Systemic fungal infections in neonates
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ABSTRACT
Advances in neonatal management have led to considerable improvement in newborn survival. However, early (<72 hours) and late (>72 hours) onset systemic infections, both bacterial and fungal, remain a devastating complication and an important cause of morbidity and mortality in these babies. Most neonatal fungal infections are due to Candida species, particularly Candida albicans. The sources of candidiasis in NICU are often endogenous following colonization of the babies with fungi. About 10% of these babies get colonized in first week of life and up to 64% babies get colonized by 4 weeks of hospital stay. Disseminated candidiasis presents like bacterial sepsis and can involve multiple organs such as the kidneys, brain, eye, liver, spleen, bone, joints, meninges and heart. Confirming the diagnosis by laboratory tests is difficult and a high index of suspicion is required. The diagnosis of fungemia can be made definitely only by recovering the organism from blood or other sterile bodily fluid. Amphotericin B continues to be the mainstay of therapy for systemic fungal infections but its use is limited by the risks of nephrotoxicity and hypokalemia. Newer formulations of amphotericin B, namely the liposomal and the lipid complex forms, have recently become available and have been reported to have lesser toxicity. More recently Indian liposomal Amphotericin B derived from neutral lipids (L-Amp –LRC-1) has shown good response with less toxicity. A clinical trial with this preparation has shown to be safe and efficacious in neonatal fungal infections. Compared to other liposomal preparations, L-Amp–LRC-1 is effective at lower dose and is less expensive drug for the treatment of neonatal candidiasis.

KEY WORDS: Systemic fungal infection, neonataes, Fungisome, Amphotericin

Causes and risk factors
Most neonatal fungal infections are due to Candida species, particularly Candida albicans. Candida parapsilosis and Candida tropicalis are other species getting notorious in NICU outbreaks. The sources of candidiasis in NICU are often endogenous following colonization of the babies with fungi. The NICU babies become colonized very early. About 10% of these babies get colonized in the first week of life and up to 64% babies get colonized by 4 weeks of hospital stay.[9] The gastrointestinal tract is the first to become colonized though multiple sites may be involved. There is some evidence showing a correlation between fungal colonization and invasive disease in VLBW babies.[9–16]

Administration of contaminated intravenous solutions, notably the solutions for total parental nutrition (especially the intralipid) may result in NICU outbreaks. Spread may also occur from patient to patient or through a colonized health care worker.[1],[3],[4],[6]

Acquired late onset systemic fungal infections occur in babies with the risk factors like prematurity, use of broad spectrum antibiotics, prolonged duration of endotracheal intubation, receipt of parenteral hyper alimentation, presence of central venous catheters, surgical procedures, use of theophylline, administration of corticosteroids, presence of mucocutaneous candidiasis, perineal dermatitis or colonization with the organism.[1],[8],[15]

Congenital candidiasis is uncommon and occurs due to ascending infection through the birth canal. These are mostly localized to the skin but occasionally can cause disseminated disease. Candida is usually cultured from the gastric aspirate, or from the skin lesions. These babies are treated with amphotericin B and have a mortality rate as high as those with ac-
quired candida infections.

*M. furfur*, a lipid dependent fungus, is another cause of systemic fungemia in neonates. It frequently involves babies receiving intralipid through a central venous catheter. Mycotic thrombi on the catheters lead to mycotic emboli. 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.

**Diagnosis**

Disseminated candidiasis presents with manifestations similar to bacterial sepsis. The signs and symptoms are non-specific and include temperature instability, refusal of feeds, respiratory distress, abdominal distension, apnoea, lethargy, bradycardia, decreased perfusion or seizures. End organ damage is more common and severe in systemic fungal infections and can involve the kidneys, brain, lungs, eyes, liver spleen, bones and joints.[7] Widespread infection despite negative cultures is common.[8] Pulmonary fungal affection can occur either due to haematogenous spread or through bronco-pulmonary spread; the latter is seen in newborns after prolonged ventilation. The renal manifestations can be in the form of acute renal failure, hypertension or flank masses. Endophthalmitis is a complication of invasive disease and needs urgent intervention.[9]

Confirming the diagnosis by laboratory tests is difficult and a high index of suspicion is required. The diagnosis of fungemia can be made definitely only by recovering the organism from blood or other sterile body fluids. The blood must be cultured in a Dupont isolator. All indwelling catheter aspirates, blood, urine must be examined for hyphae or budding yeast. Budding yeast can be seen onuffy coat preparations also. Rapid diagnosis of invasive candida infection by detection of circulating cell wall or cytoplasmic antigen is possible though less reliable. Prompt and aggressive use of antifungal treatment is justified in a clinically septic neonate, especially the one with a raised serum concentration of C reactive protein, who does not show a satisfactory response to antibiotics.

**Therapy**

Amphotericin B continues to be the mainstay of therapy for systemic fungal infections. The optimal daily dosage for adequate treatment of systemic candidiasis in neonates is estimated to be 20–30 mg/kg. In children with CNS infections conventional amphotericin B has been used even up to 12 weeks with a maximum cumulative dose of 800–1000 mg.[10] Its efficacy in treating CNS infections is greatly enhanced by concurrent administration of 5-Fluorocytosine. Although resistance to amphotericin B is not a major problem, its use is limited by the risks of nephrotoxicity and hepatotoxicity. Some of the other side effects being thrombocytopenia, hypokalemia and hypomagnesaemia. Hence monitoring of serum potassium and magnesium is imperative during the therapy. There is a serious search for the use of alternative drugs that can give equal or superior efficacy in treating fungal infections with lesser side effects than conventional amphotericin B. Liposomal amphotericin B and lipid complex of amphotericinB may serve as useful alternatives with equal effectiveness but less toxicity. Liposomal encapsulation of Amphotericin B has been shown to reduce the toxicity of the drug while retaining its antifungal activity. More recently liposomal amphotericin B derived from neutral lipids (L-AMP-LRC-1) was studied in 25 neonates with systemic candidiasis and showed good response with less of toxicity. This preparation would be economical compared to the marketed liposomal preparation.[11] In a prospective study of 67 babies with systemic candidiasis, cure rates were 67.6%, 83.3% and 57.1% for conventional amphotericin B, liposomal amphotericin B and ABCD, respectively.[12] However, the optimum duration of therapy as well as the maximum dose that can be used safely have not yet been defined. The maximal dose of liposomal amphotericin B used in a newborn without apparent side effects is 750 mg (150 mg/kg) and the maximum duration being 12 weeks after negative fungal cultures.[13]

Fluconazole, a triazole that has far less toxicity, has been used with some success. It has the additional advantage of being available as an oral formulation. It is used in the dose of 5–6 mg/kg per day orally or intravenously. In a study 24 neonates with culture proven candidiasis treated with fluconazole, both clinical and microbiological cure was achieved in 96% babies and two babies experienced adverse events. Fluconazole appears to be safe and effective for treatment of systemic candidal infection in the neonate although more data are required regarding its use in very low birth weight (VLW) infants.[14] We have treated babies with fluconazole, mostly as monotherapy and have found a variable response. Of the nine cases of systemic fungal infection presenting over the past 6 months, fluconazole used as monotherapy was effective in three cases.

The Neonatal Candidiasis Study Group has published a consensus statement on the management of systemic fungal infections. About 95% of respondents have cared for an infant with systemic candidiasis in the past 2 years. Fluconazole and liposomal amphotericin were used to some extent by 90 and 69% of respondents, respectively. A single blood culture positive for Candida led to a recommendation for immediate treatment by 99%; amphotericin B was the preferred therapy for candidemia (88%). More than 80% of respondents would request cerebrospinal fluid, urine and repeat blood cultures and ophthalmologic examination in the evaluation of candidemia. If a cerebrospinal fluid culture is positive, 25% would use amphotericin B alone whereas 62% would add fluocytosine. There was no consensus concerning duration of therapy, use of amphotericin B test dose or management of a central catheter in place during candidemia. Thus this study group derived no consensus regarding the duration of therapy, the use of fluconazole in systemic fungal infections, antifungal susceptibility testing and the removal of central venous catheters in cases of catheter related candidiasis.[15]

Systemic candidiasis is an iatrogenic disease of modern neonatal intensive care that deserves urgent attention for its
prevention as well as effective treatment in order to minimize neonatal morbidity and mortality.

References