Case Report

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Francesca Cossovel * , Silvia Nider , Jenny Bua , Elena Ghirigato , Monica Piccoli , Paolo Manzoni , Laura Travan

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Congenital *Candida krusei* Sepsis in an Extremely Preterm Baby: Case Report and Literature Review

Cossovel F. [1,*], Nider S. [1], Bua J. [1], Ghirigato E. [2], Piccoli M. [3], Manzoni P. [4] and Travan L. [1]

[1] Department of Neonatology, Institute for Maternal and Child Health, IRCCS "Burlo Garofolo", Trieste, Italy
[2] Department of Medical, Surgical and Health Sciences, University of Trieste, Trieste, Italy
[3] Department of Obstetrics and Gynecology Institute for Maternal and Child Health, IRCCS Burlo Garofolo, Trieste, Italy
[4] Department of Pediatrics and Neonatology, University Hospital Degli Infermi, Biella, Italy
* Correspondence: francesca.cossovel@burlo.trieste.it; Tel.: +39-0403-785-371

Abstract: A preterm neonate born at 24+5 weeks gestation developed congenital *Candida krusei* sepsis, diagnosed via placental culture, axillary swab, and elevated beta-glucan levels. Despite initial negative blood cultures, early antifungal therapy with amphotericin B and later micafungin was effective. Prompt diagnosis, HeRo monitoring, and tailored therapy ensured a favorable outcome, highlighting the importance of timely management in neonatal fungal infections

Keywords: congenital candida; *Candida krusei*; preterm baby

1. Introduction

Congenital sepsis is a life-threatening condition in neonates, caused by a variety of bacterial and fungal pathogens. Among fungal infections, *Candida* spp. is the most commonly implicated microorganism in neonatal invasive candidiasis [1]. *Candida krusei* is an emerging pathogen in this context, increasingly recognized for its distinct resistance profile and the therapeutic challenges it presents [2].

One of the main difficulties in managing *C. krusei* infections is its intrinsic resistance to fluconazole and its ability to form biofilms, which further complicates treatment [3]. The pathogenesis of congenital *Candida* sepsis can involve either vertical transmission from the mother or horizontal transmission after birth. Vertical transmission occurs when *Candida* spp. ascends from the vaginal canal or crosses the placenta, leading to intrauterine infection [4]. This risk is particularly high in preterm infants, whose underdeveloped immune defenses make them highly susceptible to invasive fungal infections.

Diagnosing congenital *Candida* sepsis remains a significant challenge. Mothers may be asymptomatic or exhibit non-specific signs, and typical neonatal sepsis workups focus primarily on bacterial pathogens. Consequently, fungal infections may go unrecognized, leading to delays in appropriate antifungal treatment.

2. Case Presentation

A female baby was born at 24+5 weeks of gestation via spontaneous vaginal delivery due to unstoppable labor. Four days before the mother experienced severe abdominal pain and after MRI the hypothesis of pyelonephritis was proposed; she was treated with antibiotic therapy (piperacillin-tazobactam, meropenem, vancomycin). Steroids as prophylaxis for respiratory distress syndrome (RDS) and magnesium sulfate were administered. Two days after delivery the mother was eventually diagnosed a phlegmonous appendicitis.

At birth, the neonate showed good adaptation (Apgar score 8-9) and was referred to the Neonatal Intensive Care Unit on non-invasive ventilation. Approximately four hours after birth, intratracheal surfactant was administered using the IN-REC-SUR-E technique (intubation-

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recruitment-surfactant-extubation) due to respiratory distress with need of FiO2 >0.3, resulting in significant clinical improvement. Antibiotic therapy with ampicillin and tobramycin was started, but discontinued after 36 hours after negative blood culture result. Fluconazole prophylaxis 3 mg/kg every 72 hours was administered due to the placement of an umbilical venous catheter in an extremely low birth weight infant (ELBWI). On day-of-life (dol) 3, we were informed by the Microbiology Unit that *Candida krusei* was growing from the mother's placenta culture. In the light of the extremely high risk condition of this newborn, an axillary skin swab was done on the baby and turned out to be positive on dol 4.

On dol 5, persistent high HeRO was detected together to a decreased reactivity. However, the neonate continued showing stable vital signs, negative reactive protein C and procalcitonin, and stable respiratory conditions under non-invasive ventilation. Given the concomitant consistent positivity for *Candida krusei* of the cultures from both mother's placenta and neonate's axillary skin, systemic antifungal therapy using amphotericin B was initiated together with empiric oxacillin and tobramycin . A sample for Beta-glucan level was collected: the result was strikingly positive (1000 pg/ml; normal values 7-10), while the complete blood count, inflammatory markers remained negative; cultures from blood, catheter tip and cerebrospinal fluid were negative as well.

Considering the high level of Beta-glucan, on dol 8 a another blood culture was repeated and this time it yielded positivity for *Candida krusei* after only 23 hours since incubation. Amphotericin B was therefore replaced after 48 hours with Micafungin, an antifungal agent that more effectively penetrates both old- and young- biofilms [1]. This antifungal regimen was maintained for 21 days, being discontinued after obtaining two consecutively negative blood cultures together with a normalization of beta-glucan levels. The neonate maintained good general conditions throughout the course of the NICU stay, and continued requiring only non-invasive respiratory support.

During antifungal therapy, the central catheter was replaced 48 hours after the initiation of the treatment.

During hospitalization, end-organ fungal dissemination workup was performed weekly to rule out possible sanctuaries, and this included repeated ophthalmologic examinations, abdominal and cranial ultrasounds, all of which remained normal. At 38 weeks of corrected gestational age, a brain MRI was performed and was normal for gestational age.

The infant was weaned off the respiratory support on dol 51 and achieved full feeding autonomy on dol 85, being thereafter discharged in good general conditions on dol 91.

3. Discussion

Congenital candidiasis is a rare yet severe complication in neonatology, particularly affecting extremely preterm infants with underdeveloped immune defenses and disrupted skin and mucosal barriers. Among the Candida species, *Candida krusei* poses a notable clinical challenge due to its intrinsic resistance to fluconazole and its tendency to form biofilms on medical devices and epithelial surfaces [5]. Although *Candida albicans* remains the most frequently isolated species in congenital infections, an increasing proportion of neonatal fungal sepsis cases are attributed to non-albicans species, particularly in settings with widespread antifungal prophylaxis [6].

4. Epidemiology and Transmission

Vertical transmission of Candida can occur in utero, intrapartum, or postnatally. In the case of in utero transmission, fungal organisms may ascend from the maternal genital tract following premature rupture of membranes or via hematogenous spread from the mother through the placenta [7]. C. *krusei* colonization of the maternal genital tract is uncommon but has been reported, and it is often associated with prior antifungal exposure that selects for resistant strains [8]. While intrapartum transmission is more frequently described for Candida albicans, our case suggests a probable congenital (in utero) transmission route, supported by prolonged maternal antibiotic therapy, clinical presentation within the first 24 hours of life, skin colonization at birth, and absence of postnatal exposure.

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The rarity of C. *krusei* as a congenital pathogen, combined with its resistance profile, elevates the importance of early diagnosis and targeted treatment. Prompt initiation of therapy is critical, as untreated or delayed fungal infections in neonates are associated with significant morbidity, including neurodevelopmental impairment, bronchopulmonary dysplasia, and mortality [9].

5. Clinical Presentation and Role of HeRO Monitoring

Congenital candidiasis may present as localized cutaneous disease or progress to systemic involvement, particularly in premature infants. Typical clinical signs include respiratory distress, apnea, hypotonia, poor feeding, and skin lesions such as diffuse erythematous rashes or pustules. However, these manifestations are non-specific and often indistinguishable from bacterial sepsis or other neonatal conditions [10].

In our case, the early use of HeRO (Heart Rate Observation) monitoring provided a critical diagnostic adjunct. This system continuously evaluates heart rate variability and deceleration events to generate a predictive index of neonatal sepsis risk. Several studies have demonstrated that HeRO monitoring enables earlier detection of sepsis-related physiologic changes, often before clinical deterioration becomes apparent [11]. In this instance, the elevated HeRO score preceded overt symptoms, prompting timely laboratory workup and empirical antifungal therapy. This suggests a promising role for advanced physiologic monitoring in guiding early intervention, particularly when traditional clinical signs are subtle or delayed.

6. Diagnostic Challenges and Utility of β-D-Glucan

Confirming the diagnosis of neonatal fungal infection is fraught with difficulty. Blood cultures, though considered the gold standard, have limited sensitivity, with false negatives occurring in up to 50% of neonatal cases due to intermittent fungemia and low circulating organism load [12]. Moreover, the slow growth kinetics of fungi often delay confirmation, underscoring the need for more rapid and sensitive diagnostic tools.

In this context, (1→3)-β-D-glucan (BDG), a polysaccharide component of most fungal cell walls, has emerged as a useful biomarker. BDG assays offer a non-culture-based method to detect invasive fungal infections and have been validated in adult and pediatric critical care populations [13]. However, data on their application in neonates remain limited, and interpretation must account for age-specific confounders, including exposure to intravenous immunoglobulin, blood products, and mucosal colonization.

Despite these limitations, our patient exhibited markedly elevated BDG levels in the absence of other inflammatory markers or bacterial growth. This prompted preemptive initiation of antifungal therapy, which was justified by positive skin cultures for C. krusei. Notably, serial BDG monitoring revealed a downward trend that paralleled clinical improvement, suggesting its potential utility not only in diagnosis but also in monitoring treatment response [14]. Recent studies propose that rising or persistently elevated BDG levels in neonates should raise concern for ongoing fungal infection and prompt reevaluation of therapy [15].

7. Therapeutic Considerations and Antifungal Strategy

Management of congenital C. *krusei* infection necessitates prompt initiation of systemic antifungal therapy with agents active against this species. Amphotericin B deoxycholate has long been the cornerstone of neonatal antifungal therapy due to its broad-spectrum activity and fungicidal effects. However, its nephrotoxicity, electrolyte imbalances, and infusion-related adverse events pose significant risks, particularly in preterm neonates with fragile renal function and fluid balance [16].

In our case, treatment was initiated with amphotericin B, but due more effectively penetration both old- and young- biofilms, a transition to micafungin was undertaken. Echinocandins, including micafungin and caspofungin, inhibit β-(1,3)-D-glucan synthase, impairing fungal cell wall synthesis. They have demonstrated excellent efficacy against C. krusei, and unlike amphotericin B, possess

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activity against biofilm-embedded fungal cells, which is particularly relevant in the context of central lines and endovascular infection [17].

While echinocandin use in neonates has historically been limited due to sparse pharmacokinetic data, recent studies support their safety and efficacy when appropriately dosed. High-dose micafungin regimens have been evaluated in neonatal trials, showing favorable therapeutic outcomes without significant hepatotoxicity or hematologic toxicity [18]. Our patient responded well to micafungin, with resolution of signs of sepsis and normalization of BDG levels.

8. Multidisciplinary Management and Outcome

Successful management of neonatal fungal infections, especially those caused by rare and resistant organisms, requires close collaboration among neonatologists, infectious disease specialists, microbiologists, and pharmacists. In this case, the decision-making process was facilitated by prompt laboratory communication, real-time monitoring, and a proactive approach to diagnostic and therapeutic escalation. Multidisciplinary discussions guided antifungal selection, monitoring of renal and hepatic function, and decisions about treatment duration and follow-up.

Despite the traditionally poor prognosis associated with C. *krusei* and other non-albicans species in preterm infants, our patient had a favorable outcome. This likely reflects a combination of factors: extremely early detection, appropriate therapeutic adjustments, and consistent follow-up. A growing body of literature supports the notion that early, aggressive intervention in fungal infections—particularly in high-risk neonates—can significantly improve outcomes [19].

9. Implications for Practice and Future Directions

This case contributes to a limited but growing body of evidence on congenital C. *krusei* infections. It reinforces the need for vigilance in recognizing early signs of sepsis in neonates, particularly when standard bacterial cultures are negative. BDG testing, although not yet standard in all neonatal intensive care units, represents a promising adjunct for early detection and therapy guidance.

There is also a clear need for additional research on antifungal pharmacodynamics and pharmacokinetics in neonates, particularly for newer agents such as echinocandins and azoles like voriconazole or isavuconazole. Expanding clinical experience with echinocandins, supported by prospective multicenter trials, could help standardize dosing protocols and safety monitoring in this vulnerable population [20].

Finally, this case underscores the importance of maternal screening, especially in high-risk pregnancies with prolonged rupture of membranes or prior antifungal exposure. While routine screening for fungal colonization is not currently recommended, targeted screening in selected scenarios may warrant reconsideration, especially in settings where resistant Candida species are prevalent.

10. Conclusion

To our knowledge, this is the first reported case of congenital, vertically transmitted *Candida krusei* infection in an extremely preterm neonate, successfully managed with early antifungal therapy guided by advanced monitoring and biomarker evaluation. It highlights the diagnostic challenges of neonatal fungal sepsis, the therapeutic potential of echinocandins in this setting, and the vital role of multidisciplinary collaboration. Our experience supports further incorporation of non-culture diagnostics like BDG and expanded use of real-time physiologic monitoring to improve early recognition and outcomes in neonatal fungal infections.

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Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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