SYSTEMIC FUNGAL INFECTIONS EMERGING INFECTION IN NEWBORN

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INTRODUCTION

Fungal infections in general and Candida species in particular are increasingly being recognized to cause late onset sepsis (> 3 day) and compete with bacteria today as one of the leading causes of nosocomial infections[1]. Most fungal infections in neonates are due to Candida species; a much smaller number of infections may be attributed Malassezia, Zygomycetes, or Aspergillus pathogens. Candida produce infections that range from nonlife-threatening mucocutaneous illnesses to invasive processes that may involve virtually any organ system. Preterm infants and sick term infants in NICUs have a specific, increased risk for invasive fungal infection.

INCIDENCE

The cumulative incidence of invasive candidiasis is upto 5% of low-birth-weight babies and is inversely proportional to birth weight[2]. About 20% of babies weighing less than 1000 g develop invasive fungal infections. The overall mortality rate for disseminated fungal infections in this group of babies is very high, often approaching 50%[3]. Candida colonization can be detected in approximately 30% of infants weighing less than 1500 g birth weight. Colonization increases with decreasing birth weight[4,5]. Colonization is not an independent risk factor for subsequent candidiasis. Acquiring Candida does not always translate into systemic infection, but previous colonization is a required step before the occurrence of invasive candidiasis[6]. Nearly 80% of cases diagnosed in premature infants occur in the first 42 days of life[7]. In term newborns the incidence of candidemia is 10 fold less and is especially related to congenital anomalies especially of the gastrointestinal tract.

CANDIDA SPECIES

Candida organisms are saprophytic yeasts that are ubiquitous and are constituents of the normal microbial flora of humans. All Candida species form pseudohyphae that are important in invasion. Candida albicans is the predominant species associated with maternally acquired neonatal disease[8]. Candida parapsilosis is a common species in nosocomially acquired infection (central line infection), and other species such as Candida stellatoidea, Candida lusitania, Candida krusei, and Candida glabrata are reported less frequently[9]. Any Candida species may cause disease in neonates.

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PATHOGENESIS

Neonates may acquire Candida by vertical or nosocomial transmission (person to person contact or via infusates). In vertical transmission, acquisition may occur either during gestation or at the time of delivery. A combination of infecting dose and host factors play a role in the development of candidiasis. The organism produces multiple virulence factors such as adhesins, proteinases, and phospholipases that promote attachment and invasion. After penetration of epithelial or endothelial barriers, in this setting, Candida can penetrate into lymphatics, blood vessels, and deep tissues, resulting in disseminated infection. Disseminated candidiasis can cause disease in any organ system.

Table 1 : Risk factors for candidiasis

Gestational age < 32 week	**Umbilical catheters**
Birth weight 1500 g	Peripheral or central venous catheters
Apgar score < 5 at 5 minutes	Abdominal surgery
Intubation/mechanical ventilation	Use of intralipid / TPN
Prolonged administration of antibiotics	Corticosteroid use
The most important of these factors appears to be the number of prior antibiotics and the duration of therapy.	

Risk factors for candida colonization and sepsis are similar

CLINICAL MANIFESTATIONS

Clinical manifestations vary depending on the location and extent of the infection. The classic clinical picture of systemic candidiasis in neonates is indistinguishable from bacterial sepsis[2]. Symptoms are often more subtle and indolent. Among these, respiratory dysfunction and apnea were the most common presenting signs in large series[10]. A significant proportion of neonates will present simultaneously with localized signs of candidal infection at one or more other sites. In addition to fungaemia, infants may present with pneumonia, meningitis, renal tract infection, ophthalmitis, osteomyelitis, endocarditis, liver abscesses, and skin abscesses[11]. Candida species. Always should be considered in the differential diagnosis of sepsis in the neonate, particularly late onset sepsis[12]. Up to 75% of cases of neonatal candidiasis present with infection of two or more organs.

Table 2 : Clues to fungal infection

- Ashen grey skin complexion
- Indolent clinical course
- Persistently elevated C Reactive protein
- New-onset or persistent thrombocytopenia
- Sepsis with Negative blood culture

DIAGNOSIS

Documented invasive candidiasis is defined as a positive culture from normally sterile body fluid. No special medium is required for growth of Candida in the laboratory. The isolation of Candida from wounds, skin, urine, or stool specimens is not diagnostic of disease. On the other hand, growth of Candida spp. From sterile specimens (e.g., blood or CSF) is always diagnostic of infection. Candida species grow robustly in the routine blood culture media used in most clinical laboratories, and these media usually yield the organism within 48 to 72 hours of incubation. Widespread infection despite negative cultures is common[13].

Overgrowth of bacteria on nonselective media can easily inhibit or hide the growth of fungi. Selective culture media can be made inhibitory to bacteria by maintaining a low pH (e.g., Sabouraud dextrose agar) or by including antibacterial agents in the media (e.g., gentamicin and chloramphenicol). To date PCR testing is not widely available for clinical use.

Screening for disseminated disease

Prolonged symptoms, persistent candidemia (>5d), or laboratory evidence of end-organ damage should prompt investigation for disseminated disease[14,15]. Dissemination affects length of treatment. A thorough evaluation to rule out disseminated candidial infection in infants with this syndrome should be done routinely by:

- completing a microbiological evaluation of blood, urine, and CSF.
- Indirect opthalmoscopy evaluation of the retina
- an echocardiographic evaluation of the heart
- a renal ultrasound

Consequences of missed or delayed diagnosis

Delayed treatment results in increased rates of intraventricular hemorrhage, chronic lung disease, retinopathy of prematurity requiring surgical therapy, and up to a four fold increase in long-term neuro developmental delays[16]. The associated mortality with invasive candidiasis is three times higher than that of uninfected infants of similar gestational age and birth weight. Untreated, the mortality exceeds 80%.

TREATMENT

Empiric Treatment

Some studies have reported use of empiric antifungals pending culture results while some have used clinical scores. These have not been studied in prospective controlled trials. There is lack of evidence for routine empiric treatment. In certain circumstances, empiric antifungal therapy for 48-72 hours may be warranted in infants with negative initial culture results who still have signs and symptoms of sepsis after 48 hours of antibacterial treatment and who are recultured[17]. In

addition, the infants must have one of the following criteria:

- Thrombocytopenia (<100 X 109/L)
- Necrotising enterocolitis or focal bowel perforation
- Weight of less than 750 g or a gestational age of less than 26 weeks

Definitive treatment[18]

Isolation of candida from sterile site warrants definitive therapy. Amphotericin B is the drug of choice for invasive fungal infections. It is effective against most Candida species causing disease in neonates except for C lusitaniae Test doses are not required because the drug is better tolerated in neonates than in adults. Age and underlying disease are not associated with increased risk of nephrotoxicity. Lipid formulations of amphotericin B are very much expensive and do not appear to be more efficacious than conventional amphotericin B deoxycholate, and their use should be limited to patients who are either refractory to, or intolerant of, the regular amphotericin B preparation Flucytosine is not recommended as monotherapy because resistance develops rapidly, but the antifungal is given occasionally in combination with amphotericin B for central nervous system infections. The lack of a parenteral formulation limits the utility of flucytosine. Fluconazole is both safe and effective for invasive fungal infections. 50% of C glabrata and 100% of C krusei isolates have been reported to be resistant to fluconazole. Breakthrough (or persistence of) candidemia in the face of ongoing antifungal therapy suggests the possibility of an infected intravascular device, significant immunosuppression, or microbiological resistance.

Table 3 : Antifungal Agents

DRUG	DOSE	Toxicity	Comments
Amphotericin B	1 mg/kg/d q 24h IV	Anemia, hypokalemia, nephrotoxicity	Monitor blood urea nitrogen, creatinine, and K+ daily initially and twice weekly if stable after 1 week; hold dose until K+ <3 mEq/dL is corrected. Give infusion over 2-4 h.
Lipid formulations of amphotericin B	3–7 mg/kg/d q 24h IV	Less nephrotoxic than amphotericin B	Monitor renal function and K+ as above
Flucytosine	50–150 mg/kg/d q 6h PO	Bone marrow suppression, hepatotoxicity, and gastrointestinal symptoms	Good penetration into CSF; must reduce dosage in patients with renal failure
Fluconazole	3–6 mg/kg/d q 24h PO, IV	Good penetration into CSF	Drug interaction with cytochrome P-450 system
Itraconazole	5 mg/kg/d q 24h PO		Limited experience

Additionally, caspofungin an echinocandin, and voriconazole and posaconazole the newest azole agents, are promising future treatment options due to their excellent broad-spectrum activity against Candida species. Published data on the use of these medications in infants are limited.

Duration of treatment

In the absence of deep tissue involvement or abscess formation, treatment usually is continued 5 to 7 days after clinical improvement. At least 14 days of therapy after the last positive blood-culture result is recommended for neonates with candidemia in the absence of disseminated disease. Prolonged antifungal therapy (i.e. 6 weeks) is frequently required for chronic disseminated candidiasis, endocarditis, endophthalmitis, and osteomyelitis.

Monitoring lab parameters during treatment

- Liver and renal function should be evaluated at the time of diagnosis (or if candidemia is persistent) because they may suggest liver or renal dissemination and the need for ultrasonography.
- Antifungal treatment can affect serum electrolytes and the hematologic, hepatic, and renal systems and should be monitored during treatment.
- In patients with persistent candidemia of longer than 5 days, repeat screening tests for vegetation or abscess
- Persistent thrombocytopenia may indicate therapeutic failure.

Anti fungal Prophylaxis

There is insufficient evidence to support the use of prophylactic oral antifungal agents in very low birth weight infants in the neonatal intensive care unit.[19] Prophylaxis with intravenous fluconazole in VLBW/ELBW infants showed significant reduction in invasive fungal infections. This finding should be interpreted cautiously.[20] For some NICUs with high rate of infection, and those with large populations of < 1000 gram infants, prophylaxis may be appropriate. One concern with fluconazole prophylaxis is the potential for the emergence of resistance over time, and this issue is under further study. Further trials are needed to provide more precise estimates of effect size, and to assess the effect on mortality, neurodevelopment, and the emergence of antifungal resistance.[21,22]

Malassezia furfur[17], a lipid dependent fungus, is another cause of systemic fungemia in neonates. It frequently involves babies receiving intralipid through a central venous catheter. Lung lesions, pulmonary vasculitis, septic thrombi are the chief affections and involvement of other organ systems is uncommon. Although Amphotericin B has been used in these cases, they usually resolve on removal of indwelling central catheters and omitting intralipid.

Aspergillosis[17] contamination through the ventilation system is one of the predisposing factors. One presentation involves injured skin areas that rapidly (over 24 h) progress to necrotic eschars. Diagnosis is made by demonstrating septate hyphae with 45° angles characteristic of Aspergillus species.

Table 4 : Good practices to reduce fungal infections

- Increased compliance with hand hygiene standards
- Improved accuracy of the diagnosis of bacteremia
- Reduced line and line connection (hub) bacterial contamination
- Maximal barrier precautions for central line placement
- Improve nursing practices to maintain skin integrity. Avoid skin abrasions.
- Decreased number of skin punctures
- Decreased duration of IV lipid infusion
- Decreased duration of central venous line use
- Early enteral nutrition preferably by breast milk.
- Remove a central venous catheter on suspicion of severe fungal infection or within 24 hours of a positive culture for fungus
- Avoid use of antacids as gastric pH favors fungal colonization.
- Use narrowest spectrum antibiotics possible
- Reduce duration of antibiotics. Stop antibiotics if cultures negative.
- Use HEPA filtration ventilation systems and take measures for containment of dust, especially during hospital renovation and construction

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