A Clinical Guideline

For use in: Neonatal Intensive Care Unit

By: Neonatal Medical and Nursing staff

For: Preterm infants

Division responsible for document: Women and Children’s Services

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Joint Trust Guideline for the Use of Antifungal Prophylaxis on the Neonatal Intensive Care Unit

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1. Quick reference guideline

Antifungal prophylaxis is **recommended** for infants in **either** of the following groups:

a) All infants ≤750grams birthweight or < 27 weeks gestational age.

b) Other preterm infants who, during the first 4 weeks of life:
   - Have had diagnosed NEC or undergone abdominal surgery **and**
   - Have a percutaneous long line in situ and are receiving parenteral nutrition.

Antifungal prophylaxis should be **considered** for the following group of infants:

c) Preterm infants colonised with candida with 1 or more of the following additional risk factors.
   - Endotracheal tube in-situ for more than one week.
   - Received ≥2 courses of antibiotics of ≥ 5 days duration.
   - Received postnatal steroids.

**Prophylaxis Regime**

Fluconazole: 3 mg/kg/dose Intravenous every 72 hours for maximum of 6 weeks

Reduce dose interval to every 48 hours after 2 weeks of age

If a baby develops proven fungal sepsis whilst on prophylaxis:

- Stop fluconazole prophylaxis.
- Start Amphotericin B (liposomal) as first line antifungal therapy (test dose of 100 micrograms/kg then 1mg/kg daily as a single dose).
- Subsequent antifungal treatment, including dosage, will be guided by a Consultant Microbiologist and the unit pharmacist.
2. **Objective of Guideline**

   To guide prophylactic therapy, for infants at high risk, with a view to reducing the incidence of fungal colonisation and invasive fungal sepsis.

3. **Rationale for the recommendations**

   Colonisation with candida is common in infants born extremely preterm or at extremely low birth weight and in those with a range of other risk factors, including the use of broad spectrum antibiotics, central venous catheterisation, endotracheal intubation and the need for abdominal surgery.

   In such cases, prevalence rates of 5% or more are reported. Progression to invasive infection is associated with substantial morbidity and mortality, especially in preterm infants – published mortality rates range from 20% to 50%. Even with appropriate treatment, disseminated disease, prolongation of hospitalisation, and the development of long-term sequelae are common. Prior to the introduction of anti-fungal prophylaxis, the incidence of candidiasis in neonatal intensive care units had risen substantially.

   It is now recognised that a preventive strategy for invasive candidiasis is needed, and emerging evidence supports the use of prophylactic antifungal agents to reduce colonisation and the development of invasive disease.

   Fluconazole has been shown to be a suitable drug for prophylaxis because of its long half-life and high CSF penetration. The drug is metabolised by the liver, although 80% is excreted unchanged in the urine. These characteristics allow for long dosing intervals, excellent tissue penetration, and easy elimination. Fluconazole prophylaxis, even at low dose, is efficacious in the prevention of invasive fungal infection in high-risk preterm infants when initiated in the first 5 days of life.

4. **Broad recommendations**

   Infants should receive anti-fungal prophylaxis if they meet the following criteria:

   EITHER

   a) ≤750grams birthweight or < 27 weeks gestational age – start prophylaxis on admission to the neonatal unit

   OR

   b) Other preterm infants who, in the first 4 weeks of life:

   - Have had diagnosed NEC or undergone abdominal surgery.

   and

   - Have a percutaneous long line in situ and are receiving parenteral nutrition.
Consideration should be given to starting antifungal prophylaxis in infants who meet the following criteria:

c) Colonisation with candida and 1 or more of the following:
   - Endotracheal tube in-situ for more than one week.
   - Received ≥2 courses of antibiotics of ≥ 5 days duration.
   - Received postnatal steroids.

**Prophylaxis Regime**

**Fluconazole: 3 mg/kg/dose Intravenous every 72 hours for maximum of 6 weeks**

Reduce dose interval to every 48 hours after 2 weeks of age

**Contraindications:**

- Liver failure (defined as hepatomegaly, jaundice, conjugated hyperbilirubinemia, and serum transaminases more than twice the upper limit of normal values).

**Caution:**

- Dose may need to be reduced in severe renal impairment.

**Drug interaction**

- Fluconazole decreases midazolam excretion (monitor patients on midazolam infusions for increased sedation).

**Reasons to discontinue prophylaxis**

Prophylaxis should be discontinued if:

- Infant reaches 6 weeks of age.
- Central venous access is no longer required.
- Antifungal therapy is initiated for presumed/proven invasive fungal infection.
- Infant develops possible fluconazole-related adverse effects.

**Monitoring:**

While receiving fluconazole prophylaxis each baby should have a weekly full blood count with differential white blood cell count and renal and hepatic function tests.
If a baby develops proven fungal sepsis whilst on prophylaxis:

- Stop fluconazole prophylaxis.
- Start Amphotericin B (liposomal) as first line antifungal therapy (test dose of 100 micrograms/kg then 1mg/kg daily as a single dose).
- Subsequent antifungal treatment, including dosage, will be guided by a Consultant Microbiologist and the unit pharmacist.

5. Clinical Audit Standards derived from guideline

a. All preterm infants < 27 weeks gestational age or \( \leq 750\) g birthweight should receive fluconazole prophylaxis from day 1 of admission to the neonatal unit.

b. All other preterm infants with additional risk factors as defined should receive fluconazole prophylaxis.

c. Fluconazole prophylaxis should be stopped at 6 weeks of age or at the earliest appropriate date.

6. Summary of development and consultation process undertaken before registration and dissemination

The author drafted the guideline on behalf of the Paediatric Department. It was discussed at the Departmental Guidelines Meeting and circulated to the Neonatal Consultants and Specialist Registrars, Neonatal SHOs and ANNPs. Consultants in medical microbiology were actively involved in authoring the guideline. The neonatal unit pharmacist has reviewed the guideline.

Suggestions for improvement have been incorporated in subsequent drafts and this version represents a final draft upon which agreement by all parties has been reached.

7. Distribution list/ dissemination method

a. Hospital intranet.

b. Neonatal Unit.

8. References/ source documents


2. Benjamin DK, Garges H, Steinbach WJ. Candida bloodstream infection in neonates. Seminars in Perinatology; 2003: 27(5); 375-83


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12. Kaufman D. Fungal infection in the very low birth weight infant. Current Opinion in Infectious Disease; 2004; 17(3); 253-59

