

Systemic Candidiasis in Extremely Low Birthweight (ELBW) Neonates Despite the Routine Use of Topical Miconazole Prophylaxis: Trends, Risk Factors and Outcomes over an 11-Year Period

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Abstract

Introduction: This study aims to determine the incidence, trends of systemic candidiasis and meningitis in extremely low birthweight (ELBW) neonates (<1000 gms) despite the routine use of topical miconazole prophylaxis and to compare the risk factors, adverse outcomes and comorbidities with controls. **Materials and Methods:** Retrospective cohort study of ELBW neonates with systemic candidiasis and meningitis over an 11-year period (1997 to 2007). Matched case control analyses were performed to determine the risk factors and comorbidities which were severe intraventricular haemorrhage (IVH), severe retinopathy of prematurity (ROP), patent ductus arteriosus (PDA) requiring treatment, necrotising enterocolitis (NEC), chronic lung disease (CLD) and cholestatic jaundice. Mortality and end organ involvement secondary to systemic candidiasis were identified as adverse outcomes. **Results:** Of the 757 ELBW neonates, 51 (6.7%) had evidence of systemic candidiasis with a significant 3-fold increase in trend noted in 2007 as compared against 1997 (12.1% vs 3.8%) (RR 1.2, 95% CI, 1.06 to 1.36, $P < 0.001$). This corresponds to a significant increasing trend of preceding or co-existent bacterial blood stream infections (BSI) in neonates with systemic candidiasis (0% in 1997 vs 7.1% in 2007, RR 1.40, 95% CI, 1.04 to 1.25, $P = 0.005$). On logistic regression analysis, decreasing gestational age was an independent risk factor for systemic candidiasis (OR 2.0, 95% CI, 1.52 to 2.63, $P < 0.001$). Candida meningitis was detected in 4/38 (10.5%) and end organ involvement in 17 (33%). The organisms isolated were *Candida parapsilosis* 31 (61%), *Candida albicans* 17 (33%) and *Candida glabrata* 3 (5.8%). Significantly higher mortality was seen in cases when compared to controls 10/51 (19.6%) vs 76/706 (10.7%) (OR 2.02, 95% CI, 1.02 to 4.40, $P < 0.001$). **Conclusion:** Increasing trend in the incidence of systemic candidiasis despite routine use of topical miconazole prophylaxis is of concern and future studies comparing the use of systemic fluconazole versus oral nystatin may need to be considered.

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Introduction

Systemic candidiasis in extremely low birth weight (ELBW) neonates is associated with a high mortality, as well as short- and long-term morbidities. The incidence of systemic candidiasis in the very low birth weight neonates is less than 10% but it is higher in the ELBW cohort.¹ It varies in different centres with some reporting an increasing trend.^{2,3} Numerous risk factors predisposing to systemic candidiasis have been implicated. Extreme prematurity with relative immunodeficiency⁴ and presence of immature and fragile skin⁵ are considered as important host factors. Other risk factors are the use of third-generation cephalosporins,

H₂-receptor antagonists, parenteral steroids, prolonged ventilatory support, presence of central venous catheters, previous gastrointestinal (GI) surgery and prolonged hyperalimentation.⁶

Pre-existing fungal colonisation and increased density of colonisation of the skin and mucosal surfaces are significant risk factors for systemic disease.⁷ Strategies have focused on prevention of systemic disease from the colonised sites by use of topical antifungal agents with limited success.⁸ By comparison, prophylactic systemic antifungals have shown promising results.

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Mortality and end organ involvement secondary to systemic candidiasis still remains high but a declining trend is noted with improved neonatal care.⁹ In this study, we evaluated the incidence, trends and clinical presentation of ELBW neonates with systemic candidiasis and compared the risk factors, mortality and comorbidities in neonates with and without systemic candidiasis in our institution over an 11-year period.

Materials and Methods

Study population consisted of all ELBW neonates with evidence of systemic candidiasis/candida meningoencephalitis admitted to the neonatal intensive care unit (NICU) at KK Women's and Children's Hospital (KKH) Singapore, between January 1997 and December 2007. KKH is the largest tertiary perinatal centre in Singapore with approximately 12,000 deliveries annually. Control population included all ELBW neonatal survivors beyond 72 hours of life without systemic candidiasis. Maternal, perinatal and neonatal data were prospectively captured from a standardised very low birth weight (VLBW) database and review of case records. Approval was obtained from the hospital ethics committee.

Topical miconazole prophylaxis was used for all ELBW neonates commencing from the day of admission and continued until full enteral feeds were established. The preparation that is used in our institution is Daktarin oral gel™ (Miconazole 20 mg in 1 g), which is applied with an applicator to cover the mucosal surface of the oral cavity. Strict handwashing and hand hygiene measures were practised with periodic audits.

Antibiotic policy was based on customised antibiograms but neonates with presumed nosocomial infection would be initially treated with cloxacillin and an aminoglycoside pending antibiotic sensitivity. Neonates with confirmed bacterial blood stream infection (BSI) would be treated with 2 weeks of appropriate broad spectrum antibiotic therapy, or 3 weeks, if there was proven meningeal involvement in the presence of gram negative infections. Routine surveillance cultures for detecting fungal colonisation was not a practice in our institution.

Definitions

Systemic candidiasis was defined as isolation of candida species from a peripheral blood culture. Blood cultures were drawn between 3rd and 5th day after appropriate antifungal therapy to document clearance of systemic infection. Persistence of systemic candidiasis was defined as isolation of candida species from peripheral venous culture 10 days after the first isolate despite appropriate treatment. Mortality secondary to systemic candidiasis was

defined as death within one week of documented sepsis. Combined adverse outcomes analysed were mortality and end organ involvement secondary to systemic candidiasis. Evidence of end organ involvement was performed within 2 weeks after commencing therapy and involvement of the central nervous system, hepatobiliary system and kidneys were scanned by ultrasonography to look for evidence of fungal abscess. 2D echocardiography was done to look for vegetations. Ophthalmological evaluation was done to look for fungal chorioretinitis. Candida meningitis was diagnosed if the cerebrospinal fluid (CSF) showed pleocytosis or isolation of candida species from CSF cultures.

Antenatal risk factors analysed were use of antenatal steroids, presence of maternal chorioamnionitis, pregnancy induced hypertension and mode of delivery. Postnatal risk factors analysed were birthweight, gestation, Apgar scores at 1 and 5 minutes of age, need for intubation during resuscitation, surfactant therapy, presence of pneumothorax, presence of umbilical lines prior to the onset of sepsis, use of parenteral steroids and need for GI surgery, duration of ventilator support in the form of positive pressure ventilation and duration of percutaneously inserted central catheters (PICC). Presence of bacterial BSI either preceding the onset of systemic candidiasis or occurring concomitantly was also evaluated. The risk factors evaluating the combined adverse outcomes were the types of candida species, presence of PICC beyond 48 hours of positive cultures and persistence of positive cultures beyond 10 days of appropriate therapy.

Associated comorbidities secondary to systemic candidiasis analysed were presence of chronic lung disease (CLD), severe intraventricular haemorrhage (IVH), necrotising enterocolitis (NEC), severe retinopathy of prematurity (ROP) and patent ductus arteriosus (PDA) requiring treatment. CLD was defined as requirement of supplemental oxygen at 36 weeks post-conceptual age indicating severe form of CLD.¹⁰ The Papile grading system was used to define the different grades of IVH.¹¹ Severe IVH was defined as Grade III/IV IVH. ROP was considered severe if grading by the paediatric ophthalmologist was Stage III ROP or presence of plus disease.¹² Necrotising enterocolitis (NEC) was graded using Bell's classification.¹³ Stage II or more was considered as a significant morbidity. Haemodynamically significant PDA confirmed by 2D echocardiography would be treated medically and failure of resolution would warrant surgical ligation. Duration of hospitalisation and duration of total parenteral nutrition (TPN) were also evaluated as associated comorbidities as there was an increased need for resource utilisation.

Amphotericin as a single agent was used for treatment of systemic candidiasis and combination of antifungal drugs (flucytosine, fluconazole) was used only in the presence of end organ involvement or persistence of cultures beyond

10 days of monotherapy. Amphotericin at 1 mg/kg/day was commenced and a cumulative dose of 20 mg was used in the absence of end organ involvement and 40 mg in the presence of end organ involvement.

Microbiology

In neonates with presumed sepsis, one millilitre of blood was drawn by a venipuncture using standardised sterile precautions. Blood for bacterial culture was inoculated into Bactec Paed (d2) blood culture vials and incubated for 5 days in Bactec 9240 (BD, USA), a continuous monitoring blood culture system. *Candida* isolates were identified using API 20C AUX (bioMérieux, France). The isolate was plated on cornmeal agar to determine its microscopic morphology.

Computerised data were analysed using SPSS software version 14. Categorical data were analysed using Fischer's exact test or chi-square tests and continuous data using Student's t-test. Parametric data were expressed as mean $\pm$ standard deviation and non-parametric data expressed as median (range). Logistic regression model was used for trend analysis and for predicting risk factors. Significance was declared at P values <0.05 and odds ratio with 95% confidence interval was expressed.

Results

There were a total of 757 ELBW neonates during the study period. Of them, 51 (6.7%) had systemic candidiasis with a total of 55 episodes (7.3%). The mean gestation and the mean birthweight of the study population were 24.5 ± 1.2 weeks (range, 23 to 29 weeks) and 673 ± 127 g (range, 390 to 1000 g) respectively. A 3-fold increase in the incidence of systemic candidiasis was noted from 3.8% in 1997 to

12.1% in 2007 and logistic regression analyses showed a significant increase in the trend of systemic candidiasis over the years (RR 1.2, 95% CI, 1.06 to 1.36, $P < 0.001$ (Fig. 1)). *Candida meningitis* was detected in 4/38 (10.5%) and 2 of them had evidence of cerebral abscess. Thirteen neonates had no cerebrospinal fluid (CSF) analyses done as they were critically ill. CSF analysis was performed between 2 to 18 days (median 5 days) in neonates with systemic candidiasis. The mean age of onset of sepsis was 20.4 ± 13.7 days (range, 7 to 60 days) and the mean duration to clearance of sepsis was 10.4 ± 5.4 days (range, 3 to 28 days).

Of the 51 cases, *C. parapsilosis* was the predominant organism isolated in 31 (61%), followed by *C. albicans* in 17 (33%) and *C. glabrata* in 3 (5.8%). Clinical presentation at the onset of illness was increased respiratory distress requiring ventilatory support in 48 (94%), hypotension requiring inotropes in 27 (54%), feed intolerance in 27 (52%) and neurological symptoms like lethargy and seizures in 4 (7.8%) cases.

Maternal, perinatal and neonatal demographic risk factors in the study and control groups are described in Table 1.

On univariate analysis, significant risk factors for systemic disease were maternal chorioamnionitis, need for intubation during resuscitation, lower birth weight and decreasing gestation, surfactant therapy, presence of pneumothorax, duration of umbilical lines prior to the onset of systemic candidiasis, need for GI surgery and bacterial blood stream infections. It is interesting to note that not only was there a significant increase in the presence of preceding or concomitant bacterial (BSI) in neonates with systemic candidiasis compared to controls 29 (51%) vs 166 (23.5%) (OR 4.2, 95% CI, 2.31 to 7.97, $P < 0.001$) but also a significant increase in trend in the incidence of bacterial

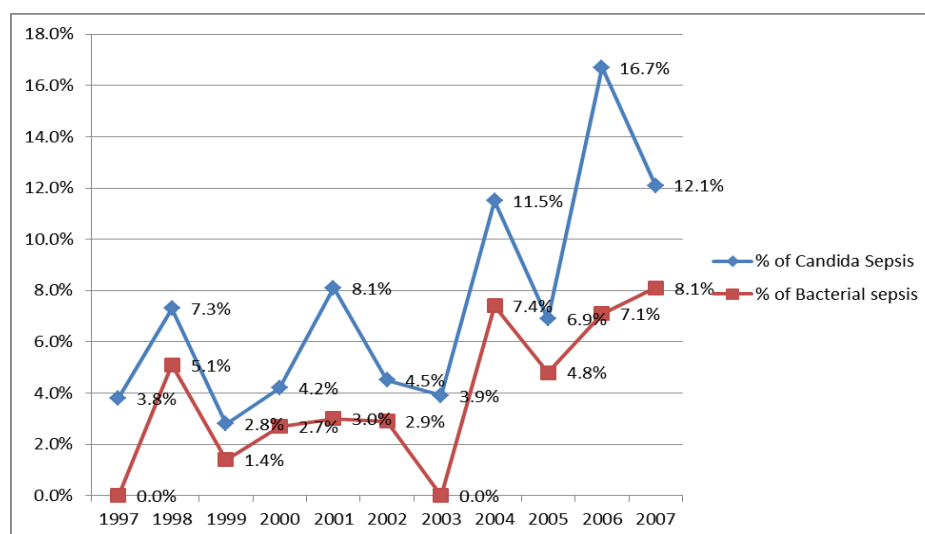


Fig. 1. Trends in the incidence of systemic candidiasis and comparison with the trend of preceding or co-existent bacterial BSI (January 1997 – December 2007).

Table 1. Patient Demographics and Risk Factors Associated with Systemic Candidiasis: Univariate Analysis

Risk Factors	Numbers	Cases (%)	Controls (%)	OR	95% CI	P Value
Number of cases	n = 757	n = 51	n = 706			
Maternal chorioamnionitis	735	25 (49)	212 (31)	2.1	(1.20 – 3.79)	0.008
Antenatal steroids	752	38(76)	521 (74)	1.1	(0.56 – 2.15)	0.78
Cesarean section	757	34 (67)	310 (44)	2.6	(1.40 – 4.65)	0.002
Maternal pregnancy-induced hypertension	754	4 (8)	163 (23)	0.3	(0.1 – 0.79)	0.037
Need for positive pressure ventilation	709	48 (94)	515 (78)	0.2	(0.07 – 0.73)	0.007
Apgar scores <7 at 5 minutes	750	37 (72)	563 (80)	0.6	(0.33 – 1.21)	0.168
Surfactant therapy	753	44 (86)	454 (65)	3.4	(1.52 – 7.73)	0.002
Birthweight (g) Mean ($\pm$ 2SD)	757	673 $\pm$ 127	810.47 $\pm$ 136.23	1.0	(0.991 – 0.996)	<0.001
Gestation (weeks) Mean ($\pm$ 2SD)	757	24 $\pm$ 1	26.81 $\pm$ 2.16	2.2	(1.4 – 2.8)	<0.001
Postnatal parenteral steroids	691	17 (44)	150 (23)	258	(1.33 – 4.99)	0.004
Presence of pneumothorax	755	14 (27)	72 (10)	3.3	(1.71 – 6.43)	<0.001
Gastrointestinal surgery	757	12 (24)	41 (5.8)	4.9	(2.27 – 10.7)	<0.001
Preceding or concomitant bacterial sepsis	757	29 (57)	166 (23.5)	4.2	(2.31 – 7.97)	<0.001
Duration of umbilical arterial catheter prior to the onset of sepsis (days) Mean ($\pm$ SD)	692	8 $\pm$ 5	5 $\pm$ 5	1.1	(1.04 – 1.14)	0.003
Duration of umbilical venous catheter prior to the onset of sepsis (days) Mean ($\pm$ SD)	696	6 $\pm$ 3	4 $\pm$ 2.9	1.2	(1.11 – 1.34)	<0.001
Duration of TPN (days) Mean ($\pm$ SD)	696	45.66 $\pm$ 29.38	28.39 $\pm$ 17	2.65	(22.49 – 12.06)	0.00
Duration of PICC (days) Mean ($\pm$ SD)	757	41 $\pm$ 25	27 $\pm$ 17	1.02	(1.02 – 1.04)	0.00
Duration of ventilatory support (days) Mean $\pm$ SD	750	49 $\pm$ 40	20 $\pm$ 29	1.01	(1.01 – 1.02)	0.00

OR: Odds ratio; TPN: Total parental nutrition; PICC: Peripherally inserted central catheter

BSI between 1997 and 2007 (0% vs 7%) (RR 1.14, 95% CI, 1.04 to 1.25, $P = 0.005$) (Fig. 1). There were 29 (57%) cases of bacterial BSI preceding or concomitantly occurring in neonates with systemic candidiasis. Gram-negative BSI occurred in 18/29 (62%), gram-positive in 7/29 (24%) and a combination of gram-positive and gram-negative organisms were present in 4/29 (14%). There is a preponderance of gram-negative organisms in this cohort with a corresponding use of broad spectrum antibiotics like the third-generation cephalosporins and the carbapenams. It was noted in our study that 36/51 (76%) of neonates with systemic candidiasis received broad spectrum antibiotics. In the control group, there were 166 (23.5%) cases of bacterial BSI of which 81/166 (49%) were gram-negative organisms, 70/166 (42%) were gram-positive and 15/166 (9%) were a combination of both. However, logistic regression analysis revealed that the only significant risk factor for predicting sepsis was decreasing gestational age (OR 2.0, 95% CI, 1.52 to 2.63, $P < 0.001$). Presence of pregnancy-induced hypertension appears to have protective effect 7.8% vs 23%, (OR 0.28, 95% CI, 0.1 to 0.79, $P \leq 0.01$).

In neonates with systemic candidiasis, the overall mortality was 16/51 (31%) but deaths secondary to systemic candidiasis occurred only in 10 neonates (19.6%). End organ involvement occurred in 17 (33%) neonates and the sites were hepatic abscesses in 4 (24%), renal fungal balls in 2 (12%), cerebral abscess in 2 (12%) and cavitatory lung lesions in 1 (6%) neonate; gastrointestinal perforation occurred in 8 (47%) neonates, of whom 6 had mycelia isolated from histopathology specimens resected during surgery. Risk factors associated with significant adverse outcomes (mortality secondary to systemic candidiasis and end organ involvement) were presence of *C. albicans* sepsis $P = 0.034$ (Table 2) and the presence of PICC beyond 48 hours of positive cultures ($P = 0.00$, OR 3.13, 95% CI, 1.10 to 7.92) (Table 3). Persistence of culture positivity >10 days despite appropriate antifungal treatment was not associated with a significant increase in mortality or end organ involvement in our series as the mean day of clearance of sepsis was 10.4 ± 5.4 days (OR 1.79, 95% CI, 1.97 to 6.45, $P = 0.46$). Thirty (59%) babies needed only amphotericin deoxycusate while 21(41%) cases needed

Table 2. Comparison of Types of Candida Species Predicting Adverse Outcomes

Adverse Outcomes	No. of Cases n = 51	<i>C. Albicans</i> n = 17 (35%)	<i>C. Parapsilosis</i> n = 31 (61%)	<i>C. Glabrata</i> n = 3 (4%)	P Value
Mortality secondary to systemic candidiasis	10 (19.6%)	6 (35%)	2 (6.5%)	2 (67%)	0.02
End organ involvement secondary to systemic candidiasis	17 (33%)	6 (35%)	10 (32%)	1 (34%)	0.45
Combined adverse outcomes	27 (53%)	12 (71%)	12 (39%)	3 (100%)	0.04

Table 3. Risk Factors for Predicting Adverse Outcomes Secondary to Systemic Candidiasis

Risk Factors for Predicting Adverse Outcomes Mortality n = 10 End Organ n = 17	Neonates with Systemic Candidiasis n = 51	Adverse Outcomes Present n = 27 (53%)	Adverse Outcomes not Present n = 24 (47%)	OR 95% CI	P Value
Removal of PICC <48 hours after culture positivity	22 (43%)	8/22 (36%)	14/22 (64%)	OR 3.12 95% CI, 1.10 – 7.92	P = 0.00
Removal of PICC >48 hours after culture positivity	29 (57%)	19/29 (66%)	10/29 (34%)		
Persistence of systemic candidiasis >10 days of appropriate therapy	28 (55%)	13/28 (46%)	15/28 (54%)	OR 1.79 95% CI, 1.97 – 6.45	P = 0.46
Clearance of systemic candidiasis <10 days after appropriate therapy	23 (45%)	14/23 (61%)	9/28 (39%)		

PICC: Peripherally inserted central catheter; OR: Odds ratio

Table 4. Comparison of Mortality and Comorbidities in ELBW Neonates With and Without Candidiasis

Mortality and Comorbidities	Numbers n = 757	Cases (%) n = 51	Controls (%) n = 706	OR	95% CI	P Value
Overall mortality	757	16 (31.3%)	76 (10.7%)	3.78	(1.906 – 7.474)	0.00
Mortality secondary to systemic candidiasis	757	10 (19.61%)	76 (10.7%)	2.02	(1.021 – 4.396)	0.009
Stage II and above NEC/GI perforation	757	12 (24%)	58 (8%)	3.43	(1.60 – 7.25)	0.00
PDA requiring treatment and surgical ligation	746	45 (90%)	442 (64%)	5.1	(2.02 – 13.19)	0.00
Severe IVH	755	11 (22%)	81 (12%)	2.1	(1.07 – 4.41)	0.028
Chronic lung disease at 36 weeks (in survivors)	689	28/35 (50%)	177/644 (25%)	10.5	(4.3 – 27)	0.001
Severe ROP (in survivors)	677	22/36 (61%)	123/641 (19%)	6.6	(3.29 – 13.30)	0.00
Duration of hospitalisation (days) Mean (± SD)		121 ± 78	97 ± 52	8.04	(8.48 – 40.06)	0.037
Cholestatic jaundice	756	26 (51%)	194 (28%)	2.74	(1.49 – 5.05)	0.005
Duration of TPN (days) Mean (± SD)	696	45.66 ± 29.38	28.39 ± 52.42	2.65	(22.49 – 12.06)	0.00

ELBW: Extremely low birth weight; NEC: Necrotising enterocolitis; GI: Gastrointestinal; IVH: Intraventricular haemorrhage; ROP: Retinopathy of prematurity; TPN: Total parental nutrition; OR: Odds ratio

a combination therapy with flucytosine/fluconazole for clearance of sepsis.

Neonates with systemic candidiasis had a significantly higher incidence of comorbidities such as CLD, severe IVH, PDA requiring treatment, NEC, cholestatic jaundice and severe ROP compared to controls (Table 4). Resource utilisation in the form of prolonged duration of TPN and duration of hospital stay were also significantly higher in those with systemic candidiasis.

Discussion

Despite significant improvement in the survival of VLBW neonates, the surviving neonates are immunocompromised and susceptible to systemic blood stream infections. *Candida* species is an emerging pathogen with *C. albicans* reported as the third most frequent organism in neonates with nosocomial sepsis.¹ In our institution, there was a significant rise in the trend of systemic candidiasis with an incidence of 3.7% in 1997 to 12.1% in 2007 despite the routine use of topical miconazole as a prophylactic agent. Except for a decline in the incidence in 2005 to 6.9%, there appears to be an increase noted since 2004. Bacterial BSI before the onset of systemic candidiasis is an important risk factor for systemic candidiasis.¹² We noted in our study that not only was there a significant increase in the incidence of preceding or concomitant BSI in neonates with systemic candidiasis when compared to controls 29 (56.9%) vs 166 (23.5%)) but also a significant increase in trend in the incidence of bacterial blood stream infections from 0% in 1997 to 7.1% in 2007. It is interesting to note that the incidence of gram-negative infections preceding or occurring concomitantly in those with systemic candidiasis was 62%, leading to the use of broad spectrum antibiotics. Though the antibiotic policy in our institution for nosocomial infection is cloxacillin and an aminoglycoside in the presence of proven blood stream infection secondary to gram-negative infection, broad spectrum antibiotics like the third-generation cephalosporins or carbapenem would be used for 2 weeks depending on the antibiotic sensitivity pattern. Prolonged antimicrobial use promotes colonisation of the neonate with *Candida* species and this could be one of the reasons for the rising trend of systemic candidiasis noted in our institution. We also cannot ignore the fact that there was use of broad spectrum antibiotics in 76% of the cases prior to the onset of systemic candidiasis. High density colonisation of the skin and mucosal surfaces is important for spread of systemic disease and is associated with prolonged antimicrobial use especially third-generation cephalosporins.⁶

Other risk factors commonly implicated are lower birthweight and decreasing gestation, use of parenteral steroids, duration of central lines, duration of assisted ventilation and previous GI surgery similar to our study.^{6,14,15}

Pregnancy-induced hypertension was noted to be protective with a lower incidence of sepsis in our study similar to the study reported by Cotten et al.³

Systemic candidiasis predominantly occurs between 2nd and 3rd week of life but in our study, the mean age of onset of sepsis was between the 3rd and 4th week of life.¹⁶ The clinical presentations are non-specific and difficult to distinguish from other bacterial infections. However, positive cultures can usually be obtained within 72 hours¹⁷ and aids physicians to discontinue empiric antifungal therapy if warranted. In our study, all positive cultures were available within 72 hours.

C. albicans was considered the predominant pathogen for systemic disease but recent trends show that *C. parapsilosis* is the predominant organism in the NICU¹⁶ and this was also noted in our study. Systemic candidiasis is associated with a high mortality rate of more than 25%⁹ and our series also showed a rate of 19.6%. End organ involvement secondary to dissemination is well documented with systemic candidiasis and was seen in 17 (33%) of our cases.¹⁸ Screening for end organ involvement is essential to guide duration of treatment and aids in prognostication.

Spontaneous intestinal perforation, described as a distinct clinical entity in ELBW neonates, is associated with systemic candidiasis or coagulase negative staphylococcal infection.¹⁹ In our study, 8 (16%) babies had isolated intestinal perforation, of which, 6 had evidence of myelia in the histopathology specimens. Increased incidence of mortality and end organ involvement are reported in those with *Candida albicans* sepsis, persistently positive cultures and failure of removal of PICC more than 24 hours after detection of candida sepsis.^{20,21} In our study, removal of PICC beyond 48 hours and presence of *Candida albicans* sepsis were associated with significant combined adverse outcomes. Persistence of culture positivity >10 days despite treatment was not associated with significant adverse outcomes in our series as the mean duration to clearance of sepsis in our series was (10.4 ± 5.4) days.

Associated comorbidities like CLD, severe IVH, cholestatic jaundice, significant PDA and severe ROP were reported to be significantly higher in neonates who survive candida sepsis both in our study and in the literature.^{22,23}

Amphotericin B is used as monotherapy in proven fungal sepsis.²⁴ Amphotericin was used in 30 (59%) of our cases with combination of antifungals being used only in the presence of complications.

The limitations of the study are failure to evaluate some of the essential risk factors in the cohort between cases and controls, like the use of third-generation cephalosporins, use of H2 blockers and fungal surveillance cultures. It would indeed be useful to identify the above-mentioned risk factors which are commonly implicated as predisposing factors to

subsequent development of systemic infection. This would certainly help us in future to look at our antibiotic policies and use of H2 blockers.

Systemic candidiasis is associated with a high disease burden in the VLBW neonates and therefore strategies to decrease the incidence of systemic candidiasis have been extensively studied. The use of prophylactic antifungal agents in the VLBW neonates has been of great interest recently as it decreases the intensity of fungal colonisation and thereby preventing systemic spread.²⁵

The prophylactic antifungal agents evaluated are topical miconazole, oral nystatin and systemic fluconazole. Selection of prophylactic agents will depend on the disease burden in the nursery, safety and efficacy of the agent and cost-benefit analysis.

Use of topical miconazole was studied by Warner et al,²⁶ showing a reduction in the incidence of fungal colonisation but no difference in the rates of systemic candidiasis. Miconazole as a topical prophylactic agent was used for all high-risk neonates in our unit and despite the routine use, we noted a steady rise in the incidence of systemic candidiasis in the ELBW neonates. We understand that the increase in incidence of systemic candidiasis is likely to be due to multifactorial causes. However, we need to address the rising trend of candida sepsis in our institution by considering the use of other antifungal prophylactic agents. Systemic oral nystatin as a prophylactic agent has been successfully shown to decrease the incidence of systemic candidiasis.²⁷⁻²⁹

Concerns about use of oral nystatin as a prophylactic agent is due to the high osmolality of the medication and its association with gastrointestinal morbidities (NEC and solitary intestinal perforation).³⁰

Fluconazole as a systemic prophylactic antifungal agent has been evaluated with promising results and has shown significant decline in the incidence of systemic candidiasis.³¹⁻³³ Despite the success, concerns still exist on reports of reversible elevated liver enzymes, fluconazole resistant candida species and emergence of filamentous fungi as pathogens with the use of routine fluconazole prophylaxis.³⁴⁻³⁶ A prospective study comparing the efficacy of nystatin and systemic fluconazole has shown promising results with the use of nystatin with minimal GI side effects.³⁷

Conclusion

The incidence of systemic candidiasis in our institution has shown an increasing trend despite the routine use of prophylactic topical miconazole of *C. parapsilosis* which was the predominant pathogen in our nursery. Systemic candidiasis was associated with a significantly high mortality and morbidity. The limited impact of topical antifungal prophylaxis has prompted physicians to consider use of

systemic agents like fluconazole targeted to neonates <800 gms. With ongoing concerns about the use of systemic agents, a prospective randomised trial comparing the efficacy of fluconazole with nystatin should be considered.

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