**ABSTRACT:**

The incidence of candidemia in the neonatal intensive care unit (NICU) is steadily increasing, with an estimated incidence of 1.6 to 9% in very-low-birth-weight infants and 15% in extremely-low-birth-weight infants. Here we report the case of a refractory candidemia by *Candida parapsilosis* successfully treated with caspofungin in a premature infant. The use of lysis centrifugation blood culture permitted to isolate *Candida parapsilosis* and the infant responded well to antifungal treatment, with a prompt improvement of his clinical condition. Caspofungin seems to be a valid option for infants with invasive candidiasis refractory to conventional antifungal therapy.

**Key words:** NICU, Candidiasis, *Candida parapsilosis*, Treatment failure, Caspofungin.

**INTRODUCTION**

The incidence of candidemia in the neonatal intensive care unit (NICU) is steadily increasing, with an estimated incidence of 1.6 to 9% in very-low-birth-weight infants and 15% in extremely-low-birth-weight infants. Although *Candida albicans* is the organism most often associated with serious fungal infections, other *Candida* spp. have emerged as clinically important pathogens associated with opportunistic infections. *Candida parapsilosis* is the second most common yeast species isolated from blood in Europe and South America and it is particularly associated with bloodstream infections in neonates and with catheter-associated candidemia.

Our report describes the case of a refractory candidemia by *Candida parapsilosis* in a premature infant, which was successfully treated with caspofungin.

**CASE REPORT**

In August 2010, a male infant weighing 2.6 kg was delivered at 35 weeks by cesarean section, after a twin pregnancy, and was admitted to our NICU for respiratory distress syndrome. His mother did not refer any disease during pregnancy and her laboratory exams were all normal. After delivery, the infant needed surfactant therapy and nasal respiratory support. Some hours after delivery, the infant required intubation, a new dose of surfactant and endotracheal respiratory support for nearly one month (for ten days in High Frequency Oxygen Ventilation (HFOV)). Chest X-ray at admission showed an image compatible with hyaline membrane disease grade IV. A Peripheral Inserted Central Catheter (PICC) was placed and empiric ampicillin plus gentamicin therapy as well as parenteral nutrition was started. Moreover, fluconazole prophylaxis at a dose of 6 mg/kg/die was begun. Echocardiogram showed a persistent ductus arteriosus Botalli, treated with ibuprofen for three days, and decreased myocardial kinesis, requiring dopamine and dobutamine. The child also underwent a Chest Computed Tomography Scan in order to exclude lung malformations.

Since the admission, surveillance cultures were performed. Twenty days after admission, the child showed
an increased request of $O_2$, hypopreactivity, fever and signs of thrombocytopenia. Peripheral blood cultures (Isolator™ 1.5 microbial tubes - ISO 1.5 Wampole Laboratories, Princeton, NJ, USA) and mannan Candida antigen (Platelia® Candida antigen kits-Bio-Rad Laboratories) were performed. Blood culture was positive for Candida parapsilosis as well as the mannan antigen test. Liposomal amphotericin B (L-AmB, at a dose of 3 mg/kg/die) was started on day 20 and fluconazole was for one day, then decreased at 35 mg/m².

Three days later the infant had a prompt clinical improvement, while thrombocytopenia and hypertransaminasemia resolved after 20 days. After 15 days of caspofungin therapy, the infant was extubated. Blood cultures and mannan antigen at day 10 and 18 of caspofungin treatment were negative. As a consequence, PICC was removed and caspofungin was discontinued, while the child was discharged with oral fluconazole for other 30 days (Table 1).

Pediatric neurologic evaluation was performed using the assessment of spontaneous motility according to Prechtl⁶ at 1 and 3 months, with a normal result in both the assessments. A further neurological assessment was performed at 18 months using the Hammersmith Infant Neurological Examination⁷, obtaining a score within the normal range.

**DISCUSSION**

In our report we describe the case of a premature infant with a bloodstream infection due to Candida parapsilosis, which was successfully treated with caspofungin.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Day 0</th>
<th>Day 20</th>
<th>Day 30</th>
<th>Day 40</th>
<th>Day 58</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood culture</td>
<td>Negative</td>
<td>C. parapsilosis</td>
<td>C. parapsilosis</td>
<td>Negative</td>
<td>Negative</td>
</tr>
<tr>
<td>Stool</td>
<td>Negative</td>
<td>C. parapsilosis</td>
<td>C. parapsilosis</td>
<td>Negative</td>
<td>-</td>
</tr>
<tr>
<td>Gastric aspirate</td>
<td>Negative</td>
<td>C. parapsilosis</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Mannan Antigen</td>
<td>&lt;0.25 (negative)</td>
<td>0.58 (positive)</td>
<td>0.52 (positive)</td>
<td>&lt;0.25 (negative)</td>
<td>&lt;0.25 (negative)</td>
</tr>
<tr>
<td>White blood cell count</td>
<td>25,840</td>
<td>31,580</td>
<td>21,220</td>
<td>12,210</td>
<td>9,200</td>
</tr>
<tr>
<td>(cells/µl)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Quantitative C</td>
<td>1.07</td>
<td>2.28</td>
<td>3.81</td>
<td>1.19</td>
<td>&lt;0.10</td>
</tr>
<tr>
<td>Reactive Protein (mg/dl)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Platelets (/µl)</td>
<td>205,000</td>
<td>16,000</td>
<td>12,000</td>
<td>130,000</td>
<td>544,000</td>
</tr>
<tr>
<td>Antimicrobial Treatment</td>
<td>Imipenem,</td>
<td>Fluconazole</td>
<td>Caspofungin</td>
<td>Caspofungin</td>
<td>Stop therapy</td>
</tr>
<tr>
<td>Amikacin</td>
<td>Ambsome</td>
<td>3 mg/kg</td>
<td>50 mg/m²</td>
<td>35 mg/m²</td>
<td>Removed</td>
</tr>
<tr>
<td>Gentamicin</td>
<td>Flucnazole</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peripheral Central Catheter</td>
<td>Inserted</td>
<td>Removed</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Candida infections can be a life-threatening problem in long-term hospitalized adult and pediatric patients, especially in NICU⁸. Several investigators have described a predominance of Candida albicans and Candida parapsilosis as the etiologic species in neonates, accounting for 40 to 50% of neonatal candidemia each⁹,¹⁰. The identified risk factors for neonatal candidemia are low-birth weight, use of central venous catheters, parenteral nutrition, and broad-spectrum antibiotics¹¹-¹⁴. Our patient had several risk factors for a Candida infection, such as preterm birth, endotracheal intubation, a history of exposure to antibiotics before the onset of candidemia (ampicillin, gentamicin and imipenem therapy), the presence of PICC (18 days before the onset of candidemia). Our patient had severe pneumonia possibly linked either to candidemia infection or to a chronic lung dysplasia without involvement of other solid organs. The gastrointestinal tract seems to be the site most frequently implicated in systemic dissemination¹⁵, as a matter of fact both gastric aspirate and stool research for Candida were positive in our patient. Thus, it is important in Candida infections to verify a possible colonization of the gastrointestinal tract.

Conventional antifungal regimens, according to the Clinical Practice Guidelines for the Management of Candidiasis 2009¹⁶, include amphotericin B and its lipid formulations and fluconazole as first step therapy. Although in vitro resistance to these drugs, especially for Candida albicans and Candida parapsilosis, is extremely low, recent studies and newer testing techniques report resistance rates of 2 to 7%¹⁷. In contrast, clinical treatment failure or persistence of the infection despite treatment with an appropriate dose is well recognized. Persistent infections could occur because an agent fails to reach an infected site in sufficient quantity, or because the patient’s immune status is unable to eliminate the fungus even though its growth has been inhibited and, rarely, because of true drug resistance¹⁸.

Current treatments for refractory invasive fungal infection remain inadequate even in adults, though newer
drugs such as echinocandins have shown encouraging results. The clinical efficacy of caspofungin in neonatal candidemia have been described by several reports. Eun Sun Seo et al\(^\text{19}\) described a case of *Candida albicans* candidemia in a VLBW infant, resistant to fluconazole and amphotericin B liposomal, successfully treated with caspofungin at high dose (4-6 mg/kg/day). They did not report any side effects for this protocol therapy. Nevertheless, one year before, Natale F et al\(^\text{20}\) described a case of refractory *Candida krusei* candidemia in a VLBW preterm infant, resistant to other antifungal therapies, treated with caspofungin at standard dose, and they described acute liver failure due to the antimicrobial treatment. Elevation of liver enzymes and direct bilirubin values during caspofungin therapy have been previously reported in neonates\(^\text{21}\). In January 2009, Filippi et al. published two cases of neonatal liver abscesses due to *Candida albicans* infection effectively treated with caspofungin, the first one treated at a dose of 1 mg/kg daily, which is the lowest efficacious dose reported in literature\(^\text{22}\), the second one with a dose of 5 mg/kg daily, without reporting any side effects. In the same year, Haase et al\(^\text{23}\) described a case of *Candida albicans* sepsitcemia in a preterm infant with congenital ichthyosis successfully treated with a combination therapy of L-AmB and caspofungin. In our report, we decided to introduce caspofungin as a salvage therapy, when clinical condition of the patient seriously deteriorated despite the usage of conventional antifungal drugs, which is similar to the findings of previous studies. Caspofungin treatment for 18 days did not show any increase of liver enzymes during the treatment and/or other side effects. We also think that the removing of PICC was helpful in the resolution of infection.

**CONCLUSIONS**

The caspofungin seems to be a valid option for patients with invasive candidiasis refractory to conventional antifungal therapy.

**CONFLICT OF INTERESTS:**

The Authors declare that they have no conflict of interests.

**REFERENCES**