Trichosporon Fungemia in a Tertiary Pediatric Hospital: A Case Series

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ABSTRACT

Background: *Trichosporon asahii* is an opportunistic fungal pathogen increasingly recognized in immunocompromised patients, including children. Although rare, *T. asahii* fungemia carries significant morbidity and mortality, particularly in those with hematologic malignancies or prolonged immunosuppression.

Objectives: This case series aimed to describe the clinical characteristics, risk factors, microbiological profiles, and treatment outcomes of pediatric patients diagnosed with *T. asahii* fungemia over a 13-year period at a tertiary care children's hospital.

Methods: A retrospective review was conducted of all cases of *T. asahii* fungemia diagnosed between 2010 and 2023 in patients under 18 years of age. Data collected included patient demographics, underlying conditions, immunosuppressive status, presence of central venous catheters (CVCs), neutrophil counts, antifungal susceptibility profiles, treatments administered, and clinical outcomes.

Results: Most cases occurred in immunocompromised patients, mainly those with neutropenia and a CVC. Half of the patients died. *T. asahii* isolates were generally susceptible to voriconazole and other azoles but showed partial resistance to amphotericin B. Clinical improvement was mainly associated with early antifungal treatment (particularly voriconazole) and supportive measures, including immunosuppression reduction, neutrophil recovery, and CVC removal.

Conclusions: Voriconazole appears to be a reasonable empiric treatment option for pediatric *T. asahii* fungemia, a condition associated with a very poor prognosis. Successful management may also require early recognition of risk factors and interventions aimed at reversing immunosuppression and eliminating potential sources of infection such as CVCs.

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KEY WORDS: central venous catheter (CVC), children, hematologic disorders and malignancies, *Trichosporon* fungemia, voriconazole

*T*richosporon species are yeast-like fungi, mostly causing a superficial infection. However, in immunocompromised patients they may act as an important and opportunistic pathogen, causing an invasive and disseminated disease with significant morbidity and mortality. The main pathogenic species are *T. asahii* and *T. cutaneum* [1]. Most cases occur in oncologic patients, especially neutropenic. Other risk factors include the presence of central venous catheters (CVC), prosthetic valve surgery, organ transplantation, peritoneal dialysis, low birth weight premature infants, and critically ill patients treated with broad spectrum antibiotics [2]. In addition, antifungal prophylaxis with agents lacking anti-*Trichosporon* activity (e.g., echinocandins) may result in breakthrough infection [3]. The clinical presentation includes fever and neutropenia with possible involvement of different organs, mostly but not limited to the lungs, kidneys and skin.

Data on *Trichosporon* fungemia in children is scarce. There are several studies, mostly case series, which review *Trichosporonosis* in children, the majority of which focus on children with hematological disorders and malignancies. Our large tertiary care hospital is a leading pediatric medical center with an active hematology–oncology department (approximately 1200 hospitalizations per year) and both solid organ and hematopoietic stem cell transplantation units. Our objective was to describe the incidence as well as clinical and microbiologic aspects of *Trichosporon* fungemia at our hospital, highlighting risk factors and local antimicrobial susceptibility patterns.

PATIENTS AND METHODS

We evaluated the cases of all patients with positive blood cultures for *Trichosporon species* between January 2010 and March 2023 at Schneider Children's Medical Center. All positive blood cultures were processed using BAC-

TEC™ pediatric culture vials (Becton Dickinson, USA). Final fungal identification was performed with the Vitek2 automated system (bioMérieux SA, France), and antifungal susceptibility testing was conducted using either the Vitek2 (bioMérieux SA) or Sensititre™ (Thermo Fisher Scientific, USA) automated platforms.

An invasive fungal infection was defined as *Trichosporon* fungemia, positive cultures from other normally sterile sites, and radiological abnormalities consistent with an infectious process [4]. Cases with a sole positive culture from a site other than the blood (e.g., sputum, urine, ear) were excluded, as they were considered colonization and were not associated with a clinical disease in the patient. Demographic, clinical course, and microbiologic data were recorded for each case. Antifungal susceptibility profiles were based on the Clinical and Laboratory Standards Institute [5].

RESULTS

Between January 2010 and March 2023, a total of four patients were identified with positive blood cultures for *Trichosporon* species. *Trichosporon asahii* was isolated in all four cases [Table 1].

PATIENT 1

Patient 1 was a 3-year-old girl with a history of bone marrow transplantation for aplastic anemia one month prior to the infection. She was receiving cyclosporine for graft-versus-host disease prophylaxis and had an implanted port-a-cath. Her past treatments included corticosteroids and broad-spectrum antibiotics for a previous bacterial infection. During hospitalization, she presented with febrile neutropenia and respiratory distress, with bilateral pulmonary infiltrates on chest X-ray and evidence of diffuse fungal infection on bronchoscopy. She was treated with intravenous and inhaled voriconazole for 30 days in addition to central venous catheter removal. She achieved full recovery. The fungemia persisted for 11 days.

PATIENT 2

Patient 2 was also a 3-year-old girl, born prematurely at 31 weeks of gestation. She presented with short bowel syndrome following necrotizing enterocolitis. She was dependent on total parenteral nutrition (TPN) via a Hickman line. She presented with fever and received broad-spectrum antibiotics prior to the diagnosis of *Trichosporon* fungemia. She was neither neutropenic nor known to be immunocompromised. Following Hickman line removal, she was treated with intravenous fluconazole for 4 days, followed by two additional weeks of oral therapy, leading to complete recovery.

PATIENT 3

Patient 3 was a 2-month-old boy with infantile acute myeloid leukemia, carrying a port-a-cath and receiving chemotherapy and corticosteroids, as well as TPN. He presented with prolonged fever and neutropenia and was treated with broad-spectrum antibiotics. He was subsequently diagnosed with invasive *Trichosporonosis*, involving fungemia and disseminated infection of the lungs, liver, and spleen, confirmed by imaging and positive cultures from blood, abdominal fluid, urine, and liver biopsy. Treatment included voriconazole in combination with micafungin (later switched to anidulafungin) and liposomal amphotericin B. Despite aggressive antifungal therapy, the patient developed severe sepsis and died.

PATIENT 4

Patient 4 was an 18-year-old female with surgically repaired tetralogy of Fallot and a prosthetic pulmonary valve, carrying a peripherally inserted central catheter (PICC). She presented with fever and seizures, with a normal neutrophil count. She was initially admitted to the cardiac intensive care unit with *Streptococcus mitis* infective endocarditis (IE) and right ventricular dysfunction. She underwent surgical graft replacement and subsequently developed *Trichosporon* fungemia documented in three cultures. Echocardiography and chest computed tomography did not reveal evidence of fungal IE. She was initially treated with anidulafungin, later switched to voriconazole, but ultimately died of cardiogenic and septic shock 2 days later.

DISCUSSION

In this case series, we described four cases of Trichosporon fungemia in children over a 13-year span. All of them presented with significant co-morbidities. The one common characteristic for all four patients was the presence of a CVC. While most of the literature describes a background of hematological disorders and malignancies as the primary underlying disease in Trichosporon fungemia [1,3,6,7], there are also reports, although fewer, of patients with a history of heart disease, presence of CVC, and prematurity in neonates [2].

Even though neutropenia is considered the primary risk factor for fungemia, it was only seen in two of the

TABLE 1. Demographic and clinical data of the patients with invasive *Trichosporonosis*

	Patient 1	Patient 2	Patient 3	Patient 4
Age	3 years	3 years	2 months	18 years
Sex	Female	Female	Male	Female
Ethnicity	Arab	Jew	Jew	Jew
Underlying diagnosis	Aplastic anemia, S/P BMT, mental retardation	SBS S/P NEC, NDD	Infantile AML	Tetralogy of Fallot, S/P surgical repair and insertion of prosthetic valve, *S. mitis* endocarditis
Absolute neutrophile count (K/micl)	0	2.2	0	10.6–17.5
Central venous catheter	Implanted port-o-cath catheter	Hickman Line	Implanted port-o-cath catheter	Peripherally inserted central catheter (PICC)
Additional risk factors	Steroid treatment, immunosuppressive Tx (cyclosporine), previous wide spectrum Abx Tx (23 days), mechanical ventilation	Previous wide spectrum Abx Tx (2 days)	Cytotoxic treatment, steroid treatment, TPN, previous wide spectrum Abx Tx (30 days)	Congenital heart defect, prosthetic valve
Clinical manifestations	Fever, skin lesions, dyspnea, fluid retention	Fever, rhinorrhea, Erythema around PEG	Fever, abdominal pain and distention (Typhlitis), respiratory distress	Fever, seizures
Imaging	CXR (bilateral infiltrates and LLL consolidation); bronchoscopy (diffuse fungal infection); head, chest, abdominal, and pelvic CT scan, no evidence of fungal infection	None	CXR (bilateral alveolar opacities with air bronchogram), CT scan (hypodense foci in liver and spleen)	CXR (bilateral alveolar opacities and hypoventilation of bases), head, chest, abdominal and pelvic CT scan and echocardiography (no evidence of fungal infection)
Additional systemic/ organ involvement	Pulmonary	None	Hepatosplenic, pulmonary, abdominal	None
Site of positive cultures	Blood, BAL, sputum	Blood	Blood, abdominal fluid, liver biopsy, urine	Blood
Antifungal susceptibility	S – VOR, FLU, ITR; R – AMB, AFN, CFN	Unavailable	S (VOR, FLU, ITR) R (AMB)	S – VOR, FLU, ITR; R – AMB, AFN, CFN, MFN, FC
Other positive fungal cultures	Candida, knee synovial fluid (chronic synovitis)	None	None	Candida (sputum)
Initial treatment	IV + Inh VOR	IV FLU	IV VOR + MFN (changed to AFN), IV Liposomal AMB	IV VOR, IV AFN
Treatment after susceptibility results	VOR	No available antibiogram	VOR	VOR, AFN
Complications	Septic shock, cardiogenic shock	None	Septic shock	*Klebsiella pneumoniae* and *Pseudomonas aeruginosa* bacteremia, hemodynamic instability
Additional treatment	Removal of port-a-cath	Removal of Hickman	–	–
Clinical outcome	Full recovery	Full recovery	Death	Death

Abx Tx = antibiotic treatment, AFN = anidulafungin, AMB = amphotericin, AML = acute myeloid leukemia, BAL = bronchoalveolar lavage, BMT = bone marrow transplantation, CFN = caspofungin, CT = computed tomography, CXR = chest X-ray, FC = flucytosine, FLU = fluconazole, Inh = inhaled, ITR = itraconazole, IV = intravenous, LLL = left lower lobe, MFN = micafungin, NDD = neurodevelopmental disorder, NEC= necrotizing enterocolitis, PEG = percutaneous endoscopic gastrostomy, S/P = status/post, SBS = short bowel syndrome, S. mitis = *Streptococcus mitis*, TPN = total parenteral nutrition, VOR = voriconazole B, S = susceptible, R = resistant

patients in our small cohort, both also receiving systemic steroid therapy. Both patients presented with a disseminated disease, while the patients without neutropenia showed fungemia alone. Wide spectrum antibiotic therapy is also a possible risk factor. Three patients were being treated for different periods of time (2–30 days) prior to their diagnosis of *Trichosporon* fungemia. Interestingly, the two patients whose CVC was removed reached recovery, while the other two died. It is noteworthy that the latter two patients had disseminated disease with

multi-organ involvement, including the central nervous system and liver, in contrast to the more localized infections observed in the two patients who recovered.

Since our patient cohort was relatively small, the role of the removal of CVC in the treatment of *Trichosporon* fungemia cannot be determined, although it should be strongly considered.

The presence of prosthetic valves and CVC is considered a risk factor for fungal IE, which is associated with a very unfavorable prognosis, and may warrant surgical

intervention [8]. Fungal IE caused by *Trichosporon species* may present even many years after heart surgery, and is often associated with massive valve vegetations, which is seen on echocardiography or other imaging methods [8]. Therefore, in cases of *Trichosporon* fungemia in patients with endovascular grafts, a high index of suspicion is required, even in immunocompetent patients, and the diagnosis must be ruled out (patient 4).

The choice of treatment regime for invasive disease may be difficult since the affected patients usually have significant underlying diseases and different levels of immunodeficiency. It has been therefore suggested that a key part in the treatment will include the reduction of immunosuppression, if possible, and the elevation of the neutrophile count [9].

Triazoles antifungals are the drugs of choice for the treatment of *Trichosporon* fungemia [3], while other drugs may prove inferior, including reported resistance to other azoles (such as fluconazole), echinocandins, and amphotericin B [1,4]. In in vitro susceptibility testing, all azoles have shown activity against *T. asahii*, with voriconazole considered the most effective and fluconazole the least [10]. Therefore, voriconazole is the anti-mycotic drug of choice [4], even though in our local susceptibility profile, fluconazole and itraconazole were also appropriate [Table 1]. As described in the literature [3,4], all strains of *T. asahii* were found to be resistant to echinocandins and amphotericin B.

All three patients with available antibiogram results (patients 1, 3, and 4) were treated empirically with voriconazole, while patient 2 received fluconazole. Even though the susceptibility profile was not available for patient 2, local susceptibility patterns indicated sensitivity to this drug, in addition to the fact that she had her central catheter removed early and no other risk factors. All these conditions could have led to the patient's full recovery.

In our hospital, neutropenic patients with persistent or secondary fever are empirically treated with voriconazole, which has anti-yeast and anti-mold activity. This treatment may explain the small number of *Trichosporon* fungemia cases in our institute. Given the potential risk of resistant strains of *Trichosporon species* to other triazoles such as fluconazole, and to echinocandins, voriconazole should be considered as a reasonable choice for empiric treatment in the case of prolonged or secondary neutropenic fever.

Our study is limited as it depicts only a small number of patients, reflecting on the rarity of *Trichosporon* fungemia. A future prospective multicenter study with more cases may assist in creating a national database for infections with such rare pathogens.

CONCLUSIONS

Although rare, we identified only four cases over nearly 13 years, *Trichosporon* fungemia can result in substantial morbidity and mortality. It should therefore be considered in the differential diagnosis of fungal infections in severely ill patients with persistent fever, particularly in those who are neutropenic or immunocompromised, as well as in any patient with a CVC or endovascular graft. Medical management should include appropriate antifungal therapy, reduction of immunosuppression when feasible, correction of neutropenia, and prompt removal of the CVC.

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