Fungal infection in neonates

Immune function is sub-optimal at the extremes of life. In the neonate this is manifest chiefly as defective cell-mediated immunity leading to increased susceptibility to infection with intracellular bacteria, viruses and fungi. Invasive therapeutic and monitoring devices heighten this susceptibility.

Fungal infection occurs in about 5% of premature low birth weight infants, with Candida spp. being the most frequent cause. This may be acquired from the mother's genital tract during delivery; infection thereafter is usually associated with central venous catheters, used for parenteral nutrition (Knox, Hooton & Barson, 1987), endotracheal tubes or intra-ventricular shunts. Nosocomial outbreaks of infection have been reported in infants (Vaudry, Tierney & Wenman, 1988). Colonization of the oropharynx and gastrointestinal tract may lead to oral thrush or napkin rash, but in pre-term infants Candida spp. may gain entry into the bloodstream by invading the gut wall. In the latter case mortality is high; the diagnosis often being made at post-mortem examination (Keller et al., 1977). Babies of very low birth-weight (< 1500 g) (Johnson et al., 1984), babies receiving antibiotics (Baley, Kliegman & Fanaroff, 1984), and those who have had mucocutaneous candidosis (Faix et al., 1989) are also at greater risk of developing systemic candida infection.

The clinical features of disseminated candidosis in the neonate are non-specific but include deteriorating respiratory function, abdominal distension and temperature instability. Focal infection such as meningitis, osteomyelitis or skin abscesses is rare, although more common in neonates than in older children or adults.

The isolation of Candida spp. (especially more than once), from sterile sites such as suprapubic aspiration of urine (SPA) or blood cultures is nearly always significant. However, systemic infection is not always associated with the recovery of the fungus from these sites. Examination of Gram-stained buffy coat smears may be useful (Cattermole & Rivers, 1987). Detection of candida cell wall antigens (such as mannan) in serum is possible using ‘in house’ methods (Schreiber, Maynard & Lew, 1984) or commercially available kits (Barnes, 1990; Jones, 1990) but levels can be elevated in subjects who are heavily colonized, or absent from patients with proven disseminated candidosis. Serial measurements of C-reactive protein (CRP) is a useful, if non-specific, guide to the presence of fungal infection (Cattermole & Rivers, 1987). At present no single test can reliably diagnose systemic candidal infection; a high index of suspicion is necessary in infants whose condition is deteriorating. Blood cultures and SPA should be done while serial measurements of serum CRP and candida antigen levels may give useful information.

Although C. albicans is the most frequent isolate, other Candida spp. such as C. parapsilosis (Weems et al., 1987) and C. lusitaniae (Sanchez & Cooper, 1987) as well as other yeasts such as C. glabrata (Walter, Gingras & McKinney, 1990) and Hansenula anomala (Murphy et al., 1986) have been reported in neonatal infections, often in association with central venous catheters or ventriculo-peritoneal shunts.

Malassezia furfur is a lipophilic yeast which may be a normal skin commensal as well as causing pityriasis versicolor. Systemic infection with this yeast have been described and include pulmonary vasculitis (Redline & Dahms, 1981) and fungaemia in neonates receiving parenteral lipid solutions via central venous catheters (Powell et al., 1984). There are no specific diagnostic features of systemic infection but fever and thrombocytopenia are common findings. The organism may be seen in peripheral blood buffy coat preparations. Conventional blood culture systems are not optimal for the recovery of M. furfur; Sabouraud’s dextrose agar with olive oil and 0.2% Tween 80 are required for isolation (Dankner et al., 1987). Improved methods for the isolation of M. furfur have been described by Leeming & Notman (1987). The source of M. furfur and the route by which it enters the blood remain unclear. It colonizes the skin in up to 64% of neonates in intensive care units (Powell et al., 1987). In a recent study (Azimi et al., 1988) M. furfur was grown from only four of ten intravenous catheter tips, but from all 11 samples of fluid from lines connecting the central venous
catheter and lipid emulsion, although the organism could not be grown from the emulsions. This suggests contamination of the intermediate line at either end, rather than direct entry of the organism into the bloodstream via an infected exit site or contaminated parenteral solution.

The yeast *Trichosporon beigelli* is a normal commensal of skin, and respiratory and gastrointestinal tracts. Although known as the cause of white piedra, it is now recognized as an opportunistic pathogen in immunocompromised patients, including the neonate (del Palacio et al., 1990). Disseminated infection presents in a similar way to systemic candidosis and mortality is high. The organism can be isolated on routine fungal media and should be distinguished from other yeasts, as it is often resistant to amphotericin B (Walsh et al., 1987).

Fungal infections with *Cryptococcus* spp. and *Aspergillus* spp. appear to be very rare in this group of patients.

Removal of central lines, stopping broad spectrum antibiotics and intralipid preparations are all important initial steps in the management of systemic fungal infections in neonates. Although in adults these measures may be all that is needed for the resolution of infection, antifungal treatment should be given to the neonate.

Amphotericin B remains the treatment of choice for systemic candidosis and appears to be better tolerated by infants than adults (Starke et al., 1987). However, the volume of distribution, renal clearance and serum levels are variable and the drug may accumulate. Nephrotoxicity is minimal if the dose is kept to a maximum of 1 mg/kg/day, although the interval between doses may need to be increased in pre-term infants. Combined therapy with flucytosine (100 mg/kg/day) may be needed to treat species other than *C. albicans* and for infections of the central nervous system into which the penetration of amphotericin B is poor. The duration of antifungal therapy depends upon the severity and site of infection. Short course therapy (< 14 days) may be appropriate in cases of catheter-associated fungaemia. Serial CRP measurements are useful in determining the response to treatment (Timonen & Koistinen, 1985).

Patients with systemic *M. furfur* infection which persists despite stopping the administration of parenteral lipid solution, or those who have severe thrombocytopenia require systemic treatment with amphotericin B. Flucytosine has variable activity in *vitro* and the majority of strains are resistant (Marcon et al., 1987).

Optimal treatment for trichosporinosis is unknown. About 60% of isolates are susceptible to amphotericin B *in vitro*, and flucytosine has very little activity. Theazole antifungals, such as miconazole and ketoconazole, may be effective but more data on the value of these and of combined therapy are needed (Anaissie, Bodey & Rinaldi, 1989).

Recently available antifungal drugs such as fluconazole, have not been fully evaluated in neonates. However, this drug has been used successfully by the intravenous route in a baby with heavy colonization by *Candida* sp. (Viscoli et al., 1989) and candidaemia (G. Phillips, unpublished observation) without evidence of toxicity. Fluconazole might be considered for babies who have persistent fungaemia and whose condition is such that clinicians may wish to avoid the use of amphotericin B.

G. PHILLIPS

CLAYTON GOLLEDGE

*Medical Microbiology Department, University of Dundee Medical School, Ninewells Hospital, Dundee DD1 9SY;

*Central Microbiological Laboratories, Western General Hospital, Edinburgh EH4 2XU, UK

References


neonatal trichosporosis associated with the hemophagocytic syndrome. *Pediatric Infectious Disease Journal* 9, 520-2.


