Management of systemic fungal infection in the newborn

Introduction
Premature infants are at particular risk of invasive fungal infections because of their relative immunodeficiency. Reported incidence of invasive candidal infection in very preterm (<32 weeks) or VLBW infants is 1%-5%, rising to up to 20% in <750g and <26 weeks gestation infants.\(^1\) The overall incidence of fungal septicaemia on neonatal units had been rising due to increased survival of VLBW neonates and the use of broad spectrum antibiotics but there is evidence that rates are now falling.\(^2\) 89.6% of invasive fungal infections are caused by \textit{Candida} species\(^2\) and are associated with significant morbidity and mortality. \textit{C albicans} is responsible for most neonatal infections (62%), whereas \textit{C parapsilosis} and \textit{C tropicalis} account for 23% and 1% of infections respectively.\(^2\)

Candida colonisation
Fungal colonisation can result from vertical transmission from mother or postnatal acquisition. Initial site of colonisation is usually the gastrointestinal tract. 50% of NICU infants are colonised at 1 week of age.\(^4\) Colonisation with fungal organisms is an independent risk factor for subsequent invasive fungal infection.\(^4\)

Candidiasis/Candidaemia: Infection/ isolation of candida species in the blood. It carries an overall mortality of 19%.\(^3\)

Invasive/ Disseminated Candidiasis: Isolation of candida from other normally sterile body fluids or a persistent infection after removal of catheter. Candida is capable of invading all vital organs and following candidaemia, end organ dissemination is more likely with persistent candidaemia of more than 7 days. Disseminated candidiasis involving the CNS has a mortality rate of 30% and survivors have a high incidence (up to 50%) of neurodevelopmental impairment. Usual CNS involvement includes Meningitis (15%) and ventriculitis (4%). Candida also results in other end-organ damage such as, endophthalmitis (3%), endocarditis (4%), and renal fungal balls which may calcify (5%).

Risk factors:
Risk factors for candidiasis include:
- low birth weight (<1500g)
- low gestational age (<28 weeks)
- use of broad spectrum antibiotics and/or multiple antibiotics
- central venous catheters
- parenteral nutrition/NBM
- \(\text{H}_2\) receptor blockers
- Fungal colonisation in VLBW infants.

Clinical Manifestations
The clinical picture of systemic fungal infection in neonates is indistinguishable from bacterial sepsis. Diagnosis is often delayed because of this. Signs and symptoms are generalised such as apnoea, worsening cardio-respiratory function, abnormal renal function and/ or seizures. Candidiasis can also present with GIT symptoms similar to NEC, where there may be paucity of classic radiological signs of necrotising enterocolitis.

Diagnosis
Isolation of candida from blood or other sterile body fluids is diagnostic. Sensitivity of fungal cultures is limited by small volumes of blood. Always consider candida in the differential diagnosis of neonatal sepsis, particularly late-onset sepsis. Thrombocytopenia is an almost invariable feature in candidaemia but is also often seen in bacterial sepsis, thus it may not be helpful in distinguishing between bacterial or fungal infection.

Management
Following positive cultures for candida appropriate antifungal therapy should be started (see below) following discussion with consultant neonatologist (+/- microbiologist). Central vascular catheters should be removed/replaced if possible. Further assessment should be undertaken to exclude disseminated infection. This work-up should include:
- Urine MC+S (with fungal culture specifically requested)
- Renal USS (fungal balls)
- Cranial USS (ventriculitis)
- Lumbar Puncture (meningitis)
- Ophthalmological Examination (ophthalmitis)
- ECHO cardiogram (endocarditis)

Serial blood cultures should be sent to guide duration of antibiotic therapy

**Drug Treatment**

There is one small study that compares efficacy of antifungal in systemic infection in neonates with insufficient data to inform practice.\(^5\) Our units practice is to use Ambisome as 1\(^{st}\) line for systemic infection.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Mode of Action</th>
<th>Monitor</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>AMBISOME</strong> (Liposomal Amphotericin)**</td>
<td>3mg/kg/day IV</td>
<td>Fungicidal – binds to ergosterol in fungal cell membrane and cause leakage of cations – cell death</td>
<td>Renal function Serum K and Mg</td>
</tr>
<tr>
<td>1(^{st}) line in systemic fungal infection</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>FLUCONAZOLE</strong></td>
<td>12mg/kg/day IV/PO</td>
<td>Fungistatic- inhibits fungal cytochrome P-450. Enzyme inducer Urinary concentration 10x that in plasma</td>
<td>Transamminases weekly</td>
</tr>
<tr>
<td>1(^{st}) line in fungal UTI</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2(^{nd}) line in systemic fungal infections</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>CASPOFUNGIN</strong></td>
<td>25mg/m2 OD IV</td>
<td>Fungicidal- inhibits enzyme (1→3)-β-D-glucan synthase (disrupts cell wall). Poor CSF penetration. Excellent soft tissue penetration.</td>
<td>LFTs weekly</td>
</tr>
<tr>
<td>Can be given alongside above agents if poor response to treatment</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Alternative:** Flucytosine can be used as an adjunct to Amphotericin, only available PO.

**Note:** Ambisome not licensed in babies <1 month of age.

**Duration of Antifungal therapy:** please liaise with neonatal consultant and microbiologist. The appropriate duration of therapy for candidial infections in infants is controversial; there are insufficient data to precisely determine necessary treatment periods.

<table>
<thead>
<tr>
<th>Condition</th>
<th>Duration of Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fungaemia</td>
<td>14-21 days after clinical improvement and negative blood culture and removal/change of central line.</td>
</tr>
<tr>
<td>Endocarditis</td>
<td>Minimum of 6 weeks, surgery often required for cure</td>
</tr>
<tr>
<td>Endophthalmitis</td>
<td>6-12 weeks after vitrectomy</td>
</tr>
<tr>
<td>Meningitis</td>
<td>Minimum of 4 weeks after resolution of signs and symptoms</td>
</tr>
<tr>
<td>Simple UTI</td>
<td>2 weeks</td>
</tr>
</tbody>
</table>

**Prophylaxis:** Fluconazole prophylaxis is effective in reducing the rate of colonisation and progression to systemic infection in neonatal units with a high rate of fungal infection (>10%). In our unit the incidence of systemic fungal infection is very low; 0.2% in all babies but increasing slightly to 0.6% in VLBW babies. The NNT to prevent one case on the unit is around 555, and even in VLBW infants the NNT to prevent a case of fungal sepsis is 125. Given this, Fluconazole prophylaxis is currently not indicated.

**References:**


D Gallacher, S Barr, R Barnes August 2014, to be reviewed August 2017.