1 **Title:** *Schizophyllum radiatum*, an emerging fungus from human respiratory tract

2 **Running title:** *S. radiatum* from human clinical specimens

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12 **Abstract**

13 *Schizophyllum* is an important genus of basidiomycetes that, apart from having
14 genetic and biotechnological interest, is also reported as a plant and animal pathogen.
15 *Schizophyllum commune* is the best-known species, and the only one reported from
16 clinical specimens thus far, being recovered mainly from the respiratory tract. The aim
17 of this study was to determine the species diversity of 23 clinical isolates of
18 *Schizophyllum* from the USA, using a multi-locus phylogenetic analysis, and their *in*
19 *vitro* susceptibility against six drugs. The markers used for sequencing were the internal
20 transcribed spacer (ITS), a portion of the nuclear large subunit rDNA (LSU), the RNA
21 polymerase II second largest subunit (*RPB2*), and the translation elongation factor 1-
22 alpha (*EF-1α*) gene. The analyses revealed that 22 of the clinical isolates were placed in
23 the *Schizophyllum radiatum* clade, with high support values, and one isolate in the *S.*
24 *commune* clade. This is the first report of this species in clinical samples. The two
25 mentioned species show very similar morphological features in culture (i.e., white,

cottony, unsporulated colonies composed of hyphae with clamp connections), making morphological discrimination impossible between the two. An epitype is designed for *S. radiatum* and its sequences deposited in GenBank. The antifungal that showed the greatest *in vitro* activity against the strains tested was shown by amphotericin B. In general, the strains of *S. radiatum* showed higher MICs than *S. commune.*

Introduction

Schizophyllum (*Schizophyllaceae*, *Agaricales*) comprises one of the most commonly found mushrooms on the planet (1). The most common species of the genus is *S. commune*, a ubiquitous fungus, well-known as a wood decay organism able to cause white rot (1, 2), but also by its biotechnological applications (3). It has been used as an ethanol producer (4) and some of its metabolites have anticancer (5) and antimicrobial properties (6, 7). It also has been studied for many years as a model for understanding mating interactions (8, 9). In recent years, *S. commune* has become clinically relevant as an etiological agent of respiratory infections in humans (10–15). However, other types of infections have also been reported, such as a brain abscess (16, 17), meningitis (18), an eye infection (19), palate ulceration (20), and onychomycosis (21). Infections have also been reported in other mammals (22–24) and in both immunocompromised and immunocompetent individuals (25, 26).

The most effective treatment options for infections by *S. commune* are yet to be determined, although various treatment modalities have been used (14, 25–29). Most susceptibility patterns for these fungi are restricted to individual cases; however, studies by Gonzalez et al. (30) and Chowdhary et al. (31), with five and 26 strains, respectively, indicated that amphotericin B, itraconazole, and voriconazole had good *in vitro* activity against the isolates tested, while elevated MICs were observed for flucytosine and fluconazole.

The identification of *S. commune* and other filamentous basidiomycetes from clinical specimens is often problematic. Key morphological features necessary for the recognition of these fungi are the presence of clamp connections on hyphae and the development of fruiting bodies (32). However, many clinical isolates of *S. commune* do not form such structures and, in culture, only show colonies with white cottony surfaces, a rapid growth rate, and droplets of exudate (33), which are clearly not distinctive for either species or genus recognition. *Schizophyllum* includes nearly 20 species (http://www.mycobank.org). However, ex-type strains for many of those species do not exist; only a limited number of strains for a few species identified by specialists have been deposited into different public culture collections (i.e. *S. commune*, *S. fasciatum*, *S. radiatum*, and *S. umbrinum*). In addition, some species such as *S. commune* and *S. radiatum* have long been considered conspecific due to their morphological similarity (2). Recently, molecular methods have more successfully discriminated between various basidiomycetous moulds (13, 33, 34). Singh et al. (34) proposed sequencing the ITS and D1/D2 regions for the identification of basidiomycetes. However, when the sequences of these two regions are submitted in the GenBank database for comparison, there is a low level of discrimination due mainly to the lack of reliable sequences, therefore making a conclusive identification impossible (35). Although it is well-known that databases may contain poor quality sequences, the discordant results may also be related to the deposition of misidentified strains. Therefore, the occurrence of *S. commune* may have been overestimated and other species may in fact have been involved in both human and animal infections. Hence, the real distribution of the species of this genus in clinical samples is unknown. Therefore, the aim of this study was to assess the spectrum of *Schizophyllum* spp. in a set of clinical isolates from the USA, comparing representative reference strains of different

Schizophyllum species, and using a multi-locus phylogenetic analysis to clarify their taxonomy. Additionally, the *in vitro* antifungal susceptibility of the fungi investigated was determined against six antifungal agents to determine if the susceptibility profiles of the USA strains differ from those of strains isolated from other parts of the world.

Material and Methods

Fungal isolates

A total of 33 *Schizophyllum* strains were included in this study, 23 of which were clinical isolates from across the USA and received in the Fungus Testing Laboratory at the University of Texas Health Sciences Center at San Antonio (UTHSCSA) for identification, antifungal susceptibility testing, or both. The USA isolates were of human (n=21) and animal (n=2) origins, and were mainly recovered from the respiratory tract (n=19, 82.6%), i.e. sinuses (43.5%), bronchoalveolar lavage (26.1%), sputum (8.7%) and lung (4.3%). Additionally, one isolate was from a lymph node and the other from a spinal mass, and two other isolates were of unknown origin. The remaining 10 isolates were obtained from different international culture collections as reference strains for comparison (Table 1).

DNA extraction, amplification and sequencing

Total genomic DNA was extracted from potato dextrose agar (PDA; Pronadisa, Madrid, Spain) cultures after 7 days of incubation at 25ºC using the FastDNA® Kit and the FastPrep® Instrument (MP Biomedicals, Irvine CA, USA), according to the manufacturer's specifications. Four DNA targets were amplified using the following primer pairs: ITS4 and ITS5 for the internal transcribed spacer 1 (ITS1), the 5.8S gene, and ITS2 regions (36); LR0R and LR5 for a portion of the large subunit (LSU) gene of the rDNA (37); EF-983F and EF-2218R for the translation elongation factor 1α (*EF-1α*) gene (38); and 5F and 7CR for the RNA polymerase II second largest subunit (*RPB2*)

gene (39). PCR products were sequenced in both directions, using the same primers, at Macrogen Europe (Macrogen Inc., Amsterdam, The Netherlands). Sequences were assembled and edited using Sequencher 4.1.4 (Gene Codes Corporation©, Ann Arbor MI, USA).

Molecular identification and phylogenetic analyses

The phylogenetic analyses were carried out first individually for each gene and, after the topologies proved to be congruent, a concatenated study was performed. All sequences used for the analyses were obtained from the strains included in this study. For multiple sequence alignment, the ClustalW tool was used together with the MUSCLE tool inside MEGA v.6 software (40), with manual adjustments. The Maximum Likelihood (ML) phylogenetic method was also run with MEGA v.6 software, as well as the estimation of the best nucleotide substitution method. Support of the internal branches was assessed by the Bootstrap (bs) method with 1000 replications, where values ≥70 were considered significant. The Bayesian Inference (BI) method was performed using MrBayes v.3.1.2 software (41). The evolutionary models that best fit each gene were assessed by MrModelTest v.2 software (42). Markov chain Monte Carlo (MCMC) sampling was performed with two simultaneous runs for 3 million generations, with samples taken every 100 generations. The 50% majority rule consensus trees and posterior probability values (pp) were calculated after removing the first 25% of the resulting trees for burn-in. A pp value of ≥0.95 was considered in the tree.

Antifungal susceptibility testing

The *in vitro* susceptibility profiles of the isolates were determined by CLSI M38-A2 method with a few modifications (43). The modifications included working inocula, obtained from colonies on PDA with 7 to 10 days of incubation at 30ºC, of 2.5

x 10^4 to 5.0 x 10^4 hyphal fragments/ml, and the microplates were incubated at 35°C for 72 h. The six antifungal agents tested were amphotericin B (AMB) (Sigma Aldrich Quimica S.A., Madrid, Spain), itraconazole (ITC) (Jansen Pharmaceuticals, Beerse, Belgium), posaconazole (PSC) (Schering-Plough Res., Inst., NJ, USA), voriconazole (VRC) (Pfizer S.A., Madrid, Spain), caspofungin (CFG) (Merk & Co., Inc., Rahway, USA), and terbinafine (TBF) (Sigma Aldrich Química S.A., Madrid, Spain). The minimal inhibitory concentration (MIC) was defined as the lowest drug concentration that produced 100% inhibition of visible fungal growth for the AMB and the azoles (ITC, PSC and VRC) or 80% for TBF. The minimum effective concentration (MEC) was determined for CFG and was defined microscopically as the lowest concentration of drug that led to the growth of small, rounded, compact hyphal forms as compared with the long, unbranched hyphal clusters that were seen in the growth control. Two quality control strains (*Candida parapsilosis* ATCC 22019 and *Candida krusei* ATCC 6258) were used in each test, and their MIC ranges were within the CLSI reference ranges. All tests were carried out in duplicate, on different days, for reproducibility. Results were statistically analyzed using the Prism software for Windows v.6.0 (GraphPad Software, San Diego, CA).

Nucleotide sequence accession numbers

Sequences newly generated in this study were deposited in GenBank under accession numbers shown in Table 1.

Results

The phylogenetic analyses of the individual markers proved that the rDNA regions tested (ITS and LSU) were much conserved, not discriminating well between the closely-related species *S. commune* and *S. radiatum*. The LSU, *EF-1α*, and *RPB2* markers showed consistency and were used to perform a concatenated study. The ITS

region was not included in the combined alignment because, apart from not being informative for differentiating between the above-mentioned species, some strains were difficult to amplify and sequence. For example, the ITS sequence could not be obtained for MUCL 20578, UTHSCSA DI14-4 and UTHSCSA DI14-7 (Table 1).

The concatenated sequence alignment consisted of 2622 base pairs (LSU, 838 bp; *EF-1α*, 971 bp; *RPB2*, 813 bp), from which 539 bp were variable sites (LSU, 30 bp; *EF-1α*, 248 bp; *RPB2*, 261 bp) and 282 bp parsimony informative (LSU, 2 bp; *EF-1α*, 116 bp; *RPB2*, 164 bp). The topologies of the trees obtained with ML and BI analyses were basically the same, with only minor differences in the support values of internal nodes observed. Figure 1 shows the phylogenetic tree constructed using the LSU, *EF-1α*, and *RPB2* markers. Two main clades were observed in the phylogenetic tree. One clade included the strains of *S. commune* (i.e., 7 reference strains and one clinical isolate), and the other clade included the only reference strain of *S. radiatum* (CBS 301.32) used in the study together with the 22 remaining clinical isolates. Both clades showed high support values (values of bootstrap/posterior probability of 99/1 and 100/0.87, respectively). The reference strains of *S. umbrinum* and *S. fasciatum* acted as outgroups since the genetic distance to the clades of *S. radiatum* and *S. commune* were elevated (around 11.5% for *S. umbrinum*, and around 9% for *S. fasciatum*, for the LSU, *EF-1α* and *RPB2* markers). The average genetic distance between the clades of *S. radiatum* and *S. commune* was 4.0%, and the differences within the clades were 1.8% and 2.7% for the *S. radiatum* and *S. commune*, respectively.

In general, all the drugs tested showed activity against the *Schizophyllum* isolates tested. However, the antifungal with the greatest potency was AMB, followed by CFG and TBF (geometric mean MICs of 0.29 µg/ml, 0.58 µg/ml, and 0.79 µg/ml, respectively), while the least effective agents were ITC and PSC (geometric means of

1.67 µg/ml, and 2.93 µg/ml, respectively). Significant variation in *in vitro* activity was noted among the strains, especially for TBF, with MIC values ranging from 0.03 to 16.0 µg/ml. The drug displaying the most consistent results was CFG, with MICs ranging from 0.25 to 1.0 µg/ml. *Schizophylum radiatum* showed clearly higher geometric mean MICs for all the antifungals tested than *S. commune*, especially for ITC and PSC. The results of the *in vitro* susceptibility test are summarized in Table 2.

Taxonomy

Schizophyllum was described by Fries in 1815 (44) with *S. commune* as the type species. The same author transferred the morphologically similar species *Agaricus radiatum* to *Schizophyllum* (45), which was accepted by Linder in 1933 (46). By contrast, Cooke in 1961 considered both as varieties of the same species and treated *S. radiatum* as a synonym of *S. commune* (2). However, in the absence of modern taxonomic studies on this genus, due mainly to the lack of ex-type strains, the Index Fungorum (http://www.indexfungorum.org) and MycoBank (http://www.mycobank.org) databases list the species as different taxa.

According to our phylogenetic analysis, the clade formed by the confirmed strain of *S. radiatum* and most of the clinical isolates from the USA constitutes a well-supported monophyletic lineage with enough genetic differences to be considered a species distinct from *S. commune,* which forms a sister clade. For the purpose of taxonomic stability of the name *S. radiatum* and based on the current recommendations (47, 48), we selected the strain CBS 301.32 as epitype (CBS H-22699, MBT372269) for this species. This strain was collected in the same region as the type strain (Panama and Jamaica, respectively), and was identified by D. H. Linder (46) based on the original description provided by Fries (45). Among numerous specimens, Linder examined the authentic material of *S. radiatum*, which is deposited in the Farlow Herbarium at

Harvard University (46). Sequence data from the ex-epitype may be useful for future phylogenetic studies of *Schizophyllum* species, especially for the identification of non-sporulating isolates of *S. radiatum* involved in human infections, and to determine whether this species is also predominant among the *Schizophyllum* species in other parts of the world.

Our results also show that *S. commune* represents a species complex, which was already mentioned by Linder (46), since the genetic variation within the clade ranged from 0.9 % (between MUCL 20578 and UTHSCSA DI14-5) to 3.5 % (between MUCL 31016 and FMR 14713), with a mean variation of 2.7%. Nonetheless, further studies are needed to solve taxonomic differentiation within the *S. commune* clade.

Discussion

Schizophyllum is a very common and cosmopolitan genus of basidiomycetes that has been associated with human infections for over 60 years (11, 21). The most recent reviews of infections by *S. commune* were by Buzina et al. (33), who reported 16 published cases, and Chowdhary et al. (13) with 71 cases. More recently, 15 additional cases have been reported (14, 15, 17, 19, 49–59). Here, we studied 23 isolates of *Schizophyllum* from different clinical specimens and, although histopathological evidence for the corresponding infections is not available, this number of isolates from a single country reinforces the growing importance of *Schizophyllum* in the clinical setting. The different clinical manifestations highlight the versatility of this pathogen (13); however, the pulmonary and respiratory sites appear to be the most common sites of recovery. In Colombia, *S. commune* was the second most common agent of fungal rhinosinusitis, following *Aspergillus* (60). In our study, 43.5% of the strains were isolated from sinuses, and a total of 82.6% of strains from patients with respiratory conditions. Interestingly, in a study on the distribution and seasonal diversity of

pathogenic fungi in outdoor air in the northeastern United States, which used quantitative real-time PCR plus pyrosequencing, *S. commune* was the most abundant species, particularly in spring (61). However, the identification exclusively of *S. commune* in all those studies should be taken with caution due to the lack of phylogenic studies that have clarified the taxonomy of closely-related species in *Schizophyllum*, such as *S. commune* and *S. radiatum*.

Although in nature these fungi mainly adopt the form of a gilled mushroom (62), when they are isolated from clinical specimens and growing in culture, *Schizophyllum* strains often remain sterile (63). This precludes their morphological identification. In routine laboratories, the induction of sporulation usually requires about 3 weeks and is associated to high failure rates (34). Therefore, molecular methods, such as DNA sequence analysis, are required for accurate identification of this kind of fungi that fails to sporulate (13). The most commonly sequenced markers in *Schizophyllum* are the ITS and D1/D2 regions of LSU (13, 33, 34). However, *Schizophyllum* has a highly conserved ITS region, which is often difficult to amplify and to sequence. Singh et al. (34) reported this difficulty, being unable to amplify three of 27 strains they identified as *S. commune*. Although the LSU region is more informative, in general, its resolution is only at the genus level. In addition, Romanelli et al. (35) demonstrated, with filamentous basidiomycetes that included *Schizophyllum*, that a comparison in the GenBank database can cause disagreement between results when both ITS and LSU regions of the same strain are searched; of the 15 *Schizophyllum* strains (9 *S. commune* and 6 *S. radiatum*) identified by ITS sequencing, only one strain of *S. radiatum* by the LSU region agreed with the identification. Moreover, two strains identified as belonging to *Phlebia* by the ITS, were identified as *Schizophyllum* spp. by the LSU region. The inconsistency of results made it impossible to assign a conclusive identification to over

70% of the isolates included in that study (35). It would seem clear then that other, more appropriate, markers need to be adopted for reliable species identification. In the present study, the use of three combined markers (LSU, and *EF-1α*, and *RPB2*) provided enough phylogenetic information for this purpose. We were able to demonstrate that more than one species may be involved in *Schizophyllum* infections; and, contrary to general belief, *S. radiatum* was shown to be, almost exclusively, the species identified from clinical isolates of a US reference center. In addition, this study provides a set of 33 strains (4 species) of *Schizophyllum* spp. for future comparison.

Optimum management of infections by *S. commune* has not yet been determined (14, 31, 34). However, treatment with antifungal drugs has given encouraging results. AMB is reported to be the most potent *in vitro* against *S. commune* and other antifungal drugs have also shown good activity (14, 16, 31, 64). It is worth mentioning, however, that at least one patient with allergic bronchopulmonary infection and treated with itraconazole for 10 months showed no clinical improvement (65, 66). In fact, a correlation between *in vitro* data and clinical efficacy has not been well established (54). In agreement with other studies (30, 31), AMB showed the highest *in vitro* potency against most *Schizophyllum* isolates tested. The strains of *S. commune* tested here had low MICs for PSC and VRC (0.20 µg/ml for both) similar to previous reports (30, 31). For *S. radiatum*, our results revealed high variability among strains, especially for the azoles and for TBF (Table 2). In the case of PSC, MIC values of *S. radiatum* were significantly higher than those of *S. commune* (GM of 7.46 µg/ml and 0.20 µg/ml, respectively; $p < 0.0001$), compared using the Mann-Whitney U test. For ITC and VRC, the differences were not statistically significant even though the MICs of *S. radiatum* were apparently higher than those of *S. commune* (GM of 2.82 µg/ml and 0.37 µg/ml for ITC, and 1.72 µg/ml and 0.20 µg/ml for VRC). For the echinocandin tested, CSP, in

general low MIC values were observed (0.25–1.0 µg/ml), contrary to Singh et al. (34) who reported high MICs (2–8 µg/ml) of the same drug for *S. commune*. Considering that echinocandins have been reported as ineffective against clinically relevant basidiomycetes (67, 68), our discrepant results might be due to variations in the method (incubation time, preparation of the inoculum with hyphal fragments, etc.). Since there is no standardized method for antifungal susceptibility testing of filamentous basidiomycetes and non-sporulating fungi (68), studies often modify the CLSI protocol (31, 34) in an attempt to obtain reproducible results, as in our case. Therefore, before standardization of these protocols, inter-laboratory results cannot be properly compared.

In conclusion, the importance of *Schizophyllum* in the clinical setting has been demonstrated by the number of reported cases and strains isolated. The present study, on this collection of isolates from the USA, has shown that *S. radiatum*, rather than *S. commune*, is the most frequently recovered species, and provides informative targets for the molecular discrimination between the two species.

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Fig 1 − Maximum likelihood tree obtained from the combined LSU, *EF-1α*, and *RPB2* sequences of the isolates. Branch lengths are proportional to phylogenetic distance. Bootstrap support values/Bayesian posterior probability scores over 70/0.95 are indicated on the nodes. The fully supported branches (100/1) and reference strains are shown in bold. CBS: CBS Fungal Biodiversity Centre (The Netherlands); FMR: Facultat de Medicina de Reus (Spain); MUCL: Université Catholique de Louvain (Belgium); UTHSCSA: University of Texas Health Science Center (San Antonio, USA).

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Table 1 − Origin and GenBank accession numbers of the sequences of *Schizophyllum* strains included in this study

Species			GenBank accession number			
(no. isolates)	Strain	Origin	ITS	LSU	*EF-1α*	*RPB2*
S. commune	CBS 132304	Man, India	LT217530	LT217561	LT217595	LT217629
(8)	CBS 476.64	Unknown, USA	LT217531	LT217562	LT217596	LT217630
	FMR 14713	Sputum, India	LT217532	LT217563	LT217597	LT217631
	MUCL 20578	*Fagus sylvatica*, Belgium	-	LT217564	LT217598	LT217632
	MUCL 29305	Man, Brazil	LT217533	LT217565	LT217599	LT217633
	MUCL 30748	*Saccharum officinarum*, Africa	LT217534	LT217566	LT217600	LT217634
	MUCL 31016	Hay, Belgium	LT217535	LT217567	LT217601	LT217635
	UTHSCSA DI14-5	Sinus-nasal, USA	LT217536	LT217568	LT217602	LT217636
S. radiatum	CBS 301.32	Unknown, Panama	LT217537	LT217569	LT217603	LT217637
(23)	UTHSCSA DI14-1	Unknown, USA	LT217539	LT217571	LT217605	LT217639
	UTHSCSA DI14-2	Lymph node[a], USA	LT217540	LT217572	LT217606	LT217640
	UTHSCSA DI14-3	Lung[a], USA	LT217541	LT217573	LT217607	LT217641
	UTHSCSA DI14-4	BAL, USA	-	LT217574	LT217608	LT217642
	UTHSCSA DI14-6	Sputum, USA	LT217542	LT217575	LT217609	LT217643
	UTHSCSA:DI14-7	Maxillary sinus, USA	-	LT217576	LT217610	LT217644
	UTHSCSA:DI14-8	BAL, USA	LT217543	LT217577	LT217611	LT217645
	UTHSCSA DI14-9	Sinus-nasal, USA	LT217544	LT217578	LT217612	LT217646
	UTHSCSA DI14-10	BAL, USA	LT217545	LT217579	LT217613	LT217647
	UTHSCSA DI14-11	Sinus-nasal, USA	LT217546	LT217580	LT217614	LT217648
	UTHSCSA DI14-12	Sphenoid sinus, USA	LT217547	LT217581	LT217615	LT217649
	UTHSCSA DI14-13	Spinal mass, USA	LT217548	LT217582	LT217616	LT217650
	UTHSCSA:DI14-14	Sphenoid sinus, USA	LT217549	LT217583	LT217617	LT217651
	UTHSCSA:DI14-15	BAL, USA	LT217550	LT217584	LT217618	LT217652
	UTHSCSA:DI14-16	BAL, USA	LT217551	LT217585	LT217619	LT217653
	UTHSCSA DI14-17	Sputum, USA	LT217552	LT217586	LT217620	LT217654
	UTHSCSA DI14-18	Abscess, USA	LT217553	LT217587	LT217621	LT217655
	UTHSCSA DI14-19	BAL, USA	LT217554	LT217588	LT217622	LT217656
	UTHSCSA DI14-20	Maxillary sinus	LT217555	LT217589	LT217623	LT217657
	UTHSCSA DI14-22	Sinus-nasal, USA	LT217556	LT217590	LT217624	LT217658
	UTHSCSA DI14-23	Ethmoid sinus, USA	LT217557	LT217591	LT217625	LT217659
	UTHSCSA DI14-26	Maxillary sinus, USA	LT217558	LT217592	LT217626	LT217660
S. fasciatum	CBS 267.60	Unknown, USA	LT217559	LT217593	LT217627	LT217661
S. umbrinum	MUCL 43017	Unknown, USA	LT217560	LT217594	LT217628	LT217662

BAL: bronchoalveolar lavage fluid specimen; CBS: CBS Fungal Biodiversity Centre (The Netherlands); FMR: Facultat de Medicina de Reus (Spain); MUCL: Université Catholique de Louvain (Belgium); UTHSCSA: University of Texas Health Science Center (San Antonio, USA); ITS: internal transcribed spacer regions of the rDNA and 5.8S region; LSU: partial large subunit of the rDNA; *EF-1α*: partial translation elongation factor gene; *RPB2*: partial RNA polymerase II second largest subunit. [a]Animal origin.

TABLE 2 − Results of *in vitro* antifungal susceptibility test for 31 isolates of *Schizophyllum* spp.

Species (no. isolates)	Parameter	MIC or MEC (µg/ml) for:					
		AMB	CFG	ITC	PSC	TBF	VRC
S. commune (8)	GM	0.09	0.41	0.37	0.20	0.61	0.20
	MIC range	0.03–0.25	0.25–1.0	0.25–1.0	0.12–0.5	0.12–>16	0.12–0.5
	Mode	0.25	0.25	0.25	0.25	0.25	0.25
S. radiatum (23)	GM	0.43	0.66	2.82	7.46	0.86	1.72
	MIC range	0.06–2.0	0.25–1.0	0.12–>16.0	0.25–>16.0	0.03–>16.0	0.06–>16.0
	Mode	0.5	1.0	>16.0	>16.0	0.5	>16.0
	MIC_{90}	2.0	1.0	>16.0	>16.0	>16.0	>16.0
Total (31)	GM	0.29	0.58	1.67	2.93	0.79	0.99
	MIC range	0.03–2.0	0.25–1.0	0.12–>16.0	0.12–>16.0	0.03–>16.0	0.06–>16.0
	Mode	0.5	1.0	0.25	>16.0	0.25	0.12
	MIC_{90}	2.0	1.0	>16.0	>16.0	>16.0	>16.0

AMB, amphotericin B; CFG, caspofungin; ITC, itraconazole; PSC, posaconazole; TBF, terbinafine; VRC, voriconazole; MIC, minimum inhibitory concentration; MEC, minimum effective concentration, for CFG; GM, geometric mean.

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