Background changing patterns of neonatal fungal sepsis in a developing country

by Daynia E. Ballot,1 Noma Bosman,2 Trusha Nana,2 Tanisha Ramdin,1 and Peter A. Cooper1
1Department of Paediatrics and Child Health, University of the Witwatersrand, Johannesburg, South Africa
2Department of Clinical Microbiology and infectious diseases, Faculty of Health Sciences, University of the Witwatersrand, PO Box 2115, Houghton 2041

Correspondence: Daynia E. Ballot, Department of Paediatrics and Child Health, School of Clinical Medicine, University of the Witwatersrand Private Bag X 39, Johannesburg 2000. Fax: 0865534650. E-mail <Daynia.ballot@wits.ac.za>

Summary

Background: Candida albicans is the predominant isolate in many neonatal fungal bloodstream infections (BSIs), so fluconazole is used as empiric antifungal therapy.

Aim: To determine the predominant organisms, antifungal sensitivity patterns, clinical and demographic risk factors and crude mortality rate in neonatal fungal BSI cases.

Subjects and Methods: This is a review of all neonatal fungal BSI cases between January 2007 and December 2011.

Results: Fifty-nine patients were included in the study. Candida parapsilosis (54.2%) was isolated in majority of the cases, followed by C. albicans (27.1%). Fluconazole resistance was present in 16 of 32 cases of C. parapsilosis versus 1 of 16 cases of C. albicans (P = 0.003). Mortality rate was 45.8%. Surgical problems were present in 55.9%. Death was significantly associated with lower birth weight (P = 0.046) and necrotizing enterocolitis (P = 0.034).

Conclusions: The increase in neonatal fungal BSI and resistant organisms highlights the need to review use of routine empiric fluconazole and to implement preventive measures.

Key words: fungal bloodstream infections, neonates, Candida, fungal sepsis

Background

Fungal sepsis (FS) is an important problem in sick newborn infants, with a mortality rate between 21% [1] and 76% [2]. FS should be suspected in the critically ill neonate with negative blood cultures [3]. Risk factors include very low birth weight, gestational age <30 weeks, intravenous hyperalimentation, exposure to H2 receptor antagonists, lack of antenatal care, use of central catheters, prolonged hospitalization, mechanical ventilation, endotracheal intubation, use of broad-spectrum antibiotics/steroids and previous colonization with Candida albicans [1, 3–12].

Early diagnosis and aggressive treatment improves the outcome of FS [3]. Definite diagnosis of neonatal FS is difficult and pathogenes take time to isolate, so babies with suspected FS are treated with empiric antifungal therapy while awaiting culture results.

Funding

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Methods
This is a review of neonates with fungal BSI at the neonatal unit of CMJAH between 1 January 2007 and 31 December 2011. A neonate was considered to be any patient admitted to the neonatal unit within 28 days of birth or those neonates who were born in the hospital and had not ever been discharged, e.g. a preterm infant now 40 days old would still be included in the study.

All neonates with a fungal organism isolated on blood culture were included in the study. The same organism isolated from the same patient within 7 days was considered to be a single episode of fungal BSI. The duration of incubation, identification of the organism and mean inhibitory concentrations (MICs) of fluconazole and voriconazole were obtained from the culture result. The different Candida species isolated were classified as resistant based on species-specific MIC cut-off levels for fluconazole or voriconazole, as published by Pfaller et al. [17]. Clinical and demographic information was obtained from the neonatal computer database, admission registers and microfilmed patient records. Ethics approval for the study was obtained from the Human Research Ethics Committee of the University of the Witwatersrand. Patients were started on empiric antifungal therapy at the discretion of the attending physician. Treatment was adjusted according to the fungal isolate and sensitivity pattern, as soon as this information was available. Fluconazole was used as first-line empiric antifungal therapy. This did not change during the whole study period, and amphotericin was not used in any patient as empiric therapy. There was no prophylactic use of fluconazole in the neonatal unit at the time of the study.

Although indwelling catheters are known risk factors for FS, this information was not available for review, as it was not routinely recorded in patient information. Similarly, information regarding individual antibiotic therapy received by patients with FS was not available. At the start of the study period, empiric antibiotic therapy for nosocomial sepsis was piperacillin – tazobactam with vancomycin. This changed to meropenem with vancomycin. This changed to meropenem with vancomycin. At the start of the study period, empiric antibiotic therapy for nosocomial sepsis was piperacillin – tazobactam with vancomycin. This changed to meropenem with vancomycin. This was followed by amikacin and extended-spectrum beta-lactamase Klebsiella pneumonia.

Statistical analysis
Statistical analysis was done using IBM SPSS statistics version 20. The data were described using conventional statistical methods. Continuous data with a normal distribution were described using mean and standard deviation, and skewed data were described using median and interquartile range (IQR). Categorical data were described using frequencies and percentages. Comparisons were done between survivors and non-survivors and between patients with C. albicans and C. parapsilosis. Categorical data were compared using chi-square analysis. Fisher exact test was used where a cell in the 2X2 table was <5. The distribution of birth weight, gestational age and duration of intensive care unit stay was skewed, so non-parametric analysis was done for comparison. A P value <0.05 was considered as significant.

Results
There were 63 patients with fungal BSI in the CMJAH neonatal unit during the study period. Adequate clinical data could not be obtained on four patients, so these were excluded from the study. The final sample therefore comprised 59 neonates.

Microbiology
The most common organism isolated was C. parapsilosis (54.2%), followed by C. albicans (27.1%) (Table 1). There was an increase in both in the incidence of fungal BSI and NAC isolates over the duration of the study (Fig. 1), although this did not reach significance (P = 0.06 χ² = 40.498). There was also an increase in FS as a percentage of total admissions over the study period—from 0.6% in 2007 to 1.8% in 2011 (Fig. 1).

Significantly more C. parapsilosis were resistant to fluconazole as compared with C. albicans (16/32 vs. 1/16 P = 0.003 Fisher exact test). Eight of the C. parapsilosis as compared with none of the C. albicans isolates were resistant to voriconazole (P = 0.0394 Fisher exact test). All of the voriconazole-resistant C. parapsilosis isolates were resistant to fluconazole as well. The mean duration of incubation to a positive culture was 37.11 h (standard deviation 13.35). There was no difference in the duration of incubation between C. parapsilosis and C. albicans.

Clinical and demographic information
Patient clinical and demographic characteristics are shown in Table 2. Babies with fungal BSI were predominantly preterm and of extremely low birth weight (ELBW): median birth weight 956 g (IQR 1000 g) and median gestational age 28 weeks (IQR 8 weeks). The median duration of ventilation was 9 days (IQR 32 days). The majority were male (57.6%), and the mortality rate was 45.8%. Surgical problems were present in 33 patients (55.9%)—14 of whom had necrotizing enterocolitis (NEC), seven abdominal wall defects and seven intestinal atresia. There was no difference in the incidence of fungal infection or species of fungus isolated in inborn vs. outborn babies (χ² 0.951).

The birth weight of babies who died was significantly lower than those who survived (median 1000 g...
Gestational age was not different between the survivors and non-survivors. The only significant association with death was NEC ($\chi^2 8.662 \ P = 0.034$). There was no other significant difference for any other clinical or demographic factor between survivors and non-survivors. There was no significant difference in the death rate over time (i.e. death rate by year) ($\chi^2 0.759$). There was no significant difference between the group of patients with \textit{C. parapsilosis} and those with \textit{C. albicans} infections for any of the demographic or clinical characteristics, including mortality.

**Discussion**

Fungal BSI is an important cause of morbidity and mortality in sick newborn infants. This study showed an increase in the incidence of fungal BSI over time—from 0.6% in 2007 to 1.8% in 2011, despite similar patient numbers and demographics. This is in contrast to reports from the USA [18, 19] and Kuwait [7], where a decline in neonatal fungal BSI has been noted over a similar time.

The neonates in the current study were premature and of ELBW. This is in close agreement with many other reports [7, 11, 18, 20, 21]. The majority (79.7%) of the current neonates received assisted ventilation—69.2% mechanical ventilation and 10.5% nasal continuous positive airway pressure. Mechanical ventilation has been described as a risk factor for neonatal fungal BSI [9–11], although nasal continuous positive airway pressure has not been identified previously. The present mortality rate was 45.8%, which is close to the 42.8% reported by Celebi \textit{et al.} [22] from Turkey, but much lower

**TABLE 1**

<table>
<thead>
<tr>
<th>Organism</th>
<th>Number</th>
<th>%</th>
<th>Fluconazole resistance</th>
<th>Voriconazole resistance</th>
<th>Resistance to both</th>
</tr>
</thead>
<tbody>
<tr>
<td>\textit{Candida parapsilosis}</td>
<td>32</td>
<td>54.2</td>
<td>16</td>
<td>8</td>
<td>8</td>
</tr>
<tr>
<td>\textit{Candida albicans}</td>
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<td>27.1</td>
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<td>0</td>
<td>0</td>
</tr>
<tr>
<td>\textit{Candida tropicalis}</td>
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<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>\textit{Candida glabrata}</td>
<td>2</td>
<td>3.4</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>\textit{Candida dublinensis}</td>
<td>1</td>
<td>1.7</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>\textit{Candida lusitaniae}</td>
<td>1</td>
<td>1.7</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>\textit{Hansenula polymorpha}</td>
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<td>1.7</td>
<td>0</td>
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<td>0</td>
</tr>
<tr>
<td>\textit{Saccharomyces cerevisiae}</td>
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<td>1.7</td>
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</tr>
</tbody>
</table>

**TABLE 2**

<table>
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<tr>
<th>Characteristic</th>
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<tr>
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<td></td>
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<tr>
<td>Male</td>
<td>34</td>
<td>57.6</td>
</tr>
<tr>
<td>Female</td>
<td>25</td>
<td>42.4</td>
</tr>
<tr>
<td>Died</td>
<td>27</td>
<td>45.8</td>
</tr>
<tr>
<td>Place of birth</td>
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<tr>
<td>Inborn</td>
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<td>52.5</td>
</tr>
<tr>
<td>Referred</td>
<td>28</td>
<td>47.5</td>
</tr>
<tr>
<td>Antenatal steroids</td>
<td>10</td>
<td>16.9</td>
</tr>
<tr>
<td>HIV exposed</td>
<td>12</td>
<td>20.3</td>
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<tr>
<td>Surgical diagnosis</td>
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<td>41.1</td>
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<tr>
<td>Surgical procedure</td>
<td>24</td>
<td>40.7</td>
</tr>
<tr>
<td>NEC</td>
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<td>23.7</td>
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<tr>
<td>Central catheter</td>
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<td>16.9</td>
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<tr>
<td>Parenteral nutrition</td>
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<td>44.1</td>
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<tr>
<td>PDA</td>
<td>5</td>
<td>8.5</td>
</tr>
<tr>
<td>IVH</td>
<td>14</td>
<td>25.4</td>
</tr>
<tr>
<td>Ventilated</td>
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<td></td>
</tr>
<tr>
<td>IPPV</td>
<td>41</td>
<td>69.5</td>
</tr>
<tr>
<td>NCPAP</td>
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<td>10.2</td>
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</table>

NEC: necrotizing enterocolitis; NCPAP: nasal continuous positive airway pressure; IPPV: intermittent positive pressure ventilation; IVH: intraventricular haemorrhage; PDA: patent ductus arteriosus.

Fig. 1. \textit{Candida} isolates by year. Numbers in blocks indicate percentage of total admissions.
than the 76% reported from a public hospital in Brazil [2, 11]. The present study showed a high prevalence of surgical problems (44%), including 23.7% with NEC in patients with fungal BSI. C. albicans infection has been described as an uncommon cause of intestinal perforation and NEC [23]. Abdominal surgery has been found to be a risk for candidaemia, irrespective of birth weight [21].

In the present study, there was an increase in the incidence of NAC neonatal BSI over time, particularly C. parapsilosis, although no differences could be identified between patients with C. albicans and C. parapsilosis, similar to a report from Taiwan [24]. The most common Candida isolate varies between neonatal units. C. albicans is more common than C. parapsilosis in the USA and Venezuela [8, 18, 21], with few resistant organisms [18] and little variation over time [19], whereas C. parapsilosis was the predominant organism in neonatal units in Kuwait [7] and Barcelona. Half of the C. parapsilosis isolates in the current study were resistant to fluconazole, and eight of these were resistant to both fluconazole and voriconazole. Only one of the C. albicans isolates was resistant to fluconazole. A linear relationship has been reported between the MICs to voriconazole and fluconazole, suggesting that cross-resistance occurs [25].

The use of prophylactic nystatin or fluconazole administration in preterm very-low-birth-weight infants prevents fungal colonization and invasive fungal disease [4, 26], without an increase in naturally occurring fluconazole-resistant organisms [27]. However, a report from Helsinki mentions emergence of fluconazole resistance in C. parapsilosis after >10 years of fluconazole prophylaxis in neonatal intensive care units [28]. There was a high incidence of fluconazole resistance in the C. parapsilosis in the present study, so the routine use of prophylactic fluconazole in this setting would be debatable.

There was an increase in 2009 in total neonatal fungal BSI as well as that due to C. parapsilosis in the present study and the incidence of both continued to rise. The reason for this is unknown. There was, however, an increase in nosocomial infections due to multiresistant bacteria during the study period, and the empiric antibiotic therapy changed from piperacillin–tazobactam at the start of the study period to meropenem in the latter half. Exposure to broad-spectrum antibiotics is a known risk factor for FS [12], so this could be a contributory factor.

The increase in FS is a cause for concern. One successful method of reducing the incidence of nosocomial infection is through the implementation of ‘Care bundles’ [29]. In this approach, four to five evidence-based methods of reducing infection are ‘bundled’ together and presented to staff on an ongoing basis with a targeted outcome (decreased infection rates). CMJAH will be participating in Best Care Always programme (www.bestcare.org.za), which uses this approach to reduce nosocomial infection rates. As resistant C. parapsilosis has become a frequent cause of neonatal fungal BSI, the protocol for empiric antifungal therapy in the present neonatal unit has been adjusted to the use of amphotericin B as first-line therapy.

Conclusion

Fungal BSI is an important problem in neonates in CMJAH, with a high mortality rate and significant incidence of resistant organisms. Neonates with FS are most likely to be premature and of ELBW. There is also a strong association with surgical conditions, particularly NEC. The use of prophylactic fluconazole in this setting is questionable, and empiric antifungal therapy with fluconazole may not be effective. Fungal BSI isolates and their sensitivity must be monitored on an ongoing basis. The increase in both FS and resistant organisms is a cause for concern, and strategies to address hospital-acquired infection must be implemented.

Study limitations

Certain important risks for neonatal fungal BSI, including the use and duration of indwelling catheters, details of broad-spectrum antibiotic therapy and exposure to H2 receptor antagonists, could not be evaluated in this study. Detailed information regarding risk factors should be included in the ongoing surveillance programme.

References


