

A Study On Clinico-Mycological Profile of Systemic Fungal Infection In Neonates: An Indian Perspective

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Abstract :

Objectives: To analyze clinical presentation and mycological profile of systemic fungal infection in neonates.

Material and Methods: A hospital based prospective, observational study was done over a period of one year in the department of Pediatrics of Burdwan Medical College. The study included 254 neonates who were admitted in newborn care unit (inborn and outborn) and were started on intravenous fluid.

Results: Fungal culture was positive in 19 neonates (7.48%). The mean birth weight and gestational age of the neonates with positive fungal cultures were 1.539 ± 0.593 kg and 33.368 ± 2629 weeks respectively. *Candida Parapsilosis* was the most common organism in <1500 gm group whereas *Candida albicans* and *Candida parapsilosis* were mostly found in 1500-2499 gm group. The predominant presenting signs were related to the gastrointestinal system (68.4%). A significant difference was found in the repeat CRP between the two groups with the *C. albicans* group having a much higher CRP count ($p=0.041$).

Conclusion- An idea of the organisms responsible for systemic fungal infection, help us to choose appropriate antifungals depending upon the resistance pattern.

Keywords: Fungal Infection, Neonate, Organism, Antifungals.

I. Introduction

In the developing world 1.6 million of neonatal deaths are due to neonatal sepsis. [1] Neonatal sepsis is defined as a clinical syndrome with features of infection, usually systemic, in the first 28 days of life. [2] With advances in neonatal care and change in patient population in neonatal intensive care unit (NICU), fungal infections have emerged as a significant cause of morbidity and mortality among such neonates. [3] Systemic fungal infection is an important entity in very low birth weight infants. [4] Infections due to invasive fungal infection account for 15% of all blood stream infections in NICU. [5] Although *Candida albicans* accounts for approximately 65% of cases of fungal infections in neonates, over 10 other species including *Candida parapsilosis*, *Candida tropicalis* and *Candida glabrata* have been reported to cause disease in neonates. [6] The manifestation of systemic neonatal candidiasis is indistinguishable from bacterial sepsis. [7] Diagnosis and treatment is further delayed because of difficulty in culture of the organism from blood, cerebrospinal fluid or urine. So, a high index of suspicion and additional laboratory tests may be required. Till now, there are very few previous studies in India on the profile of fungal sepsis in neonates. So, the present study was done to observe the clinical presentation and mycological profile of systemic fungal infections in neonates, admitted in a tertiary care hospital of Eastern India.

II. Material And Methods

A hospital based, prospective, observational study was conducted in the department of Pediatric Medicine of a tertiary care hospital of eastern India over a period of one year. The study was approved by the Institutional Ethics Committee for human research. Written informed consent was taken from the parents/ caregivers of the included neonates.

Newborn babies who were admitted in newborn care unit (inborn and outborn) and were started on intravenous fluid, were included in this study. Study population was broadly divided into two groups : (a) Newborn weighing less than 1500 grams at birth and (b) Newborn weighing more than or equal to 1500 grams at birth. Initial CBC (Complete blood count), CRP (C-reactive protein) and bacteriological culture were sent before starting intravenous antibiotics. Blood for **fungal culture** was performed after seven days of antibiotic therapy. 0.5-1 ml of blood was collected under aseptic precautions in biphasic blood culture bottle. The samples were processed and growths were identified by standard methods, i.e, morphology on SDA (Sabouraud dextrose agar) and *Candida* species on gram stain. Culture and microscopy were also done from oral thrush and urine specimen. Patients with fungemia were subjected to cerebro-spinal fluid study for fungal growth. Extent of disease was evaluated by ultrasonography abdomen, X-ray chest/abdomen as required. Recruitment of cases for this study was done on every Monday of the month. Neonates with major congenital anomalies, neonates who

had expired before the report came for fungal culture and neonates whose parents/ caregivers did not consent to participate were excluded.

Statistical analyses were done using SPSS Version 17.0. Descriptive statistics were used to summarize important characteristics of the population. For categorical variables, contingency tables were analyzed and Fisher's exact two-tailed P values were reported. Continuous variables were tested for normality of distribution by Kolomogorov-Smirnov and Shapiro-Wilks tests. For variables following normal distribution, independent samples t-test was used to compare means between two groups. P value < 0.05 was considered to be statistically significant.

III. Results

Two hundred seventy one neonates were recruited for the present study. But, after exclusion of neonates meeting the exclusion criteria, 254 neonates were included in the final analyses (Figure 1). Among them, fungal culture was positive in only 19 cases (7.48%). The mean birth weight and gestational age of the neonates with positive fungal cultures were 1.539 ± 0.593 kg and 33.368 ± 2629 weeks respectively. Ten of them were female (52.6%) and nine were male (47.4%). (Figure 1) Sixty eight percent (68.2%) of the patients were very low birth weight. *Candida Parapsilosis* was the predominant organism in <1500 gm group whereas *Candida albicans* along with *Candida parapsilosis* were mostly found in 1500-2499 gm group. In babies weighing ≥ 2500 gm *Candida tropicalis* was isolated in only one case. (Figure 2).

The common presenting signs are related to the gastrointestinal system (68.4%), followed by respiratory system and metabolic e.g. hyperglycemia/hyoglycemia. The three most common presentations are shock (42.1%), temperature instability (31.6%) and abdominal distension (42.1%). Most patients had a complete blood count (CBC) and C-Reactive Protein (CRP) done as a part of the work up. The majority (63.2%) of the patients had a normal total leucocyte count (TLC) but only 6 (31.5%) having leukopenia (TLC < 5000/cmm). Sixty eight percent of the patients had thrombocytopenia ($< 150 \times 10^9/l$) in the initial report and 73% in the repeat report. CRP came to be positive in 63% and 78% of the initial and repeat report respectively. There is no organism specific difference between the initial and repeat CBC with respect to the white cell count and platelets. However, there is a significant difference in the repeat CRP between the two groups with the *C. albicans* group having a much higher CRP count ($p = 0.041$) [Table 1] Among the commonly isolated species *C. albicans* isolates are 100% susceptible to amphotericin and 83.3% to fluconazole. Seven (87.5%) of *C. parapsilosis* isolates are susceptible to amphotericin B and eight (100%) to fluconazole. None of the isolates are resistant to both amphotericin B and fluconazole.

IV. Discussion

Recent advances in newborn care have resulted in longer survival of the premature neonates and hence, prone to interventions and nosocomial infections. Fungal sepsis is emerging as an important cause of sepsis in the neonatal population. One study found an eleven-fold increase in the rate of candidemia. [8] *Candida* species rank as the third and fourth most common organisms isolated in the neonatal units of the UK and the USA respectively. [9] There are few studies on epidemiology of fungal sepsis from developing countries like India. In the present study, isolation rate is 7.5% (19 fungal cultures positive out of 254 neonates), while Agarwal et al showing isolation rate of 13.6%. [10] Isolation rate in Indian study ranges from 3.2% to 13.6%. [11] Systemic candidiasis has been reported by Narang et al in 3.2% of admissions in NICU. [12] *Candida parapsilosis* is the predominant pathogen (42.1%) in our study followed by *Candida albicans* (31.6%), *Candida glabrata* (15.8%) and *Candida tropicalis* (10.5%). Agarwal et al showed marked increase in non albicans *Candida* with *Candida parapsilosis* being the most prevalent isolate. [10] Kosshoff et al reported a 60% increase in the prevalence of *C. parapsilosis* over a period of five years (1991-1995). [8] In the last two decades there has been a decrease in *C. albicans* and a proportional increase in the non-albicans *Candida* species causing invasive disease. [13-15] In our study we found the similar finding with *Candida parapsilosis* as the predominant pathogen followed by *C. albicans*.

Studies reported a higher prevalence in the ELBW and VLBW group. [16,17] There is also an inverse relationship between the gestational age and acquisition of fungal sepsis. Benjamin et al reported that fungal sepsis is more common if the patient's gestational age is less than 25 weeks. [18] In the present study the mean gestational age is 33.37 weeks with standard deviation of 2.629 and the mean birth weight is 1.54 kg with standard deviation of 0.593. Thrombocytopenia occurs in 32.5% of all neonates, admitted to the NICU without fungal sepsis and the incidence is 47.3% among neonates with fungal sepsis. [19] Thrombocytopenia is used as a nonspecific marker for sepsis in the neonate. [20] This study shows that patients with fungal sepsis have lower platelet counts than patients not affected with fungal sepsis. In our study all *C. albicans* isolates are sensitive to fluconazole whereas 83.3% of fungal isolates are sensitive and 16.7% are intermediately sensitive to amphotericin B. The Sentry antimicrobial surveillance programme in the USA reported that 95% of the *C. albicans* isolates were sensitive to amphotericin B. [21] On the other hand, the TSARY surveillance programme

in Taiwan reported an increase in resistance of all isolates to amphotericin B from 0.5% in 1999 to 2.5% in 2002 and a decrease in the resistance rate to fluconazole from 8.45 to 1.9%. [22] Amongst the *C. parapsilosis* isolates of our study 87.5% are susceptible to amphotericin B and 12.5% are intermediately susceptible. They are 100% susceptible to fluconazole. In the Artemis Disk antifungal surveillance programme, 20.3% of *C. parapsilosis* isolates from South Africa were resistant to fluconazole. [23]

V. Conclusion

Recent trends are showing changes in the organism responsible for invasive fungal infection in the neonates. Therefore, choice of antifungals should be based on the changing pattern of organism as well as the resistance pattern of the common isolates. Trends are needed to be followed via a surveillance programme to identify emerging resistance as seen in the rest of the world.

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Figures And Tables

1. **Figure-1:** Flow chart showing recruitment of patients in the study

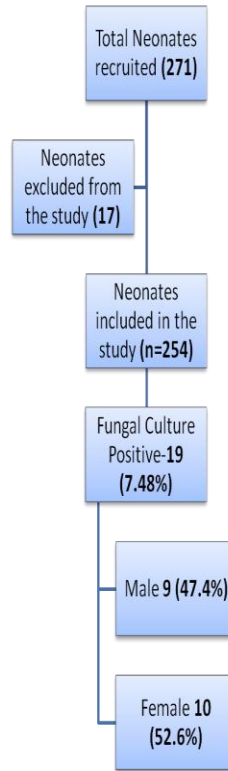


Figure-2: Bar diagram showing distribution of study population according to different fungal isolates (n=19)

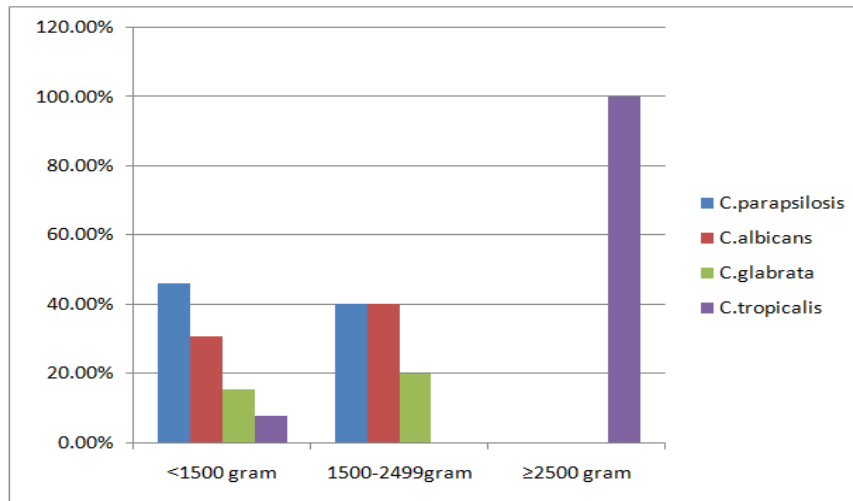


Table-1: Comparison of initial and repeat blood results between the C.albicans and the C. parapsilosis Group

Blood Results		C.albicans (n=6)	C. parapsilosis (n=8)	p-value
Initial	TLC/cmm	7612.5±4799.8	7110±3669.1	0.279
	Platelet count/cmm	13587.6±56806	148166.6±45128	0.872
	CRP mg/dl	3.2-6.4(<0.8-12.8)	3.2-6.4(<0.8-6.4)	0.923
Repeat	TLC/cmm	7437.5±4539.01	5266.66±1278.54	0.429
	Platelet count/cmm	125125±60974.0	69166±28840.36	0.64
	CRP mg/dl	3.2-6.4(<0.8-51.2)	<0.8(0.8-3.2)	0.041