**Candida utilis: a rare cause of septicemia in children**

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**Abstract**

*Candida utilis* is an emerging fungal pathogen in blood. The main aim of this study was to describe the prevalence, methods of speciation and antifungal susceptibility of *Candida utilis* at a tertiary care centre.

**Methods.** This was a retrospective study carried out at a tertiary care centre in South India. Over a period of 1 year, three *Candida utilis* were isolated from blood culture identified by MALDI–TOF MS Version 3.2 and were confirmed by ITS sequencing. Susceptibility testing was carried out by micro broth dilution.

**Results.** All three patients had a common risk factor of prolonged ICU stay but the source of infection could not be identified. *Candida utilis* isolates were identified by MALDI–TOF and confirmed by ITS sequencing. They were pansusceptible to all tested antifungal drugs. Among these, two patients who were treated in hospital had good clinical outcome and response to antifungal drugs. A third patient was lost to follow up.

**Conclusion.** *Candida utilis* was predominantly seen between 0–3 month olds. Conventional methods of speciation were unable to identify *C. utilis* to species level. Rapid identification was done by MALDI–TOF MS and confirmed by sequencing. Rapid identification leads to prompt treatment and favours a good clinical outcome.

**INTRODUCTION**

*Candida* spp are an increasingly frequent cause of sepsis in critically ill patients, cause substantial morbidity and mortality and account for 10–15% of health-care associated infections [1]. The prevalence of candidemia in India is 6–18% and there is a upward trend in non-albicans *Candida* spp causing blood stream infections. A study from Northeast India demonstrated a prevalence of 6% candidemia with a predominance of non-albicans *Candida* species of 70% [2]. *Candida utilis* is a rare cause of candidemia [3]. Its teleomorphic form, *Cyberlindera jadinii*, is used in the food industry as a yeast additive. *Candida utilis* fungaemia has mainly been reported in immunocompromised patients, neonates and following surgical intervention [4].

Previous case reports show a low mortality rate of *Candida utilis* and susceptibility to all antifungal drugs tested [4]. Matrix-Assisted Laser Desorption–Ionization Time Of Flight Mass Spectrometry (MALDI–TOF MS) can result in rapid detection and differentiation of yeasts from blood culture specimens [5]. Sequencing of the Internal Transcribed Spacer (ITS) region can also provide a quick diagnosis, with potential for identifying drug resistance in the same run, however it is expensive and technically difficult [6].

In the case of emerging pathogens, a systematic monitoring of the trends of incidence, species distribution and antifungal susceptibility profile is needed and provides learning lessons in [7, 8].

**METHODS**

This was a retrospective case series carried out at a tertiary care centre. Ethics approval was obtained from the Institutional Review Board (IRB MinNo.13343). We reviewed the electronic patient records for demographic and clinical details of all patients with *Candida utilis* isolated from blood cultures at the Department of Clinical Microbiology from...
June 2019 to June 2020. As per standard protocol, these specimens were inoculated into BacT/Alert (BioMérieux, France). Blood cultures that flagged positive underwent a Gram-stain and if yeast-like organisms were identified in broth, were inoculated onto Sabouraud's Dextrose Agar. Identification was performed by MALDI–TOF MS (BioMérieux, Version 3.2, France), CHROMagar Candida, germ tube test and confirmed by ITS sequencing. Susceptibility testing was carried out by the micro broth dilution method (CLSI M27-A3, 2008 and M60 Ed1 2017) with quality controls ATCC 22019 Candida parapsilosis and ATCC 6258 Candida krusei.

We identified three cases of Candida utilis causing septicemia.

**CASE 1**
A 10 day old neonate (Table 1) was referred from another hospital with complaints of failure to cry at birth and was treated for neonatal seizures in intensive care unit (ICU) for 10 days. On examination the baby was lethargic, floppy, anterior fontanelle flat and reflexes not elicitable. The random blood sugar was 49 mg dl⁻¹. Blood culture done on day 1 of admission grew Candida spp within a day of incubation. It was identified as Candida utilis by MALDI-TOF MS. Sequencing confirmed this isolate as Cyberlindera jadinii. Antifungal susceptibility was carried out with amphotericin B, fluconazole, voriconazole, itraconazole, anidulafungin, posaconazole, 5-flucytosine and demonstrated a pansusceptible strain (Table 2). A diagnosis of hypoxic ischaemic encephalopathy stage three was made, with septic shock. Despite advice on the need for further intensive care, parents were unwilling to admit the baby. The child was discharged against medical advice.

**CASE 2**
A 4 day old baby (Table 1) was referred from another hospital and admitted at the ICU with complaints of poor feeding, lethargy and two episodes of seizures of unknown aetiology since day 2 of life. Antenatal history elicited high grade fever in the third month of gestation, which was not associated with a rash. A routine ultrasound scan in the third trimester had also revealed severe oligohydramnios. At 39 weeks of gestation baby was delivered by emergency Lower Segment Caesarean Section (LSCS) in view of cord around neck. Blood culture was done on day 2 of admission. The blood culture grew Candida utilis and Candida tropicalis, identified by MALDI-TOF MS. Antifungal susceptibility was carried out with amphotericin B, fluconazole, voriconazole, itraconazole, anidulafungin, posaconazole, 5-flucytosine and demonstrated a pansusceptible Candida utilis strain (Table 2). Sequencing confirmed this isolate as Cyberlindera jadinii. I/V amphotericin B was started and given for 21 days. Baby was stable at the time of discharge.

**CASE 3**
A 2 month 20 day old baby (Table 1) was admitted with complaints of interrupted feeding for 1 month, cough and

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**Table 1. Summary of case presentation**

| S. no | Age        | Outcome | Final diagnosis                          | Comorbidities                           | Concomitant infection | Treatment | No. of isolates, Source and day of isolation after admission | ICU stay |
|-------|------------|---------|------------------------------------------|------------------------------------------|-----------------------|-----------|-------------------------------------------------------------|----------|
| 1     | 10 days    | DAMA    | Hypoxemic ischaemic encephalopathy       | Neonatal seizure                        | Nil                   | DAMA      | 1, Blood, Day-1                                             | YES      |
| 2     | 4 days     | Well at discharge | Early onset neonatal sepsis, Transient SIADH | Oligohydroamnios, LSCS- cord around neck, neonatal seizures, hypocalcemia | Candida tropicalis -Blood | Inj Amp B –21 days | 1, Blood, Day –2                                             | YES      |
| 3     | 2 months and 20 days | Well at discharge | CCF, PDA, ASD, Infective endocarditis | Jaundice, late onset meningitis | CONS - Blood | Inj Amp B+flucytosine-6Ws followed by Oral fluconazole -lifelong | 6, Blood, Day –2 | YES |

**Table 2. Antifungal susceptibility of three isolates**

| Drug | Amphotericin B | Fluconazole | Voriconazole | Itraconazole | Posaconazole | Anidulafungin | 5-Flucytosine |
|------|---------------|-------------|--------------|--------------|--------------|---------------|--------------|
| Testing range (μg ml⁻¹) | 0.03–16 | 0.12–64 | 0.03–16 | 0.03–16 | 0.03–16 | 0.002–32 | 0.12–64 |
| Case 1 | 0.06 | 1.0 | 0.03 | 0.06 | 0.06 | 0.002 | 0.12 |
| Case 2 | 0.06 | 0.5 | 0.03 | 0.06 | 0.03 | 0.002 | 0.12 |
| Case 3 | 0.06 | 1.0 | 0.03 | 0.12 | 0.12 | 0.002 | 0.12 |
Cold for 1 week and rapid breathing for 1 day. Antenatal history was uneventful. Baby was delivered by LSCS, had history of jaundice on day 4 and received phototherapy for 2 days. On day 30 of life the baby developed poor feeding and lethargy, and was diagnosed as late onset neonatal meningitis in a local hospital. The CSF culture grew *Pseudomonas* species and thus I/V meropenam and vancomycin were given and continued for 21 days. In view of interrupted feeding, an echocardiogram was done and demonstrated an atrial septal defect, patent ductus arteriosus and vegetations on the tricuspid valve leaflets. A diagnosis of infective endocarditis and subsequently congestive cardiac failure (CCF) was made. Blood culture done on day 4 of admission grew Coagulase Negative *Staphylococcus aureus* (CONS) and I/V vancomycin was started. Five subsequent blood cultures taken on sixth, ninth (two cultures), 10th and 15th day of admission grew *C. utilis*. Antifungal susceptibility was carried out with amphotericin B, fluconazole, voriconzole, itraconazole, anidulafungin, posaconazole, 5-flucytosine and demonstrated a pansusceptible strain (Table 2). Sequencing confirmed this isolate as *Cyberlindera jadinii*. Surgical removal of the vegetation was advised, however deferred due to the high risk associated with it and a medical management was planned instead. Amphotericin B (IV) and flucytosine was given for 6 weeks followed by advice on lifelong oral fluconazole. The parents were counselled about the need for long term treatment and follow up which was planned to continue at a local hospital.

**DISCUSSION**

Over a period of 1 year, a total of 221 *Candida spp* were isolated from blood cultures, of which 173 were non-albicans *Candida spp*. MALDI-TOF MS identified three *C. utilis* which accounts for 1.5%. All patients were in the age group 0–3 months and referred from another hospital. These babies had a history of poor feeding, neonatal seizures and lethargy requiring hospital admissions and investigations. Common predisposing factors among these three babies were intensive care admissions and previous use of antimicrobials. Previously reported *Candida utilis* cases have had the same risk factors [8]. These isolates, though unidentified by conventional methodology (Table 3), were detected by MALDI-TOF MS facilitating early diagnosis and treatment. Sequencing of the Internal Transcribed Spacer region also confirmed the diagnosis as *Cyberlindera jadinii*, the teleomorphic stage of *Candida utilis* (Table 1). Antifungal susceptibility of all isolates revealed wild-type isolates, according to the reported epidemiology cut-off values and as previously described, the MICs of all drugs tested here, with the exception of fluconazole (Table 2), demonstrated MIC values corresponding to the least drug concentration tested, which is similar to previous data [5, 9]. A concomitant infection of *Candida tropicalis* was observed in one patient and CONS in another.

Patients admitted to ICU often harbour *Candida* species, as did the three babies in the current study. One of these babies had fungal endocarditis as a complication.

| Sl no | Year | Authors                        | Title                                                  | Country | Total no: of cases |
|-------|------|--------------------------------|--------------------------------------------------------|---------|-------------------|
| 1     | 2011 | Lukić-Grič et al. [4]          | *Candida utilis* candidaemia in neonatal patients      | Croatia | 3 cases           |
| 2     | 2014 | Scoppettuolo et al. [10]        | *Candida utilis* catheter-related bloodstream infection | Rome    | 1 case; 66 year old |
| 3     | 2016 | Shivadasan et al. [8]           | *Candida utilis* causing neonatal Candidemia           | India   | 1 case            |
| 4     | 2018 | Treguer et al. [9]              | *Cyberlindera jadinii* (teleomorph *Candida utilis*) | France  | 1 case; 21 year old |
| 5     | 1993 | Bougnoux et al. [11]            | Resolutive *Candida utilis* fungemia in a nonneutropenic patient | France  | 1 case; 68 year old |
| 6     | 1988 | Alsina et al. [12]              | Cather-associated *Candida utilis* fungemia in a patient with acquired immunodeficiency syndrome: species verification with a molecular probe | Tennessee | 1; 5 year old     |
of therapy was prolonged in the presence of infective endocarditis. Despite this, identification and prompt treatment led to a good outcome.

We present what we believed to be the first case series of Candida utilis in India. Table 4 describes the literature for previously reported Candida utilis. We highlight the importance of rapid diagnostics for the detection of new and emerging fungi.

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Author contributions
S.T.S.: data curation, investigation, writing, original draft preparation. M.M.N.: conceptualization, writing, reviewing, Supervision Arul Premanand: investigation, reviewing. A.C., investigation, reviewing. R.D.S.: investigation, reviewing, supervision. J.S.M.: conceptualization, writing, visualisation, reviewing, supervision.

Conflicts of interest
The authors declare that there are no conflicts of interest.

Ethical statement
IRB No 13343. Consent to publish was obtained.

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