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Update on the Genus *Trichosporon*

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Abstract *Trichosporon* spp. are widely distributed in nature and can occasionally belong to the human microbiota. For many years, the unique species of the genus, *Trichosporon beigelli*, was only known as an environmental and saprophytic fungus occasionally found as the etiological agent of white piedra. However, case reports of invasive trichosporonosis have been frequently published and the genus is currently considered the second most common agent of yeasts disseminated infections. Based on molecular analysis, the taxon *T. beigelli* was replaced by several species and the taxonomy of the genus was progressively modified. Despite the reported increase of *Trichosporon* infections refractory to conventional antifungal drugs, there are only a few studies investigating in vitro susceptibility of *Trichosporon* spp. to new compounds. Difficulties on different species identification as well as the lack of standardized sensitivity tests in vitro, contribute to the limited information available on epidemiology, diagnosis and therapeutics of trichosporonosis.

Keywords Emergent pathogen · Yeast identification · Epidemiology · *Trichosporon* · Antifungal drugs

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Trichosporon spp. are widely distributed in nature and can predominantly be found in environmental substrates, such as soil and decomposing wood. These fungi can occasionally belong to the permanent gastrointestinal microbiota of humans as well as transiently colonize the skin and respiratory tract [1–4].

The genus *Trichosporon* is characterized for the ability to form arthroconidia, blastoconidia, hyphae and pseudohyphae. Nevertheless, some species posses other morphological structures that may help to differentiate them: appresoria, macroconidia or meristematic conidiation. All the species of this genus are able to assimilate different carbohydrates and carbon sources and to degrade urea. Cell cultures on Sabouraud dextrose agar grow as yeast colonies with colors ranging from white to cream, showing, most of the time, particular aspects, such as cerebriform and radial surfaces [5].

The genus *Trichosporon* was created in 1890 to group fungal isolates related to superficial mycoses in humans. The word *Trichosporon* is derived from the Greek and represents a combination of *Trichos*, which means hair, with *sporon* which means spores. The genus as well as the species *Trichosporon beigelli*, was originally described from the visualization of nodules on body and head hair of patients. For many years, *T. beigelli* was only known as an environmental and saprophytic fungus occasionally found as the etiological agent of white piedra. A case report of systemic infection caused by *Trichosporon* sp. was firstly described only in 1970 [6]. Currently,

the clinical relevance of the genus *Trichosporon* and its ability to cause invasive infection in immunocompromised patients are well recognized among the emergent pathogens [7–11]. This genus is strictly anamorphous and has a long and controversial history. The first description of clinical isolates of *Trichosporon* spp. was in 1867, where white piedra nodules were cultured and surrounded cells obtained from colonies were observed under light microscopy. The etiological agent was erroneously classified as the algae *Pleirococcus beigelli* [12, 13]. Latter on, in 1890, Behrend [14] described in detail the fungus causing white piedra on a man beard and named it as *Trichosporon ovoides*. Since then, other *Trichosporon* species have been reported. In 1902, Vuillemin considered all *Trichosporon* species as *Trichosporon beigelli*, which means arthrospored yeast [12, 13].

In 1909, Beurmann cultured the cells collected from a cutaneous lesion and denominated the fungus isolated as *Oidium cutaneum*, which was subsequently renominated as *Trichosporon cutaneum* by Ota in 1926. Nevertheless, Diddens and Lodder (1942) apud Gueho et al. [12, 13] considered *T. beigelli* and *T. cutaneum* to be the same species. This situation led to a dramatic simplification of the genus to only two names with clinical relevance: *Trichosporon beigelli*, adopted by physicians and *Trichosporon cutaneum*, preferred by environmental mycologists [12, 13].

Traditional taxonomy based on morphological, ecologic and physiological approaches used to group the genus *Trichosporon*, generates inconsistent results, because it groups in the same *taxon* isolates with heterogeneous behavior. This genus traditionally englobed few species until the taxonomic review proposed by Guého et al. [13], through the employment of molecular studies of nucleic acids correlated to morphological, physiological and biochemical characteristics. The criteria used to reclassify *Trichosporon* species, based on new taxonomic concepts were: the analysis of the ultra-structure of septal pores, guanine-cytosine content (mol% G-C), DNA reassociation values, nutritional profile and part of the sequence of the 26S region of ribosomal DNA (rDNA).

Based on molecular analysis, the *taxon T. beigelli* was replaced by several species and the taxonomy of the genus was progressively modified by powerful molecular tools which were able to discriminate phylogenetically closely related species [13, 15, 16]. According to these authors, the taxon *T. beigelli* was replaced by the following six human pathogens: *T. cutaneum*, *T. asahii*, *T. asteroides, T. mucoides, T. inkin* and *T. ovoides*. Guého et al. [17], Sugita et al. [15, 16] reviewed the genus *Trichosporon* and proposed a new classification, including 17 species and five varieties of *Trichosporon*. In 2002, Sugita et al. [18] proposed 25 species for the genus *Trichosporon*, and suggested that eight of them should be considered relevant as potential human pathogens, including the two emergent species *T. domesticum* and *T. montevideense*. Thereafter, the same group published a paper in 2004 recognizing now 36 *Trichosporon* species, including five new species proposed by Middelhoven et al. [19]: *T. vadense*, *T. smithiae*, *T. dehoogii*, *T. scarabaeorum* and *T. gamsii*. They also separated the order Trichosporonales into four clades, named: Gracile, Porosum, Cutaneum and Ovoides (Table 1). In the same year, Sugita et al. [20] included the clade Brassicae to the order Trichosporonales, which englobed some species considered as belonging to the clade Gracile by Middelhoven et al. [19] (Table 1). A new *Trichosporon* species isolated from the hindgut of the lower termite *Mastotermes darwiniensis*, recognized as an important detoxifier of mycotoxins has been described by Molnar et al. [21] and named *T. mycotoxinivorans*, belonging to the clade Gracile. In 2007, Fuentefria [22] proposed a new *Trichosporon* species isolated from the gut of insects from Panama and artesian cheese prepared in Brazil. The new species was included in the Ovoides clade. It is important to mention that the old taxon *T. pullulans*, which was considered to belong to the genus *Trichosporon* by Diddens & Lodder (1942) for a long time, was now reassigned to a new genus and is currently named *Guehomyces pullulans* [23].

Human Infections Caused by the Genus *Trichosporon*

Trichosporon species are mostly associated with benign superficial lesions, particularly white piedra, which is characterized by the presence of irregular nodules on the affected hair. These nodules can exhibit white or light brown colors. White piedra is a cosmopolitan infection that can be found on the beard, moustache, armpit, and genital area [16, 17, 24, 25].

Table 1 *Trichosporon* species currently accepted and their subdvision within clades according to different authors

No	*Trichosporon* species	Clade
1	*T. brassicae*[a]	Brassicae[b]
2	*T. domesticum*[a]	
3	*T. montevideese*[a]	
4	*T. scarabaeorum*[a]	
5	*T. cutaneum*	Cutaneum
6	*T. debeurmannianum*	
7	*T. dermatis*	
8	*T. jirovecii*	
9	*T. moniliiforme*	
10	*T. mucoides*	
11	*T. smithiae*	
12	*T. terricola*	
13	*T. mycotoxinivorans*[c]	Gracile
14	*T. dulcitum*	
15	*T. gracile*	
16	*T. laibachii*	
17	*T. multisporum*	
18	*T. vadense*	
19	*T. veenhuisii*	
20	*T. aquatile*	Ovoides
21	*T. asahii*	
22	*T. asteroides*	
23	*T. caseorum*	
24	*T. coremiiforme*	
25	*T. faecale*	
26	*T. inkin*	
27	*T. japonicum*	
28	*T. lactis*	
29	*T. ovoides*	
30	*T. insectorum*[d]	
31	*T. dehoogii*	Porosum
32	*T. gamsii*	
33	*T. guehoae*	
34	*T. lignicola*[e]	
35	*T. loubieri*	
36	*T. porosum*	
37	*T. sporotrichoides*	
38	*T. wieringae*	

[a] Classified as belonging to the clade Gracile by Middelhoven et al. [19]

[b] According to Sugita et al. [20]

[c] Classified by Molnar et al. [21]

[d] Classified as belonging to the clade Ovoides by Fuentefria et al. [22]

[e] Classified as *Hyalodendron lignicola* by Middelhoven et al. [19]

White piedra is predominantly caused by *T. inkin* (on pubic hair) and *T. ovoides* (on head hair). In addition, *Trichosporon* spp. can also cause other superficial infections, such as onycomycosis, where the more frequently isolated species is *T. cutaneum* [24]. In addition, *T. loubieri* has been recently reported in literature as an emergent species mainly related to superficial infections in humans [16, 17, 26–28].

Some Mexican authors have documented that the isolation of *Trichosporon* spp. from *tinea pedis* and onychomycosis ranged from 2.81 to 42.8% of cases [26, 29, 30]. In Brazil, *Trichosporon* species have also been reported as colonizing agents of the anus and causing genitopubic white piedra in HIV positive patients (2.7% and 5.6%, respectively). The species isolated were *T. inkin* (four cases) and *T. asahii* (1 case) [31].

In Japan, several authors have reported that *T. asahii* can cause allergic pneumonia [4, 24, 25, 32–34]. In addition to infections, *Trichosporon* species are responsible for summer-type hypersensitivity pneumonitis (SHP) leading to type III and IV allergies by repeated inhalation of arthroconidia which contaminate home environments during summer season which is very hot, humid and rainy in western and southern Japan [20]. SHP is an immunologically induced lung disease whose pathogenesis mechanisms involve an initial immune complex-mediated lung injury, followed by cell-mediated tissue damage [35]. Mizobe et al. [36] have already characterized the antigenic components involved in SHP as glucoronoxylomannan, a (1–3)-linked mannan backbone attached to short side chains of (1–4)-linked mannose and a small portion of (1–2)-linked xylose residues by substituting the 2- or 4-portions of the (1–3)-linked mannose residues of the main group.

Invasive infections caused by *Trichosporon* spp. are usually preceded of respiratory and gastrointestinal tract colonization, and are commonly associated with the use of central venous catheters [1–4]. In patients with malignant hematological diseases, this genus has been reported as the second most common agent of yeast disseminated infections, only behind the genus *Candida*, leading to 80% of mortality rates, despite treatment with amphotericin B [4, 27, 37].

More recently, *T. asahii* and *T. mucoides* have been described as emergent opportunistic pathogens related to disseminated infections in immunocompromised

patients [4, 24]. The incidence of invasive mycoses caused by opportunistic fungal species has been considerably growing over the last two decades. This finding is probably secondary to several factors including the increased occurrence of degenerative diseases, the higher number of organ transplant recipients, the higher use of immunosuppressive therapies and chemotherapy as well as the use of broad spectrum antibiotics and the progressive number of invasive medical procedures performed recently. It is important to emphasize that emergent fungal infections are usually difficult to diagnose, refractory to conventional antifungal drugs and associated with high mortality rates [4, 38–41].

Trichosporon spp. have been recognized as causative agents of fungemia, especially in patients who have neutropenia and cancer. Of note, trichosporonosis may resemble hematogenous candidiasis both in clinical presentation and in histopathologic appearance.

In 1970, Watson and Kallichun apud Arce et al. [6] described the first case report of invasive trichosporonosis due to *T. cutaneum* as the etiological agent of cerebral abscess. Since then, several cases of invasive trichosporonosis have been described in different clinical scenarios. For instance, Manzella et al. [42] reported a case of fungemia with cutaneous dissemination due to *Trichosporon* sp. documented in a leukemic patient that evoluted to death [42]. Some years later, Reinhart et al. [43] reported a case of endocarditis caused by *Trichosporon* sp. in a patient who previously has had rheumatic disease [43]. In 1997, Lopes et al. [44] described a case of peritonitis due to *T. inkin* in a diabetic patient successfully treated with fluconazole (100 mg/day). Moretti-Branchini et al. [45] reported two cases of *Trichosporon* invasive infections involving two bone marrow transplanted patients hospitalized at the Clinical Hospital of The University of Campinas (Unicamp), Sao Paulo. One of the patients had intravascular catheter tip and anal swab positive cultures for *T. inkin.* This patient was successfully treated with fluconazole. The second patient had severe neutropenia due to chemotherapy and developed an episode of fungemia. The yeast isolate was at first misidentified as *Candida* sp. Subsequently, it was correctly identified as *Trichosporon asahii* var. *asahii*. Despite treating the patient with amphotericin B, the death could not be avoided. Recently, a case of chronic dissemination infection due to *Trichosporon* sp. with multiple liver abscesses has been reported by Meyer et al. [46]. Abdala et al. [47] reported a case of invasive *T. asahii* infection in a non-neutropenic patient submitted to orthopic liver transplantation. Despite treatment with amphotericin B, the patient died of sepsis resulting in multiple organ failure.

The largest retrospective multicentric study on invasive trichosporonosis and geotrichosis in patients with malignal hematological diseases was conducted by Girmenia et al. [48], including data of *Trichosporon* and *Geotrichum* infections documented during a period of 20 years. The authors included a review of 287 cases of trichosporonosis and 99 cases of geotrichosis documented all over the world. The most common underlying conditions related to trichosporonosis were hematological diseases, peritoneal dialysis and solid tumor. Trichosporonemia occurred in 115/154 (74.7%) of patients and disseminated infection in 78/154 (50.6%) of cases. The majority of the cases of trichosporonosis and geotrichosis were reported in North America medical centers (33.9%), followed by Europe (27.6%) and Asia (23.3%). Only six isolates from South American institutions were reported, including five Brazilian isolates and one isolate from Argentina. Despite the large number of *Trichosporon* isolates included in this review, only thirty of them were accurately identified to the species level and eight to the old taxon *T. pullulans* (recently named *G. pullulans*), while the other 257 isolates were only identified as *Trichosporon* sp.

According to the literature, besides fungemia and fever, the clinical manifestations described for *Trichosporon* hematogenic dissemination may include multiple cutaneous lesions, the presence of pulmonary infiltrates, neurological damage, corioretinitis and even septical shock with renal failure. In patients with disseminated infection, *T. asahii* has been described as the most frequently isolated species [8, 9, 11, 46, 49]. Most cases of human trichosporonosis have been reported in immunosuppressed patients, such as cancer, diabetes and neutropenic individuals. However, Rastogi et al. [50] reported a rare case of meningoencephalitis and pneumonia due to *T. asahii* in an immunocompetent patient who presented clinical improvement when treated with fluconazole. This fact demonstrates the pathogenic role of *Trichosporon* species to cause human diseases.

Phenotypic and Molecular Identification of *Trichosporon* Species

Several methods used for *Trichosporon* species identification have been reported, including morphological and biochemical tests and the use of molecular tools. Despite the fact that phenotypic methods are more suitable for routine in general microbiology laboratories, the accuracy for the identification of *Trichosporon* spp. seems to be limited [4, 12, 15, 16]. On the other hand, molecular methods are more precise for identification but are still costly for routine laboratories [18, 51].

It is important to mention that both *Trichosporon* and *Geotrichum* species are able to produce arthroconidia. In routine laboratories, when artrochonidia are visualized, it is recommended to perform the urease test. Differently form *Geotrichum* spp., all the species belonging to the genus *Trichosporon* are able to hydrolyze urea [5]. Although these genera are phenotypically similar, they are genotypically very distinct. Their nucleotide ITS sequences are less then 80% similar [52]. Subsequently, specific diagnostic PCR can also be performed to differentiate the two genera [53].

Phenotypic methods for *Trichosporon* species identification are based on the characterization of micromorphological aspects of the colonies as well as the biochemical profiling. Performing a slide microculture to search for arthroconidia is a very useful tool for *Trichosporon* spp. triage. However, other morphological aspects and biochemical tests do not allow the complete identification of *Trichosporon* isolates to the species level.

Table 2 shows the expected results for six different *Trichosporon* species (old denomination *T. beigelli*) when control organisms are tested with different conditions by three reference laboratories: Sugita et al. [16], De Hoog et al. [5], ID32C bioMérieux—Pincus et al. [54]. Significant differences in the results generated by the same organisms tested by different authors can be observed in regard to biochemical and physiological tests performed with different substrates used in yeast identification keys. Therefore, it is possible to conclude that this methodology presents limited accuracy and reproducibility for *Trichosporon* spp. identification.

Despite limitations, several commercial non-automated and automated systems have been used in the identification of *Trichosporon* spp. Besides the problems already mentioned for the biochemical tests, it is important to emphasize that most of these methods do not include the new taxonomic categories in their databases. Consequently, the identification of the genus *Trichosporon* is oversimplified with incomplete databases and classificatory keys [5, 16, 54].

Considering all the mentioned limitations of the phenotypic methods used to accurately identify *Trichosporon* spp. at the species level, it is now easy to understand why most of the reports only refer to the genus *Trichosporon* with no species determination or

Table 2 Experience of three different reference laboratories relative to biochemical and physiological characterization of *Trichosporon* species relevant in medical mycology

Strains	*T. asahii*			*T. cutaneum*			*T. inkin*			*T. mucoides*			*T. ovoides*			*T. asteroides*		
Tests	Authors																	
	1	2	3	1	2	3	1	2	3	1	2	3	1	2	3	1	2	3
Assimilation																		
L-arabnose	+	+	+	+	+	n	−	−	v	+	+	+	v	−	n	+	+	n
Sorbitol	−	v	v	+	v	n	−	v	v	+	+	+	−	v	n	v	v	n
Melibiose	−	−	−	+	−	n	−	−	−	+	+	+	−	−	n	−	+	n
Myo-Inositol	−	v	v	+	+	n	v	+	+	+	+	+	−	+	n	+	+	n
Growth at 37°C	+	+	+	−	−	n	+	+	+	+	+	+	v	v	n	+	v	n
Growth in the presence of 0.1% cicloheximide	+	n	v	−	n	n	v	v	n	+	n	v	+	n	n	v	n	n
Apressorium formation	−	−	n	−	−	n	+	+	n	−	−	n	+	+	n	−	−	n

1- Sugita et al. [16]; 2- De Hoog et al. [5]; 3- ID32C bioMérieux-Pincus et al. [54]. (+) positive; (−) negative; (v) variable; (n) not informed

simply identify the clinical isolates as *T. asahii* or *T.* non-*asahii*.

The lack of accurate laboratory tools for the complete identification of *Trichosporon* strains in routine laboratories impairs the understanding of epidemiological and clinical peculiarities as well as differences in terms of clinical response to conventional antifungal therapy possibly related to the six medically most important species of this genus, previously named *T. beigelli* [1, 55–57].

In order to improve the identification of this microorganism, DNA based methods have been progressively used [58].

Some authors suggest that the evaluation of specific nucleotide sequences can be a precise method to resolve taxonomic problems generated by the inconsistent phenotypic identification of *Trichosporon* species. In this regard, ribosomal genes represent consistent evolutive markers, including alternating conserved and variable regions, which may be useful for species identification and phylogenetic studies [53, 59].

Sugita et al. [53] constructed a phylogenetic tree with the small subunit (SSU) region sequences of rDNA from different pathogenic yeasts obtained from DNA libraries. The pair of primers TRF and TRR, which amplify part of the SSU region, were designed for the specific identification of the genus *Trichosporon*, because these oligonucleotides do not amplify conserved regions in the ribosomic gene of other medically important yeasts rather than *Trichosporon* [18].

Subsequently, Sugita et al. [60] have sequenced and analyzed the interespacer regions (ITS1 e ITS2) genes of rDNA from *Trichosporon* spp. and proposed 17 species and five varieties for this genus. Therefore, the authors concluded that the six medically relevant species could be accurately identified by their ITS sequences.

However, in a recent study, Sugita et al. [18] analyzed the sequence of the intergenic spacer region (IGS1), which is localized between the 26S and 5S genes of rDNA, in 25 isolates of *Trichosporon*. The IGS1 region ranged in size from: 195 base pairs (bp) to 704 bp. The comparative analysis of the nucleotide sequences suggested higher variations in the IGS1 region than in the ITS region. Therefore, the use of ITS region sequencing is not suitable for *Trichosporon* identification. In addition, these authors could also identify five different genotypes of *T. asahii* among 43 strains. They also observed that the majority of Japanese isolates belonged to the genotype 1 and that the strains from the American continent (including two Brazilian isolates) belonged to the genotypes 3 or 5. Rodriguez-Tudela et al. [61] also evaluated sequence polymorphisms of IGS1 region of *T. asahii* isolates from Argentina, Brazil and Spain and reported the presence of six different genotypes for this species. While most of the strains belonged to the genotype 1, Spanish strains belonged to all genotypes, except to genotype 2, whereas South American isolates belonged to the 1, 3, and 6 genotypes. Therefore, the use of this region of rDNA for sequencing has a high potential as a diagnostic and epidemiologic tool in trichosporonosis, besides it can also be used for phylogenetic studies.

Diaz et al. [62] used Luminex 100, a novel flow cytometer, for the detection of medically important species of the genus *Trichosporon*. The assay is based on the use of PCR-biotinylated amplicon target DNA, which is inoculated into microsphere bead mixtures containing species-specific probes of interest. By adding a reporter molecule (streptavidin R-phycoerythrin), all hybridized species-specific amplicons captured by their complementary nucleotide sequence on the microsphere beads are recognized by the fluorescence of the reporter molecule. The authors have used capture probes designed to target the D1/D2 and ITS region of rDNA when these sequences were sufficiently discriminatory, whereas the IGS region was chosen for closely related species, such as *T. asahii*, *T. japonicum*, and *T. asteroides*.

A summary of molecular methods more commonly used for *Trichosporon* identification is described in Table 3.

It is, therefore, evident that phenotypic methods are no longer appropriated for the accurate identification of species belonging to the genus *Trichosporon*. The use of molecular methods evaluating specific DNA sequences, such as the IGS region of rDNA must be employed. As a consequence, it is necessary that *Trichosporon* spp. isolates are sent to reference laboratories enabled to properly identifying these species using molecular techniques.

Antifungal Susceptibility Tests for *Trichosporon* spp and Challenges for Therapy

Despite the reported increase of *Trichosporon* infections refractory to conventional antifungal drugs,

Table 3 Specific molecular methods for *Trichosporon* species identification most currently used

Method	rDNA specific region	Description
Diagnostic PCR	18S	Primers TRF and TRR are sufficiently discriminatory for the identification of the genus *Trichosporon* [53]
DNA sequencing	ITS	Universal primers ITS1 and ITS4 are sufficiently discriminatory for the identification of a considerable number of species of the genus *Trichosporon*. However, this rDNA region is not able to distinguish closely related species such as *T. domesticum* and *T. montevideese* [18]
DNA sequencing	IGS1	*Trichosporon* specific primers 26F and 5SR are suitable for satisfactory identification of all the species of this genus currently described [18]
Luminex 100 flow cytometry	26S (D1/D2), ITS and IGS1	Probes were specifically designed to distinguish even closely related species, such as *T. asahii*, *T. japonicum* and *T. asteroides* [62]

SSU, small subunit; ITS1-ITS2, internal transcriber spacers 1 and 2; IGS1, intergenic spacer 1; PCR, polymerase chain reaction; bp, base pairs

there are only few studies investigating in vitro susceptibility of *Trichosporon* spp. to new compounds. Difficulties on different species identification within the genus as well as the lack of standardized sensitivity tests in vitro, contribute to the limited information available on this subject. Currently, the optimal therapy for trichosporonosis has not yet been identified.

Clinical Laboratory Standards Institute (CLSI) documents for antifungal susceptibility testing of yeasts do not include the genus *Trichosporon.* Most of the studies available evaluating *Trichosporon* spp. susceptibility to antifungal drugs in vitro use the CLSI (2002) methods currently standardized for *Candida* spp. and *Cryptococcus neoformans* [55]. However, Rodrigues-Tudela et al. [51] have used an adaptation of the guideline for antifungal susceptibility test recommended by The European Committee for Antimicrobial Susceptibility Testing (EUCAST). Again, the recommendations of this document are only standardized for the genus *Candida*, and do not encompass yeasts which are not able to ferment glucose [63].

Despite the fact that the CLSI methodology may be successfully adapted to test *Trichosporon* strains, several authors have suggested that broth microdilution method is not satisfactory in detecting isolates resistant to amphotericin B because it generates narrow MIC variation within different clinical strains. Therefore, MIC breakpoints have not yet been established for amphotericin B assays [64, 65]. Some authors have suggested that E-test may be a useful alternative to the CLSI methodology when testing fungal isolates susceptibility to amphotericin B. Apparently, E-test may better discriminate susceptible and resistant isolates to amphotericin B when compared to the CLSI broth microdilution method. CLSI susceptibility tests for *Trichosporon* isolates are usually performed by using RPMI-1640 at 35 C with an inoculum size of 0.5 to 2.5 $\times$ 10^3 CFU/ml. The readings are taken after 48 h of incubation. Of note, E-test assays are performed using the same conditions. EUCAST method differs from CLSI because the same culture medium (RPMI-1640) is added 2% glucose, and the inoculum size used is 0.5–2.5 $\times$ 10^5 CFU/ml. In addition, the readings should be taken at 24 $\pm$ 2 h of incubation.

The majority of the studies regarding sensitivity tests in *Trichosporon* spp. still consider the old nomenclature *T. beigelli* [56, 57, 66, 67]. Therefore, sensitivity to antifungal drugs within the different species of the genus *Trichosporon* is still not largely investigated.

After the resolution of the genus *Trichosporon*, some authors have suggested that *T. asahii* is more resistant to amphotericin B and more sensitive to triazolics as compared to other *Trichosporon* species [67]. Rodriguez-Tudela et al. [51] properly identified 49 *Trichosporon* clinical isolates using IGS1 region sequencing and tested their susceptibility to antifungal drugs. The authors have demonstrated that all *T. asahii* isolates tested had MICs $\geq$ 2 μg/ml. On the other hand, they observed that the majority of *T. coremiiforme* and *T. faecale* were also resistant to amphotericin B, while the other species tested had MICs $<$ 1 μg/ml.

Antifungal therapy with amphotericin B has controversial results in trichosporonosis. Laboratorial studies have demonstrated that some *Trichosporon* isolates may be resistant to this drug [68–70]. Some isolates can be inhibited using safe concentrations of the drug in serum, but fungicidal activity has not been observed in neutropenic patients [71]. Experimental data suggest that fluconazole may be more suitable than amphotericin B in treating disseminated trichosporonosis [68, 72].

Disseminated trichosporonosis has unfavorable prognostic, with mortality rate higher than 80% [27]. In a series of 25 neutropenic patients who developed systemic trichosporonosis and were treated with amphotericin B, only four of them survived [8]. The recent series published by Girmenia et al. [48] showed a retrospective analysis of the clinical outcome of 55 patients with hematological diseases and disseminated thichosporonosis that were treated with amphotericin B. Clinical response to amphotericin B was documented in only 13/55 (24%) of the patients evaluated. It has been suggested by different authors that neutropenia recovery is essential to guarantee better clinical outcome in cancer patients. Therefore, it is possible to suggest that the improvement of cancer patients with disseminated trichosporonosis is only marginally related to the antifungal drugs used, and mostly related to the recovery of host response to the infection.

Despite the increasing relevance of the genus *Trichosporon* in contemporary medicine, treating patients with trichosporonosis remains a challenge once that we still have very few data available on the in vitro and in vivo antifungal activity of conventional and new antifungal drugs among different species of the genus. Trichosporonosis therapeutic failure, when fluconazole, amphotericin B, or when both drugs were used in combination has been reported. In the same direction, *T. asahii* strains naturally resistant to amphotericin B, fluconazole, itraconazole, and 5-fluorocytosine have already been described [25, 67, 73–77].

Apparently, echinocandins have low activity against *Trichosporon* spp. and are not recommended for trichosporonosis treatment [4]. Breakthrough *Trichosporon* infections have been reported in patients treated with echinocandins (caspofungin and micafungin). Despite treatment with caspofungin acetate, an isolate of *Trichosporon* sp. was recovered from a sinovial liquid culture of a patient after day 6 of bone marrow transplant. However, the patient was successfully treated with fluconazole [78]. Goodman et al. [78] described a trichosporonemia case report in a bone marrow transplantation patient, receiving caspofungin prophylactic therapeutics. Other authors have reported that caspofungin has no reliable activity for trichosporonosis treatment [4, 79, 80].

Combination therapy of amphotericin B and caspofungin was successfully used to treat a patient with trichosporonosis. Bassetti et al. [81] described a case report of fungemia caused by *T. asahii* in a patient with intense neutropenia and acute myeloid leukemia. The patient was not cured after treatment with fluconazole, voriconazole, and liposomal amphotericin B. However, the individual was successfully treated with caspofungin combined with amphotericin B. The authors did not inform if there was neutropenia recovery. Other antifungal combinations already used to treat patients with trichosporonosis include amphotericin B and azoles or 5 fluorocytosine [48].

In vitro and in vivo results suggest that voriconazole may be useful for treating patients with trichosporonosis, including cases of acute leukemia and myelodisplasic syndrome with disseminated infection [67, 82, 83]. Matsue et al. [84] reported four cases of invasive trichosporonosis by *T. asahii* in Japan, including three patients with acute myeloid leukemia and one patient with myelodisplasic syndrome. All patients were initially treated with micafungin, (150 mg/day), but clinical improvement was observed in only one of the cases after recovery from neutropenia and therapy with voriconazole. These data confirmed the results obtained by Paphitou et al. [67] which suggested that the new triazolics (voriconazole, ravuconazole and posaconazole) are more effective than amphotericin B for trichosporonosis treatment.

In conclusion, it is possible to suggest that there is a lack of epidemiological and clinical data about infections due to different *Trichosporon* species. The standardization of laboratory methods for *Trichosporon* identification and antifungal susceptibility test evaluation are necessary to conduct studies with reliable and consistent information on the biological, clinical, and epidemiological aspects of invasive infections due to different species of this emergent pathogen.

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