by lower concentrations of the liposomal formulations in the kidneys,[23] which are prime locations for end-organ damage due to candidiasis in infants.[4] Few data are available to guide dosing of amphotericin B lipid products, although a dose of 5 mg/kg/day of liposomal amphotericin B is generally considered reasonable.

5-fluorocytosine

5-fluorocytosine (5-FC) is an antifungal agent that is converted to 5-fluorouracil (5-FU) by fungal cells. 5-FU is then converted to other metabolites that disrupt fungal DNA and RNA synthesis. 5-FC is almost exclusively used in combination with other antifungal therapies, as monotherapy with 5-FC can lead to resistant organisms. 5-FC may be associated with delayed clearance of *Candida* from the CSF in neonates.[3] 5-FC toxicity is a concern particularly in infants of low birth weight who may be at risk for developing high

concentrations of drug due to renal immaturity.[24] 5-FC is also poorly tolerated and can cause gastrointestinal upset, resulting in delayed feeding. This product is not recommended for use in the nursery, but if it is used, therapeutic drug monitoring is necessary.[25]

Triazoles

The triazole antifungal class includes fluconazole, itraconazole, posaconazole, and voriconazole. These drugs represent an oral alternative to intravenous antifungal therapies. Triazoles inhibit a cytochrome P–450-dependent enzyme (lanosterol c14 demethylase) that is needed to make ergosterol, a sterol of fungal cell membranes. Fluconazole has excellent activity against *Candida* and is used routinely in infants. Itraconazole, posaconazole, and voriconazole can also be used to treat *Candida*, although their primary use is their extended spectrum activity against molds.

Of the mold-active agents, only voriconazole has been studied in infants. Pharmacokinetic analysis of voriconazole has revealed extreme variability in serum concentration with respect to weight-based dosage.[26] The unpredictable pharmacokinetic response combined with known hepatotoxicity of this agent underscores the need for therapeutic drug monitoring. Thus, except in rare cases of *Aspergillus* infection or infection with *Candida* species resistant to fluconazole (such as *C. glabrata* or *C. krusei*), voriconazole should be considered a drug of last resort in the intensive care nursery.

Fluconazole has been shown to be safe and effective in the treatment of invasive candidiasis in infants.[27] Although fluconazole is renally excreted with minimal hepatic metabolism, its most concerning side effect is hepatotoxicity that is not related to amount or duration of exposure. Fluconazole dosing adjustments therefore are made based on renal function rather than liver function. Because fluconazole exhibits fungistatic activity that is time-dependent, optimal dosing incorporates area-under-the-curve (AUC) dosing target. Adult dosing of fluconazole in stable patients consists of a loading dose of 800 mg (12 mg/kg) followed by 400 mg (6 mg/kg) daily.[24] This dosing provides adequate drug for adults to maintain an AUC of 400–800 mg*hr/L. To achieve similar exposures, infants require 12 mg/kg/day.[16,28] In addition, a loading dose of 25 mg/kg results in more rapid achievement of therapeutic levels and was found to be safe in a small cohort of infants.[29] Because more immature infants have delayed clearance of fluconazole, infants who are less than 30 weeks gestational age and less than 2 weeks postnatal age who have a creatinine level >1 mg/dL should be given a loading dose of 12 mg/kg.[16] Creatinine level should be monitored, and if creatinine remains >1 mg/dL, then 6 mg/kg/day dosing should be considered; if creatinine drops to <1 mg/dL, then 12 mg/kg/day should be continued.[16]

Echinocandins

The echinocandins (anidulafungin, caspofungin, and micafungin) act at the fungal cell wall and inhibit 1,3-β-D-glucan synthesis. These agents do not penetrate the CSF, but they are able to penetrate brain tissue. The echinocandins do not, however, penetrate the vitreous; infants being considered for treatment with these agents must undergo dilated retinal exam to exclude endophthalmitis. Based on data from randomized controlled trials, the echinocandins are recommended as first-line agents in adults and older children for

candidemia and disseminated candidiasis.[24] In the intensive care nursery, the echinocandins are emerging as an alternative therapy for *Candida* infections. Most of the available neonatal pharmacokinetic data are for micafungin. Several pharmacokinetic studies of micafungin at doses ranging from 1.5–15 mg/kg/day have been performed in infants.[30–33] The current recommended dose is 10 mg/kg/day, with no adjustment needed for renal or hepatic impairment.

Anidulafungin and caspofungin have been studied in older children, but few data are available to guide dosing in infants.[34] Only a low dose of caspofungin (25 mg/m^2/day) has been studied, and there is a risk for central nervous system under-dosing.[35] Thus, anidulafungin and caspofungin are not first-line agents for candidiasis in the intensive care nursery.

Summary and recommendations

Candidiasis in the intensive care nursery results in substantial morbidity and mortality. Prevention of infection is possible via modification of risk factors. Early diagnosis is critical, and treatment should be initiated promptly with appropriate antifungal agents. Empirical antifungal therapy should be considered when *Candida* is suspected in ELBW infants. When infection with *Candida* is diagnosed, the following steps should be followed:

1) Central venous and arterial catheters should be removed. Temporary, peripheral access should be used for several days while the patient is receiving antifungal therapy until documentation of negative blood cultures.

2) First-line therapy for candidiasis should be initiated. Choice of therapy includes:

- Fluconazole 12 mg/kg/day (25 mg/kg loading dose)
- Amphotericin B deoxycholate 1 mg/kg/day
- Liposomal amphotericin B 5 mg/kg/day (if urine cultures are negative)
- Micafungin 10 mg/kg/day (if eye involvement is excluded)

3) Microbiologic clearance should be documented by exhaustive search, including CSF culture, urine culture, two negative blood cultures separated by greater than 24 hours, dilated retinal exam by an ophthalmologist, and echocardiogram. Abdominal or central nervous system imaging should be considered if there is concern about invasive candidiasis in these areas.

4) For uncomplicated candidemia or candiduria, length of therapy should be 21 days after microbiologic clearance. If cultures continue to be positive by day 7, the addition of a second agent should be considered.

5) Patients should undergo follow-up to assess neurodevelopmental outcome with intervention if needed.

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