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REVIEW ARTICLE

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Prognostic factors in 264 adults with invasive *Scedosporium* spp. and *Lomentospora prolificans* infection reported in the literature and FungiScope®

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ABSTRACT

Invasive *Scedosporium* spp. and *Lomentospora prolificans* infections are an emerging threat in immunocompromised and occasionally in healthy hosts. *Scedosporium* spp. is intrinsically resistant to most, *L. prolificans* to all the antifungal drugs currently approved, raising concerns about appropriate treatment decisions. High mortality rates of up to 90% underline the need for comprehensive diagnostic workup and even more for new, effective antifungal drugs to improve patient outcome. For a comprehensive analysis, we identified cases of severe *Scedosporium* spp. and *L. prolificans* infections from the literature diagnosed in 2000 or later and the FungiScope® registry. For 208 *Scedosporium* spp. infections solid organ transplantation ($n = 58$, 27.9%) and for 56 *L. prolificans* infection underlying malignancy ($n = 28$, 50.0%) were the most prevalent risk factors. *L. prolificans* infections frequently presented as fungemia ($n = 26$, 46.4% versus $n = 12$, 5.8% for *Scedosporium* spp.). Malignancy, fungemia, CNS and lung involvement predicted worse outcome for scedosporiosis and lomentosporiosis. Patients treated with voriconazole had a better overall outcome in both groups compared to treatment with amphotericin B formulations. This review discusses the epidemiology, prognostic factors, pathogen susceptibility to approved and investigational antifungals, and treatment strategies of severe infections caused by *Scedosporium* spp. and *L. prolificans*.

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Introduction

Advances in medical care led to increasing numbers of patients with non-*Aspergillus* mold infections. Scedosporiosis is of particular concern due to intrinsic resistance to antifungal therapy (Douglas et al. 2016).

The most relevant pathogens causing invasive scedosporiosis and lomentosporiosis are *Scedosporium apiospermum* species complex [comprising amongst others *S. apiospermum, S. boydii* (traditionally and wrongly thought to be the teleomorph state of the anamorphic fungus *S. apiospermum*)], *S. aurantiacum*, and *Lomentospora prolificans* (formerly *Scedosporium prolificans* but renamed due to phylogenetic differences to *Scedosporium* spp.) (Lackner et al. 2014). In the absence of effective surveillance systems, data on the incidence of *Scedosporium*- and *Lomentospora*-related infections is scarce and differs by region (Tintelnot et al. 2009). In Spain, a population-based survey on clinically relevant fungi identified *Scedosporium* spp. as the second most relevant filamentous fungus after *Aspergillus* spp. (Alastruey-Izquierdo et al. 2013). In Italy, incidence of proven scedosporiosis was 0.08% among acute leukaemia patients (Caira et al. 2008). For Houston, Texas incidence increased from 0.82 to 1.33 cases per 100,000 inpatient days between 1993 and 2005 (Lamaris et al. 2006).

Patients with compromised immune status are at highest risk of developing invasive scedosporiosis or lomentosporiosis. In particular, those with prolonged neutropenia, solid organ transplant, and patients with inherited or acquired immunodeficiency. It has long been recognized that *Scedosporium* spp. can also cause severe infections in immunocompetent hosts, e.g. after near drowning in polluted water and after penetrating trauma (Panackal and Marr 2004; Katragkou et al. 2007). Clinical presentation depends on the route of infection and immune status and ranges from superficial and subcutaneous disease to deep tissue involvement and dissemination (Ishii et al. 2015; Daniele et al. 2017). *Scedosporium* spp. and *L. prolificans* infections can involve the central nervous system, in immunocompetent patients through contiguous spread from the sinuses, and in immunocompromised patients through haematogenous spread (Tortorano et al. 2014). *L. prolificans* is more prone to cause invasive disease than *Scedosporium* species, as it produces conidia in body fluid and tissue and disseminates through the bloodstream (Husain et al. 2005; Cooley et al. 2007; Tortorano et al. 2014).

Current treatment guidelines recommend combination of voriconazole or amphotericin B-based formulations with surgery (Rodríguez-Tudela et al. 2009; Tortorano et al. 2014; Lass-Flörl and Cuenca-Estrella 2017). *Scedosporium* spp. is often resistant to amphotericin B-based formulations but susceptible to posaconazole and voriconazole, whereas *L. prolificans* is usually pan-resistant (Cuenca-Estrella et al. 1999; Carrillo and Guarro 2001; Espinel-Ingroff 2001; Bouza and Muñoz 2004; Patterson et al. 2016). Mortality rates rise up to 90% owing to pathogenicity and limited treatment options (Blyth et al. 2014).

In this study, we comprehensively review scedosporiosis and lomentosporiosis cases selected from relevant literature and the FungiScope® registry, with an emphasis on assessing predictors of mortality.

Methods

FungiScope® is a registry study on rare invasive fungal diseases (IFD) currently active in 74 countries. Its methodology has been described elsewhere (Seidel et al. 2017). Data of scedosporiosis and lomentosporiosis cases were extracted and included for analysis.

In addition, we performed an electronic literature search for case reports in PubMed on August 18, 2017 using the search filter "(Scedospori* OR Pseudallescheri* OR Lomentospori*) AND ((invasive OR disseminated OR infection) AND (case OR patient OR report))". Articles in English, French, German, Italian, and Spanish were chosen for further selection. Records presenting cases of invasive *Scedosporium* spp. or *L. prolificans* infection were selected on the basis of the title and abstract. Reference lists of the identified articles were checked for further studies. We chose the case reports with diagnosis made in 2000 or later, i.e. after marketing authorization of voriconazole for scedosporiosis and other IFD in 2002, and the compassionate use of voriconazole in the preceding years (Agatha et al. 2014). Each report was reviewed for demographics, fungal pathogens, underlying diseases and risk factors for IFD, site of infection, signs and symptoms at the time of diagnosis of IFD (imaging findings, fever, cough, dyspnoe, neurological signs), antifungal and surgical therapy from first sign of IFD, susceptibility assessed according to European Committee on Antimicrobial Susceptibility Testing (EUCAST) and Clinical & Laboratory Standards Institute (CLSI) reference method (Institute CaLaS 2008; The European Committee on Antimicrobial Susceptibility Testing 2017), clinical outcome, and autopsy findings. Observation time was defined from day of first sign of IFD to last patient contact.

Underlying conditions were selected as follows: treatment of hematological malignancy, allogeneic hematopoietic stem cell transplantation (HSCT), long-term immunosuppression (prolonged use of corticosteroids, treatment with other recognized

T cell immunosuppressants, such as cyclosporine, TNF-α blockers, monoclonal antibodies, inherited severe immunodeficiency), HIV/AIDS, solid organ transplantation (SOT), cystic fibrosis (CF), diabetes mellitus (DM), near drowning, surgery, trauma, history of pulmonary tuberculosis (TB), and others. For each patient the main risk factor was identified. For example, in a car accident with traumatic injuries and near drowning, inhalation of polluted water was chosen as the dominating risk factor, if the primary site of infection was related to the near drowning event and not the injuries. In patients with lung transplant on a background of CF or TB, SOT would dominate.

Proven and probable IFD were included (De Pauw et al. 2008). Disseminated infection was defined as a positive blood culture or infection at $\geq$2 non-contiguous sites.

In vitro susceptibility was tested for approved antifungals and the novel orotomide antifungal olorofim (F901318) that inhibits the dihydroorotate dehydrogenase (Oliver et al. 2016; McCarthy et al. 2017) for eight *S. apiospermum* and seven *L. prolificans* isolates collected in FungiScope® using broth microdilution for filamentous fungi according to CLSI document M38-A2 (25).

For comparison analysis, cases were grouped according to the causative pathogen: (1) infection due to *Scedosporium* species including *S. apiospermum*, *S. boydii* and *S. aurantiacum* and (2) infection due to *L. prolificans* together with one case that had a mixed infection with *S. apiospermum* (Lackner et al. 2014).

Statistical analyses were performed using SPSS 25 (IBM Corp., USA). Characteristics of the patient population were compared by calculating the frequencies, means and medians. For the comparison analysis, Chi^2, Fisher's Exact Test or *t*-test were used as appropriate. Kaplan–Meier method was used to estimate survival and curves were compared statistically using the log rank test. The *p* value $\leq$0.05 was considered statistically significant. Mean survival of time to death was calculated using the mean and 95% confidence interval (CI 95%). Minimum inhibitory concentrations (MIC) were compared by calculating medians.

Results

We identified 273 cases with invasive *Scedosporium* spp. and *L. prolificans* infection, 232 from the literature and 41 from the FungiScope® registry (D'Hondt et al. 2000; Muñoz et al. 2000; Bhatk and Naseeruddin 2001; Canet et al. 2001; Greig et al. 2001; Kiraz et al. 2001; Lavy et al. 2001; Luu et al. 2001; Nguyen 2001; Tirado-Miranda et al. 2001; Campagnaro et al. 2002; Farina et al. 2002; Levine et al. 2002; Mellinghoff et al. 2002; Miele et al. 2002; O'Bryan et al. 2002; Raj and Frost 2002; Safdar et al. 2002; Talbot et al. 2002; Taylor et al. 2002; Wu et al. 2002; Zaas 2002; Bosma et al. 2003; Chaveiro et al. 2003; Fernández-Mosteirín et al. 2003; Fietz et al. 2003; Gosbell et al. 2003; Horré et al. 2003; Howden et al. 2003; Leck et al. 2003; Nulens et al. 2003; Ochiai et al. 2003; Pennekamp et al. 2003; Posteraro et al. 2003; Saracli et al. 2003; Ahmed et al. 2004; Danaher and Walter 2004; Figueroa et al. 2004; German et al. 2004; Kanafani et al. 2004; Kowacs et al. 2004; Perlroth and Miller 2004; Reimann et al. 2004; Riddell et al. 2004; Shand et al. 2004; Shu et al. 2004; Tan et al. 2004; Thiagalingam et al. 2004; Larocco and Barron 2005; O'Doherty et al. 2005; Schaenman et al. 2005; Singh and McCluskey 2005; Uenotsuchi et al. 2005; Vagefi et al. 2005; Verghese et al. 2005; Bates and Mims 2006; Buzina et al. 2006; Farina et al. 2006; Musk et al. 2006; Porte et al. 2006; Symoens et al. 2006; Tascini et al. 2006; Abgrall et al. 2007; Baumgartner et al. 2007; Bhat et al. 2007; Chen et al. 2007; Jain et al. 2007; Kooijman et al. 2007; Lainscak et al. 2007; Leechawengwongs et al. 2007; Oh et al. 2007; Pellón Dabén et al. 2007; Rogasi et al. 2007; Sahi et al. 2007; Sarvat and Sarria 2007; Shankar et al. 2007; Tong et al. 2007; Ananda-Rajah et al. 2008; Guignard et al. 2008; Li et al. 2008; Mesfin et al. 2008; Nochez et al. 2008; Satirapoj et al. 2008; Bibashi et al. 2009; Cardoso et al. 2009; Carod-Artal et al. 2009; Chanqueo et al. 2009; Elm et al. 2009; Ezzedine et al. 2009; Foo et al. 2009; García-Vidal et al. 2009; Grenouillet et al. 2009; Horré and Marklein 2009; Ikewaki et al. 2009; Matsumoto et al. 2009; Morales et al. 2009; Ngai et al. 2009; Sheu et al. 2009; Ahmad et al. 2010; Al-Jehani et al. 2010; Azofra et al. 2010; Baradkar et al. 2010; Beier et al. 2010; Gelabert-González et al. 2010; Kimura et al. 2010; Morio et al. 2010; O'Hearn et al. 2010; Ortmann et al. 2010; Sarva et al. 2010; Sireesha et al. 2010; Spanevello et al. 2010; Fernández Guerrero et al. 2011; Gottesman-Yekutieli et al. 2011; Lackner et al. 2011; Luijk et al. 2011; Makino et al. 2011; Nakamura et al. 2011; Nguyen and Raychaudhuri 2011; Ohashi et al. 2011; Ong et al. 2011; Rivier et al. 2011; Ruinemans et al. 2011; Solé 2011; Stur-Hofmann et al. 2011; Takeuchi et al. 2011; Tammer et al. 2011; Bose et al. 2012; Ceccarelli et al. 2012; Cetrulo et al. 2012; Harrison et al. 2012; Mays et al. 2012; Yoneda et al. 2012; Allen et al. 2013; Ergin et al. 2013; Fadzillah et al. 2013; Henao-Martínez et al. 2013; Holmes et al. 2013; Husain et al. 2013; Kubisiak-Rzepczyk et al. 2013; Larbcharoensub et al. 2013; Lin et al. 2013; Nakamura et al. 2013; Sayah et al. 2013; Slone et al. 2013; Wilson and Kennedy 2013; Yu et al.

2013; Agatha et al. 2014, Abela et al. 2018; Campa-Thompson et al. 2014; Kepez Yildiz et al. 2014; Moloney and Park 2014; Nishimori et al. 2014; Shimizu et al. 2014; Trubiano et al. 2014; Uno et al. 2014; Alpaydın et al. 2015; Boyce and Collins 2015; Clement et al. 2015; Cruz et al. 2015; He et al. 2015; Ishii et al. 2015; Kim et al. 2015; Ochi et al. 2015; Patel et al. 2015; Patel and Orlandi 2015; Sharma and Singh 2015; Smita et al. 2015; Strunk et al. 2015; Thomson et al. 2015; Balandin et al. 2016; Bui and Carvounis 2016; Chen et al. 2016; Denton et al. 2016; Goldman et al. 2016; Guber et al. 2016; Kelly et al. 2016; Kite and Heng 2016; Lahmer et al. 2016; Leek et al. 2016; Mohan and Gopakumar 2016; Ogawa et al. 2016; Roy et al. 2016; Tamaki et al. 2016; Tilakaratne et al. 2016; Wang et al. 2016; Williams et al. 2016; Ghosh et al. 2017; Hu and Chen 2017; Jain et al. 2017; Kim et al. 2017; Masukane et al. 2017; Mei et al. 2017; Signore et al. 2017; Stoneham et al. 2017; Tóth et al. 2017; Tsuji et al. 2017). Five cases were already included in the comprehensive review of 162 *Scedosporium (Lomentospora) prolificans* infections by Rodríguez-Tudela et al. (2009) (Greig et al. 2001; Taylor et al. 2002; Gosbell et al. 2003; Howden et al. 2003; Singh and McCluskey 2005). Nine cases with unknown species were omitted from further analysis. Distribution and reported cases per million population by the country are given in Figure 1(A,B).

Scedosporium spp.

IFD due to *Scedosporium* spp. was reported in 208 patients. Five patients had mixed infection, four with *Aspergillus* spp., one with *Candida* spp. The majority were proven IFD ($n = 183$, 88%). Median age at diagnosis was 56 years (IQR 39–65 years), 128 (61.5%) patients were males.

Predisposing factors

The most common risk factors in immunocompromised patients ($n = 118$, 56.7%) were SOT ($n = 58$, 49.2%) and malignancy ($n = 29$, 24.6%) (Table 1). Concerning solid organ transplantation, most transplants were kidney or lung transplants ($n = 22$ each, 37.9%). IFD occurred in median after 365 days (IQR 98–1460 days) in kidney and after 82 days (IQR 26–461 days) in lung transplant patients. Eleven of 13 CF patients received a lung transplant. Regarding patients with underlying malignancy, most had leukaemia or lymphoma ($n = 21$, 72.4%). In total, eight (27.6%) patients received allogeneic hematopoietic stem cell transplantation for haematological malignancy. In 10 (34.5%) patients with underlying malignancy, neutropenia was reported. Nineteen of 33 (57.6%) patients with DM were immunocompromised due to SOT, malignancy or other long-term immunosuppression.

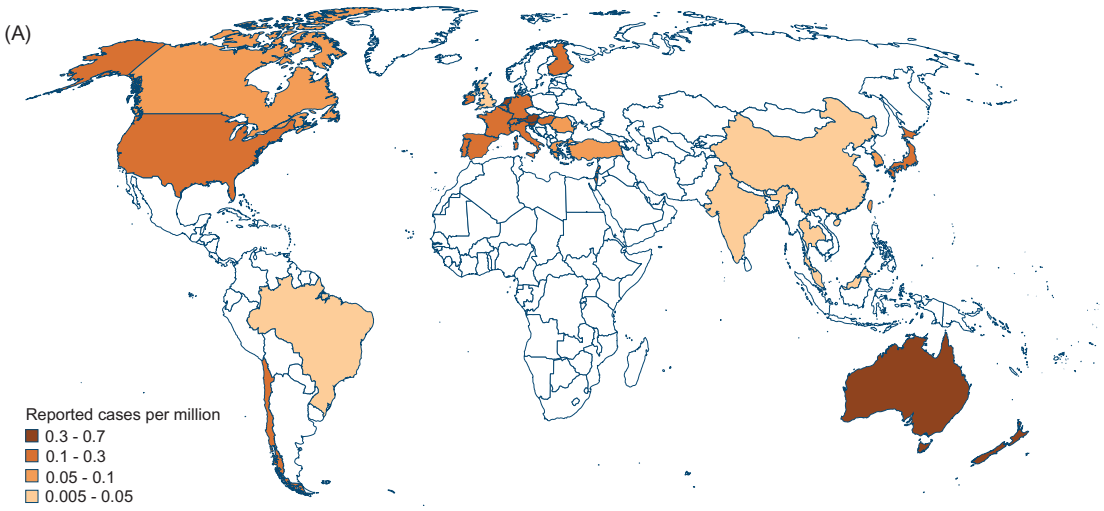
In immunocompetent patients ($n = 90$, 43.3%) surgery or trauma were the most prevalent risk factors ($n = 17$, 18.9% each). The most frequent traumatic events were eye lacerations and penetrating injuries. DM was the sole known risk factor in five patients.

Clinical presentation

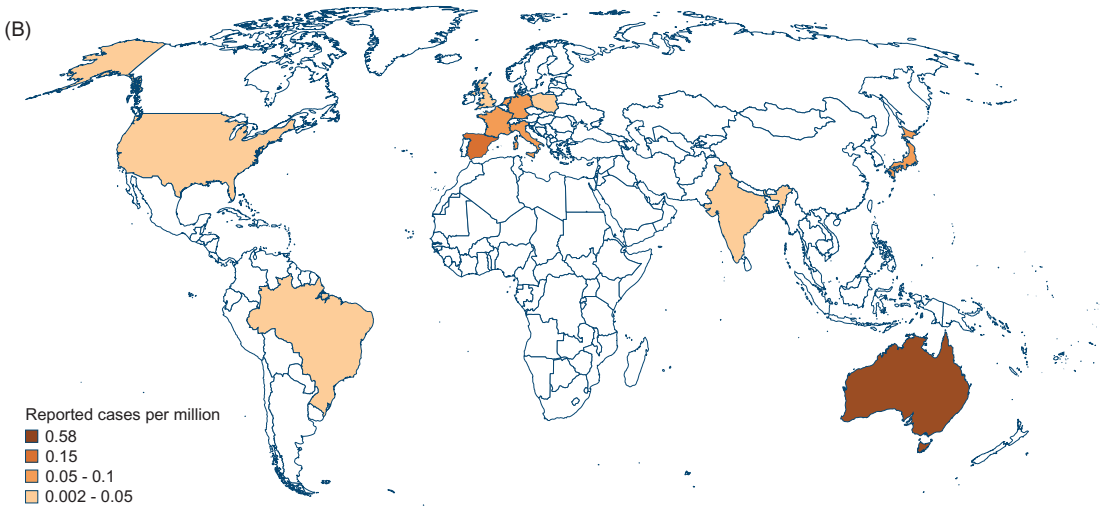
Fever at onset of the *Scedosporium* spp. infection was reported for 53 (25.5%) patients, similar for immunocompromised (30/118, 25.4%) and immunocompetent (23/90, 25.6%) patients. Fever was most frequent in HSCT recipients, other patients treated for malignancy and near drowning victims (62.5%, 42.9% and 50% respectively) but rarely reported for trauma patients (5.9%).

Scedosporiosis affected skin, lung, CNS, and eye in the majority of patients ($n = 58$, 27.9%; $n = 51$, 24.5%; $n = 50$, 24%; $n = 47$, 22.6%, respectively) (Table 1). Lung was frequently involved in patients with underlying malignancy, primarily in HSCT recipients (6/8, 75%) and near drowning victims (6/12, 50%) (Table 1). Pulmonary infection was identified in 13 of 24 (54.2%) patients receiving a lung transplant, but in none of the patients receiving a kidney or liver transplant. Four of the 51 patients with lung infection presented with cough, five with dyspnoea, and six with both. Chest pain was reported for only three immunocompromised patients. Abnormal computed tomography (CT) findings were presented for 17 (33.3%) patients with lung infection, mostly infiltrates, cavities with surrounding infiltrates and nodular lesions. No difference in imaging findings of the lung between immunocompetent ($n = 5$) and immunocompromised ($n = 12$) patients could be identified.

The CNS was frequently affected in transplant recipients and near drowning victims. The majority of the patients with CNS infection showed neurological symptoms (27/50, 54%), mostly decreased consciousness, confusion but also hemiparesis in few cases, and complained about headache (17/50, 34%). Occurrence of neurological symptoms were similar in immunocompetent and immunocompromised patients, but pain was reported more frequently in the immunocompetent group (50% versus 21.4% in immunocompromised patients). Lesions suggestive of IFD were detected by magnetic resonance imaging (MRI) in 23 (46%) patients



United States (n=57), Australia, Germany (n=17 each), India (n=16), Japan (n=14), France (n=11), Spain (n=10), China, Italy, The Netherlands (n=7 each), South Korea, Turkey (n=5 each), Austria (n=4), Belgium, Canada, Thailand (n=3 each), Chile, New Zealand, Portugal, Taiwan, Switzerland, United Kingdom (n=2 each), Brazil, Finland, Greece, Hungary, Ireland, Israel, Lebanon, Malaysia, Romania, Slovenia (n=1 each).



Australia (n=14), Japan, United States (n=8 each), Spain (n=7), France, Germany (n=5 each), India, Italy, United Kingdom (n=2 each), Brazil, The Netherlands, Poland (n=1 each).

Figure 1. Geographical distribution of (A) 208 scedosporiosis cases and (B) 56 lomentosporiosis cases identified in the literature and FungiScope® presented as number of cases per million population. United States ($n = 57$), Australia, Germany ($n = 17$ each), India ($n = 16$), Japan ($n = 14$), France ($n = 11$), Spain ($n = 10$), China, Italy, The Netherlands ($n = 7$ each), South Korea, Turkey ($n = 5$ each), Austria ($n = 4$), Belgium, Canada, Thailand ($n = 3$ each), Chile, New Zealand, Portugal, Taiwan, Switzerland, United Kingdom ($n = 2$ each), Brazil, Finland, Greece, Hungary, Ireland, Israel, Lebanon, Malaysia, Romania, Slovenia ($n = 1$ each). Australia ($n = 14$), Japan, United States ($n = 8$ each), Spain ($n = 7$), France, Germany ($n = 5$ each), India, Italy, United Kingdom ($n = 2$ each), Brazil, The Netherlands, Poland ($n = 1$ each).

with CNS infection and by CT in additional six (12%) patients.

Eye infections were localized in 28 (59.6%) patients and were involved in disseminated disease in 13 (27.7%). In additional six (12.7%) patients, infection affected adjacent sinuses or CNS. For 14 (29.8%) patients with eye infections, impaired or complete loss of vision was reported; for 21 (44.7%) pain in the eye was noted. Whereas impaired vision was reported slightly more frequently in immunocompromised patients (35% versus 25.9% in immunocompetent patients), pain was more frequently addressed in immunocompetent patients (48% versus 40% in immunocompromised patients).

Table 1. Site of infection by dominant risk factor in 208 *Scedosporium* spp. and 56 *L. prolificans* infections.

		Persistently immunocompromised					Immunocompetent					
	Total $n=208$	Total $n=118$	SOT $n=58$	Malignancy $n=21$	HSCT $n=8$	Other $n=31$[a]	Total $n=90$	Surgery $n=17$	Trauma $n=17$	Near drowning $n=12$	Other $n=28$[b]	Unknown $n=16$
Scedosporium spp.												
Blood	12 (5.8)	7 (5.9)	6 (10.3)	–	1 (12.5)	–	5 (5.6)	2 (11.8)	–	–	1 (3.6)	2 (12.5)
CNS	50 (24)	28 (23.7)	18 (31)	3 (14.3)	4 (50)	3 (9.7)	22 (24.4)	5 (29.4)	2 (11.8)	7 (58.3)	6 (21.4)	2 (12.5)
Eye	47 (22.6)	20 (16.9)	10 (17.2)	7 (24.1)	–	3 (9.7)	27 (30)	4 (23.5)	8 (47.1)	2 (16.7)	8 (28.6)	5 (31.3)
Sinuses	19 (9.1)	5 (4.2)	2 (3.4)	1 (3.4)	–	2 (6.5)	14 (15.6)	1 (5.9)	1 (5.9)	–	6 (21.4)	6 (37.5)
Heart	11 (5.3)	7 (5.9)	6 (10.3)	–	–	1 (3.7)	4 (4.4)	4 (23.5)	–	–	–	–
Lung	51 (24.5)	36 (30.5)	15 (25.9)	9 (42.9)	6 (75)	6 (19.4)	15 (16.7)	4 (23.5)	–	6 (50)	5 (17.9)	–
Deep Tissue	9 (4.3)	6 (5.1)	2 (3.4)	–	–	4 (12.9)	3 (3.3)	2 (11.8)	–	–	1 (3.6)	–
Skin	58 (27.9)	46 (39)	23 (39.7)	7 (24.1)	–	16 (51.6)	12 (13.3)	3 (17.5)	5 (29.4)	–	1 (3.6)	3 (18.8)
Bone/joints	31 (14.9)	11 (9.3)	11 (19)	–	–	–	20 (22.2)	5 (29.4)	6 (35.3)	1 (8.3)	6 (21.4)	2 (12.5)
Other[c]	28 (13.5)	17 (14.4)	14 (24.1)	1 (4.8)	1 (12.5)	1 (3.7)	11 (12.2)	2 (11.8)	–	3 (25)	5 (17.9)	1 (6.3)
Disseminated	46 (22.1) $n=56$	31 (26.3) $n=39$	23 (39.7) $n=7$	3 (14.3) $n=19$	2 (25) $n=9$	3 (11.1) $n=4$[d]	15 (16.7) $n=17$	5 (29.4) $n=7$	2 (11.8) $n=5$	4 (33.3) $n=0$	2 (7.1) $n=3$[e]	2 (12.5) $n=2$
L. prolificans												
Blood	26 (46.4)	23 (59)	1 (14.3)	16 (84.2)	5 (55.6)	1 (25)	3 (17.6)	1 (14.3)	1 (20)	–	1 (33.3)	–
CNS	6 (10.7)	6 (15.4)	1 (14.3)	4 (14.3)	–	1 (25)	–	–	–	–	–	–
Eye	12 (21.4)	9 (23.1)	2 (28.6)	6 (31.6)	1 (11.1)	–	3 (17.6)	1 (14.3)	1 (20)	–	1 (33.3)	–
Sinuses	3 (5.4)	2 (5.1)	–	1 (5.3)	1 (11.1)	–	1 (5.9)	–	–	–	–	1 (50)
Heart	11 (19.6)	7 (17.9)	2 (28.6)	4 (21.1)	1 (11.1)	–	4 (23.5)	2 (28.6)	1 (20)	–	1 (33.3)	–
Lung	22 (39.3)	18 (46.2)	4 (57.1)	8 (42.1)	5 (55.6)	1 (25)	4 (23.5)	2 (28.6)	–	–	1 (33.3)	1 (50)
Deep Tissue	1 (1.8)	–	–	–	–	–	1 (5.9)	1 (14.3)	–	–	–	–
Skin	6 (10.7)	4 (10.3)	1 (14.3)	1 (5.3)	2 (22.2)	1 (25)	2 (11.8)	1 (14.3)	1 (20)	–	–	–
Bone/joints	7 (12.5)	3 (7.7)	1 (14.3)	–	1 (11.1)	1 (25)	4 (23.5)	1 (14.3)	3 (60)	–	–	–
Other[f]	12 (21.4)	9 (23.1)	2 (28.6)	5 (26.3)	2 (22.2)	–	3 (17.6)	3 (42.9)	–	–	–	–
Disseminated	33 (58.9)	29 (74.4)	4 (57.1)	17 (89.5)	7 (77.8)	1 (25)	4 (23.5)	2 (28.6)	1 (20)	–	1 (33.3)	–

Number of sites (% in brackets) for each risk group and overall are superadditive.
CNS: central nervous system; SOT: solid organ transplantation; DM: diabetes mellitus; HSCT: hematopoietic stem cell transplant recipients; TB: tuberculosis.
Malignancy excludes hematopoietic stem cell transplant recipients.
[a]Long-term immunosuppressed patients (asthma, rheumatic arthritis, chronic pulmonary disease, others), HIV/AIDS patients ($n=4$).
[b]incl. Bronchiectasis, cystic fibrosis, chronic kidney disease/Diabetes Mellitus, contact lens, chronic pulmonary disease, dialysis, extracorporeal membrane oxygenation, glaucoma, intravenous drug abuse, tuberculosis, viral pneumonia
[c]Colon, kidney, liver, lymph node, mediastinum, meninges, peritoneum, spine, testicle, thyroid.
[d]Long-term immunosuppressed patients (asthma, rheumatic arthritis, chronic granulomatous disease).
[e]Bronchiectasis, contact lens, intravenous drug abuse.
[f]Kidney, liver, pancreas, peritoneum, spine.
Multiple underlying conditions: *Scedosporium* spp. (Malignancy: pneumonia (3), trauma (1), diabetes mellitus (3); Longterm immunosuppression: diabetes mellitus (3), trauma (2), COPD (1), surgery (1); HIV and TB (1); Surgery: diabetes mellitus (4); Trauma: diabetes mellitus (2), intravenous drug abuse (1); Other: cystic fibrosis and diabetes mellitus (1); *L. prolificans* (Malignancy: diabetes mellitus (1), chronic renal failure (1); Longterm immunosuppression: trauma (1); Surgery: diabetes mellitus (1)).

Table 2. Treatment administered to 208 patients with *Scedosporium* spp. and 56 *L. prolificans* infection.

	Scedosporium spp.	*L. prolificans*
Antifungal prophylaxis (%)	20 (9.6)	13(23.2)
Posaconazole, voriconazole	7 (35)	10 (76.9)
Other[a]	13 (65)	3 (23.1)
Antifungal treatment		
Antifungal and surgery	117 (56.3)	24 (42.9)
Antifungal	87 (41.8)	31 (55.4)
Surgery	2 (1)	–
No treatment	2 (1)	1 (1.8)
Antifungal drugs (%)[b]		
Amphotericin B	63 (30.3)	27 (48.2)
Voriconazole	137 (65.9)	38 (67.9)
Posaconazole	15 (7.2)	8 (14.3)
Itraconazole	57 (27.4)	8 (14.3)
Other azoles[c]	20 (9.6)	4 (7.1)
Terbinafine	26 (12.5)	22 (39.3)
Echinocandin[d]	22 (10.6)	17 (30.4)
Monotherapy	102 (49)	16 (28.6)
Consecutive monotherapy	53 (25.5)	10 (17.9)
Combination therapy	49 (23.6)	28 (50)
Sequential	30 (61.2)	13 (23.2)
Treatment length overall median days (IQR)	90 (34–217)	21 (5–150)
Observation period median days (IQR)	180 (50.5–374)	49 (6–300)
Observation period if alive	285 (142.5–652.5)	330 (180–603.5)
Observation period if dead	30 (10–98.5)	15 (4.5–35)

[a]*Scedosporium* spp.: Itraconazole (5), fluconazole (4), amphotericin B (3), caspofungin (1); *L. prolificans*: fluconazole (2), itraconazole (1).
[b]superadditive.
[c]*Scedosporium* spp.: Fluconazole (13), isavuconazole (1), miconazole (3), ketoconazole (4); *L. prolificans*: Fluconazole (3), isavuconazole (1).
[d]*Scedosporium* spp.: Caspofungin (16), micafungin (6); *L. prolificans*: Caspofungin (11), micafungin (6), anidulafungin (2).

Disseminated *Scedosporium* spp. infection was present in 31 (26.3%) of the immunocompromised, mainly in transplant recipients, and 15 (16.7%) of immunocompetent patients. Lung, CNS, skin, and eye were the most frequently involved organs in disseminated disease overall ($n = 25$, 54.3%; $n = 22$, 47.8%; $n = 19$, 41.3%; $n = 13$, 28.3%, respectively) (Supplementary Table 1(A)). In 12 (5.8%) patients with confirmed blood stream infection, the pathogen was isolated from at least one other organ (mostly CNS, heart or lung). If infection affected contiguous organs these were eyes, sinuses and/or CNS in all but two cases with deep soft tissue infection with involvement of the bone.

Treatment

All but four patients received antifungal drugs for treatment of scedosporiosis, in median for 90 days (IQR 34 – 217 days) (Table 2). Surgical resection, debridement or drainage of the infected site was performed in 62 (52.5%) immunocompromised patients and in 57 (63.3%) immunocompetent patients. Most patients with eye infections underwent vitrectomy, keratoplasty, enucleation or surgical drainage of abscesses (32/47, 68%). Pulmonary infections were mainly treated with systemic antifungals (49/51, 96%), eight (15.7%) infections were managed surgically in addition, of which six had localized disease. Brain lesions were resected or surgically drained in 15 of 50 (30%) patients, of which eight were immunocompromised and seven immunocompetent.

The majority of the patients received systemic voriconazole, amphotericin B-based formulation (amphotericin B) or itraconazole (65.9%, 30.3%, and 27.4%, respectively) for treatment of scedosporiosis (Table 2). The most frequent monotherapies were voriconazole and itraconazole (Supplementary Table 2). In 31 of 46 (67.4%) patients treated with other than these two first line antifungals, treatment was switched to voriconazole. Switch of any antifungal drug to amphotericin B was rare. Most patients treated with any combination therapy, received more than one regimen. In the majority of the cases, voriconazole was co-administered, mostly with terbinafine or amphotericin B. Posaconazole was rarely used, never as first line monotherapy, but rather as salvage or in combination.

Outcome and presumed prognostic factors

All-cause mortality for each risk group and for disseminated *Scedosporium* spp. infection is shown in Table 3.

Table 3. All-cause mortality overall and at day 42 in patients with *Scedosporium* spp. ($n = 205$) and *L. prolificans* ($n = 55$) infection.

	Scedosporium spp. ($n = 205$)				*L. prolificans* ($n = 55$)			
Risk group	Events overall/total	% overall	Events day 42 /total	% day 42	Events overall/total	% overall	Events day 42 /total	% day 42
SOT	23/58	39.7	10/52	19.2	4/7	57.1	2/7	28.6
Localized	5/35	14.3	3/33	9.1	1/3	33	0/3	0
Disseminated	18/23	78.3	7/19	38.9	3/4	75	2/4	50
Malignancy	16/29	55.2	8/26	30.8	24/28	85.7	20/28	71.4
Localized	12/24	50	7/22	31.8	2/4	50	1/4	25
Disseminated	4/5	80	1/4	25	22/24	91.7	19/24	79.2
HSCT	6/8	75	4/8	50	7/9	77.8	6/9	66.7
Localized	4/6	66.7	3/6	50	1/2	50	1/2	50
Disseminated	2/2	100	1/2	50	6/7	85.7	5/7	71.4
Other immunocompromised	12/30	40	6/29	20.7	1/4	25	1/4	25
Localized	10/27	37	5/26	19.2	0/3	0	0/3	0
Disseminated	2/3	66.7	1/3	33.3	1/1	100	1/1	100
Surgery	7/17	41.2	3/16	18.8	2/8	25	1/8	12.5
Localized	3/12	25	1/12	8.3	1/6	16.7	0/6	0
Disseminated	4/5	80	2/4	50	1/2	50	1/2	50
Trauma	2/16	12.5	0/16	0	1/3	33.3	1/3	33.3
Localized	0/14	0	0/14	0	0/3	0	0/3	0
Disseminated	2/2	100	0/2	0	1/1	100	1/1	100
Near drowning	3/12	25	0/12	0	–	–	–	–
Localized	3/8	37.5	0/8	0	–	–	–	–
Disseminated	0/4	0	0/4	0	–	–	–	–
Other immunocompetent	12/28	42.9	6/27	22.2	1/3	33.3	1/3	33.3
Localized	11/26	42.3	5/25	20	0/2	0	0/2	0
Disseminated	1/2	50	1/2	50	1/1	100	1/1	100
Unknown	3/15	20	3/15	20	0/2	0	0/2	0
Localized	1/13	7.7	1/13	7.7	0/2	0	0/2	0
Disseminated	2/2	100	2/2	100	–	–	–	–

SOT: solid organ transplantation; HSCT: allogeneic hematopoietic stem cell transplantation.
Disseminated: positive blood culture or infection at ≥2 non-contiguous sites.

Day 42 and overall mortality were higher in immunocompromised (22.2% and 43.6% respectively) compared to immunocompetent patients (14% and 30.7%, respectively). Mortality in patients with malignancy (55.2% overall), particularly in HSCT recipients (75%), was higher than in SOT recipients (39.7%) and other immunocompromised patients (40%) (Supplementary Figure 1 (A), Table 3). Disseminated disease was associated with higher mortality in all risk groups, except near drowning, where four patients with CNS and lung or eye infection survived. All 12 patients with fungemia died and death was mostly attributed to IFD. Overall, attributable mortality was 76%; results for each risk group are presented in Supplementary Table 3.

Mean survival time varied depending on the risk group and dissemination of the infection (Supplementary Figure 1, Figure 2). HSCT recipients had a shorter mean survival time of 93 days (CI 95% 30–157) compared to patients with underlying malignancy without HSCT (236 days, CI 95% 41–156), SOT (271 days, CI 95% 230–312), and other conditions requiring long-term immunosuppression (220 days, CI 95% 156–283). Overall, for immunocompromised patients with disseminated *Scedosporium* spp. infection mean survival time was 156 days (CI 95% 98–214); in the seven patients with blood stream infection 42 days (CI 95% 0–107). If infection was localized, mean survival time was 270 days (CI 95% 236–305). In immunocompetent patients with disseminated disease, mean survival time was 175 days (CI 95% 87 – 262); in the five patients with blood stream infection 12 days (CI 95% 5–19). If infection was localized, mean survival time was 293 days (CI 95% 261–325) accordingly.

Bivariate analysis revealed that in SOT recipients, infection of the CNS and disseminated infection were associated with higher mortality (Supplementary Table 4(A)). In patients with underlying malignancy, infection of the lung predicted worse outcome. This holds true if HSCT recipients were excluded (Log Rank Test $p = 0.011$, data not shown). In immunocompromised patients who developed CNS complications, the 42-day mortality was higher compared to those with other infected sites, both in patients with localized (33.3% versus 15.9%) and disseminated disease (60% versus 18.8%). In immunocompetent patients with localized infection, CNS involvement was associated with higher 42-day mortality compared to other affected organs (23.1% versus 6.5%, Fisher's Exact Test $p = 0.095$). No difference in 42-day mortality was identified in immunocompetent patients with disseminated disease with versus without CNS involvement (33.3% versus 33.3%).

Table 4. Median minimum inhibitory concentrations in *Scedosporium* spp. and *L. prolificans* clinical isolates assessed using the EUCAST and CLSI procedures.

	Scedosporium spp.			*L. prolificans*		
	n	MIC Median (IQR) mg/L		*n*	MIC Median (IQR) mg/L	
Amphotericin B	28	12	(2.5–16)	18	16	(4–16)
Flucytosine	7	128	.[a]	8	128	(80–128)
Terbinafine	5	16	(3–32)	–	–	–
Fluconazole	10	24	(16–56)	8	128	(128–224)
Isavuconazole	8	3	(1.3–13)	7	32	.[a]
Itraconazole	18	2	(1–16)	11	16	(16–32)
Posaconazole	21	1.5	(0.5–2)	10	32	(28–32)
Voriconazole	32	0.5	(0.3–1)	17	8	(6–16)
Caspofungin	10	3	(1.6–10)	–	–	–
Micafungin	–	–	–	6	24	(0.9–32)
F901318	8	0.0039	.[a]	7	0.0039	.[a]

[a]same MIC in all isolates tested.

Surgical treatment of eye infections was not associated with better overall survival in this case series. Day 42 mortality was 6.3% (2/32) and 13.3% (2/15) in patients with and without surgically treated eye infection, respectively (Fisher's Exact Test $p = 0.602$). In patients with and without surgically treated brain infection, day 42 mortality was 20% (3/15) and 37.1% (13/35), respectively (Fisher's Exact Test $p = 0.328$).

Overall, patients who received voriconazole for the treatment of scedosporiosis had a longer mean survival time compared to the patients treated with amphotericin B (276 days, CI 95% 248–304 versus 144 days, CI 95% 78–209) (Supplementary Figure 3(A)). For voriconazole similar mean survival times were seen in immunocompromised and immunocompetent patients (274 days, CI 95% 235–312 versus 280 days, CI 95% 238–321; Log Rank Test $p = 0.651$), whereas for amphotericin B survival time was longer in immunocompetent than in immunocompromised patients (206 days, CI 95% 104–309 versus 95 days, CI 9% 19–170; Log Rank Test $p = 0.065$).

Day 42 mortality was lower in patients treated with voriconazole compared to those treated with any formulation of amphotericin B in immunocompromised (11.3% versus 58.8%, Fisher's Exact Test $p < 0.001$) and immunocompetent (14% versus 23.1%, Fisher's Exact Test $p = 0.416$) patients. Treatment with voriconazole was associated with lower day 42 and overall mortality in localized and disseminated disease compared to treatment with amphotericin B.

Antifungal susceptibility

In vitro susceptibility to antifungals was available for clinical isolates of *Scedosporium* spp. from 34 patients (Table 4). Median MIC values were lowest for olorofim (0.0039 mg/L for all isolates), voriconazole (0.5 mg/L, IQR 0.25–1 mg/L) and posaconazole (1.5 mg/L, IQR 0.25–1 mg/L), and high for amphotericin B (12 mg/L, IQR 2.5–16 mg/L) and terbinafine (16 mg/L, IQR 3 – 32 mg/L). Highest MICs were determined for fluconazole (24 mg/L, IQR 16 – 56 mg/L), and flucytosine (128 mg/L for all isolates). In rare cases low MICs ($\leq$0.5 mg/L) were determined for amphotericin B, itraconazole as well as for echinocandins but not for terbinafine, fluconazole and flucytosine for which MICs were >2 mg/L for all isolates.

Lomentospora prolificans

Fifty-six patients with *L. prolificans* infection were identified. Three had a mixed IFD with additional identification of *Aspergillus* spp., *Exserohilum* spp. or *S. apiospermum*. The majority were proven IFD ($n = 52$, 92.9%). Median age at diagnosis was 58 years (IQR 42–67 years), 32 (57.1%) patients were male.

Predisposing factors

Of 56 patients with *L. prolificans* infection, the majority were immunocompromised ($n = 39$, 69.6%), most related to an underlying malignancy ($n = 28$, 71.8%) or a SOT ($n = 7$, 17.9%) (Table 1). Leukaemia and lymphoma were the most frequent haematological diseases ($n = 19$, 67.9% and $n = 4$, 14.3%). Nine (32.1%) patients received HSCT and overall, for 13 (46.4%) patients neutropenia during treatment of the underlying malignancy was reported. Transplant patients had received a lung ($n = 4$), kidney ($n = 2$) or heart ($n = 1$). Lomentosporiosis was reported in 17 immunocompetent patients, mainly in surgical and trauma patients ($n = 7$, 41.2% and $n = 5$, 29.4%, respectively).

Clinical presentation

Fever was present before diagnosis of *L. prolificans* infection in 41% (16/39) of immunocompromised patients, mostly those with malignancy (15/28, 53.7%),

and in 29.4% (5/17) of immunocompetent patients, mostly surgical patients (4/7, 57.1%). In none of the patients with traumatic injuries, long-term immunosuppression and in only one kidney transplanted patient fever was reported before diagnosis of IFD.

L. prolificans infection most frequently affected lung, eye, and heart ($n = 22$, 39.3%; $n = 12$, 21.4%; $n = 11$, 19.6%, respectively). Ten of 11 patients with infection of the heart had disseminated disease, seven with positive blood culture. Disseminated infection was more frequent in immunocompromised patients ($n = 29$, 74.4% versus $n = 4$, 23.5% of immunocompetent patients) and was mostly associated with fungemia in both groups (Table 1, Supplementary Table 1). Overall, in 8 of 26 (30.8%) patients with fungemia, no other infected organ was reported. In the other 18 fungemia cases as well as in cases with disseminated infection without reported blood stream infection ($n = 7$), on average a total of three affected organs was identified. Here, lung and/or heart were most frequently reported (Supplementary Table 1(B)). In 10 (45.5%) patients with lung infections, radiological signs were seen. CT scans showed mostly pulmonary areas of nodular consolidation without cavitation and less frequently infiltrates; halo or air-crescent signs were not reported. For seven (31.8%) patients with lung infection, dyspnoea or cough was reported.

Eye infections were localized in four (33.3%) patients. Pain in the eye was reported for four patients, for one of them and additional three patients, blurred vision was reported. Infection of the CNS was diagnosed in immunocompromised patients only ($n = 6$, 10.7%), in five the infection was disseminated, four with blood stream infection. Lesions on head MRI and CT scans were presented for four of these cases.

Overall, *L. prolificans* infection was localized in 10 (25.6%) immunocompromised patients and 13 (76.5%) immunocompetent patients; lung ($n = 8$), bone ($n = 6$) or eye ($n = 4$) were most frequently affected. For four of eight (50%) patients with localized lung infection, dyspnoea or cough before diagnosis was reported.

Treatment

All but one patient with *L. prolificans* infection received antifungals for treatment (Table 2). One patient with disseminated infection received intravitreal injection only and died after a few days. Nine (23.1%) immunocompromised and 15 (88.2%) immunocompetent patients underwent surgery. Two of 22 lung infections were treated with lobectomy, both patients were immunocompetent. Seven of 12 patients with eye infection underwent vitrectomy or enucleation. None of the brain infections were operated on.

Antifungals most frequently used for treatment of lomentosporiosis were voriconazole, amphotericin B, terbinafine, and echinocandins (67.9%, 48.2%, 39.3%, and 30.4%, respectively) (Table 2). Median treatment duration was 21 days (IQR 5–150 days). Sixteen patients received monotherapy, mostly amphotericin B, voriconazole or itraconazole for a median of 11 days (IQR 4–35 days). Two patients with fungemia and treated with echinocandin monotherapy died within 2 weeks. Half of the patients received combination therapy, mostly with voriconazole plus terbinafine or amphotericin B (Supplementary Table 2) for a median of 35 days (IQR 15–330 days). In 13 (26%) patients treated with combination therapy, more than one regime was administered.

Outcome

Overall mortality, as shown in Table 3 for each risk group, was higher in immunocompromised than in immunocompetent patients with *L. prolificans* infection (74.4% versus 25%, Fisher's Exact Test $p = 0.001$), being highest in patients with malignancy (85.7%), similar for patients with and without HSCT, and SOT (57.1%) (Supplementary Figure 1(B), Table 3). Of the 14 patients with available information on attributable death, 10 (71.4%) died due to infection (Supplementary Table 3), all of which had disseminated disease, eight with confirmed blood stream infection.

Day 42 mortality was 59% in immunocompromised patients and 17.6% in immunocompetent patients (Fisher's Exact Test $p = 0.004$). In patients with underlying malignancy, day 42 mortality was 71.4%, 90% of those had confirmed fungemia. Overall mortality and day 42 mortality in patients with disseminated disease was higher in all risk groups compared to the localized infection (Table 3).

Mean survival time in immunocompromised patients was 114 days (CI 95% 66–163) (Supplementary Figure 2(B)), in patients with blood stream infection 22 days (CI 95% 9–37). Mean survival time of patients with underlying malignancy and SOT was 63 days (CI 95% 21–105) and 242 days (CI 95% 127–357), respectively. Immunocompetent patients had a mean survival time of 302 days (CI 95% 239–367).

In patients with malignancy, disseminated disease was associated with a worse outcome and surgical intervention as antifungal treatment was associated with improved outcome overall (Supplementary Table 4(B)). Of five patients with eye infection who were not

surgically treated, all died within 49 days, 4 had fungemia. Of seven patients with surgically treated eye infection, one patient with fungemia died after three weeks and six patients were alive with median follow up time of 180 days.

Overall mortality was lower in patients who received voriconazole for treatment compared to other antifungals (52.6% versus 68.8%, Fisher's Exact Test $p = 0.37$) (Supplementary Figure 3(B)). Treatment with voriconazole together with terbinafine was not associated with improved day 42 and overall survival in patients with lomentosporiosis compared to treatment with voriconazole without terbinafine overall and in any of the tested subgroups (e.g. blood stream infection and localized disease, HSCT and no HSCT, all immunocompromised and all immunocompetent patients). Overall mortality was similar in patients treated with voriconazole and patients treated with voriconazole and terbinafine (50% and 55.3%, Chi^2 $p = 0.757$).

Antifungal susceptibility

In vitro susceptibility to antifungals were available for 18 clinical isolates from different patients (Table 4). Median MIC were low for olorofim (0.0039 mg/L for all isolates). For all other antifungals tested, median MIC was 8 mg/L or higher. Occasionally isolates show MIC of 1 mg/L or lower for echinocandins, amphotericin B or voriconazole. Other than these, MICs were at least 4 mg/L for all antifungals in all isolates tested.

Discussion

Scedosporium spp. and *L. prolificans* infections are rare diseases as reflected by their reported frequency. Through literature search and in FungiScope® we identified 264 individual cases of severe IFD caused by *Scedosporium* spp. or *L. prolificans* that were diagnosed between 2000 and 2017. This translates to an average of only 16 reported cases per year. This may be due to a diagnostic and a reporting bias, and thus not reflect true epidemiology. Overall, *Scedosporium* spp. and *L. prolificans* infections account for less than 1% of all mold infections (Caira et al. 2008), and affect less than 1 in 60 000 in-patients in general (Mügge and Schömig 2017). Regional differences in incidences, such as seen with the relatively high incidence of these infections in Australia compared to other countries, may be due to climatic and environmental conditions that favour growth of the fungi. Soil pH has been suggested to play a role (Kaltseis et al. 2009). Similar pH ranges of the soil as in Australia are found in Mid East USA and Canada, Eastern South-America, Southern Europe, North and South Africa, and Mid and Central Asia (Global Soil Data Task 2014). Reported cases were predominately from those regions. Most *Scedosporium* spp. infections were reported in patients after organ transplantation, whereas *L. prolificans* infections were mostly diagnosed in patients with an underlying malignancy. Effective prophylaxis is particularly difficult in the case of *L. prolificans*, due to pan-resistance to virtually all systemically active antifungal agents currently available. Thus, incidence of break-through infections in haematological patients receiving posaconazole or voriconazole as first line antifungal prophylaxis is likely to be higher for *L. prolificans* than for *Scedosporium* spp.

Clinical manifestation differed between scedosporiosis and lomentosporiosis as well as between patient populations. Infection with *Scedosporium* spp. frequently disseminates to distant organs, often to the CNS even in immunocompetent patients, without primary bloodstream infection. *L. prolificans* infection often presents as fungemia, while brain infections are reported less commonly (Horré et al. 2000; Mellinghoff et al. 2002). Tropism for blood vessels and haematogenous spread is considerable in both diseases (Kowacs et al. 2004). Disseminated disease is independently associated with worse outcome, fungemia being the key determinant. In our dataset, fungemia proved fatal in all immunocompromised patients and in all but one immunocompetent patients.

Infection of the CNS was found to be associated with worse outcome in SOT patients with *Scedosporium* spp. infection. The true impact of brain infection on survival, also in other risk groups, is difficult to assess. Several aspects need to be considered. Despite CNS being reported as the sole site of infection for several patients, in the absence of previous brain injury or surgery, it is highly unlikely to be the primary site (O'Bryan 2005). If not all potentially infected sites are examined thoroughly, the additional impact of brain infection may be underestimated. On the contrary, CNS infections may not be identified before death. Reasons are manifold, involvement of the CNS is not suspected, patient's condition does not allow transport to radiology or invasive diagnostic procedures, imaging findings may be inconclusive, or results from microbiological workup may remain negative. With fewer autopsies being performed nowadays, brain infections may not be reported altogether (Tietz et al. 2005). Due to low susceptibility of the fungus and low permeability of the blood-brain barrier for many antifungal drugs, it is undisputed that CNS infection is

particularly difficult to treat, and mortality is high (Kantarcioglu et al. 2008).

With voriconazole, known for its ability to cross the blood-brain barrier, an antifungal became available for successful treatment of brain lesions (Schwartz et al. 2005). Voriconazole showed high *in vitro* activity against *S. apiospermum* isolates (Meletiadis et al. 2002). Current guidelines recommend the use of voriconazole along with surgical resection (Tortorano et al. 2014). A comprehensive study on treatment efficacy in 107 scedosporiosis patients treated with voriconazole showed successful response in 57% of patients overall (Troke et al. 2008). In our analysis, day 42 and overall mortality was numerically lower in immunocompromised patients with scedosporiosis and lomentosporiosis treated with voriconazole compared to those treated with amphotericin B. Differences between voriconazole alone or in combination with amphotericin B were not seen. Combination therapies are widely used to exploit synergistic effects. Terbinafine for example, although demonstrating limited *in vitro* activity alone, showed synergy in combination with azoles in several *in vitro* studies (Ryder and Leitner 2001; Meletiadis et al. 2003). The additional value of terbinafine in combination treatment of patients with mold infections is controversial. Poor tissue penetration of terbinafine casts doubt on the clinical meaning of such synergy. Our analysis did not identify synergy of terbinafine. Olorofim is a new antifungal agent that shows promising antifungal activity *in vitro*. In our analysis, olorofim had low MICs against all *Scedosporium* spp. and *L. prolificans* strains, confirming recently published results (Wiederhold et al. 2017; Biswas et al. 2018). A clinical efficacy study on olorofim is upcoming. Similarly, APX001 (E1210) a novel antifungal agent that disrupts fungal cell wall assembly, showed good *in vitro* activity against *Scedosporium* spp. and *L. prolificans* and is currently tested in phase I clinical trial in patients with acute leukaemia (clinicaltrials.gov 2017; Castanheira et al. 2012).

Route of entry of *Scedosporium spp.* and *L. prolificans* is frequently through the respiratory tract, which explains the high incidence of lung lesions. In this case series, lung involvement predicted worse outcome of scedosporiosis in patients with malignancy in univariate analysis. Furthermore, disseminated infection was associated with worse outcome in patients with *Scedosporium spp.* infection post SOT and in patients with *L. prolificans* infection and malignancy. In our analysis, we did not identify additional potentially important predictors. Proper control of confounders is difficult due to heterogeneity of hosts and diverse clinical patterns of IFD, leaving us with small numbers not allowing multivariate analysis. Trends determined in univariate analysis need further confirmation in a larger dataset.

Infections caused by *Scedosporium* spp. and *L. prolificans* resemble other mold infections on cytological and histological examination, challenging timely diagnosis and targeted treatment (Guarro et al. 2006). High virulence of certain species, in particular *L. prolificans*, and less predictable susceptibility patterns urge for prompt pathogen identification. We detected low voriconazole MICs and slightly higher MICs for itraconazole and posaconazole in most *Scedosporium* spp. strains. In comparison, for *L. prolificans* MICs were higher for all antifungals and low voriconazole MICs were determined in individual cases only. Amphotericin B or echinocandin MICs were low in few *Scedosporium* spp. strains, which may offer a treatment option in respective patients. Supportive experimental *in vivo* data are scarce with varying results on efficacy of single and combination therapy with amphotericin B or echinocandins (Rodriguez et al. 2009; Lackner et al. 2014). The clinical predictive value of *in vitro* susceptibility of amphotericin B or echinocandins and thus, the additional therapeutic benefit for patients is still unknown.

Successful treatment of *L. prolificans* infections seems almost impossible. Currently available antifungals are ineffective against the vast majority of strains and surgical treatment is rarely an option due to the poor general condition of most patients and because disease presents as fungemia or complex disseminated disease in most cases. Thus, most patients are left with virtually no treatment option. This dilemma is clearly reflected by the high mortality rates in these patients and short survival time compared to *Scedosporium* spp. infections.

Despite being a feasible approach to comprehensively investigate the epidemiology and treatment patterns of these rare diseases, this study has obvious limitations. Due to recent changes in the taxonomy of *Scedosporium* and various standards in mycological diagnostics in different countries, reported species may or may not be correctly identified. Furthermore, one cannot be certain on the correct diagnosis of an invasive infection, due to lack of data in some cases. Predisposing host factors are sometimes difficult to assess, hampered by the frequently rapid deterioration of the fungal infection until death. Thus, impaired immune system may not have been recognized and patients may have been wrongly deemed immunocompetent. Nonetheless, *Scedosporium spp.* and *L. prolificans* infections have been reported in several

immunocompetent patients with devastating outcome. Through direct wound inoculation potentially everyone is at risk for invasive fungal infections.

Infections caused by *Scedosporium* spp. and *L. prolificans* are extremely rare and patient populations at risk are diverse. CNS involvement, disseminated disease, and immunosuppression determine prognosis. During clinical management and eventually clinical trial design, these factors should be considered.

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