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Original Article

Scedosporiosis/lomentosporiosis observational study (SOS): Clinical significance of *Scedosporium* species identification

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Abstract

Scedosporiosis/lomentosporiosis is a devastating emerging fungal infection. Our objective was to describe the clinical pattern and to analyze whether taxonomic grouping of the species involved was supported by differences in terms of clinical presentations or outcomes. We retrospectively studied cases of invasive scedosporiosis in France from 2005 through 2017 based on isolates characterized by polyphasic approach. We recorded 90 cases, mainly related to *Scedosporium apiospermum* ($n = 48$), *S. boydii*/*S. ellipsoideum* ($n = 20$), and *Lomentospora prolificans* ($n = 14$). One-third of infections were disseminated, with unexpectedly high rates of cerebral (41%) and cardiovascular (31%) involvement. In light of recent *Scedosporium* taxonomic revisions, we aimed to study the clinical significance of *Scedosporium* species identification and report for the first time contrasting clinical presentations between infections caused *S. apiospermum*, which were associated with malignancies and cutaneous involvement in disseminated infections, and infections caused by *S. boydii*, which were associated with solid organ transplantation, cerebral infections, fungemia, and early death. The clinical presentation of *L. prolificans* also differed from that of other species, involving more neutropenic patients, breakthrough infections, fungemia, and disseminated infections. Neutropenia, dissemination, and lack of antifungal prescription were all associated with 3-month mortality. Our data support the distinction between *S. apiospermum* and *S. boydii* and between *L. prolificans* and *Scedosporium* sp. Our results also underline the importance of the workup to assess dissemination, including cardiovascular system and brain.

Lay Summary

Scedosporiosis/lomentosporiosis is a devastating emerging fungal infection. Our objective was to describe the clinical pattern and to analyze whether taxonomic grouping of the species involved was supported by differences in terms of clinical presentations or outcomes.

Key words: scedosporiosis, *Scedosporium* sp., *Lomentospora prolificans*, outcome, cardiovascular localization.

Introduction

Invasive scedosporiosis/lomentosporiosis is a devastating emerging mycosis caused by *Scedosporium* spp. and *Lomentospora prolificans* (previously known as *Scedosporium prolificans*).^{1–3} This mycosis usually affects immunocompromised patients with hematological malignancies (HMs) or after solid organ transplantation (SOT),^{4–8} but it has also been reported in immunocompetent patients in the setting of near-drowning or inoculation.^{9,10} The predominant clinical presentations are pulmonary and cerebral, but they can also manifest with disseminated infections.^{5,8,11–13} Invasive scedosporiosis/lomentosporiosis can also occur in cystic fibrosis patients, especially in case of lung transplantation.¹⁴

Invasive scedosporiosis/lomentosporiosis represents 13–33% of infections due to non-*Aspergillus* moulds, depending on geographical localization and underlying disease.^{15,16} An increase in cases of non-*Aspergillus* mould infections has been reported over the last two decades,^{17,18} and is associated with high overall mortality rates (up to 35–40% nowadays), especially in the setting of HM and when infection is due to *L. prolificans*.^{11,15}

Overall, data regarding invasive scedosporiosis are scarce and have mostly been obtained from reviews of case reports or small case series.^{2,3,10,15,19–21} Prior original studies have mostly focused on specific at-risk populations, such as patients with hematological conditions or recipients of solid organ and allogeneic stem cell transplantation.^{4,7,8} To date, only one recent study of 264 cases, based on a literature analysis of 232 cases and aggregating 41 additional cases from the FungiScope[®] registry, has assessed the prognostic factors associated with *Scedosporium* spp. and *L. prolificans* infections.²²

The nomenclature and taxonomy of the genus *Scedosporium* have been revised on several occasions.^{23–26} The first was the separation of *S. apiospermum* and *Pseudallescheria boydii* (traditionally thought to be a sexual form of *S. apiospermum*) into two distinct species.^{23,27} More recently, *Scedosporium* was adopted as the generic name over *Pseudallescheria*, and *S. prolificans* was renamed as *L. prolificans*.^{23,25} At present, the genus *Scedosporium* comprises 10 distinct species: *S. aurantiacum*, *S. minutisporum*, *S. deboogii*, *S. desertorum*, *S. cereisporum*, *S. apiospermum*, *S. boydii*, *S. ellipsoideum*, *S. angustum*, and *S. fusoidium*. Finally, Lackner et al. have proposed grouping the latter five species into the *S. apiospermum* complex.^{25,26} Overall, few studies have considered these taxonomic changes in the clinical description of cases of scedosporiosis. Furthermore, even taxonomists question the relevance of identification at a species level among the *S. apiospermum* complex because of the potential for interspecies recombination and the lack of clinical data supporting species differentiation.²⁸

The National Reference Center for Invasive Mycoses and Antifungals (NRCMA) conducted a retrospective scedosporiosis/lomentosporiosis observational study (SOS) of all proven

and probable cases of invasive scedosporiosis diagnosed over a 12-year period in France. Our objective was to describe the infections and the various species involved in France and to analyze whether taxonomic grouping was supported by differences in terms of clinical presentation or outcome.

Methods

Type of study and sources of data

Cases of proven or probable invasive scedosporiosis/lomentosporiosis (thereafter referred to as DeepScedo) from January 2005 to March 2017 were retrospectively studied based on the isolates of *Scedosporium* spp. or *L. prolificans* already characterized at the NRCMA.

Database management and case validation

Data were recorded anonymously on a standardized questionnaire hosted on a secured web site using Voozoo[®] (Epiconcept, Paris, France). Each case was reviewed at the NRCMA by two clinicians (D.B. and F.L.) and classified according to the 2019 European Organization for Research and Treatment of Cancer/Mycoses Study Group criteria.²⁹ The only modification was the inclusion of trauma as a risk factor when there was a temporal relationship with the onset of DeepScedo. Only proven and probable DeepScedo were included.

Definitions

Six main underlying conditions were considered but only one was assigned to each patient in the following order: (i) malignancies (HM or solid tumor); (ii) SOT in the absence of malignancies, (iii) systemic inflammatory disease (SID) in the absence of HM or SOT; (iv) contamination through trauma, injury, surgery, and near-drowning in the absence of HM, SOT, or SID (trauma/inoculation); (v) ‘others’ in case of miscellaneous underlying medical conditions; and (vi) no risk factor in the absence of all previous factors. For each patient, we determined the number of associated underlying conditions such as neutropenia, allogeneic hematopoietic stem cell transplantation (HSCT), chronic renal or respiratory insufficiency, diabetes mellitus, or corticosteroid administration.²⁹

Infections were considered as disseminated (two noncontiguous sites involved and/or positive blood culture)¹¹ or localized and thus categorized as involving the pleura or lung parenchyma (lung), bones, muscles or skin (osteoarticulation/skin), sinus/ear, or others (including brain and digestive tract). Breakthrough infections were defined by infections developing while the patient had received antifungal therapy for at least 7 days. Prior colonization was defined by presence of *Scedosporium* in a site without sign of infection. Death occurring within 8 days of diagnosis (including post-mortem diagnosis) was considered as early death.

Polyphasic identification of isolates

All strains were identified at the NRCMA by polyphasic approach. Purity was first assessed on Sabouraud chloramphenicol agar plates. Subcultures were done on 2% malt agar (MEA), incubated at 30°C to promote sporulation, and morphology was studied on cultures grown for 5–7 days. Molecular identification was performed by sequencing the ITS1-5.8S-ITS2 region of the ribosomal DNA³⁰ and a partial region of the β -tubulin gene.²⁷ Consensus sequences were obtained by using the Sequencher[®] version 5.4.6 sequence analysis software (Gene Codes Corporation, Ann Arbor, MI, USA) and pairwise sequence identification was carried out against curated databases available at the online MycoBank database (<http://www.mycobank.org/>). The β -tubulin sequences were aligned using MAFFT v.7.388 with default settings and the alignment was submitted to neighbor-joining (NJ) analysis implemented on MEGA7 program.³¹ For NJ analyses, the model used was Kimura two-parameter gamma and robustness of the branches was assessed by bootstrap analysis with 1000 replicates.

Antifungal susceptibility testing

In vitro susceptibility testing was performed according to the European Committee on Antimicrobial Susceptibility Testing procedure³² with modifications as described before.³³ Six antifungal agents (all purchased from ALSACHIM, Strasbourg, France) were included: amphotericin B, itraconazole, voriconazole, posaconazole, caspofungin, and micafungin.

Ethical issues

Research was approved by the Institut Pasteur Internal Review Board (2009-34/IRB) and by the Commission Nationale de l'Informatique et des Libertés in accordance with French law. All clinical data were recorded anonymously through a secured database using Voozano[®] (Epiconcept, Paris, France).

Statistical analysis

All species were analyzed individually. Since *S. ellipsoideum* status is still on debate,²⁶ it was grouped with *S. boydii* for comparison with *S. apiospermum*. Univariate analysis was performed with the chi-squared or Fisher's exact test when needed for discrete variables. Comparison of two distributions was based on the Wilcoxon–Mann–Whitney test. Comparison of more than two distributions was based on the Kruskal–Wallis equality-of-populations rank test. Survivals were determined by the Kaplan–Meier method and compared by the log-rank test. Data were analyzed using Stata[®] software (version 15; College Station, TX, USA).

Results

Characterization of the isolates and susceptibility testing

A total of 147 isolates of *Scedosporium* spp. or *L. prolificans* were characterized at the NRCMA corresponding to 146 cases. Fifty-six cases were excluded due to missing data ($n = 24$), noninvasive infections ($n = 14$), and colonization ($n = 18$). Ninety cases of DeepScedo were eventually included (65 proven and 25 probable infections). One patient had mixed proven infection due to *L. prolificans* and *S. apiospermum* and was thereafter excluded from the species comparison analysis.

All isolates were identified to the genus *Scedosporium* or *Lomentospora* by microscopic observation (Fig. 1) of branched or solitary conidiophores, with pale or melanized thin- or thick-walled sessile conidia for *Scedosporium* spp., and inflated flask-shaped conidiophores and pale to melanized conidia aggregated on slimy heads for *L. prolificans*. The latter grew dark velvety colonies compared to suede-like greyish black colonies for *Scedosporium* spp. In parallel, the alignment of the tubulin sequences allowed for the identification of 8 species among the 91 isolates studied (Fig. 2). Overall, we identified 48 *S. apiospermum*, 15 *S. boydii*, 14 *L. prolificans*, 5 *S. ellipsoideum*, 4 *S. dehoogii*, 2 *S. aurantiacum*, 2 *S. minutisporum*, and 1 *S. angustum*.

Antifungal susceptibility pattern was determined for all isolates (Table 1 and Supplementary Table 1). *Lomentospora prolificans* exhibited the highest minimal inhibitory concentrations (MICs) for all antifungals (Table www1). The MICs for azoles were consistently lower for *S. boydii* than for *S. apiospermum*, whereas MICs for echinocandins were similar. Of note, micafungin MICs were lower than caspofungin MICs.

Characteristics of the patients

Patient characteristics are presented in Table 2. The most common underlying condition was malignancy. Twenty-eight patients had HM, including 12 with acute leukemia (7 myeloid [AML], 5 lymphoid [ALL]) and 11 with other lymphoid malignancies. Half of these patients (14/28) were neutropenic. Nine patients had undergone allogeneic HSCT (matched related [$n = 3$] or unrelated [$n = 6$]), three of which were complicated by grade 3–4 graft-versus-host disease. The median interval between diagnosis of HM or HSCT and DeepScedo was 503 days (range: 11–4904 days) and 186 days (range: 19–3809 days), respectively.

Trauma or 'direct' inoculations were the second most common underlying conditions. These included road accidents ($n = 5$), farming or gardening injuries ($n = 4$), falls ($n = 4$), contaminations through medical procedures ($n = 3$), near-drowning ($n = 1$), or other traumas ($n = 2$). SOT was the third most frequent underlying condition, with DeepScedo occurring a median

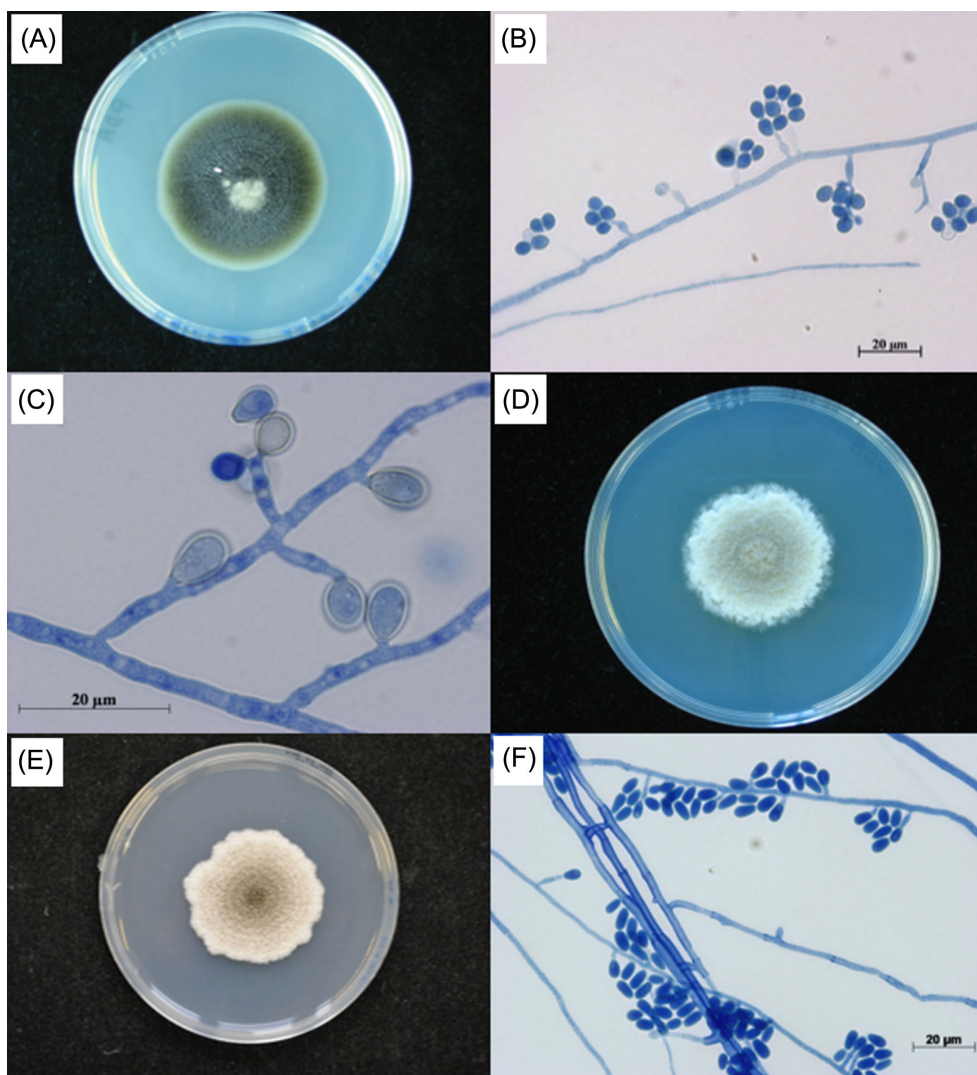


Figure 1. Colony morphology on potato dextrose agar after 7 days at 30°C: (A) *L. prolificans*, (D) *S. apiospermum*, and (E) *S. boydii*. Conidiogenous cells and conidia: (B) *L. prolificans*, (C) *S. apiospermum*, and (F) *S. boydii*.

of 155 days (range: 28–2181 days) after transplantation. Lastly, SID was the main underlying condition in eight patients (9%), of whom six received corticosteroids and seven another immunosuppressive therapy.

Six children with a mean age of 9 years (range: 0–14 years) had DeepScedo. The main underlying conditions were malignancy (including two with ALL), inoculation/trauma (one near-drowning and one dog bite with telluric contamination), and two had chronic granulomatous disease.

Characteristics of DeepScedo cases

The median delay between onset of first symptoms and diagnosis of DeepScedo was 29 days (range: 1–1080 days). Cases were divided into localized or disseminated infections (Table 2). Localized infections were mostly musculoskeletal/cutaneous and pulmonary, whereas disseminated infections most often in-

involved the lungs, skin, brain, and the cardiovascular system. Blood cultures were performed in 52 patients and were positive in 11 (21%).

Clinical presentation differed according to the main underlying medical condition

When considering the six categories of underlying conditions (HM, SOT, SID, inoculation, others, and no risk factor), we discovered significant differences in terms of clinical presentation, with patients with HM or SOT experiencing significantly more disseminated infections (Table 3). Dissemination was reported in 86% of patients with AML compared to less than 50% in patients with other HMs (40% for ALL and 46% for other lymphoid malignancies). In cases of disseminated infection, SOT recipients more often had cerebral (71% vs. 24%, $P = .028$), cardiovascular (57% vs. 18%, $P = .053$), and osteoarticular

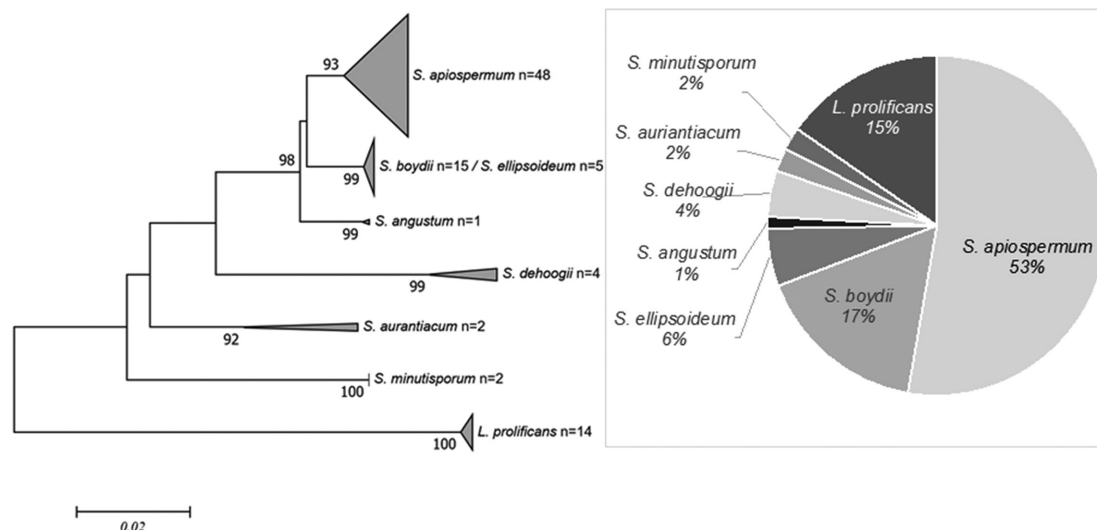


Figure 2. Characterization and proportion of the 91 isolates responsible for DeepScedo. (A) Condensed phylogenetic tree. Constructed from partial gene sequences of β -tubulin using the NJ method based on the Kimura two-parameter gamma model. Support bootstrap values for NJ are provided on the branches and scale bar = substitutions/site. (B) Distribution of *Scedosporium* and *Lomentospora* species.

Table 1. *In vitro* susceptibility profiles (mg/l) of *Scedosporium* species and *L. prolificans* to six antifungal drugs.

	MIC50/MIC90 (range) ^a		
	<i>L. prolificans</i> (n = 14)	<i>S. apiospermum</i> (n = 48)	<i>S. boydii</i> (n = 15)
Itraconazole	16/16 (16–16)	1/16 (0.25–16)	0.5/2 (0.125–16)
Voriconazole	8/16 (2–16)	0.5/1 (0.06–2)	0.25/0.5 (0.25–0.5)
Posaconazole	16/16 (16)	1/2 (0.25–2)	0.5/16 (0.125–16)
Amphotericin B	8/16 (8–16)	8/16 (1–16)	8/16 (8–16)
Caspofungin	4/8 (2–8)	1/2 (0.5–8)	1/2 (0.125–2)
Micafungin	4/8 (0.25–8)	0.25/1 (0.125–1)	0.25/1 (0.125–2)

^aMIC50 and MIC90: MIC inhibiting 50% and 90% of the isolates tested, respectively.

(43% vs. 0%, $P = .004$) localizations compared to patients with HM. Localized infections were more prevalent in the other groups, with patients with SID or trauma/inoculation-related infections predominantly experiencing either pulmonary or osteoarticular and soft-tissue infections. Patients with no risk factors consistently had localized sinusitis or invasive otitis.

Overall, patients with malignancies and SOT recipients had a shorter interval of time between onset of symptoms and diagnosis of DeepScedo, and more frequently experienced breakthrough infections than patients in other categories.

Scedosporiosis/lomentosporiosis presentation and outcomes differ according to causative species

Comparison of *S. apiospermum* vs. *S. boydii* infections (Table 4)

The distribution of underlying risk factors differed between the two groups, with malignancy being more prevalent in the 47 patients with *S. apiospermum* infection (36%, mainly HM, including 1 AML, 4 ALL, 8 lymphoid, and 2 others), and SOT

(40%, including 5 lung transplantations) in the 20 patients with *S. boydii*/*S. ellipsoideum* infections. Chronic respiratory failure, prior *Scedosporium* colonization, and localized lung infections were more frequently reported in patients with *S. boydii* infections. In cases of disseminated infections, *S. apiospermum* more frequently involved cutaneous localizations, whereas cerebral infections and fungemia were more frequent with *S. boydii*. Overall, 60% (12/20) of infections caused by *S. boydii* affected the lungs, in contrast to 30% (14/47) of those due to *S. apiospermum* ($P = .020$). Early deaths (before day 8) were significantly more frequent in patients infected with *S. boydii*.

Lomentospora prolificans infections differed from *Scedosporium* spp. infections (Table 5)

Significantly more patients infected with *L. prolificans* had an underlying HM (9/13, 69%, including 5 AML, 1 ALL, 2 lymphoid malignancies, and 1 other) compared to patients infected with *Scedosporium* spp. (20/76, 26%, 2 AML, 4 ALL, 9 lymphoid, and 5 others) ($P = .002$). Neutropenia, breakthrough infections, dissemination, and fungemia were significantly more prevalent

Table 2. Characteristics of 90 episodes of probable or proven invasive scedosporiosis/lomentosporiosis recorded in France (SOS, 2005–2017).

	Number of patients (%) ^a
Median age (range) in years	61 (0–86)
Male	67 (74%)
Main risk factor	
Malignancy	33 (37%)
HM	28 (31%)
Solid tumor ^b	5 (6%)
Trauma/inoculation	19 (21%)
SOT ^c	15 (17%)
SID ^d	8 (9%)
Other risk factors ^e	11 (12%)
No risk factor	4 (4%)
Associated risk factor	57 (63%)
Chronic renal insufficiency	14/88 (16%)
Chronic respiratory diseases	19/89 (21%)
Type 2 diabetes	18 (20%)
Corticosteroid therapy	29 (32%)
Prior <i>Scedosporium</i> spp. infection/colonization	9/89 (10%)
Breakthrough infection (ongoing antifungal treatment)	20 (22%)
Infection localization	
Localized infection	61/90 (67%)
Osteoarticular	19/61 (31%)
Cutaneous	8/61 (13%)
Pleuropulmonary	18/61 (30%)
Sinus and ear ^f	9/61 (15%)
Brain ^f	6/61 (10%)
Others	3/61 (5%)
Disseminated	29/90 (32%)
Pleuropulmonary	17/29 (59%)
Cutaneous	14/29 (48%)
Brain	12/29 (41%)
Cardiovascular	9/29 (31%)
Osteoarticular	5/29 (17%)
Fungemia	11/26 (42%)
Therapeutic management	87/90 (97%)
First-line antifungal therapy ^g	80/87 (92%)
Single drug prescribed	53/80 (66%)
Voriconazole alone	48/54 (89%)
Others ^h	6/54 (11%)
Antifungal combination including	24/87 (28%)
Voriconazole	19
Caspofungin	13
Terbinafine	7
Liposomal amphotericin B	7
Posaconazole	3
Median (range) duration in days	189 (8–1497)
Curative surgery	43/87 (49%)
Global mortality at 3 months	21/83 (25%)

^aDenominator represents the number of patients for whom the information was available (not stated when it was available for all patients).

^bMetastatic lung adenocarcinoma, rectal adenocarcinoma with peritoneal carcinomatosis, esophagus epidermoid cancer, glioblastoma, and metastatic femoral osteosarcoma (one each), all with ongoing chemotherapy.

^cLung ($n = 6$, for cystic fibrosis), kidney ($n = 3$), heart ($n = 3$), liver ($n = 2$), liver and small bowel ($n = 1$), liver and kidney ($n = 1$), kidney and pancreas ($n = 1$).

^dChronic inflammatory rheumatism ($n = 4$), Horton disease or polymyalgia rheumatica ($n = 2$), autoimmune hepatitis ($n = 1$), and autoimmune hemolytic anemia ($n = 1$).

^eChronic respiratory disease ($n = 5$), chronic granulomatous disease ($n = 2$), type 2 diabetes mellitus ($n = 2$), chronic renal failure ($n = 1$), stay in intensive care unit complicated with malnutrition ($n = 1$).

^fTwo patients had invasive sinusitis or otitis associated with CNS extension.

^gExcluding patients diagnosed post-mortem ($n = 3$).

^hPosaconazole ($n = 3$), liposomal amphotericin B ($n = 1$), and caspofungin ($n = 1$).

Table 3. Characteristics of 90 invasive scedosporiosis/lomentosporiosis episodes according to the main risk factor.

	Malignancies (n = 33)	SOT (n = 15)	SID (n = 8)	Trauma/ inoculation (n = 19)	Others (n = 11)	No risk factor (n = 4)	P-value
Median age (range) in years	59 (7–85)	52 (16–70)	75 (72–79)	55 (0–86)	66 (13–79)	78 (68–85)	<.001
Male, n (%)	27 (82%)	10 (67%)	6 (75%)	12 (63%)	8 (73%)	3 (75%)	.728
Associated risk factor, n (%)	28 (85%)	15 (100%)	8 (100%)	3 (16%)	3 (28%)	–	<.001
Neutropenia	14 (45%)	1 (7%)	–	–	–	–	<.001
Corticosteroids	10 (30%)	5 (87%)	5 (63%)	–	1 (9%)	–	<.001
Diabetes	6 (18%)	5 (33%)	3 (38%)	1 (5%)	3 (28%)	–	.206
Chronic respiratory diseases	5 (16%)	7 (47%)	1 (23%)	1 (5%)	5 (45%)	–	.012
Breakthrough infection	10 (30%)	6 (40%)	–	1 (5%)	3 (15%)	–	.057
Median delay (range) in days between first symptoms and diagnosis	18 (1–80)	29 (2–110)	60 (15–155)	43 (6–720)	120 (6–260)	180 (53–1080)	<.001
Type of infection							
Localized infection, n (%)	16 (49%)	8 (53%)	7 (88%)	18 (95%)	8 (73%)	4 (100%)	.005
Lung	8/16 (50%)	4/8 (50%)	1/7 (14%)	2/18 (11%)	4/8 (50%)	–	.038
Osteoarticulation/skin	2/16 (13%)	3/8 (38%)	5/7 (71%)	15/18 (83%)	2/8 (25%)	–	<.001
Brain	–	2/8 (25%)	1/7 (14%)	1/18 (6%)	1/8 (13%)	1/4 (25%)	.005
Disseminated infection, n (%)	17 (51%)	7 (47%)	1 (13%)	1 (5%)	3 (27%)	–	.005
Lung	11/17 (65%)	3/7 (43%)	–	1/1 (100%)	2/3 (67%)	–	.675
Osteoarticulation/skin	9/17 (53%)	5/7 (71%)	5/1 (100%)	–	3/3 (100%)	–	.376
Fungemia	7/23 (30%)	2/10 (20%)	0/3 (0%)	1/10 (10%)	1/6 (17%)	ND	.589
Brain	4/17 (24%)	5/7 (71%)	1/1 (100%)	1/1 (100%)	1/3 (33%)	–	.058
Cardiovascular	3/17 (18%)	4/7 (57%)	–	1/1 (100%)	1/3 (33%)	–	.139
Others	6/17 (35%)	3/7 (43%)	–	–	1/3 (33%)	–	1.000
Therapeutic management							
First-line antifungal therapy, n (%) ^a	28/30 (93%)	15/15 (100%)	8/8 (100%)	15/19 (79%)	10/11 (91%)	4/4 (100%)	.236
Voriconazole alone or combined	25/28 (89%)	14/15 (93%)	8/8 (100%)	13/15 (87%)	6/10 (60%)	4/4 (100)	.102
Antifungal combination	10/27 (37%)	5/14 (36%)	1/8 (13%)	4/14 (29%)	4/10 (40%)	–	.537
Surgical treatment, n (%)	8/30 (27%)	10/15 (67%)	5/8 (63%)	14/19 (74%)	3/11 (27%)	3/4 (75%)	.006
Global outcome							
Death within 30 days, n (%)	10/33 (23%)	1/15 (7%)	1/8 (13%)	2/18 (11%)	0/11	0/4	.145
Death within 3 months, n (%)	15/31 (48%)	2/15 (13%)	1/7 (14%)	2/17 (12%)	1/10 (10%)	0/3	.023

Denominator represents the number of patients for whom the information was available (not stated when it was available for all patients).

^aExcluding patients diagnosed post-mortem.

in cases of *L. prolificans* infection. Of note, a skin injury was reported in three cases of *L. prolificans* infection. Patients with *L. prolificans* infection were also more frequently prescribed combination therapy than the others (Table 3).

Outcomes

Overall mortality was 16% (14/89) at 30 days and 25% (21/83) at 3 months. Almost all deaths were attributable to DeepScedo, and all patients deceased by day 30 had proven DeepScedo. The proportion of patients treated with voriconazole alone or in combination (total of 70/87, 80%) did not differ between survivors and non-survivors at 3 months (52/60 [87%] vs. 12/14 [86%]). Combination therapy was more frequently prescribed among those who died (8/13 [62%] vs. 14/59 [24%]). Curative surgery was significantly more frequent in patients with SOT, SID, and

trauma than in the remaining patients. The 3-month mortality rate was higher in patients with malignancy (15/32, 47%) than in all other groups (6/51, $P = .001$).

In multivariate analysis, neutropenia, dissemination, infection by *L. prolificans*, and lack of antifungal drug prescription after diagnosis were independent predictors of mortality at 3 months (Table 6 and Fig. 3).

Infection due to rare species

Nine cases were related to rare *Scedosporium* spp. *Scedosporium dehoogii* was recovered in four cases (one patient with malignancy, two with SID, and one with trauma/inoculation). Three were localized infections (two musculoskeletal or cutaneous infections) and one was disseminated case. *Scedosporium aurantiacum* was involved in two pleuropulmonary infections (one

Table 4. Comparison of patient's characteristics and disease presentation and outcome for invasive scedosporiosis caused by *S. apiospermum* or *S. boydii* (SOS, France 2002–2017).

	<i>S. apiospermum</i> (n = 47)	<i>S. boydii</i> ^a (n = 20)	P-value
Median age (range) in years	65 (14–86)	61 (13–80)	.181
Male, n (%)	32 (68%)	17 (85%)	.153
Main risk factor, [*] n (%)			.010
Malignancies	17 (36%)	5 (25%)	
SOT	6 (13%)	8 (40%)	
SID	6 (13%)	–	
Trauma/inoculation	12 (26%)	2 (10%)	
Other risk factors	3 (6%)	5 (25%)	
No risk factor	3 (6%)	–	
Associated medical condition, n (%)	29 (62%)	11 (55%)	.609
Neutropenia	6/46 (13%)	1/18 (6%)	.388
Chronic respiratory deficiency [*]	5/46 (11%)	11 (55%)	<.001
Prior <i>Scedosporium</i> colonization [*]	2 (4%)	6 (30%)	.003
Breakthrough infection	5 (11%)	51 (25%)	.131
Characteristics of the infection, n (%)			
Proven invasive infection	35 (77%)	13 (65%)	.374
Median duration of symptoms before diagnosis (range) in days	39 (6–720)	30 (2–260)	.403
Body site involved			
Localized infection	35 (74%)	13 (65%)	.431
Lung [*]	7/35 (20%)	8/13 (62%)	.012
Osteoarticular/skin	16/35 (46%)	4/13 (31%)	.512
Disseminated	12 (26%)	7 (35%)	.431
Lung	7/12 (58%)	4/7 (57%)	1.000
Skin	8/12 (67%)	2/7 (29%)	.170
Brain	4/12 (33%)	5/7 (71%)	.170
Fungemia [*]	1/25 (4%)	4/10 (40%)	.006
Therapeutic management			
First-line antifungal therapy ^b	44 (94%)	16/20 (80%)	.095
Voriconazole alone or not	42 (95%)	13/16 (81%)	.078
Antifungal combination	10/41 (24%)	5/16 (31%)	.597
Curative surgery	26 (55%)	10 (50%)	.689
Global outcome			
Death within 8 days, [*] n (%)	1 (2%)	3 (15%)	.042
Death within 30 days, n (%)	4 (9%)	3/20 (15%)	.445
Death within 90 days, n (%)	8/41 (20%)	5/20 (25%)	.623

Denominator represents the number of patients for whom the information was available (not stated when it was available for all patients).

^a*Scedosporium boydii* and *S. ellipsoideum* have been regrouped for analysis.

^bFor patients who survived 7 days after diagnosis.

^{*}P < .05.

near-drowning syndrome and one lung transplant recipient). One case of spondylodiscitis was caused by *S. angustum* in a patient with diabetes mellitus and chronic renal failure. *Scedosporium minutisporum* was responsible for one pulmonary infection in a patient with malignancy and one invasive sinusitis in a patient with no risk factor. None of the patients infected with these rare species died within 3 months.

Discussion

Our study collected 90 nationwide cases in France, which were recorded through a predetermined questionnaire with central-

ized case validation and characterization of the isolates at a reference laboratory. This provided a unique opportunity to analyze the species involved and the correlation between species identification, clinical presentation, and outcome.

Our data from 90 well-documented cases of scedosporiosis show a significant difference in terms of clinical presentations, risk factors, and outcome between *S. apiospermum* and *S. boydii* infections, which has not been previously reported in the literature. We provide evidence that patients with DeepScedo caused by *S. boydii* had different risk factors, more frequent pulmonary involvement and fungemia, and worse early outcomes when compared to infections caused by *S. apiospermum*. Very

Table 5. Characteristics of the invasive infections due to *L. prolificans* compared to *Scedosporium* species.

	<i>L. prolificans</i> (n = 13)	<i>Scedosporium</i> spp. (n = 76)	P-value
Median age (range) in years	52 (7–80)	62 (0–86)	.203
Male, n (%)	10/13 (77%)	55/76 (72%)	1.000
Main risk factor			.140
Malignancies	9 (69%)	24 (32%)	
SOT	–	15 (20%)	
SID	–	8 (11%)	
Trauma or inoculation	3 (23%)	16 (21%)	
Other risk factors	1 (8%)	9 (12%)	
No risk factor	–	4 (5%)	
Associated medical condition, n (%)			.094
Neutropenia	6 (46%)	9/73 (12%)	.003
Central venous catheter	8 (62%)	20 (26%)	.011
Diabetes	–	18 (24%)	.049
Breakthrough infection	8 (62%)	12 (16%)	.001
Characteristics of the infection, n (%)			
Proven invasive infection	11 (85%)	53 (70%)	.337
Median duration of symptoms before diagnosis (range) in days	13 (1–180)	30 (2–1080)	.058
Localized infection	5 (38%)	56 (74%)	.011
Lung	1/5 (20%)	18/56 (32%)	1.000
Osteoarticular/skin	3/5 (60%)	24/56 (43%)	.647
Disseminated infection	8 (62%)	20 (26%)	.011
Lung	5/8 (63%)	12/20 (60%)	1.000
Skin	3/8 (38%)	11/20 (55%)	.678
Brain	2/8 (25%)	10/20 (50%)	.401
Fungemia	6/9 (67%)	5/42 (12%)	<.001
Therapeutic management			
First-line antifungal therapy	10/13 (77%)	69/76 (91%)	.143
Voriconazole alone or not	6/13 (46%)	63/76 (83%)	.003
Antifungal combination	7/11 (64%)	17/68 (25%)	.010
Curative surgery	4/13 (31%)	38/76 (50%)	.199
Global mortality			
Thirty-day mortality	7/13 (54%)	7/75 (9%)	<.001
Three-month mortality	8/12 (67%)	13/70 (19%)	<.001

Denominator represents the number of patients for whom the information was available (not stated when it was available for all patients).

few studies have compared the clinical presentation of Deep-Scedo according to *Scedosporium* sp. In a recent analysis of 65 strains of the genus *Scedosporium*, Chen et al.²⁸ conclude that occasional recombinations and lack of known clinical differences support the grouping of *S. apiospermum*, *S. boydii*, and *P. angusta* as the ‘*S. apiospermum* species complex’. Our results contradict these conclusions and suggest that it is important to pursue the identification to species level for all isolates belonging to the *S. apiospermum* complex. Additional clinical studies are warranted to confirm our findings. Furthermore, other studies should explore *in vitro* and experimental models if differences in clinical presentations are supported by difference in physiological or virulence traits.

We also show that in contrast to infections caused by *Scedosporium* spp., those due to *L. prolificans* were more prevalent in patients with HM, notably those with prolonged neutropenia, were more often responsible for disseminated infections with a

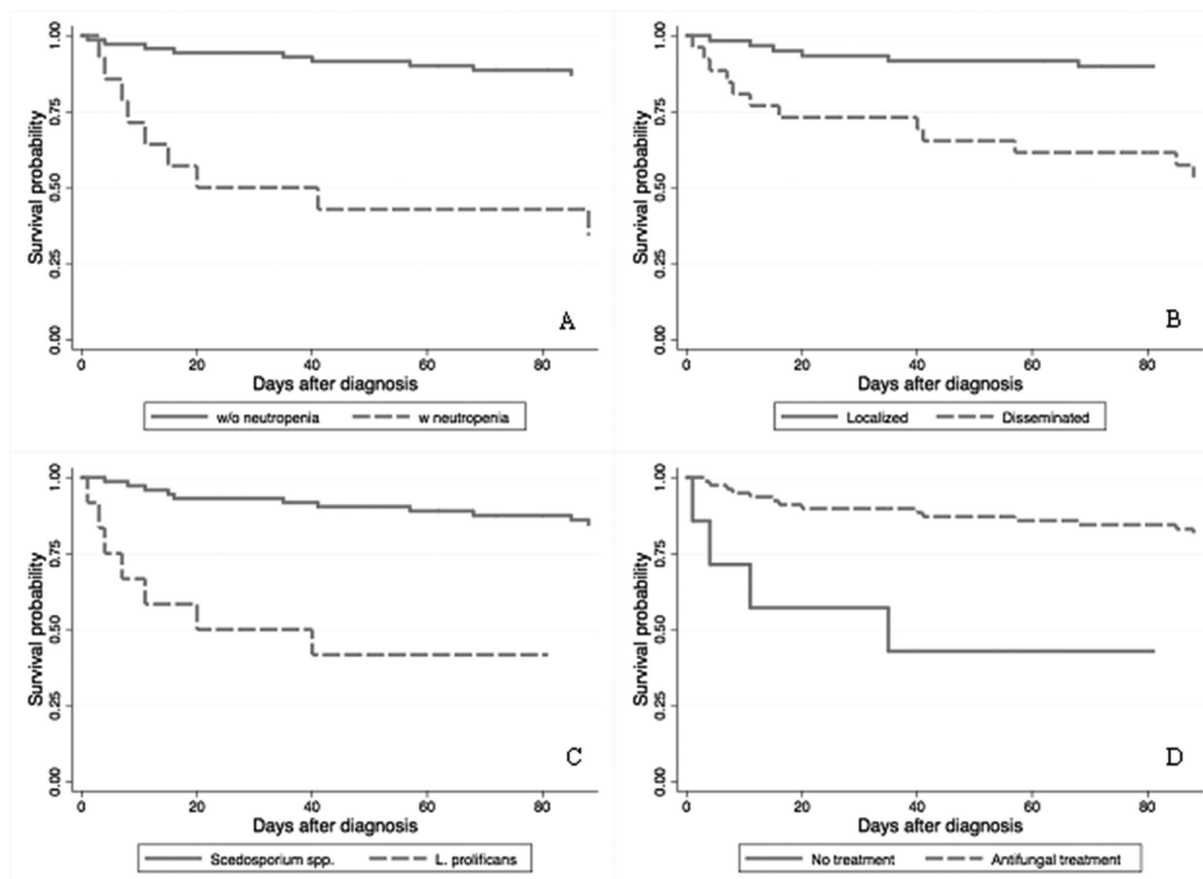
high frequency of positive blood cultures, and were associated with a more severe prognosis. The higher virulence of *L. prolificans* has previously been documented in murine models.³⁴ Our data are in agreement with previously published reports²² and further support the separation of *L. prolificans* from *Scedosporium*.^{25,26} Table 7 summarizes the main clinical differences between *L. prolificans*, *S. apiospermum* and *S. boydii* in our study.

Unsurprisingly, breakthrough infections occurred more frequently in relation with *L. prolificans* (62%). As previously reported, *L. prolificans* exhibited high MICs for all the antifungals tested,³⁵ and the vast majority of patients diagnosed with *L. prolificans* infections were patients with HM who are the target for prophylactic antifungal treatments. This raises the hypothesis that pre-exposure to antifungals participated in the selection of this species.

In our reported series, *S. apiospermum* was the main causative species, followed by *S. boydii*. These findings are in contrast with

Table 6. Univariate and multivariate analysis of parameters associated with 3-month mortality rate in 82 patients diagnosed with DeepScedo (excluding mixed infection).

Parameter	Death (<i>n</i> = 21)	Alive (<i>n</i> = 61)	Univariate analysis		Multivariate analysis	
			OR [95% confidence interval]	<i>P</i> -value	Odds ratio [95% confidence interval]	<i>P</i> -value
Male	18/21 (86%)	43/61 (71%)	2.51 [0.64–9.83]	.171		
Neutropenia	10 (53%)	4 (7%)	15.83 [4.08–61.44]	<.001	9.97 [1.83–54.35]	.008
Dissemination	15 (71%)	12 (20%)	10.21 [2.77–37.67]	<.001	7.00 [1.33–36.94]	.022
<i>L. prolificans</i>	8 (38%)	4 (7%)	8.77 [2.29–33.59]	.002	6.06 [0.91–40.25]	.062
Lack of antifungal prescription after diagnosis	14 (67%)	60 (97%)	0.07 [0.01–0.43]	<.001	0.02 [0.00–0.20]	.001

**Figure 3.** Overall survival at 3 months after the diagnosis of invasive scedosporiosis. (A) Patients presenting with and without neutropenia at baseline (log-rank test, $P < .001$). (B) Patients presenting with localized or disseminated infection at baseline (log-rank test, $p = .0001$). (C) Patients infected with *L. prolificans* or with *Scedosporium* spp. (log-rank test, $P < .0001$). (D) Patients prescribed antifungal treatment or none (log-rank test, $P \leq .0017$).

data reported from studies on the airway colonization of patients with cystic fibrosis patients diagnosed in France, for whom *S. boydii* and *S. apiospermum* accounted for 62% and 24% of cases, respectively.³⁶ These differences are meaningful since they are observed with well-characterized isolates recovered from patients living in the same geographical area, who, however, differ by both their underlying risk factors and their clinical presentation. Local ecology could be partially responsible for the rel-

atively small proportion of infections due to *L. prolificans* reported in our study. Indeed, *L. prolificans* was only recovered in 15% of SOS cases compared to 50–53% in Australian studies.^{15,21} This could be explained by the fact that it represents less than 1% of fungal species recovered from soil samples in France³⁷ compared to 43% in Australia.³⁸

Our data do not allow for discussions regarding the optimal treatment of DeepScedo. While almost all deaths were attributed

Table 7. Main differences between the three most frequent causative species in scedosporiosis/lomentosporiosis.

	<i>L. prolificans</i>	<i>S. apiospermum</i>	<i>S. boydii</i>
Main risk factors	Malignancies (AML), trauma/inoculation	Malignancies (chronic lymphoid leukemia), trauma/inoculation	SOT (lung transplantation), malignancies
Most frequent clinical manifestation	Disseminated infection	Isolated osteoarticular/skin infection	Isolated pulmonary infection
Dissemination	Very frequent (62%)	Frequent (26%)	Frequent (35%)
Fungemia	Present in 6 of 9 tested patients	Present in 1 of 25 tested patients	Present in 4 of 10 tested patients
Three-month mortality	Very high (67%)	High (20%)	High (25%)

to DeepScedo by the treating physician, outcomes were significantly influenced by the prescription of any antifungal drug. Voriconazole was prescribed in the majority of the patients with no difference in the proportion of overall mortality at days 30 and 90. The fact that combination therapy was more frequently prescribed in those who eventually died should presumably be interpreted as a consequence of a more severe clinical presentation in these patients rather than combination therapy being potentially harmful. Overall, our data do not support nor contradict the recent conclusion that voriconazole should be the favored treatment option for DeepScedo,^{2,3,22} but nevertheless highlight the fact that the prescription of antifungal drugs should not be delayed.

In conclusion, our data support the importance of distinguishing between *S. apiospermum* and *S. boydii*, as well as between *L. prolificans* and *Scedosporium* sp., insofar as the risk factors, clinical presentation, and outcomes differ between patients according to the causative species. Our results also underline the importance of a full workup to assess dissemination, including an evaluation of the cardiovascular and central nervous systems, especially in neutropenic patients and transplant recipients, as well as the need to rapidly prescribe antifungal treatment and correct neutropenia whenever possible in order to improve the severe prognosis of DeepScedo.

Supplementary material

Supplementary data are available at [MMYCOL](https://www.mycology.oup.com/mmycol) online.

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No conflict of interest during the last 3 years for all authors.

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References

- Cortez KJ, Roilides E, Quiroz-Telles F et al. Infections caused by *Scedosporium* spp. *Clin Microbiol Rev.* 2008; 21: 157–197.
- Ramirez-Garcia A, Pellon A, Rementeria A et al. *Scedosporium* and *Lomentospora*: an updated overview of underrated opportunists. *Med Mycol.* 2018; 56: 102–125.
- Mello TP, Bittencourt VCB, Liporagi-Lopes LC, Aor AC, Branquinha MH, Santos ALS. Insights into the social life and obscure side of *Scedosporium/Lomentospora* species: ubiquitous, emerging and multidrug-resistant opportunistic pathogens. *Fungal Biol Rev.* 2019; 33: 16–46.
- Caira M, Girmenia C, Valentini CG et al. Scedosporiosis in patients with acute leukemia: a retrospective multicenter report. *Haematologica.* 2008; 93: 104–110.
- Berenguer J, Rodriguez-Tudela JL, Richard C et al. Deep infections caused by *Scedosporium prolificans*: a report on 16 cases in Spain and a review of the literature. *Scedosporium prolificans* Spanish Study Group. *Medicine.* 1997; 76: 256–265.
- Tintelnot K, Just-Nübling G, Horré R et al. A review of German *Scedosporium prolificans* cases from 1993 to 2007. *Med Mycol.* 2009; 47: 351–358.
- Park BJ, Pappas PG, Wannemuehler KA et al. Invasive non-*Aspergillus* mold infections in transplant recipients, United States, 2001–2006. *Emerg Infect Dis.* 2011; 17: 1855–1864.
- Husain S, Muñoz P, Forrest G et al. Infections due to *Scedosporium apiospermum* and *Scedosporium prolificans* in transplant recipients: clinical characteristics and impact of antifungal agent therapy on outcome. *Clin Infect Dis.* 2005; 40: 89–99.
- Taj-Aldeen SJ, Rammaert B, Gamaletsou M et al. Osteoarticular infections caused by non-*Aspergillus* filamentous fungi in adult and pediatric patients: a systematic review. *Medicine.* 2015; 94: e2078.
- Kantarcioğlu AS, Guarro J, de Hoog GS. Central nervous system infections by members of the *Pseudallescheria boydii* species complex in healthy and immunocompromised hosts: epidemiology, clinical characteristics and outcome. *Mycoses.* 2008; 51: 275–290.
- Troke P, Aguirrebengoa K, Arteaga C et al. Treatment of scedosporiosis with voriconazole: clinical experience with 107 patients. *Antimicrob Agents Chemother.* 2008; 52: 1743–1750.
- Lamaris GA, Chamilos G, Lewis RE, Safdar A, Raad II, Kontoyiannis DP. *Scedosporium* infection in a tertiary care cancer center: a review of 25 cases from 1989–2006. *Clin Infect Dis.* 2006; 43: 1580–1584.
- Idigoras P, Pérez-Trallero E, Piñeiro L et al. Disseminated infection and colonization by *Scedosporium prolificans*: a review of 18 cases, 1990–1999. *Clin Infect Dis.* 2001; 32: E158–E165.
- Bouchara J-P, Le Govic Y, Kabbara S et al. Advances in understanding and managing *Scedosporium* respiratory infections in patients with cystic fibrosis. *Expert Rev Respir Med.* 2020; 14: 259–273.
- Slavin M, van Hal S, Sorrell TC et al. Invasive infections due to filamentous fungi other than *Aspergillus*: epidemiology and determinants of mortality. *Clin Microbiol Infect.* 2015; 21: 490.e1–490.e10.
- Azie N, Neofytos D, Pfaller M, Meier-Kriesche H-U, Quan S-P, Horn D. The PATH (Prospective Antifungal Therapy) Alliance® registry and invasive fungal infections: update 2012. *Diagn Microbiol Infect Dis.* 2012; 73: 293–300.
- Bitar D, Van Cauteren D, Lanternier F et al. Increasing incidence of zygomycosis (mucormycosis), France, 1997–2006. *Emerg Infect Dis.* 2009; 15: 1395–1401.
- Nucci M, Marr KA, Queiroz-Telles F et al. *Fusarium* infection in hematopoietic stem cell transplant recipients. *Clin Infect Dis.* 2004; 38: 1237–1242.
- Kantarcioğlu AS, de Hoog GS, Guarro J. Clinical characteristics and epidemiology of pulmonary pseudallescheriasis. *Rev Iberoam Micol.* 2012; 29: 1–13.
- Rodriguez-Tudela JL, Berenguer J, Guarro J et al. Epidemiology and outcome of *Scedosporium prolificans* infection, a review of 162 cases. *Med Mycol.* 2009; 47: 359–370.
- Heath CH, Slavin MA, Sorrell TC et al. Population-based surveillance for scedosporiosis in Australia: epidemiology, disease manifestations and emergence of *Scedosporium aurantiacum* infection. *Clin Microbiol Infect.* 2009; 15: 689–693.
- Seidel D, Meißner A, Lackner M et al. Prognostic factors in 264 adults with invasive *Scedosporium* spp. and *Lomentospora prolificans* infection reported in the literature and FungiScope®. *Crit Rev Microbiol.* 2019; 45: 1–21.
- Gilgado F, Cano J, Gené J, Sutton DA, Guarro J. Molecular and phenotypic data supporting distinct species statuses for *Scedosporium apiospermum* and *Pseudallescheria boydii* and the proposed new species *Scedosporium dehoogii*. *J Clin Microbiol.* 2008; 46: 766–771.
- Crous PW, Wingfield MJ, Burgess TI et al. Fungal Planet description sheets: 469–557. *Persoonia.* 2016; 37: 218–403.
- Lackner M, Hagen F, Meis JF et al. Susceptibility and diversity in the therapy-refractory genus *Scedosporium*. *Antimicrob Agents Chemother.* 2014; 58: 5877–5885.
- Lackner M, De Hoog GS, Yang L et al. Proposed nomenclature for *Pseudallescheria*, *Scedosporium* and related genera. *Fungal Divers.* 2014; 67: 1–10.
- Gilgado F, Cano J, Gené J, Guarro J. Molecular phylogeny of the *Pseudallescheria boydii* species complex: proposal of two new species. *J Clin Microbiol.* 2005; 43: 4930–4942.
- Chen M, Zeng J, De Hoog GS et al. The “species complex” issue in clinically relevant fungi: a case study in *Scedosporium apiospermum*. *Fungal Biol.* 2016; 120: 137–146.
- Donnelly JP, Chen SC, Kauffman CA et al. Revision and update of the consensus definitions of invasive fungal disease from the European Organization for Research and Treatment of Cancer and the Mycoses Study Group Education and Research Consortium. *Clin Infect Dis.* 2020; 71: 1367–1376.
- García-Hermoso D, Hoinard D, Gantier J-C, Grenouillet F, Dromer F, Dannaoui E. Molecular and phenotypic evaluation of *Lichtheimia corymbifera* (formerly *Absidia corymbifera*) complex isolates associated with human mucormycosis: rehabilitation of *L. ramosa*. *J Clin Microbiol.* 2009; 47: 3862–3870.
- Kumar S, Stecher G, Tamura K. MEGA7: Molecular Evolutionary Genetics Analysis version 7.0 for bigger datasets. *Mol Biol Evol.* 2016; 33: 1870–1874.
- Subcommittee on Antifungal Susceptibility Testing of the ESCMID European Committee for Antimicrobial Susceptibility Testing. EUCAST Technical Note on the method for the determination of broth dilution minimum inhibitory concentrations of antifungal agents for conidia-forming moulds. *Clin Microbiol Infect.* 2008; 14: 982–984.
- Guégan S, Garcia-Hermoso D, Sitbon K et al. Ten-year experience of cutaneous and/or subcutaneous infections due to coelomycetes in France. *Open Forum Infect Dis.* 2016; 3: ofw106.
- Ortoneda M, Pastor FJ, Mayayo E, Guarro J. Comparison of the virulence of *Scedosporium prolificans* strains from different origins in a murine model. *J Med Microbiol.* 2002; 51: 924–928.
- Lackner M, de Hoog GS, Verweij PE et al. Species-specific antifungal susceptibility patterns of *Scedosporium* and *Pseudallescheria* species. *Antimicrob Agents Chemother.* 2012; 56: 2635–2642.
- Zouhair R, Rougeron A, Razafimandimby B, Kobi A, Bouchara J-P, Giraud S. Distribution of the different species of the *Pseudallescheria boydii/Scedosporium apiospermum* complex in French patients with cystic fibrosis. *Med Mycol.* 2013; 51: 603–613.
- Rougeron A, Schullier G, Leto J et al. Human-impacted areas of France are environmental reservoirs of the *Pseudallescheria boydii/Scedosporium apiospermum* species complex. *Environ Microbiol.* 2015; 17: 1039–1048.
- Harun A, Gilgado F, Chen SC-A, Meyer W. Abundance of *Pseudallescheria/Scedosporium* species in the Australian urban environment suggests a possible source for scedosporiosis including the colonization of airways in cystic fibrosis. *Med Mycol.* 2010; 48: S70–S76.