Introduction

In 1996 this unit introduced prophylactic oral nystatin prophylaxis against invasive candidiasis. This consisted of three times daily 0.5 mls nystatin to all babies born under 27 weeks gestation, or with birthweight < 750g, or at the discretion of the attending neonatologist. This intervention was only one of a number of measures designed to improve skin integrity, sepsis rates and other adverse events in the extreme preterm (see the small baby guideline). Nystatin was continued until all central lines had been removed.

The decision to use oral nystatin prophylaxis was heavily influenced by the randomised controlled trial of Sims et al and the perceived lack of serious side effects of nystatin. A retrospective audit of babies born < 1500g in the 3 years prior to the introduction of prophylaxis gave an incidence of invasive (including renal and pulmonary) candidiasis of 3.5%. If the diagnosis is limited to either blood and/or CSF infection the rate was 1.5%. In the 10 years following there were four cases of blood and/or CSF infection in 1099 patients (incidence 0.36%); a fourfold reduction. One of these four cases was early (congenital) infection.

Since the introduction of prophylaxis to this unit there have been a number of publications of prophylaxis regimes and two systematic reviews, prompting this revision of our guideline.

Incidence

27% of very low birth weight babies were colonised with candida in one prospective series. Of those, 1/3rd developed mucocutaneous candidiasis and 7.7% developed invasive candidiasis. A recent multi-centre cohort of < 1000g infants reported a rate of 7%.

In the UK the reported rates for invasive candidiasis are 1% for babies < 1500g and 2.1% for babies <1000g.

In NSW and ACT newborn intensive care units the rate of blood and/or csf candidiasis in VLBW babies was 1% in 1992-1996. This has fallen to 0.57% in 1997-2006. These figures are courtesy of Barbara Bajuk, NICUS co-ordinator, NSW Pregnancy and Newborn Services Network.

A recent prospective, multi-centre surveillance study of Australian and New Zealand neonatal units from 1993 to 2006 gives the following incidence of invasive fungal infection (IFI) in units using oral nystatin prophylaxis compared with those that do not.

<table>
<thead>
<tr>
<th>Birthweight</th>
<th>With Oral Nystatin Prophylaxis</th>
<th>No Prophylaxis</th>
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<tbody>
<tr>
<td>&lt; 1000g</td>
<td>1.23%</td>
<td>2.67%</td>
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<tr>
<td>&lt; 1500g</td>
<td>0.54%</td>
<td>1.23%</td>
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Risk factors

In an 8 year clinical audit of admissions to this NICU, in 1996, only infants < 27 weeks gestation and/or < 750g were diagnosed with systemic candidiasis (unpublished). More recently, no cases have been
Systemic candidiasis is associated with very low birth weight, intubation and ventilation, antibiotic use, parenteral nutrition, aminophylline, indwelling catheters, H2 receptor antagonists and vaginal vs caesarean delivery \(^2,3,5,6,7\). The strongest association, in a case-control study was duration of antibiotic therapy \(^7\). Multivariate analysis, however, showed that only prolonged antibiotic use and duration of endotracheal intubation were significantly associated with invasive disease \(^6\). A recent prospective study in the extremely low birth weight (ELBW) has shown that independent risk factors at day 3 are lower birth weight (< 750 g vs 750-1000), lack of enteral feeds, and 3rd generation cephalosporin use. \(^3\)

**Consequences**

Untreated, the mortality exceeds 80% \(^5\). Treated, mortality ranges from 20 - 60% \(^5\). Morbidity is severe if there is CNS or endophthalamic involvement.

**Diagnosis**

Systemic candidiasis is usually a late onset infection (day 9 - 28+ in an Australian series) \(^8\). Clinical features are non-specific; lethargy, respiratory distress and an NEC like illness with sugar intolerance, abdominal distension, bile aspirates and blood in stools, but without pneumatosis. Thrombocytopenia is an almost invariable feature but may be present in 50 % of bacterial sepsis episodes and is not, therefore, diagnostic \(^5\). Late diagnosis contributes to mortality and morbidity. In some series diagnosis was made at autopsy. The delay in diagnosis ranges from 2 - 11 days \(^5\). Candida may only grow slowly in culture which contributes to the delay in diagnosis \(^5-9\).

A true congenital form is recognised and is associated with candidal vaginosis and vaginal delivery in the extremely premature infant. A skin rash is prominent in this condition \(^9\), but may be absent \(^10\).

Diagnosis is made by the isolation of a candida species from a normally sterile site. The commonest site of infection is the kidney and renal tract \(^9\). Because of the difficulty distinguishing renal candidiasis from contamination, in some publications the diagnosis of invasive candidiasis is limited to blood and/or csf isolation \(^11\).

In one series almost half of the babies with candida meningitis had a negative blood culture \(^7\).

**Prevention**

Since prolonged antibiotic use is the most consistent correlate with systemic candidiasis, a rational antimicrobial regime is indicated \(^6\), avoiding 3rd generation cephalosporins \(^3,11\). It is also empirically indicated to extubate as soon as practical. Early enteral feeding is also indicated \(^3,11\).

**Prophylaxis**

**Systemic antifungals**

A systematic review has shown that fluconazole prophylaxis is effective in reducing invasive fungal disease \(^12,13\). In 3 of the 4 included trials the drug was given intravenously for up to 6 weeks. The additional trial \(^14\), which used intravenous and/or intragastric drug, did not change the overall size of the effect. There was a non significant reduction in mortality. The number needed to treat (NNT) to prevent one case of invasive fungal disease in the very low birthweight population was 9. If, however, the same risk reduction is extrapolated to the UK population (similar to this unit) the NNT rises to 130 \(^12,13\). Further concerns have
been expressed about the cost of fluconazole compared with oral nystatin, side effects such as cholestatic jaundice, and the emergence of drug resistance.

**Oral or intragastric antifungals**

A systematic review has concluded that there is insufficient evidence to recommend prophylactic oral antifungals in the VLBW infant. There were three included studies. Individually, miconazole had no effect on mortality or invasive fungal disease whereas nystatin showed significant reduction in colonisation (6% v 44%) and renal candidiasis (6% v 32%). The trial was too small to detect an effect on mortality, however the one death occurred in the placebo group. There was no benefit from oral fluconazole over nystatin.

A recent trial in which nearly 4000 babies admitted to NICU were randomised showed that prophylactic nystatin significantly reduced invasive candidiasis (1.8%) compared with no treatment (14.2%) and nystatin targeted to colonised infants (5.6%). Although this trial was randomised it was apparently not blinded, not strictly placebo controlled, and included babies of all gestations and birth weight. From the supplied data the rates of blood and csf infection in VLBW babies were 4.7% in the prophylaxis group, 16% in the targeted group and 40% in the group that received no treatment.

Fluconazole is more expensive and has more side effects than nystatin, but has not been demonstrated to be more effective prophylaxis. We should therefore continue our present regime which appears to be effective.

**Summary**

- Rationalise antibiotics and avoid cephalosporins
- Extubate
- Early enteral feeding
- All babies < 28 weeks, < 1000g receive 0.5 ml nystatin suspension three times daily from day 1 until venous lines are removed.
- babies deemed at high risk by the specialist may receive prophylactic oral or intra gastric nystatin.

**Treatment**

**Mucocutaneous candidiasis**

is treated topically with clotimazole or miconazole and enterally with nystatin suspension. A severe, invasive form seen in the extremely immature infant should be treated with systemic antifungal agents.

**Systemic candidiasis**

Central lines should be removed since delay is associated with increased mortality, but may be re-inserted at the discretion of the neonatologist after a period of antifungal therapy.

Treatment is with amphotericin ± flucytosine (especially with CNS involvement). Serious side effects of amphotericin are less common in the neonate and the starting dose is 1mg/kg/day, to total 20-30mg/kg. Central lines are removed. Percutaneous long lines may be required for prolonged amphotericin therapy.

Treatment failures have been reported with imidazoles.

There is one small randomised trial of amphotericin vs fluconazole. There was no significant difference in mortality but fluconazole was easier to administer.

**Key Points**
<table>
<thead>
<tr>
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<th>Level of evidence</th>
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<tbody>
<tr>
<td>Prolonged intubation is associated with systemic candidiasis</td>
<td>level 2b</td>
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<tr>
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<tr>
<td>Thrombocytopenia is suggestive of candidiasis</td>
<td>level 4</td>
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<tr>
<td>Prophylactic fluconazole reduces the risk of invasive candidiasis in the</td>
<td>level 1a</td>
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<td>VLBW in high risk populations</td>
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<td>level 2b</td>
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<td>Prophylactic nystatin reduces the risk of invasive candidiasis in the</td>
<td>level 2c</td>
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<td>VLBW in low risk populations</td>
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References


18. Driessen-M; Ellis-JB; Cooper-PA; Wainer-S; Muwazi-F; Hahn-D; Gous-H; De-Villiers-FP. Fluconazole vs. amphotericin B for the treatment of neonatal fungal septicemia: a prospective randomized trial. *Pediatr Infect-Dis-J* 1996; **5**: 1107-12


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