25 Fungal Infections

In majority of cases, fungal infection is caused by candida species and rarely, it is caused by Aspergillus, Zygomycetes, Malassezia and Trichosporon. Prevention and timely management improves outcome in neonates.

Invasive candida infection

The incidence of invasive candida infection is inversely proportional to birth weight. The incidence rate in VLBW is 1 to 4 %, ELBW is 2 to 8 % and in incredibly low birth weight (< 750 gm) or gestation < 26 wks is 20%[1]. The rate of systemic fungal infection as reported by DeNIS study group from India is 3.5% (only outborn cohort)[2]. Among candida infection *C. albicans* is the most common species (50%) followed by *C. parapsilosis* (33%), *C. glabrata, C. krusei, C. tropicalis and C. pseudotropicalis.*

Risk factors[1,3,4]

Important risk factors associated with invasive candida infection are : extreme prematurity, prolonged use of antibiotics > 5 days or 2 or more antibiotic use, complicated gastrointestinal disease, lack of enteral feedings, intralipid use >7 days, use of central venous catheter, endo-tracheal intubation and mechanical ventilation, hyperglycaemia, use of steroids/ H2 blockers.

Clinical presentation

Clinical features range from localised skin infection in term neonates to disseminated infection in extreme preterm neonates. Severity depends on factors like gestation, birth weight and invasive procedures. It commonly presents after 2 weeks of age. Signs and symptoms are similar to bacteremia. Usually neonates have a smouldering course. Common features include frequent apnea, lethargy, GI symptoms (distension of abdomen, bloody stools, gastric aspirates), respiratory distress, increased oxygen requirement, thrombocytopenia, hyperglycemia, metabolic acidosis, hypotension and elevated leukocyte count. Thrombo-

cytopenia lacks specificity and sensitivity for diagnosis of invasive candidiasis. Various organ system involvements and their clinical presentation are enlisted below:

1. Renal - UTI, renal abscess
2. CNS- Meningitis, ventriculitis, abscess
3. Gastrointestinal-Peritonitis, spontaneous intestinal perforation
4. Respiratory-Pneumonia
5. End organ dissemination
    a. Eye-endophthalmitis, chorioretinitis
    b. Heart-endocarditis and thrombi
    c. Bones and joint-septic arthritis and osteomyelitis

Diagnosis

Culture of fungus from a normally sterile site (blood, urine, CSF, bone or joint, peritoneum, pleural space) is diagnostic. In case of suspected catheter related infection, culture should be obtained from both peripheral venous blood and indwelling catheters.

1. **Blood culture:** Blood culture remains the gold standard[5]. 90 % of cultures grow fungus within 72 hrs. Monitor culture for 10 days to ensure growth of slow growing species. Sensitivity of blood culture varies from 28 % to 78 % from various studies.
2. **Urine:** Urine should be collected by either suprapubic aspiration/ sterile catheterization for culture and microscopy. In microscopy visualise hyphae (true and pseudo) and budding yeast cells.
    a. Candida UTI defined as 10^4 CFU of candida species/mL urine.
3. Obtain culture from other sites depending on clinical presentations (CSF, peritoneal fluid etc).
4. **Identification of species and susceptibility:** Most of the species are susceptible to both fluconazole and amphotericin B except *C. glabrata* and *C. krusei*, which are resistant to fluconazole and *C.lusitaniae*, which is resistant to amphotericin B.
5. The following baseline investigation to be done before starting of treatment with amphotercin B

a. Hemoglobin, TLC, ANC

b. Urea and creatinine

c. Serum electrolytes

d. Bilirubin and liver enzymes

6. **End organ dissemination (EOD)** screen to be done in all confirmed blood stream infection which includes-eye examination for fungal ophthalmitis or retinitis, renal ultrasound for fungal balls, echocardiography and cranial ultrasound/ CT/ MRI.

7. Newer methods of diagnosis are molecular diagnostic assay using β-1, 3-d-Glucan, PCR, PNA FISH (peptide nucleic acid) yeast traffic light assay. All these newer methods are costly, not readily available and still needs further studies.

Treatment

Table 25.1: Drugs used in the treatment of systemic candidiasis- dose, toxicity and monitoring

Drug	Dose	Toxicity	Monitoring
Amphotericin B deoxycholate	For doses, refere to Annexture A1	Renal, hematologic, hepatic	Urine output, creatinine, potassium, magnesium, liver enzymes
Lipid formulation amphotercin B		Similar to amphotercin B; (decreased renal toxicities)	Similar to amphotercin B
Fluconazole		Hepatic, gastrointestinal	Liver enzymes
Micafungin (Echinocandin)		Renal, hepatic (minimal)	Creatinine, urine output, liver enzymes

1. Infusion related toxicity of Amphotercin B is not seen in neonates. "Lower test" dosage not required.
2. No enough evidence to support the use of liposomal or lipid formulation Amphotercin B over deoxycholate form. One study showed increased mortality with lipid formulations.
3. Primary concern for use of fluconazole is emergence of resistance. C krusei and C glabrata are resistant to fluconazole.

Amphotercin B deoxycholate, 1 mg/kg daily, is first line drug recommended for systemic candidiasis including meningitis.

Fluconazole, 12 mg/kg intravenous or oral daily, is an alternative in neonates who have not been on fluconazole prophylaxis. Lipid formulation amphotercin B, 3–5 mg/kg daily, is an alternative, but should be used with caution, it may not be effective in urinary tract infection. The addition of flucytosine, 25 mg/kg 4 times daily, may be considered as salvage therapy in meningitis in conditions with inadequate clinical response amphotercin B therapy. Echinocandins are used in treatment of fungal infections unresponsive or resistant to amphotercin B and fluconazole. The recommended duration is 2 weeks (3 weeks for meningitis) after documented clearance of candida species from the bloodstream[6]. There is no evidence to recommend empiric therapy in extreme preterm neonates.

Central venous catheter care in neonates with blood stream infection

- Administer a dose of antifungal through the 'old' CVC (for diagnostic purposes- perform a blood culture from CVC)
- Place a peripheral line
- Remove the CVC and send tip for culture
- Place a new CVC in a site other than the previous at least 36–48 h after CVC removal (ideally wait for 3 sterile blood culture)

Prophylaxis

In NICUs with high (>10%) and moderate rate (5- 10%) of invasive candidiasis, intravenous or oral fluconazole prophylaxis, 3–6mg/kg twice weekly for 6 weeks is recommended in ELBW neonates. Oral nystatin, 100,000 units 3 times daily for 6 weeks, is an alternative to fluconazole but there is not enough evidence.[6]

Evidence for prophylactic antifungal therapy[7,8]

Prophylactic systemic antifungal therapy compared to placebo/no therapy in VLBW neonates reduced incidence of invasive fungal infection (RR- 0.43, 95% CI 0.31 to 0.59). (Studies done in NICUs with high incidence of invasive infection (Cochrane 2015)).

Prophylactic oral/topical non-absorbed antifungal prophylaxis vs. placebo/no therapy resulted in decreased incidence of invasive fungal infection (RR- 0.20, 95% CI 0.14 to 0.27). However, oral/topical non - absorbed antifungal prophylaxis is not recommended due to methodological weakness in studies (Cochrane 2015).

References

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