Trichosporonosis

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Trichosporonosis is an emerging concern in preterm neonates treated with broad-spectrum antimicrobials and indwelling catheters, and in children with hematologic malignant disease receiving prophylaxis or treatment with echinocandins given their lack of efficacy against this yeast.

Trichosporon trichosporonosis

1. Introduction

Trichosporon species are basidiomycetous yeast-like fungi, which are characterized by the formation of arthroconidia that disarticulate from septate hyaline hyphae [1]. The word *Trichosporon* is derived from Greek words Tricho (hair) and Sporon (spores). *Trichosporon* species are found in nature, soil, water, mammals, birds, bats and cattle and also colonize the human skin, gastrointestinal tract and mucosal surfaces as part of the human microbiota [2][3]. They are also responsible for superficial infections (white piedra), allergic pneumonitis and rarely invasive infection [4][5][6][7][8][9][10].

Since the first case of invasive *Trichosporon* infection (ITI) reported by Watson and Kallichurum in 1970, *Trichosporon* species have emerged as important opportunistic fungal pathogens [11]. *Trichosporon asahii,* in particular, is considered to be the leading and most frequent cause of invasive disease [12]. Invasive *Trichosporon* infection may involve many organs, while *Trichosporon* fungemia (TF), including catheter-related fungemia, represents the main type of this opportunistic infection, which accounts for between 58.8 and 74.7% of infections [13][14]. In the 1980s, Walsh et al. reported ITI as the second most common cause of fungemia in patients with hematological malignancies [15]. As triazole derivatives became widely available, the incidence of ITI decreased in early the 2000s [16] followed by a re-emergence of *Trichosporon* as an increasingly common pathogen in immunocompromised hosts after the wide use of echinocandins [16][17][18][19]. Most cases of invasive infection are seen in patients with neutropenia and malignancy, especially in adults and children with hematological malignancies and intravascular indwelling catheters. Premature neonates with a low birth weight, patients with Acquired Immune Deficiency Syndrome (AIDS) and critically ill patients exposed to broad-spectrum antibiotics are also at increased risk [20][21][22][23][24][25][26][27]. Data regarding ITIs in children are based on case reports and small case series.

2. Researches ang findings

Invasive trichosporonosis is rarely documented in children and is mainly reported in premature neonates and in immunocompromised children with hematological malignancies. *T. asahii* is the predominant *Trichosporon* species that causes invasive infection, especially breakthrough infections in patients receiving prophylactic/empirical antifungal treatment [1][28][29]. It is noteworthy that all pediatric cases are reported in the second half of the 2000s, indicating the re-emergence of this opportunistic fungal pathogen. After candidiasis, trichosporonosis is considered the second most frequent yeast infection leading to fungemia in patients with hematological malignancies [30][31][32]. Moreover, a change in the geographical distribution of cases is noticeable in the second decade of 2000s, since more cases have been reported from South America and Asia. An increasing concern of physicians, as well as the wider availability of more sophisticated molecular diagnostic methods, have played a role but the real epidemiological trend remains to be established.

In pediatric cancer patients, the largest group is comprised of leukemia patients. Among them, patients with ALL are at lower risk for invasive fungal infections (IFIs) compared to children with leukemia relapse or AML. Nevertheless, ALL patients are the largest group in absolute numbers reported with IFIs in children [33]. In accordance with this, when the ANC was reported, the vast majority of children had neutropenia, highlighting the importance of neutrophil recovery in the prevention of ITI. Moreover, the use of broad-spectrum antibiotics and concomitant bacteremia play a significant role in the imbalance of the microbiota, resulting in potential IFI. Prolonged and severe neutropenia, together with the underlying immune status of the host, play a critical role in the outcome of the infection in children with hematologic or malignant disorder and in neonates [34][35]. The presence of a CVC and the disruption of the mucosal barrier might provide a portal of entry for *Trichosporon* spp. The formation of *Trichosporon* biofilms on catheter surfaces is important in the pathogenesis of invasive trichosporonosis [36]. Therefore, catheter removal as source control should be suggested whenever feasible.

Diagnosis is challenging since it relies on the isolation of a yeast-like organism from a clinical specimen. Direct examination seldom contributes to a definite diagnosis as it rarely demonstrates arthroconidia and it resembles *Candida* in histology. However, it has thinner hyphae and pseudohyphae and is slightly stained with Gomori methenamine silver (GMS) stain. Cutaneous involvement with maculopapular or pustular lesions that are sometimes necrotic is suggestive of trichosporonosis, though it may also be present in disseminated candidiasis. Biopsy and culture specimens of cutaneous lesions are helpful in establishing the diagnosis. Galligan et al. reported a child with relapsed ALL and disseminated *T. asahii* infection that had cutaneous nodules suggestive of fungal infection [37]. Despite the fact that histologic characteristics resembled Neutrophil Eccrine Hydradenitis, staining with periodic acid-Schiff stain and GMS confirmed the diagnosis of trichosporonosis. Moreover, de Almeida et al. has shown that MALDI–TOF spectrometry could be used as a valuable alternative for routine identification [30]. Direct sequencing of the IGS1 region of the ribosomal DNA is considered the reference method for species identification of *Trichosporon* isolates [38]. The timing and sensitivity of the diagnostic method is an important factor for successful management of ITIs. Invasive trichosporonosis can involve many organs, but *Trichosporon* fungemia (TF) including catheter-related fungemia, represents the main type of this opportunistic infection, as depicted in this review.

Prompt initiation of proper antifungal therapy is considered critical for obtaining a favorable outcome. Global guidelines for the management of rare yeasts from the European Confederation of Medical Mycology in collaboration with the International Society for Human and Animal Mycology and American Society for Microbiology have recently been published [39]. Various antifungal agents are available in the treatment of invasive trichosporonosis.

For the neutropenic pediatric patients with potential IFI, prophylactic/empirical treatment with echinocandins or a formulation of AMB has been recommended. Review of the literature revealed ten pediatric cases with breakthrough infections in patients receiving prophylactic echinocandins. Echinocandins are ineffective against *Trichosporon* spp. Moreover, it has been reported that their use may select for resistant fungal organisms, which explains the re-emergence of this opportunistic fungal pathogen [40]. Amphotericin B has shown some positive effectiveness against *Trichosporon* spp. in vitro, but it functions poorly with breakthrough infections, particularly in patients with profound neutropenia on high doses of AMB [41]. Walsh et al. reported that 77% of *Trichosporon* isolates were not killed at achievable AMB serum levels and this finding was correlated with refractory, disseminated trichosporonosis in neutropenic patients [42]. Poor response to AMB has also been reported in adult patients [1][13][35][43]. Nevertheless, successful results with AMB have been reported in neonatal cases with disseminated disease [44][45][46]. Variable susceptibility to AMB in vitro and in vivo may be explained by the production of a biofilm layer. The capability of *T. asahii* to produce biofilms is well documented in vitro [36]. In addition, an increased antifungal resistance to AMB has been reported to be directly proportional to increased biofilm production [47]. Therefore, the expected response to AMB may not be observed in the clinical setting, despite the in vitro sensitivity to AMB. Resistance to AMB and echinocandins is alarming not only for pediatric patients with neutropenia but also for neonates since they are both commonly used as systemic antifungal agents in preterm neonates. Early diagnosis of trichosporonosis remains a challenge since *Trichosporon* spp. may be less susceptible to empirical or prophylactic antifungal drugs that are frequently used, such as echinocandins and AMB. *Trichosporon* spp. seem to be sensitive to AMB in vitro, but this response may not be observed in vivo when a biofilm layer is produced by *Trichosporon* spp.

Although in vitro and in vivo studies have shown that *Trichosporon* species are resistant to the fungicidal effect of AMB, antifungal triazoles have been found to be fungicidal against *Trichosporon* species [35][42]. A favorable outcome in patients who received a VCZ regimen or an AMB–triazole combined regimen was reported by Liao et al. who assessed 185 cases of *Trichosporon* fungemia [48]. Moreover, Almeida et al. reported that azole-based therapy was a protective factor against adverse outcomes in 199 cases of proven infection and in 4 cases of probable infection caused by *Trichosporon* spp [30]. In accordance with this, a favorable outcome was reported in 12/16 (75%) pediatric patients receiving targeted monotherapy with VRC or combined with LAMB. However, fatal pediatric cases have been reported in children despite treatment with AMB and VRC [49].

Considering the intrinsic resistance to echinocandins and poor susceptibility to polyenes, triazoles have been proposed as the antifungals of choice for invasive trichosporonosis [50]. Azole-including therapy was more frequently used especially after 2004 [14]. Global guidelines published in 2021 moderately recommend VRC as the initial antifungal therapy, whereas fluconazole is also moderately supported, contingent on the MIC. Weak support

exists for combination antifungal therapy [39]. The first successful treatment of ITI with voriconazole was reported in 2002 [51], a finding that has been confirmed in adults and children with IT [52]. According to our results, targeted monotherapy with VRC was reported in 11 pediatric patients with malignancy or hematologic disorder, resulting in a favorable outcome in 8/11(73%) patients. Combination therapy with AMB and a triazole has not been proven to be superior to VRC alone in vitro and requires more clinical studies to be confirmed [1][30][53]. Our review suggests that azole-including therapy may be superior to echinocandin- or AMB- based therapy in children, as it is in adults. According to the recently published global guidelines for the management of rare yeast infections, azole-polyene combinations should be reserved for salvage therapy [39]. Nevertheless, lately multi-drug resistant *Trichosporon* spp. has been reported with the increased use of broad-spectrum triazoles for prophylaxis in high-risk patients [54]. Multiple drug interactions in patients receiving chemotherapy and pharmacokinetic variability may play a role in the subtherapeutic level of triazoles leading to resistance to triazoles.

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