RESEARCH PAPER

Antifungal Prophylaxis Practices in Extremely Preterm Infants: A Retrospective Cohort Study from a Tertiary Care NICU in North India

Twinkle Gupta, MD[1] **Yammanuru Pavan Kumar Reddy,** MD[2] **Kummari Divya,** MD[2] **Mounika Saladi,** MD[2]

[1] *Senior Resident, Department of Paediatrics*

[2] *Postgraduate Resident (MD Paediatrics)*

MM Institute of Medical Sciences and Research, Mullana, Ambala, Haryana, India

Correspondence: Dr. Twinkle Gupta, Senior Resident, Department of Paediatrics, MM Institute of Medical Sciences and Research, Mullana, Ambala District, Haryana – 133207

Email: twinklegupta1394@gmail.com

ABSTRACT

Background: Invasive fungal infection (IFI) is a major cause of morbidity and mortality in extremely preterm (EPT) infants admitted to the neonatal intensive care unit (NICU). Fluconazole prophylaxis is recommended in high-risk settings, yet its uptake in Indian NICUs remains inconsistent.

Objective: To describe antifungal prophylaxis practices and evaluate their association with the incidence of IFI and clinical outcomes in EPT infants at a tertiary care NICU in North India.

Methods: A retrospective cohort study was conducted from January 2022 to December 2023 at the NICU of MM Institute of Medical Sciences and Research, Mullana, Haryana. All inborn EPT infants of gestational age <28 weeks were included. Antifungal prophylaxis practices, IFI incidence, and clinical outcomes were documented. Comparisons were made between those who received and those who did not receive antifungal prophylaxis.

Results: Of 156 EPT infants included, 112 (71.8%) received antifungal prophylaxis. Fluconazole (3 mg/kg intravenous twice weekly) was used in all prophylaxed infants, initiated at a median of day 3 of life. The overall IFI incidence was 14.7% (23/156). IFI was significantly lower in the prophylaxis group than in the non-prophylaxis group (8.0% vs 31.8%; RR 0.25, 95% CI 0.12–0.52; p<0.001). IFI-attributable mortality was also significantly reduced with prophylaxis (3.6% vs 18.2%; p=0.003). Candida albicans was the predominant organism (52.2%). Drug-related adverse effects were minor and occurred in 7.1% (elevated liver enzymes), with discontinuation required in only 2.7%.

Conclusion: Fluconazole prophylaxis at a dose of 3 mg/kg twice weekly was associated with a significant reduction in IFI incidence and IFI-attributable mortality in EPT infants. Practice variation remains a challenge and institutional protocols with clear eligibility criteria are recommended.

Keywords: *Extremely preterm; antifungal prophylaxis; fluconazole; invasive fungal infection; neonatal intensive care unit; Candida*

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INTRODUCTION

Preterm birth remains the leading cause of neonatal morbidity and mortality worldwide. According to the World Health Organization, an estimated 13.4 million infants were born preterm in 2020, accounting for approximately 9.9% of all live births globally.[1] Extremely preterm (EPT) infants, defined as those born before 28 completed weeks of gestation, represent the most vulnerable subgroup and are disproportionately susceptible to infectious complications during their prolonged neonatal intensive care unit (NICU) admissions.

Invasive fungal infection (IFI), predominantly caused by *Candida* species, is a major and often preventable cause of late-onset sepsis in EPT infants. The reported incidence of IFI in extremely low birth weight (ELBW) infants ranges from 2% to 20%, with significantly higher rates documented in low- and middle-income countries, including India.[2] *Candida albicans* and *Candida parapsilosis* are the most commonly isolated species. The consequences of IFI are severe: case-fatality rates before discharge in ELBW infants with *Candida* sepsis are reported at 30–40%, and long-term follow-up studies at 18–22 months demonstrate that up to 73% of survivors develop neurodevelopmental impairment or die.[2, 3]

Several modifiable risk factors predispose EPT infants to IFI, including prolonged central venous catheterisation, total parenteral nutrition (TPN), broad-spectrum antibiotic exposure, mechanical ventilation, and abdominal surgery. Given the high

burden of these risk factors in NICU care, prophylactic strategies have been explored extensively. Randomised controlled trials and meta-analyses have demonstrated that fluconazole prophylaxis, typically administered as 3–6 mg/kg twice weekly, significantly reduces *Candida* colonisation and invasive infection in high-risk preterm infants.[4–7] The Infectious Diseases Society of America (IDSA) 2016 guidelines recommend fluconazole prophylaxis in NICUs where the IFI rate exceeds 10% in ELBW infants.[4]

Despite these recommendations, antifungal prophylaxis practices across Indian NICUs are highly variable. A nationwide survey of 151 level III NICUs conducted in 2022 found that only 28.5% of units used routine antifungal prophylaxis in all ELBW infants, while 45.7% did not use prophylaxis at all.[8] Contributing factors to this variation include uncertainty about local IFI incidence, concerns about antifungal resistance, absence of institutional protocols, and lack of robust local data.

While international evidence strongly supports prophylaxis in high-risk settings, there is a paucity of data from tertiary care centres in North India describing actual prophylaxis practices and their association with outcomes. This study aimed to document antifungal prophylaxis practices in EPT infants at a teaching hospital NICU in Haryana and to evaluate the association of prophylaxis with IFI incidence and clinical outcomes.

MATERIALS AND METHODS

Study Design and Setting

This was a retrospective cohort study conducted at the Level III NICU of MM Institute of Medical Sciences and Research (MMIMSR), Mullana, Ambala District, Haryana, India, over a two-year period from 1 January 2022 to 31 December 2023. MMIMSR is a tertiary care teaching hospital with an approximate NICU capacity of 40 beds and an annual delivery rate of approximately 4,500.

Study Population

All inborn EPT infants with a gestational age (GA) of less than 28 completed weeks were eligible for inclusion. Gestational age was confirmed by the first-trimester ultrasound scan or Ballard scoring where scan was unavailable. Infants with life-limiting congenital anomalies and those who died within the first 24 hours of birth were excluded. Outborn infants admitted after 72 hours of life were also excluded to minimise confounding from pre-admission exposures.

Data Collection

Data were extracted from electronic medical records and handwritten NICU case files using a structured data-collection form. Variables recorded included: gestational age, birth weight, sex, mode of delivery, receipt of antenatal corticosteroids, and the following risk factors during NICU stay: presence of a central venous catheter, duration of TPN, duration of broad-spectrum antibiotic exposure, use of mechanical ventilation, and postnatal corticosteroid administration. Antifungal prophylaxis details recorded included: drug name, dose, route, frequency, day of initiation, and total duration. All positive blood cultures for fungal organisms during the NICU stay were documented.

Definitions

Invasive fungal infection (IFI) was defined as a positive blood culture for a fungal organism (primarily *Candida* species) in a clinically symptomatic infant. Prophylaxis was classified as received if the infant was commenced on a systemic antifungal agent (fluconazole or otherwise) within the first seven days of life and continued for at least 14 days in the absence of a breakthrough IFI. A breakthrough IFI was defined as IFI occurring after at least 14 consecutive days of antifungal prophylaxis. IFI-attributable mortality was defined as death occurring within 30 days of a positive fungal blood culture in an infant with clinical sepsis, with no other plausible cause identified.

Statistical Analysis

Categorical variables were expressed as frequencies and percentages; continuous variables as mean ± standard deviation (SD) or median with interquartile range (IQR) as appropriate. Baseline comparisons between the prophylaxis and non-prophylaxis groups were performed using the chi-square test or Fisher's exact test for categorical variables and the independent-samples t-test for continuous variables. Relative risk (RR) with 95% confidence interval (CI) was calculated for binary outcomes. A two-tailed p-value < 0.05 was considered statistically significant. All analyses were performed using SPSS version 25.0 (IBM Corp, Armonk, NY).

Ethics

The study was approved by the Institutional Ethics Committee of MM Institute of Medical Sciences and Research, Mullana (Reference No. IEC/MMIMSR/2024/087). Waiver of written informed consent was granted in view of the retrospective design and complete anonymisation of patient data.

RESULTS

Study Population

During the study period, 168 EPT infants were born at MMIMSR. Of these, 12 were excluded (4 with lethal congenital anomalies and 8 who died within 24 hours of birth), yielding a final study cohort of 156 infants. Baseline characteristics of the study population are presented in Table 1.

Table 1. Baseline characteristics of the study population (n = 156)

Characteristic	Value (n = 156)
Gestational age (weeks), mean ±SD	26.3 ±1.2
Birth weight (grams), mean ±SD	768 ±115
Male sex, n (%)	84 (53.8%)
Singleton gestation, n (%)	118 (75.6%)
Antenatal corticosteroids received, n (%)	134 (85.9%)
Mode of delivery: LSCS, n (%)	92 (59.0%)
Central venous catheter in situ, n (%)	134 (85.9%)
Total parenteral nutrition > 5 days, n (%)	141 (90.4%)
Broad-spectrum antibiotics > 5 days, n (%)	118 (75.6%)
Mechanical ventilation, n (%)	98 (62.8%)
Postnatal corticosteroids, n (%)	42 (26.9%)
Antifungal prophylaxis received, n (%)	112 (71.8%)

The mean gestational age was 26.3 ± 1.2 weeks and mean birth weight was 768 ± 115 grams. A male preponderance was noted (53.8%). Antenatal corticosteroids were administered in 85.9% of cases. The majority of infants had multiple IFI risk factors: central venous catheter in 85.9%, TPN for > 5 days in 90.4%, and broad-spectrum antibiotics for > 5 days in 75.6%.

Antifungal Prophylaxis Practices

Of the 156 infants, 112 (71.8%) received antifungal prophylaxis. Fluconazole was used exclusively in all prophylaxed infants (100%). Details of prophylaxis practices are presented in Table 2 (baseline comparison) and Table 3 (practice characteristics).

Table 2. Comparison of baseline characteristics between prophylaxis and no-prophylaxis groups

Variable	Prophylaxis (n = 112)	No Prophylaxis (n = 44)	p-value
Gestational age (weeks), mean ±SD	26.4 ±1.1	26.0 ±1.4	0.078
Birth weight (grams), mean ±SD	774 ±112	752 ±122	0.241
Male sex, n (%)	61 (54.5%)	23 (52.3%)	0.801
Central venous catheter, n (%)	96 (85.7%)	38 (86.4%)	0.912
TPN > 5 days, n (%)	102 (91.1%)	39 (88.6%)	0.645
Broad-spectrum antibiotics > 5 days, n (%)	86 (76.8%)	32 (72.7%)	0.590
Mechanical ventilation, n (%)	71 (63.4%)	27 (61.4%)	0.811

Both groups were comparable at baseline with respect to gestational age, birth weight, sex, and major NICU risk factors (Table 2). None of the baseline differences reached statistical significance.

Table 3. Antifungal prophylaxis practice details in the prophylaxis group (n = 112)

Practice Parameter	Details (n = 112)
Antifungal agent used, n (%)	Fluconazole – 112 (100%)
Dose	3 mg/kg per dose
Route	Intravenous – 112 (100%)
Frequency	Twice weekly (every 72 hours)
Day of initiation (median, IQR)	Day 3 (IQR: 2–4)
Duration of prophylaxis (days, median, IQR)	28 days (IQR: 21–35)
Discontinued due to IFI diagnosis, n (%)	9 (8.0%)
Completed planned course, n (%)	103 (92.0%)
Abnormal liver function (ALT > 2x ULN), n (%)	8 (7.1%)
Drug discontinued due to side effects, n (%)	3 (2.7%)

Fluconazole was administered at a dose of 3 mg/kg per dose via the intravenous route in all cases. The drug was initiated at a median of day 3 of life (IQR: 2–4) and continued for a median of 28 days (IQR: 21–35). Adverse events were infrequent: elevated liver transaminases (ALT > 2× upper limit of normal) were noted in 8 infants (7.1%), and the drug was discontinued in 3 (2.7%) due to significant hepatotoxicity. None of the prophylaxed infants developed fluconazole-resistant *Candida* isolates on surveillance cultures.

Among the 44 infants who did not receive prophylaxis, the clinician-documented reasons included concern about the development of antifungal resistance (63.6%), perceived low institutional IFI risk (22.7%), and clinical instability precluding intravenous medications at the time of eligibility (13.6%).

Incidence of Invasive Fungal Infection

The overall IFI incidence in the cohort was 14.7% (23/156). The IFI rate was significantly lower in the prophylaxis group (9/112, 8.0%) than in the non-prophylaxis group (14/44, 31.8%) (RR 0.25, 95% CI 0.12–0.52; $p<0.001$). The causative organisms are described in Table 4.

Table 4. Causative organisms in invasive fungal infection cases (n = 23)

Organism	n	% of IFI cases
Candida albicans	12	52.2%
Candida parapsilosis	6	26.1%
Candida tropicalis	3	13.0%
Candida glabrata	2	8.7%
Total	23	100%

Candida albicans was the most frequently isolated organism (12/23, 52.2%), followed by *C. parapsilosis* (6/23, 26.1%), *C. tropicalis* (3/23, 13.0%), and *C. glabrata* (2/23, 8.7%). Susceptibility testing revealed no azole-resistant isolates in either group.

Clinical Outcomes

Clinical outcomes stratified by prophylaxis are presented in Table 5. All-cause mortality was 18.8% in the prophylaxis group and 29.5% in the non-prophylaxis group; this difference did not reach statistical significance (p=0.123). IFI-attributable mortality, however, was significantly lower in the prophylaxis group (3.6% vs 18.2%; RR 0.20, 95% CI 0.07–0.58; p=0.003). Other morbidities—chronic lung disease, necrotising enterocolitis, severe intraventricular haemorrhage, and retinopathy of prematurity requiring treatment—were numerically lower in the prophylaxis group but did not differ significantly between groups.

Table 5. Clinical outcomes by antifungal prophylaxis status

Outcome	Prophylaxis (n = 112)	No Prophylaxis (n = 44)	p-value / RR (95% CI)

Invasive fungal infection, n (%)	9 (8.0%)	14 (31.8%)	<0.001; RR 0.25 (0.12–0.52)
All-cause mortality, n (%)	21 (18.8%)	13 (29.5%)	0.123; RR 0.64 (0.37–1.09)
IFI-attributable mortality, n (%)	4 (3.6%)	8 (18.2%)	0.003; RR 0.20 (0.07–0.58)
Chronic lung disease, n (%)	33 (29.5%)	15 (34.1%)	0.573
NEC (Stage ≥ II), n (%)	11 (9.8%)	7 (15.9%)	0.257
Severe IVH (Grade III/IV), n (%)	14 (12.5%)	8 (18.2%)	0.337
ROP requiring treatment, n (%)	20 (17.9%)	11 (25.0%)	0.291
Duration of hospital stay (days, median, IQR)	62 (48–78)	54 (40–72)	0.189

DISCUSSION

This retrospective cohort study of 156 EPT infants from a tertiary care teaching NICU in North India demonstrates that fluconazole prophylaxis was associated with a significant and clinically meaningful reduction in IFI incidence (8.0% vs 31.8%; p<0.001) and IFI-attributable mortality (3.6% vs 18.2%; p=0.003). These findings are consistent with the body of evidence from randomised trials and meta-analyses, and provide local data supporting the role of prophylaxis in high-risk EPT infants in the Indian setting.

The overall IFI incidence of 14.7% observed in our cohort falls within the range of 2–20% reported internationally for ELBW infants,[2] but the 31.8% rate in unprotected EPT infants underscores the high endemic burden of fungal sepsis in this population. This is comparable to rates reported in resource-limited NICUs and supports the IDSA recommendation that facilities with IFI rates exceeding 10% in ELBW infants should implement fluconazole prophylaxis.[4]

Our finding that fluconazole prophylaxis reduced IFI risk by 75% (RR 0.25) aligns closely with data from the landmark Manzoni et al. multicentre randomised trial,[6] the Kaufman et al. trial,[5] and the patient-level meta-analysis by Ericson et al.[7] The 2016 Ericson meta-analysis, which pooled individual patient data from 10 randomised controlled trials, reported an odds ratio of 0.20 for invasive candidiasis with fluconazole prophylaxis compared with placebo, strikingly similar to our observed RR of 0.25.

Although all-cause mortality showed a favourable trend in the prophylaxis group (18.8% vs 29.5%), the difference was not statistically significant, likely owing to the multifactorial determinants of mortality in EPT infants. This is consistent with published data from Cleminson et al.'s Cochrane review,[11] which demonstrated no significant reduction in overall mortality with systemic antifungal prophylaxis, although trials were not individually powered for mortality as a primary endpoint. Healy et al. similarly reported elimination of *Candida*-attributable deaths following institution of fluconazole prophylaxis in ELBW infants without a concurrent reduction in all-cause mortality.[9]

Only 71.8% of eligible EPT infants received antifungal prophylaxis in our study, reflecting the practice variation documented nationally. The nationwide Indian survey by Arun et al. found that 45.7% of level III NICUs did not use prophylaxis at all, and cited concerns about resistance and low perceived IFI risk as the principal barriers.[8] In our cohort, these same reasons were documented for 63.6% and 22.7% of non-prophylaxed infants, respectively. Reassuringly, antifungal resistance was not a concern in our institution: no azole-resistant

isolates were identified in either group, consistent with data from Healy et al.[9]

The safety profile of fluconazole was acceptable in our cohort. Transient elevation in liver enzymes was noted in 7.1% of prophylaxed infants, and the drug was discontinued in only 2.7%. This adverse event rate is comparable to figures in published clinical trials and does not represent a contraindication to use in this population. Twice-weekly dosing at 3 mg/kg, as used in our study, is supported by pharmacokinetic data demonstrating sustained antifungal activity.[13]

Our study has several limitations. The retrospective design precludes causal inference, and residual confounding from unmeasured variables—such as nurse-to-patient ratio, NICU environmental contamination, and hand hygiene compliance—cannot be excluded. The decision to administer prophylaxis was not protocolised uniformly throughout the study period, introducing selection bias in the choice of prophylaxis. The relatively small sample size may have underpowered analyses of secondary outcomes such as all-cause mortality. Serial surveillance cultures were not systematically obtained, which may have led to underdiagnosis of Candida colonisation. Finally, long-term neurodevelopmental outcomes were not assessed.

Despite these limitations, this study adds to the sparse Indian literature on antifungal prophylaxis in EPT infants and provides institution-specific data to guide local policy. Our findings support development and implementation of a standardised antifungal prophylaxis protocol in this and similar high-risk NICUs. Future prospective multicentre studies from India are needed to establish robust local evidence and to inform national society recommendations.

CONCLUSION

Fluconazole prophylaxis at a dose of 3 mg/kg intravenous twice weekly was associated with a significantly lower incidence of invasive fungal infection and IFI-attributable mortality in extremely preterm infants at a tertiary care NICU in North India. The drug was well tolerated with a low rate of serious adverse effects. Significant practice variation in prophylaxis use persists, driven primarily by concerns about resistance and uncertainty about institutional IFI rates. Standardised antifungal prophylaxis protocols with clear eligibility criteria are recommended for NICUs caring for EPT infants, particularly in centres where IFI rates exceed 10%.

DECLARATIONS

Ethics Approval and Consent to Participate: Approved by the Institutional Ethics Committee, MMIMSR, Mullana (IEC/MMIMSR/2024/087). Informed consent was waived due to the retrospective design.

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Conflict of Interest: The authors declare no conflict of interest.

Author Contributions: TG conceived the study, designed the data collection tool, supervised data collection, and drafted the manuscript. YPKR and KD collected data, performed statistical analysis, and contributed to the draft. MS performed literature review and contributed to the discussion. All authors read and approved the final manuscript.

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REFERENCES

1. World Health Organization. 152 million babies born preterm in the last decade [Internet]. Geneva: WHO; 2023 [cited 2024 Jun 5]. Available from: https://www.who.int/news/item/09-05-2023-152-million-babies-born-preterm-in-the-last-decade

2. Benjamin DK Jr, Stoll BJ, Fanaroff AA, McDonald SA, Oh W, Higgins RD, et al. Neonatal candidiasis among extremely low birth weight infants: risk factors, mortality rates, and neurodevelopmental outcomes at 18 to 22 months. Pediatrics. 2006;117(1):84–92.

3. Adams-Chapman I, Bann CM, Das A, Page LC, Shankaran S, Higgins RD, et al. Neurodevelopmental outcome of extremely low birth weight infants with Candida infection. J Pediatr. 2013;163(4):961–7.

4. Pappas PG, Kauffman CA, Andes DR, Clancy CJ, Marr KA, Ostrosky-Zeichner L, et al. Clinical practice guideline for the management of candidiasis: 2016 update by the Infectious Diseases Society of America. Clin Infect Dis. 2016;62(4):e1–50.

5. Kaufman D, Boyle R, Hazen KC, Patrie JT, Robinson M, Donowitz LG. Fluconazole prophylaxis against fungal colonization and infection in preterm infants. N Engl J Med. 2001;345(23):1660–6.

6. Manzoni P, Stolfi I, Pugni L, Decembrino L, Magnani C, Vetrano G, et al. A multicenter, randomized trial of prophylactic fluconazole in preterm neonates. N Engl J Med. 2007;356(24):2483–95.

7. Ericson JE, Kaufman DA, Kicklighter SD, Bhatia J, Testoni D, Gao J, et al. Fluconazole prophylaxis for the prevention of candidiasis in premature infants: a meta-analysis using patient-level data. Clin Infect Dis. 2016;63(5):604–10.

8. Arun S, Varghese M, Cherian T, Ramaswami P. Current trends in antifungal prophylaxis for high-risk neonates in neonatal intensive care units in India: a nationwide survey. Cureus. 2023;15(3):e36136.

9. Healy CM, Campbell JR, Zaccaria E, Baker CJ. Fluconazole prophylaxis in extremely low birth weight neonates reduces invasive candidiasis mortality rates without emergence of fluconazole-resistant Candida species. Pediatrics. 2008;121(4):703–10.
10. Stoll BJ, Hansen NI, Adams-Chapman I, Fanaroff AA, Hintz SR, Vohr B, et al; NICHD Neonatal Research Network. Neurodevelopmental and growth impairment among extremely low-birth-weight infants with neonatal infection. JAMA. 2004;292(19):2357–65.
11. Cleminson J, Austin N, McGuire W. Prophylactic systemic antifungal agents to prevent mortality and morbidity in very low birth weight infants. Cochrane Database Syst Rev. 2015;10:CD003850.
12. Hope WW, Castagnola E, Groll AH, Roilides E, Akova M, Arendrup MC, et al. ESCMID guideline for the diagnosis and management of Candida diseases 2012: prevention and management of invasive infections in neonates and children caused by Candida spp. Clin Microbiol Infect. 2012;18(Suppl 7):38–52.
13. Kaufman D, Boyle R, Hazen KC, Patrie JT, Robinson M, Grossman LB. Twice-weekly fluconazole prophylaxis for prevention of invasive Candida infection in high-risk infants of <1000 grams birth weight. J Pediatr. 2005;147(2):172–9.