Systemic candidiasis caused by *Candida kefyr* in a neonate: Case report.

Stefan Weichert	extsuperscript{1*}, Konrad Reinshagen	extsuperscript{2}, Katrin Zahn	extsuperscript{2}, Gernot Geginat	extsuperscript{3}, Annebärbel Dietz	extsuperscript{3}, Anna Kristina Kilian	extsuperscript{4}, Horst Schroten	extsuperscript{1}, Tobias Tenenbaum	extsuperscript{1}

	extsuperscript{1}Pediatric Infectious Diseases, University Children’s Hospital Mannheim, Heidelberg University, Germany

	extsuperscript{2}Department of Pediatric Surgery, University Hospital Mannheim, Heidelberg University, Germany

	extsuperscript{3}Institute for Medical Microbiology and Hygiene, Medical Faculty Mannheim, Heidelberg University, Germany

	extsuperscript{4}Department of Clinical Radiology and Nuclear Medicine, Medical Faculty Mannheim, Heidelberg University, Germany

*Corresponding Author:

Stefan Weichert, MD

Pediatric Infectious Diseases

University Children’s Hospital Mannheim, Heidelberg University

Theodor-Kutzer-Ufer 1-3, 68167 Mannheim, Germany

phone +49 621 383 2324

fax +49 621 383 3818

e-mail: Stefan.Weichert@medma.uni-heidelberg.de

**Key words**

Children; candidiasis; non-\textit{albicans} *Candida* species; urinary tract infection.
**Background**

Systemic *Candida* infections in children are of major concern in preterm infants, neonates with risk factors and in immunocompromised children [1, 2]. Further risk factors such as use of central venous catheters, longer use of broad spectrum antibiotics and use of parenteral nutrition contribute as well [2]. Over the last decade non-albicans *Candida* species are emerging as causative pathogens for systemic *Candida* infections in children [3]. Here, we report of a systemic *Candida kefyr* infection in a term neonate.

**Case Presentation**

After an uneventful birth anal atresia was observed and a vesico-ureteral-reflux (VUR) grade V was detected by cystography. Renal agenesis on the left side was already diagnosed antenatally. The first surgical procedure, creating a protective colostoma, on day 2 was uneventful. The child was treated with intravenous cefotaxime for 10 days and was put hereafter on cefixime prophylaxis. On day 21 the patient developed an urosepsis caused by *Enterococcus faecalis* which was treated with piperacillin according to the antibiogramm. After initial improvement the child deteriorated again 10 days after initiation of antibiotic treatment. Antibiotic therapy was changed to imipenem, gentamicin and vancomycin. A lumbar puncture showed normal results, but the urine analysis revealed *Candida kefyr* in a significant number (10⁶ CFU/mL). Blood culture results turned out to be negative.

Primary isolation was performed on *Candida Chrom™* Agar (BD) which yielded growth of large rough pink colonies. Identification was performed by biochemical identification using the API 20 C AUX (BioMerieux) biochemical identification panel which yielded excellent identification (probability > 99.9%, profile number 7220300031). This biochemical result was
confirmed by sequencing of the internal transcribed spacer (ITS) regions using primer pairs ITS 1 and ITS-4 (ITS1: 5-TCCGTAGGTGAACCTGCGG-3, ITS4: 5-T CCTCCGCTTATTGATATGC-3 and V9D: 5-TTAAGTCCCTGCCCCTTTGTA-3 and LS266: 5-GCATTCCCAAACAAACTCGACTC-3, respectively) [6]. Both primers span the complete ITS1, 5.8S, and ITS2 regions. A databank search of the amplified sequences revealed 99% and 100% homology with the ITS region from *Kluyveromyces marxianus* which represents the teleomorph form of *Candida kefyr*. Susceptibility testing against fluconazole, amphotericin B (AMB), and caspofungin was performed by ellipsometer test (“E-test”) and showed a minimal inhibitory concentrations (MIC) of 0.25 µg, 0.047 µg, and 0.25 µg, respectively. Species-specific susceptibility breakpoints for *Candida kefyr* have neither been published by the clinical laboratory institute (CLSI) nor by the European committee on antimicrobial susceptibility testing (EUCAST). Therefore we used the EUCAST breakpoints for *Candida albicans* for the interpretation of the MICs obtained with the *Candida kefyr* isolate. According to these breakpoints the isolate was susceptible to all three antifungal agents tested. Systemic antifungal therapy was initiated with liposomal AMB which was accompanied by rapid decrease of renal function. After the availability of susceptibility data antifungal treatment was changed to fluconazole. Although the child improved clinically, a significant candiduria persisted and renal ultrasound showed persistent signs of *Candida* pyelonephritis (Figure 1). An initial contrast enema did not show a connecting fistula between bladder and rectum. But due to the clinical course a fistula was suspected and surgical repair of the anorectal atresia was performed. While undergoing surgery (creating a neo-rectum) a recto-vesical fistula was found and subsequently was resected. Since high grade reflux was prevalent in our patient AMB (1µg/mL) was successfully instilled into the child’s bladder twice daily over 7 days. The child recovered completely under systemic fluconazole therapy (8 mg/kg/day) over 3 months.
Discussion

The high burden of systemic *Candida* infection in children with risk factors led to a significant increase in fluconazole use over the last decades, which was accompanied by an increased incidence of non-*albicans* *Candida* species. Interestingly, susceptibility of the main causative pathogen *Candida albicans* to fluconazole remains stable [3, 4]. In contrast, a recent study showed only 82% susceptibility of all isolated non-*albicans* *Candida* species to fluconazole [3]. Data regarding susceptibilities of antifungal agents against *Candida kefyr* are limited. The isolated *Candida kefyr* from our patient was fully sensitive to fluconazole. In a 10.5-year world-wide surveillance study resistance to fluconazole ranged from 3.3% in the first 4 study years to 1.7% for all *Candida kefyr* isolates in the last 3 study-years [4]. So far, good susceptibilities of AMB against most non-*albicans* *Candida* species were shown, although country specific differences were observed [4, 6, 7]. According to a study from Pfaller et al. the susceptibility of *Candida kefyr* to amphotericin B appears to be quite low (4 of 10 isolates were susceptible at ≤1 µg/ml) [8]. A study conducted in Germany involving mainly adult patients showed an increased MIC of AMB for 9% of all *Candida kefyr* isolates [9], whereas a more recent study from Spain showed no increased MIC of AMB [7].

Up to now *Candida kefyr* is considered as not pathogenic to healthy individuals, but has been discussed as an emerging pathogen in patients with risk factors. Pediatric data are sparse, reporting isolation of *Candida kefyr* from 1.8% to 4% of all isolated *Candida* species from mainly preterm and low birth weight neonates [10, 11]. In adults *Candida kefyr* has been reported to cause systemic *Candida* infection in patients with neutropenic leukemia [12] and in a woman with underlying heart disease [13]. Very recently *Candida kefyr* was described as a pathogen causing invasive fungal enteritis in a patient with underlying haematological disease following bone marrow transplantation [14]. Of note, Sendid et al. report a twofold detection rate of *Candida kefyr* isolates from adult patients in oncohematology wards.
compared to patients in other wards (4.8% vs. 1.9%) [15]. Up to now, it is not known why *Candida kefyr* is found more often in these patients. Induced selection of *Candida kefyr* following antimicrobial therapy or prophylaxis is discussed, as well as factors that might influence gastrointestinal homeostasis in favour of *Candida kefyr* [15]. Furthermore, as *Candida kefyr* is commonly found in dairy products, dietary habits might influence or promote colonization and subsequent infection in patients as well [16].

**Conclusion**

As clinicians are confronted with an increasing number of non-*albicans* *Candida* species, knowledge about these pathogens and their sensitivities is of major importance.
Consent

Written informed consent was obtained from the patient for publication of this case report and any accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

SW took care of the patient and drafted and wrote the manuscript. KR took care of the patient and contributed to the draft of the manuscript. KZ took care of the patient and helped to the draft of the manuscript. GG performed and interpreted all mentioned microbiological methods and revised the manuscript. AD performed and confirmed identification of the mentioned pathogen. AK performed the ultrasound imaging studies and contributed to the draft of the manuscript. HS contributed in coordinating the manuscript and to the draft of the manuscript. TT took care of the patient and coordinated and edited the manuscript. All authors have read the manuscript and approved its final version.
References


Figure 1  **Renal ultrasound.** Hyperechogenic renal parenchyma due to persistent candida pyelonephritis and massive pelviectasis.