

## Antifungal Prophylaxis in Pre-terms Newborns – NICU - Full Paediatric Clinical Guideline

Reference no.: NIC IN 13/March 19/v2.2

### 1. Introduction

Invasive fungal infection accounts for 2 -10% of all cases of nosocomial sepsis in very low birth weight (VLBW <1500 g) infants. The incidence doubles in extremely low birth weight (ELBW) infants (<750 gms and/or gestation <26 wks) <sup>(1,2)</sup>. It is associated with significant mortality and long term morbidity in VLBW infants <sup>(3)</sup>

### 2. Aim and Purpose

To ensure medical staff are aware of the criteria for prophylactic treatment.

### 3. Definition of Invasive Fungal Infection

Presence of any of the criteria below: Culture of fungus from a sterile site:

- Blood Cultures (peripheral site, not via an indwelling catheter)
- Central intravascular catheter ("long line") tip
- Urine (suprapubic aspirate or aseptic "in-out" urinary catheter sample)
- Cerebrospinal fluid
- Bone or synovial fluid
- Peritoneal or Pleural aspirates
- Pathognomonic findings on ophthalmologic or renal ultrasound examination.

### 4. Guidance

#### Organisms

*Candida Albican* infections account for (78.3%) of nosocomial fungal infections, followed by *Candida Glabrata*(7.3%) and *Aspergillus* spp. (1.3%) <sup>(4)</sup>. Others reported are *Malassezia* and *Zygomycetes*.

#### Indications for Prophylaxis

All babies' <1500grams – with any of the predisposing factors listed below.

#### Predisposing factors for Invasive Fungal Infection <sup>(6)</sup>

- I. Fungal colonisation of multiple sites: invasive infection increased almost 10 times in colonized VLBW infants compared to non-colonized infants <sup>(7)</sup>
- II. Prolonged endotracheal intubation (> 7 days)
- III. Gastrointestinal disease or surgery e.g. NEC, cardiac / abdominal surgery
- IV. Broad-spectrum antibiotic use more than 7 days (especially third- generation cephalosporin)
- V. Histamine type 2 receptor blockers and proton-pump inhibitors
- VI. Prolonged use of parenteral nutrition/delayed enteral feeding (more than 10 days)

#### Antifungal Prophylaxis Regime

**Nystatin** -- Dose -1ml 8hrly orally/ NG tube – this is divided as 0.5mls orally and 0.5mls via NG for up to six weeks or until no risk factors present <sup>(11)</sup>

**Important side effects of Nystatin:** mostly well tolerated. Nausea, vomiting, diarrhoea, oral irritation and sensitisation, rash and rarely Steven-Johnson syndrome may develop.

Other agents that can be used –

- or Miconazole – 0.75mls 8hrly orally, Fluconazole IV/PO

### Evidence

- Austin NC, Darlow B. Prophylactic oral antifungal agents to prevent systemic candida infection in preterm infants. *Cochrane Database of Systematic Reviews 2010, Issue 1*: n=1625 VLBW infants; NNT 5; Invasive fungal sepsis RR 0.19(0.14 – 0.27); Death RR 0.88 (0.72 – 1.06) <sup>(9)</sup> (Note: These figures need to be viewed with caution as there was a high prevalence of fungal infection in the trials and also some of them had methodological flaws such as no blinding of allocation).
- A recent RCT <sup>(11)</sup> comparing nystatin with fluconazole and placebo showed that both were better than placebo in reducing invasive fungal infection and fungal colonisation and no difference between fluconazole and nystatin. There was no effect on mortality. (Note: This trial was relatively small n=278, there was no power calculation given and the trial was unblinded)

### Audit Criteria

- Compliance with guideline for prophylaxis in <1500 gms.
- Invasive fungal sepsis in <1500 gm infants, mortality due to invasive fungal infection, organism identified and sensitivit

### 5. References (including any links to NICE Guidance etc.)

1. Stoll BJ, Hansen N, Fanaroff AA, et al. Late-onset sepsis in very low birth weight neonates: the experience of the NICHD Neonatal Research Network. *Pediatrics* 2002; 110:285–91
2. Clerihew L, Lamagni TL, Brocklehurst P, McGuire W. Invasive fungal infection in very low birthweight infants: national prospective surveillance study. *Arch Dis Child Fetal Neonatal Ed* 2006; 91:F188–F192
3. Freidman S ; Richardson S. E. ; Jacobs S. E. ; O'Brein K. ;Systemic Candida infection in extremely low birth weight infants : short term morbidity and long term neurodevelopmental outcome.*Pediatr Infrct Dis J* 2000;19:499-504
4. Fridkin S K;. Jarvis W R. Epidemiology of Nosocomial Fungal Infections. *CLINICAL MICROBIOLOGY REVIEWS*, Oct. 1996, p. 499–511
5. A M Sharp, F C Odds, E G V Evans Candida strains from neonates in a special care baby unit. *Arch. Dis. Child.* 1992; 67; 48-52
6. Brecht M, Clerihew L and McGuire W. Prevention and treatment of invasive fungal infection in very low birth weight infants. *Arch. Dis. Child. Fetal Neonatal Ed.*, Jan 2009; 94: F65 - F69
7. Farmaki E, Evdoridou J, Poulidou T, et al. Fungal colonization in the neonatal intensive care unit: risk factors, drug susceptibility, and association with invasive fungal infections. *Am J Perinatol* 2007; 24:127–135
8. Austin NC, Darlow B. Prophylactic oral antifungal agents to prevent systemic candida infection in preterm infants. *Cochrane Database of Systematic Reviews 2003, Issue 4*
9. Austin NC, Darlow B. Prophylactic oral antifungal agents to prevent systemic candida infection in preterm infants. *Cochrane Database of Systematic Reviews 2010, Issue*
10. David Kaufman MD , Robert Boyle MD, Kevin C. Hazen PhD, James T. Patrie MS, Melinda Robinson RN and Leigh B. Grossman MD. Twice weekly prophylaxis for prevention of invasive candida infection in high risk infants of <1000 gms *Journal of Pediatrics*, Volume 147, Issue 2, August 2005, Pages 172-179
11. Cumhuri Aydemir, Serife Suna Oguz. Randomised controlled trial of prophylactic Fluconazole vs Nystatin for prevention of fungal colonisation and invasive fungal infection in VLBW infants, *Arch Dis Child Fetal Neonatal Ed*2011;96:F164-F168
12. Aghai ZH,Mudduluru M, Nakhla TA, et al. Fluconazole prophylaxis in extremely low birth weight infants: association with cholestasis. *J Perinatol* 2006;26:550–555
13. Brion LP, Uko SE, Goldman DL. Risk of resistance associated with fluconazole prophylaxis: systematic review. *J Infect* 2007; 54:521–529
14. Sarvikivi et al. Emergence of Fluconazole Resistance in a Candida parapsilosis Strain That Caused Infections in a Neonatal Intensive Care Unit. *Journal of Clinical Microbiology*, June 2005, p. 2729-2735, Vol. 43, no 6

15. Clerihew L, Austin N, McGuire W. Prophylactic systemic antifungal agents to prevent mortality and morbidity in very low birth weight infants. *Cochrane Database of Systematic Reviews 2007, Issue 4.*
16. L Clerihew, N Austin, and W McGuire Systemic antifungal prophylaxis for very low birthweight infants: a systematic review *Arch. Dis. Child. Fetal Neonatal Ed.*, May 2008; 93: F198 - F200
17. David Kaufman MD , Robert Boyle MD, Kevin C. Hazen PhD, James T. Patrie MS, Melinda Robinson RN and Leigh B. Grossman MD. Twice weekly prophylaxis for prevention of invasive candida infection in high risk infants of <1000 gms *Journal of Pediatrics*, Volume 147, Issue 2, August 2005, Pages 172-179
18. Huttova M, Hartmanova I, Kralinsky K, et al. Candida fungemia in neonates treated with fluconazole: report of forty cases, including eight with meningitis. *Pediatr Infect Dis J* 1998; 17:1012
19. Aghai ZH, Mudduluru M, Nakhla TA, et al. Fluconazole prophylaxis in extremely low birth weight infants: association with cholestasis. *J Perinatol* 2006;26:550–555
20. Brion LP, Uko SE, Goldman DL. Risk of resistance associated with fluconazole prophylaxis: systematic review. *J Infect* 2007; 54:521–529
21. Sarvikivi et al. Emergence of Fluconazole Resistance in a Candida parapsilosis Strain That Caused Infections in a Neonatal Intensive Care Unit. *Journal of Clinical Microbiology*, June 2005, p. 2729-2735, Vol. 43, no 6

## 6. Documentation Controls

Development of Guideline:	Dr G Joshi
Consultation with:	Neonatal Consultants, Directorate Pharmacist, Trust antimicrobial subgroup.
Approved By:	Paediatric Business Unit Guidelines Group - 6 <sup>th</sup> March 2019 Women and Children's Division- 25 <sup>th</sup> March 2019 Reviewed with no changes March 2023
Review Date:	March 2026
Key Contact:	Dr G Joshi

## 7. Appendices