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FUNGAL INFECTIONS IN TRANSPLANTATION (S SHOHAM, SECTION EDITOR)

Scedosporium and *Lomentospora* infections in lung transplant recipients

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Abstract

Purpose of Review Infections caused by uncommon or rare mould pathogens often complicate the management of lung transplant (Tx) recipients contributing to high mortality. This review explores the epidemiology, diagnosis, and management of *Scedosporium* and *Lomentospora (S/L)* infections in lung Tx recipients as well as highlighting constraints in the current management and areas for future research.

Recent Findings The number of reported *S/L* infections remains low among lung Tx recipients whilst the diagnosis and treatment of *S/L* infections remains challenging. The very few studies which evaluated clinical characteristics, prognostic factors and treatment outcomes of lung Tx patients with lomentosporiosis and/or scedosporiosis were limited by single-centre and observational study design.

Summary The requirement to standardise surveillance and culture procedure for *S/L* infections in lung Tx remains. Better diagnostic tools and antifungal agents are needed to manage *S/L* infection in this patient cohort. Prospective clinical registries or online databases for lung Tx recipients with these rare mould infections are essential to refine disease management and to improve clinical outcomes in the future.

Keywords Lung transplant · Scedosporiosis · Lomentosporiosis · Infection · Colonisation

Introduction

Infection is the leading cause of mortality during the first post-transplantation year in lung transplant (Tx) recipients, accounting for 33.0% of deaths [International Society for Heart and Lung Transplantation (ISHLT)] [1]. From 1995 to 2018, a total of 63,530 adult patients underwent lung transplantation [1]. Among the 1173 lung Tx recipients from 11 solid organ Tx centres in the USA, 143 (12.0%) developed invasive mould infections [2], with a 3-month all-cause mortality of 21.7%. *Aspergillus* spp. ranked first as the agent responsible for invasive fungal disease (IFD), and

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Scedosporium spp. ranked second [2]. Data from 17 US Tx centres between 2004 and 2007 indicated that lung Tx recipients were at greatest risk for scedosporiosis compared to other organ Tx recipients [3]. More specifically, *Lomentospora prolificans* as well as *Scedosporium* spp. have emerged as a life-threatening organism in lung Tx setting. Indeed, this saprophytic environmental fungus is frequently found as a colonising mould in the lower respiratory tract (LRT) of cystic fibrosis (CF) patients, and constitutes a major risk factor for disseminated fungal infection after lung transplantation [4]. Of note, CF is the third leading indication for lung Tx (15.0%) [1]. Since the management of IFD in lung Tx may vary greatly from one centre to another [5], the aim of this review is to provide an update on *Scedosporium* or *Lomentospora (S/L)* epidemiology, diagnosis, and management in lung Tx recipients.

To identify the relevant literatures, PubMed search using search string such as "Scedospor* OR Lomentospor* AND Lung transplant*" was conducted; the latest search was in December 2020. Studies which did not provide detailed case descriptions or information on the management of invasive scedosporiosis or lomentosporiosis were excluded. We also excluded cases that were merely *S/L* colonisation or fungal ball, or cases which focused on the management of side effects in relation to the use of antifungal agents rather than the disease management of scedosporiosis and lomentosporiosis.

Epidemiology, Risk Factors, and Clinical Features for *S/L* Colonisation and Infection

Regional Distribution Disparities for *Scedosporium* and *Lomentospora* spp. *(S/L)*

Since 2014, following molecular biology-based updates in taxonomy, the genus *Scedosporium* has comprised 10 species: *S. aurantiacum*, *S. minutisporum*, *S. desertorum*, *S. cereisporum*, *S. dehoogii*, *S. angustum*, *S. apiospermum*, *S. boydii*, *S. ellipsoideum*, and *S. fusarium.* The last five species are re-grouped in the *S. apiospermum* complex. *Scedosporium prolificans* is now *L. prolificans*, and is a genus apart [6]. The change in classification has led to difficulties in interpreting the literature on scedosporiosis, with probable misclassification of species in epidemiological studies. Worldwide distribution of this fungal species could consequently be more accurately described from 2014. *S/L* are soil saprophytes found in areas of high-density population with a decreased gradient from city centre to suburban area [7]. *Scedosporium* spp. found in environmental samples is not always retrieved from patients' respiratory samples. For instance, while *S. dehoogii* is frequent in soil sample from Western France, it has never been described as a colonising agent in CF patients [4]. Some authors suggest that *S. aurantiacum* is more virulent than *S. apiospermum* complex and as virulent as *L. prolificans* [8]. By contrast, *S. minutisporum* is present in soil and clinical samples in European countries such as France, The Netherlands, and Austria, but was not found in Australia [9, 10]. *L. prolificans* is mainly found in Australia, Spain, and the southern USA [11]. *L. prolificans* is the only *Lomentospora* species that causes diseases in humans.

Lower Respiratory Tract (LRT) Colonisation with S/L

In lung Tx setting, colonisation and infection may occur within two different periods: pre-Tx and post-Tx. There are few data regarding pre-Tx fungal colonisation rates at different times after registration on waiting list for Tx in comparison with post-Tx colonisation rates [12]. Bronchial colonisation is seldom detected prior to lung transplantation as 57.0% (8 of 14) of patients with mould infections in their explanted lungs were not diagnosed or suspected before transplantation [13]. In addition, 43.0% of 304 lung Tx recipients with mould infections of the explanted lungs developed IFD post-Tx [13]. Knowledge about the prevalence of prior fungal colonisation in lung Tx candidates remains limited [12].

Nevertheless, epidemiological studies on CF patients may provide an overview of *S/L* colonisation before Tx. *S/L* are the second most frequent colonising fungi after *Aspergillus* spp. found in CF patients [14–17]; 3.1 to 15.9% being colonised [14, 17–23]. Despite antifungal treatments, CF patients can be colonised with the same genotype for years [24, 25]. An association between the use of inhaled antibiotic and occurrence of *S/L* colonisation in paediatric CF patients has been reported [21]. Another study on risk factors for colonisation in 161 CF patients found that younger age, more allergic bronchopulmonary aspergillosis, more *Pseudomonas aeruginosa* colonisation, and less colonisation with *Haemophilus influenzae* are associated with *S/L* colonisation [26].

S/L colonisation in other chronic respiratory diseases leading to lung transplantation is less widely studied. One hypothesis is that less LRT *S/L* colonisation is seen in chronic respiratory diseases other than CF. In an Australian study including 137 lung Tx recipients, 81 (59.1%) had at least one mould grown in pre-Tx respiratory samples, more commonly in suppurative diseases than in COPD and interstitial diseases (91.0% vs 44.1%, respectively, $p < 0.001$) [27]. In a French study over a 14-year period, none of the 84 patients with chronic respiratory diseases other than CF were colonised in pre-Tx with *S/L*, whereas there were 14 (7.4%) of 187 CF patients [28]. This study also reported the impact of pre-Tx colonisation with *S/L*. All but one patient colonised with *S. apiospermum* was cleared of *S/L* LRT colonisation with antifungal prophylaxis, thereby suggesting efficacy [28]. This result was confirmed in another study where 75.0% of

patients cleared their LRT colonisation when treated with antifungal agents at 6 months after Tx [29].

In an international practice survey, half of the lung Tx centres (20/42; 48.0%) had more than one candidate colonised with *S/L* per year [30••]. However, only seven centres declared having more than one recipient infected with *S/L* per year. Progression from colonisation to infection raises questions. Even with immunosuppressive drugs, some lung Tx recipients will not develop invasive disease, although *S/L* can be cultured from pulmonary samples for years [31]. Colonisation is consequently not predictive for scedosporiosis [32]. This may differ between *Scedosporium* and *Lomentospora*. Out of 14 CF patients with *S/L* colonisation in pre-lung Tx, only one colonised with *Lomentospora* developed lomentosporiosis [28]. *L. prolificans* is known to be more associated with invasive disease than *Scedosporium* spp. in malignancy setting [33]. In 10.0% of lung Tx centres in 2017, detection of bronchial colonisation with *S. apiospermum complex* before transplantation remained a contraindication to transplantation while *L. prolificans* colonisation was a contraindication in 31.0% of the lung Tx centres surveyed [30••].

Post-Tx *S/L* colonisation may appear from 2 days to 5 years after lung Tx [28, 31, 34, 35]. Endobronchial abnormalities such as stenosis with ischemia and bronchiolitis obliterans syndrome may enhance the development of scedosporiosis after lung transplantation [31]. Clearance of the fungus may be impaired by obstruction of the small airways. Out of 303 lung Tx recipients, seven (2.3%) diagnosed with either bronchiolitis obliterans syndrome or ischemic airway stenosis, had *S/L* cultured from bronchoalveolar lavage fluid [31]. In a Spanish study, respiratory samples were positive for non-*Aspergillus* moulds at some time after lung Tx in 70 (16.9%) of 412 patients [36]. Among them, *S/L* were found in 12 patients. Despite antifungal prophylaxis, one of the 12 post-Tx colonised patient developed scedosporiosis. In a Canadian study of 75 lung Tx patients, 85 isolates of non-*Aspergillus* moulds including six *Scedosporium* spp. were identified from bronchoalveolar lavage fluid [34]. Despite strains isolated being resistant to antifungal prophylaxis, no patients with *Scedosporium* isolates developed an invasive infection. Another concern is bronchial colonisation of the donor lung. If the donor is colonised with *S/L*, fungi could reactivate after lung transplantation [33]. *S/L* can be transmitted to the recipient through the graft leading to invasive infection [37].

Infection Post-Tx

The incidence of scedosporiosis post-Tx may vary between countries but is low. Multicentre studies are nonetheless lacking. In a US single centre, only two cases out of 815 (0.2%) lung Tx recipients had scedosporiosis over 7 years [38]. In another US single-centre study, 6 out of 944 (0.6%) patients had scedosporiosis over a 10-year period [29]. In Western Australia over a 13-year period, 134 patients received lung Tx and three (2.2%) developed *S. apiospermum* complex infection [27].

Various clinical manifestations of the *S/L* infections have been described in lung Tx recipients. Fever is almost always present even though signs are non-specific [39••, 40]. When localised in the lungs, infection can lead to respiratory failure. Pulmonary radiological features are usually tree-in-bud micronodules, bronchus thickening, macronodules with or without cavitations, ground glass opacities, pleural effusions, and hilar lymph nodes with or without necrosis [41]. Bronchial obstruction is uncommon [42]. In disseminated infections with or without fungaemia, almost all organs can be affected, including cases of endocarditis, osteoarthritis, epididymo-orchitis, mycotic aneurysm, and fungus ball in the urinary tract [39••, 43–48]. Infection on prosthetic material could also occur [43]. Endophtalmitis and retinitis leading to vision loss is common [43, 46]. Dissemination may occur in almost 50.0% of infected patients, thus complete work-up with central nervous system (CNS), eyes, heart, abdomino-pelvic examination should be performed when scedosporiosis or lomentosporiosis is suspected or diagnosed [32]. 18F-FDG positron emission tomography-computed tomography can be useful to screen for distant foci of infection [49–51]. Both dissemination and CNS involvement are linked with mortality in Tx recipients, and the mortality rate is close to 100% in lung Tx recipients [39••, 52–54]. Infection with *L. prolificans* is an independent predictor of death [32].

Diagnosis

Several factors might influence the identification of colonising *S/L* in lung Tx setting. First, the type of samples and frequency of sampling needed to optimally screen for *S/L* is not well-defined in the pre-Tx period [12]. It seems important to perform fungal culture from donor's lungs and candidate's explanted lungs at the time of Tx through bronchial secretion aspirates or bronchoscopy. In the post-Tx period, bronchoalveolar lavages are performed on a regular basis, with protocols varying between centres. Second, although *S/L* grow well on standard fungal media such as Sabouraud dextrose agar (SDA), cultures must be prolonged with incubation temperature of 25 °C to 35 °C [55]. An incubation time of 16 days allows detection of a sizable portion of *S/L* isolates in CF patients, since 67.0% of them need 16 days to grow [56]. Third, the presence of *Aspergillus* spp. in the same sample hampers *S/L* growth. Using semi-selective media containing benomyl, cycloheximide, or amphotericin B could improve *S/L* growth. For instance, SceSel+, benomyl-containing medium, improves *S/L* detection [19]. Benomyl is fungicidal for

Aspergillus, *Fusarium*, *Cladosporium*, *Penicillium*, or *Paecilomyces*, allowing the growth of naturally resistant *S/L*. In CF patients, 90.6–100% of isolates cultured on SceSel+ medium are detected vs. 37.5–46.9% cultured on SDA [15, 18, 57]. Another semi-selective chemically defined medium containing benomyl, Scedo-Select III, has been tested on *S. apiospermum* complex [58] where it has shown higher efficiency to detect *S. apiospermum* complex than SceSel+ [58, 59]. Media such as SDA with added gentamicin at 30 °C, inhibitory mould agar, or Brain Heart Infusion agar have been used to screen for *S/L*, and were more effective than bacterial culture media, which detected only 15.0% of *S/L* [60]. Finally, the lack of standardisation of culture media may bias *S/L* detection [61]. A French group has implemented a protocol through a multicentre study to improve screening standardisation of sputum examination in CF patients [56]. The authors proposed mucolytic pretreatment of sputum, plating on four semi-selected culture media, and reading the plates twice a week over 16 days. This protocol can increase the sensitivity of detection up to 100% for some fungi including *C. albicans*, *A. fumigatus*, *S. apiospermum* complex, and *Exophiala* spp.

In the event of infection, *S/L* may be isolated from blood cultures although haematopoietic stem cell Tx recipients are more likely to have fungaemia than solid organ Tx recipients [52]. As the case for other fungi, (1-3)-beta-D-glucan is more useful in ruling out IFD than in confirming the diagnosis. It may nonetheless be positive during scedosporiosis [62–64]. No other specific biomarkers exist so far.

Direct detection of *S/L* in clinical specimens may be enhanced using molecular methods [65••]. Of note, validation studies on panfungal polymerase chain reaction (PCR) included very few *S/L* specimens and targeted multiplex PCR are not used in clinical setting yet. Panfungal PCR could be used to directly detect *S/L* in LRT specimens although its sensitivity is lower than that in sterile body fluids [66]. Regarding fresh or formalin-fixed, paraffin-embedded tissue, the diagnostic yield of fungal molecular methods depends on (i) type of biopsy, with open biopsy having higher diagnostic yield compared with core-needle biopsy or fine needle aspiration; (ii) positive histopathology examination [67]. Thus, PCR is a useful adjunct to culture. Mycobiome sequencing and analysis by next-generation sequencing-based methods on LRT specimens are a promising diagnostic tool [68].

Treatment and Management for *S/L* Infections in Lung Tx Recipients

Lomentosporiosis

From 2005 to 2019, 10 cases of *Lomentospora* infections in lung Tx recipients were reported in 4 single case reports [42, 48, 69, 70] and 4 case series/studies [29, 71–73] (Table 1). *L. prolificans* accounted for all cases except one co-infection with *S. apiospermum* which involved lung, pleural fluid, and mycotic emboli [70]. Two were disseminated *Lomentospora* infections, with eye, lung, heart, jejunum, kidneys [69], mediastinum, and sternum [29] involvement. Other reported *Lomentospora* cases presented with pneumonia [29, 42, 72, 73] (n = 5), pericarditis with mycotic aneurysm [48] (n = 1), and sinusitis [71] (n = 1). Colonisation with the same fungal spp. (i.e. *L. prolificans*) pre- and post-lung Tx was documented in only one and two patients, respectively. Time to lomentosporiosis ranged from 21 days to 14 years post-lung Tx.

The most frequently used first-line antifungal treatment for lomentosporiosis was voriconazole-based combination therapy, with either terbinafine (n = 3) [29, 69], or terbinafine and caspofungin or micafungin (n = 3) [48, 71, 73]. This is because all currently available antifungal agents exhibit high minimum inhibitory concentrations (MIC) against *L. prolificans* [84]. Intravitreal AmB and intravitreal voriconazole were used in one of the disseminated diseases with ocular involvement [69]. Nebulised and intrapleural voriconazole have also been administered in addition to systemic voriconazole, terbinafine, and caspofungin in a disseminated infection with lung and pleural fluid involvement [70]. The use of posaconazole and anidulafungin, with or without nebulised, intrapleural voriconazole, and nebulised LAmB as second-line antifungal treatment was reported in two cases [70, 71]. In a patient with a bronchial obstructive lesion, instillation of endobronchial topical AmB thrice weekly after bronchoscopic curettage in addition to systemic voriconazole was employed as second-line therapy, with the frequency reduced to every 3 months for the next 2 years of treatment [42].

To improve the treatment outcomes, surgical interventions such as vitrectomy, pericardiectomy, sinus surgery, and washout or daily irrigation of dilute acetic acid were also reported in several cases [29, 48, 69, 71]. In the patient with mixed disseminated *S/L* infections, unsuccessful adjunct therapy with miltefosine was reported [70]. Only two cases reported therapeutic drug monitoring (TDM) for voriconazole [48, 70]. All three patients with disseminated *S/L* infection died [29, 69, 70] while the other two patients who died were those with either pneumonia [29] or pericarditis and aneurysm [48]; only one death was attributable to IFD. Inconsistency in reporting time to death was noted across these cases [i.e. death occurred at 245 days post-lung Tx (n = 1), at 9 months post-IFD (n = 1), not clearly stated (n = 3)].

The recent global clinical practice guideline by the European Confederation of Medical Mycology (ECMM) in cooperation with the International Society for Human and Animal Mycology (ISHAM) and American Society of Microbiology (ASM) has strongly recommended using combined voriconazole and terbinafine therapy as first-

Table 1 Summary of lomentosporiosis and scedosporiosis in lung transplant recipients (case reports, series, or studies)

Author (year)	*N*; patient population (primary underlying condition before LTx)	Age/gender at the time of LTx	Initial immunosuppressive agents/induction therapy	*Scedo/LoPro*/ colonisation Pre-LTx	*Scedo/LoPro* colonisation post-LTx	Fungus spp. for IFD	Time to first isolate of *Scedo/LoPro*
Disseminated infections							
Paajanen et al. (2019) [74]	1; double LTx (CF)	18/F	Tacrolimus/MMF/Prednisolone	Y (*Scedosporium apiospermum*)	N	*S. apiospermum*	Day 60 post-LTx
Chang et al. (2019) [27]	1; single LTx (ILD)	NR	NR	NR	NR	*S. apiospermum* complex	Day 299 post-LTx
Abela et al. (2018)[a] [45]	1; LTx (CF)	33/F	NR	Y (*S. apiospermum*)	Y (*S. apiospermum*)	*S. apiospermum*	3 months post-LTx
Balandin et al. (2016) [70]	1; double LTx (CF)	27/M	Tacrolimus/ Prednisone	Y (*S. apiospermum*)	NR	*S. apiospermum*, *Lomentospora prolificans*	Day 30 post-LTx
Campa-Thompson et al. (2014) [54]	1; double LTx (Idiopathic pulmonary fibrosis & AF)	62/M	NR	NR	NR	*S. apiospermum*, *Cladosporium* spp.	Day 28 post-LTx
Johnson et al. (2014)[b] [29]	1; LTx (NR)	41/F	NR	NR	Y (*S. apiospermum*)	*S. apiospermum*, *Rhizopus* spp.	Day 15 post-LTx
	1; LTx (NR)	26/F	NR	NR	Y (*S. apiospermum*)	*L. prolificans*	Day 90 post-LTx
Miraldi et al. (2012) [75]	1; double LTx (CF)	37/F	Cyclosporine/Azathioprine/Corticosteroids/Basiliximab	NR	Y (*S. apiospermum*)	*S. apiospermum*, *Candida* spp.	2 months post-LTx
Hirschi et al. (2012) [76]	1; double LTx and liver Tx (CF)	35/M	Tacrolimus/MMF/Methylprednisolone/Basiliximab	N	NR	*S. apiospermum*, *Aspergillus fumigatus* and *Trichosporon mycotoxinivorans*	Day 29 post-LTx (autopsy)
Tarabishy et al. (2011) [77]	1; LTx (COPD)	NR	NR	NR	NR	*P. boydii*	~ 2 months post-LTx
Morio et al. (2010) [53]	1; double LTx (CF)	37/F	Tacrolimus/ MMF/ Prednisone	Y (*Scedosporium/Pseudallescheria*)	Y (*S. apiospermum*)	*S. apiospermum*/ *P. boydii*	Day 70 post-LTx
Sheu et al. (2009) [41]	1; double LTx (Pulmonary hypertension)	45/M	NR	NR	NR	*P. boydii*	19 months post-LTx
	1; single LTx (COPD)	57/F	NR	NR	NR	*P. boydii*	14 months post-LTx
	1; double LTx (CF)	20/F	NR	NR	NR	*P. boydii*	11 months post-LTx
Sahi et al. (2007)[c] [43]	1; double LTx (chronic thromboembolic pulmonary hypertension)	43/M	Tacrolimus/Azathioprine/Prednisone	NR	NR	*S apiospermum, A versicolor*	18 months post-LTx
	1; single LTx (COPD)	57/F		NR	N	*S apiospermum*	14 months post-LTx

Table 1 (continued)

			Tacrolimus/MMF/Prednisone				
	1; double LTx (CF)	19/F	Tacrolimus/Prednisone	Y (*S. apiospermum*)	Y (*S. apiospermum*)	*S. apiospermum, C. glabrata*	4 weeks post-LTx
Musk et al. (2006) [46]	1; single LTx (usual interstitial pneumonitis)	57/M	Cyclosporine/Azathioprine/Prednisolone	NR	NR	*S. apiospermum*	4 years 6 months post-LTx
	1; single LTx (Emphysema)	63/M	Cyclosporine/MMF/Prednisolone/Basiliximab	N	N	*S. apiospermum/P. boydii*	Day 93 post-LTx
Symoens et al. (2006) [78]	1; double LTx (CF)	26/F	Tacrolimus/Azathioprine/Steroids	Y (*S. apiospermum*)	Y (*S. apiospermum*)	*S. apiospermum*	3 weeks post-LTx
Vagefi et al. (2005) [69]	1; double LTx (CF)	56/F	NR	NR	Y (*L. prolificans*)	*L. prolificans*	Day 21 post-LTx
Raj and Frost (2002) [79]	1; Single LTx (Idiopathic pulmonary fibrosis)	64/F	Tacrolimus/ MMF	NR	NR	*S. apiospermum*	3 years post-LTx
Castiglioni et al. (2002) [40]	1; double LTx (CF)	30/M	Tacrolimus/ Steroids	Y (*S. apiospermum*)	NR	*S. apiospermum*	2 weeks post-LTx
Bone infections							
Denton et al. (2016) [47]	1; double LTx (CF)	21/M	Tacrolimus/MMF/Corticosteroids/Basiliximab	Y (*S. apiospermum*)	Y (*S. apiospermum*)	*S. apiospermum*	Day 319 post-LTx
Thomson et al. (2015) [35]	1; double LTx (CF)	18/F	Tacrolimus/MMF/Prednisolone	Y (*S. apiospermum*)	NR	*S. apiospermum*	5 years post-LTx
Luijk et al. (2011) [80]	1; double LTx (CF)	16/F	Tacrolimus/MMF/Prednisone	Y (*S. apiospermum*)	N	*S. apiospermum*	2 years and 8 months post-LTx
Pulmonary							
Chang et al. (2019) [27]	1; single LTx (COPD)	NR	NR	NR	NR	*S. apiospermum complex, A. fumigatus, A. niger* complex	Day 3631 post LTx
	1; HLTx (CHD)	NR	NR	NR	NR	*S. apiospermum* complex	Day 583 post-LTx
Sole et al. (2018) [81]	1; double LTx (CF)	37/F	Tacrolimus/MMF/Corticosteroids	N	Y (*S. apiospermum*)	*S. apiospermum*	Day 21 post-LTx
	1; double LTx (Emphysema)	59/M	Tacrolimus/MMF/Corticosteroids	N	NR	*S. apiospermum*	Day 31 post-LTx
	1; double LTx (CF)	31/M	Tacrolimus/ MMF/ Corticosteroids	N	NR	*S. apiospermum*, *A. ochraceous*	Day 29 post-LTx
Mitomo et al. (2018) [42]	1; double LTx (Idiopathic pulmonary hypertension)	50s/F	Tacrolimus/ MMF/ Prednisolone	NR	NR	*L. prolificans*	8 years post-LTx
Jenks et al. (2018) [73]	1; LTx (CF)	NR	NR	NR	NR	*L. prolificans*	4 years post-LTx

Table 1 (continued)

Cobo et al. (2017) [72]	1; LTx (NR)	65/M	Corticosteroid/NR	NR	NR	*L. prolificans*	NR
Peghin et al. (2016) [36]	1; single LTx (Fibrosis)	61/F	NR	Y (*S. apiospermum*)	No	*S. apiospermum*	Day 31 post-LTx
	1; double LTx (COPD)	55/F	NR	No	*Penicillium* spp.	*S. apiospermum, A. fumigatus*	Day 121 post-LTx
Johnson et al. (2014)[b] [29]	1; LTx (NR)	65/M	NR	NR	NR	*S. apiospermum*	Day 2841 post-LTx
	1; LTx (NR)	26/M	NR	NR	NR	*L. prolificans*	Day 4591 post-LTx
	1; LTx (NR)	59/F	NR	NR	NR	*L. prolificans*	Day 1388 post-LTx
	1; LTx (NR)	24/F	NR	NR	Y (*S. apiospermum*)	*S. apiospermum*	Day 73 post-LTx
Rolfe et al. (2013) [82]	1; double LTx (CF)	24/F	NR	Y (*S. apiospermum*)	N	*S. apiospermum*	2 months before LTx
Castiglioni et al. (2002) [40]	1; HLTx (Transposition of vessels and Eisenmenger's syndrome)	37/F	Tacrolimus/Azathioprine/Prednisone; rabbit antithymocyte globulin	NR	Y (*S. apiospermum*)	*S. apiospermum*	1 year post-LTx
Sinusitis							
Ference et al. (2019) [71]	1; double LTx (CF)	40/M	NR	Y (*L. prolificans*) for re-LTx	NR	*L. prolificans*	14 years post-LTx
	1; double LTx (Sweet's Syndrome)	35/F	NR	NR	NR	*S. apiospermum*	2 months post-LTx
Ocular							
Tarabishy et al. (2011) [77]	1; LTx (CF)	NR	NR	NR	NR	*P. boydii*	1 month post-LTx
Pericarditis/ aneurysm							
Sayah et al. (2013) [48]	1; double LTx (Idiopathic pulmonary fibrosis)	70/F	Tacrolimus/MMF/Prednisone/Basiliximab	NR	Y (*L. prolificans*)	*L. prolificans*	8 months post-LTx
Skin							
Scott et al. (2014) [83]	1; LTx (COPD)	50s/M	Tacrolimus/MMF/Prednisone	NR	NR	*S. apiospermum*	3 months post-LTx

Author (year)	Site(s) of isolate for *Scedo/LoPro* or clinical manifestation(s)	Initial symptoms	Antifungal prophylaxis received before diagnosis of IFD	Antifungal maintenance therapy	Surgical intervention	Other	Outcome
Disseminated infections							
Paajanen et al. (2019) [74]	Skin nodules, lung, surgical wound	Upper back pain radiated to leg, painful skin nodules with ulcerations, neurological symptoms, oozing surgical wound	CASPO 50 mg OD, nebulised AmB	VORI 200–300 mg BD for 35 months, then in between added miltefosine for 1 month	NR	TDM VORI	Alive; complete resolution with no replased at 4 years post-LTx
	Disseminated (not specify the sites)	NR	No	NR	NR	NR	

Table 1 (continued)

Chang et al. (2019) [27]							Died; day 555 post-IFD
Abela et al. (2018)[a] [45]	Knee, lung	Painful, swollen left knee	Inhaled AmB + PO ITRA, then added IV CASPO	VORI + TERBI + intrarticular VORI (20 mL of a 10 mg/mL solution)	Repeated arthroscopic debridement	NR	Alive; dtable disease
Balandin et al. (2016) [70]	Lung, pleural fluid, mycotic emboli	NR	IV VORI 200 mg BD + IV LAmB 300 mg OD + nebulised LAmB 25 mg OD	IV VORI 200 mg BD + TERBI 250 mg OD + IV CASPO 50 mg OD + nebulised VORI 40 mg OD + intrapleural VORI BD, then IV POSA 300 mg OD + ANIDULA 100 mg OD + VORI (intrapleural + nebulised) + nebulised LAmB	Miltefosine 50 mg BD	TDM VORI	Died; day 245 post-LTx
Campa-Thompson et al. (2014) [54]	Pleural fluid, tracheal aspirate, surgical incision site, kidneys, outer portion of aortic wall, thyroid gland, brain, heart and lung (postmortem)	Lethargic, unresponsive, acute respiratory distress, involuntary myoclonic movements, anasarca, marked oliguria, persistent AF	NR	IV AmB	NR	NR	Died; NR
Johnson et al. (2014)[b] [29]	Lung, wound infection	Respiratory failure	NR	AmB, CASPO, FLUCO, TERBI, VORI	NR	NR	Alive with progression of disease at 6 months
	Mediastinitis, sternal osteomyelitis	Diabetic ketoacidosis	NR	VORI, TERBI	Surgery	NR	Died; at 6 months
Miraldi et al. (2012) [75]	Cardiac mycetoma	Recurrent seizures, right-sided hemiparesis, almost complete loss of vision	ITRA 200 mg OD + aerosolised AmB (50 mg OD)	CASPO 50 mg OD + VORI 4 mg/kg BD	Trans-atrial approach under cardiopulmonary bypass	TDM VORI	Died; day 10 post-surgery
Hirschi et al. (2012) [76]	Thoracic wound, lung abscess, bronchi, heart, trachea, thyroid, liver, kidney, small bowel)	Respiratory symptoms, non-febrile sleepiness	CASPO (discontinued the next day post-LTx due to deranged LFT)	CASPO + VORI	Surgical toilet of thoracic wound	TDM VORI	Died; day 29 post-LTx
Tarabishy et al. (2011) [77]	Third nerve palsy secondary to disseminated infection	NR	NR	AmB	NR	NR	Died; day 35 of ocular diagnosis
Morio et al. (2010) [53]	Nodules on legs, blood, mitral valve, lung	Skin nodules, acute vestibular syndrome, dizziness, dysarthria	VORI 250 mg BD	VORI + CASPO 50–150 mg OD, then added TERBI 250 mg OD	Valve replacement + excision of vegetation	TDM VORI	Died; 8 months post-LTx
Sheu et al. (2009) [41]	Lung, skin abscesses, osteomyelitis	NR	NR	NR	NR	NR	Died; 12 months post-IFD
	Lung, skin and brain abscesses	NR	NR	NR	NR	NR	Died; 1 month post-IFD
	Lung, osteomyelitis, pyelonephritis, endopthalmitis	NR	NR	NR	NR	NR	Died; 5 months post-IFD
Sahi et al. (2007)[c] [43]	Lung, mediastinitis, pleuritic, knee Abscess, vertebral osteomyelitis	Pulmonary signs	NR	LAmB, then CASPO + ITRA	Mediastinoscopy	NR	Died; 31 months post-LTx
	Lung, breast implant capsulitis, pleuritic/emphysema, brain abscess, skin micro-abscesses	Chest and breast pain, swollen and erythematous left breast, multiple skin	N	VORI + TERBI, then POSA	Breast implant removal, decortication, brain abscess drainage	TDM VORI	Died; NR

Table 1 (continued)

		nodules, right eye ptosis, downward gaze palsy					
	Lung, sinus, vitreous humour, skin micro-abscesses, chest wall cellulitis, mediastinitis, vertebral osteomyelitis, septic arthritis, endobronchial plaques, urinary tract infections	Blurred vision, multiple painful skin nodules	VORI 200 mg BD	VORI, then added TERBI + CASPO + intravitreal VORI, then POSA 800–1200 mg daily + LAmB	Enucleation, chest wall abscess drainage, sinus debridement	GM-CSF, pentamidine	Died; 15 months post-LTx
Musk et al. (2006) [46]	Vitreous humour, epididymoorchitis, skin and lung nodules	Progressive breathlessness, pleuritic chest pain, reduced visual acuity, swollen scrotum	NR	PO VORI 400 mg BD + TERBI 250 mg OD + intravitreal VORI + topical VORI	Vitrectomy	NR	Alive; 8 years post-LTx; relapsed 5 weeks disconution of VORI
	Retina, vitreous humour, urinary tract	Swollen left eye, sudden loss of vision	Nebulised AmB 10 mg BD	IV VORI + IV LAmB, then VORI 200 mg BD + TERBI 250 mg OD + intraocular VORI, then VORI (irrigation + oral)	Vitrectomy , Irrigation	NR	Alive; 7+ months post-LTx
Symoens et al. (2006) [78]	Skin nodules, vitreous humour, CSF	Fever, subcutaneous skin nodules, complete loss of vision	ITRA 200 mg BD + aerolised AmB 20 mg BD	PO VORI 200 mg BD + intraocular MICO (25 μg in both eyes on day 3 and 5 of treatment)	NR	TDM VORI	Died; day 23 after uncontrolled fungal infection; relapsed 2 days after VORI discontinuation
Vagefi et al. (2005) [69]	Eye; lungs, heart, jejunum, kidneys (autopsy)	Increased blurriness and a central scotoma in the right eye	VORI + TERBI	Intravitreal AmB (0.5 μg/0.1 mL) + intravitreal VORI (50/0.1 mL) *no unit provided	Vitrectomy	NR	Died; NR
Raj and Frost (2002) [79]	Lung, blood, heart	Fever, cough, sputum production, malaise	NR	AmB, ITRA	NR	NR	Died; day 18 post-treatment
Castiglioni et al. (2002) [40]	Lungs, pleural fluid, pericardium	Renal failure, respirator insufficiency, bilateral infiltrates with pleural effusions	NR	AmB + MICO	NR	NR	Died; day 6 post-IFD diagnosis
Bone infections							
Denton et al. (2016) [47]	Sternal and lower ribs osteomyelities	Swelling and localised pain at lower sternum and ribs	VORI, followed by POSA (stopped 17 days prior to IFD due to deranged LFT)	VORI	Surgical debridement with extensive resection of the infected site; extensive 2-part reconstructive procedure and superficial skin graft	TDM VORI	Alive; complete resolution at 10 months post-treatment
Thomson et al. (2015) [35]	Vertebral osteomyelitis, abdominal aortic aneurysm	Back pain	NR	VORI, then VORI + TERBI, then VORI + MICA	Debridement of vertebral bodies and abdominal aortic replacement	TDM VORI	Alive; 4 months post-surgery
Luijk et al. (2011) [80]	L1-L4, spondylodiscitis	Lumbar pain, abscess formation at the left psoas musculus	No	VORI 200 mg BD for 3.5 years	No	No	Alive; relapsed 1 year after discontinuation of voriconazole
Pulmonary							
Chang et al. (2019) [27]	Lung	NR	No	NR	NR	NR	Alive
	Lung	NR	POSA	NR	NR	NR	Died; day 160 post-IFD
Sole et al. (2018) [81]	Tracheobronchitis and lung	Bilateral anastomotic infection	MICA 150 mg OD	POSA 300–450 mg OD + TERBI, then added topical POSA (9 weekly endobronchial	Frequent cleansing bronchoscopies	TDM POSA	Alive; resolved at day 349 post-LTx

Table 1 (continued)

				doses; 50 mg per procedure) + nebulised POSA OD for 5 months/EOD for 1 month			
	Tracheobronchitis and lung	NR	Nebulised AmB lipid complex 25 mg EOD + FLUCO 200 mg OD	IV POSA 300 mg OD, then added LAmB, TERBI and nebulised AmB lipid complex 25 mg EOD	NR	TDM POSA	Died at day 399 post-LTx; relapsed 1 month after Nebulised POSA was discontinued.
	Tracheobronchitis and lung	NR	Nebulised AmB lipid complex 25 mg EOD + MICA 100 mg OD	VORI, then POSA + TERBI, then added nebulised POSA OD for 2 months	Frequent cleansing bronchoscopies	TDM POSA	Alive; Completely resolved at Day 210 post-LTx or 2 months post-combined therapy
Mitomo et al. (2018) [42]	Lung	Abnormal shadow on CT chest during routine follow-up	NR	ITRA 200–400 mg OD, then VORI 200–400 mg OD + endobronchial topical AmB instillation weekly for 3 times then every 3 months for 2 years	NR	NR	Alive; Resolution after 2 years post-treatment
Jenks et al. (2018) [73]	Lung	POSA	POSA for 31 days	VORI + MICA + TERBI	NR	NR	Alive; stable disease at day 84
Cobo et al. (2017) [72]	Lung	Productive cough, dyspnoea	NR	VORI	NR	NR	NR; transferred to other Hospital
Peghin et al. (2016) [36]	Lung	NR	NR	VORI + nebulised LAmB for 46 days	NR	NR	Died; Day 46 post-treatment
	Lung	NR	NR	VORI + nebulised LAmB for 180 days	NR	NR	Died; NR
Johnson et al. (2014)[b] [29]	Lung	Respiratory distress, tachycardia, atrial flutter	NR	VORI	NR	NR	Alive with complete resolution at 6 months
	Lung	Dyspnoea, productive cough	NR	VORI, TERBI	NR	NR	Alive; stable disease at 6 months
	Lung	Hypoxia	NR	AmB, VORI, TERBI	NR	NR	Died; 9 months post-IFD
	Lung	Shortness of breath, chest pain, fever	NR	POSA, TERBI, VORI	Mediatinal exploration	NR	Died; at 6 months
Rolfe et al. (2013) [82]	Lung	Fever, pleuritic chest pain increased sputum production	NR	POSA, then VORI + TERBI 250 mg OD	NR	NR	Alive; resolution; 17 months post-LTx
Castiglioni et al. (2002) [40]	Lung	Fever, shortness of breath, diabetic ketoacidosis	ITRA	MICO	NR	NR	Died; day 10 post-admission
Sinusitis							
Ference et al. (2019) [71]	Sinus, lung	Nasal congestion, postnasal drip, facial pain/pressure, mucopurulent discharge	NR	VORI + TERBI + CASPO, then POSA + ANIDULA, then VORI + ANIDULA, then POSA for 4 years	Bilateral endoscopic, re-LTx Sinus surgery and washout	Daily irrigation of dilute acetic acid	Alive; resolution
	Sinus, lung	Nasal obstruction, postnasal drainage, loss of smell, and facial pressure	NR	POSA, then VORI + inhaled AmB, then ISAVU + TERBI + inhaled AmB, then POSA	Sinus surgery, right-sided endoscopic medial maxillectomy with biopsy of the bone of the posterior maxillary wall	IV immunoglobu-lin, G-CSF	Alive; resolution
Ocular							

Table 1 (continued)

Tarabishy et al. (2011) [77]	Endogenous endophthalmitis	NR	NR	Intravitreal VORI + AmB	Pars plana vitrectomy and membrane peel, evisceration	NR	Died; at 16 months of Ocular diagnosis
Pericarditis/ aneurysm							
Sayah et al. (2013) [48]	Pericardium, mycotic aneurysm	Dyspnoea	VORI 200 mg BD for 8 months	VORI + TERBI + CASPO	Pericardiectomy	TDM VORI	Died at 19 weeks post-pericardiectomy
Skin							
Scott et al. (2014) [83]	Subcutaneous nodules	Purple, painful, pustular nodules on left arm with a palpable, erythematous cord extending up to arm	NR	VORI	Surgical debridement with phlebectomy	NR	Alive; significant clinical improvement; NR

[a] Abela et al. (2018): 1 LTx recipient with *S. apiospermum* infection but without radiological signs of IFD, four LTx candidates, and one liver Tx recipient were excluded.

[b] Johnson et al. (2014): Colonised before LTx ($n = 2$); previously colonised by the same fungal spp. ($n = 3$). Median time to scedosporiosis post-Tx: among those colonised before Tx: 15 (4-90) days; not colonised before Tx: 217 (6-45,914) days (findings were not specific for LTx recipients)

[c] Sahi et al. (2007): The other two LTx recipients with colonisation were excluded

AmB, amphotericin B; ANIDULA, anidulafungin; BD, twice daily; CASPO, caspofungin; CF, cystic fibrosis; CHD, congenital heart disease; COPD, chronic obstructive pulmonary disease; *EOD* every other day, *F* female, *GM-CSF* granulocyte-macrophage colony-stimulating factor, *HLTx* heart-lung transplant, *IFD* invasive fungal disease, *ILD* interstitial lung disease, *ITRA* itraconazole, *IV* intravenous, *LAmB* liposomal amphotericin B, *LFT* liver function test, *LoPro Lomentospora prolificans*, *LTx* lung transplant, *M* male, *MICO* miconazole, *MMF* mycophenolate mofetil,;*N* no, *NR* not reported, *OD* once daily, *PO* per oral, *POSA* posaconazole, *Scedo Scedosporium*, *TDM* therapeutic drug monitoring, *TERBI* terbinafine, *VORI* voriconazole, *Y* yes

line treatment for *Lomentospora* infections; voriconazole monotherapy is recommended with moderate strength as the alternative [85•]. If the lomentosporiosis progresses, the guideline group moderately supports the use of isavuconazole or posaconazole monotherapy as second-line therapy with voriconazole monotherapy as salvage therapy. The group advises against the use of LAmB in patients with *Lomentospora* infections. The guideline group also strongly recommends the use of surgical debridement where applicable and TDM for voriconazole therapy. A minimum treatment duration of 4 to 6 months of antifungal combination therapy for lomentosporiosis is moderately recommended.

Scedosporiosis

A total of 37 cases on scedosporiosis were reported in 13 single case reports [35, 45, 47, 53, 54, 74–76, 78–80, 82, 83] and 10 case series/studies [27, 29, 36, 40, 41, 43, 46, 71, 77, 81] from 2002 to 2019 (Table 1). Disseminated *Scedosporium* infection was the most common clinical presentation in lung Tx recipients ($n = 20$) [27, 29, 40, 41, 43, 45, 46, 53, 54, 74–79], followed by scedosporiosis with lung ($n = 11$) [27, 29, 36, 40, 81, 82], bone ($n = 3$) [35, 47, 80], sinus ($n = 1$) [71], ocular ($n = 1$) [77], or skin ($n = 1$) [83] involvement. *S. apiospermum* complex or *P. boydii* accounted for all reported cases. Nine were co-infected by other fungal spp. (e.g. *A. fumigatus*, *A. ochraceous*, *A. versicolor*, *A. niger* complex, *Candida* spp., *Cladosporium* spp., *Rhizopus* spp., *L. prolificans*, *Trichosporan mycotoxinivorans*). Nearly 30.0% of the cases documented colonisation with the same fungal spp. (i.e. *S. apiospermum*) pre- and post-lung Tx. Time to scedosporiosis ranged from 15.0 days to 9.9 years post-lung Tx.

First-line antifungal treatment with either voriconazole monotherapy ($n = 8$) [29, 35, 43, 47, 74, 80, 81, 83] or voriconazole-based combination therapy (with caspofungin, terbinafine, miconazole, or LAmB) ($n = 12$) [36, 43, 45, 46, 53, 75, 76, 78] was the most frequently reported. Posaconazole salvage therapy was documented in three cases; two for pulmonary scedosporiosis [81] and one for sinusitis [71]. The use of intraarticular [45], intraocular [43, 46, 77], topical [43], or irrigation [46] voriconazole, intraocular miconazole [78], nebulised ABLC [81], AmB [71] or LAmB [36], nebulised or topical endobronchial doses of posaconazole [81], has also been documented, depending on the site of infection. One disseminated case documented the successful use of adjunctive miltefosine [74]. Combination therapy of granulocyte-macrophage colony-stimulating factor (GM-CSF) and pentamidine [43] or granulocyte colony-stimulating factor (G-CSF) and immunoglobulin [71] in addition to antifungal therapy and surgical interventions were

reported in two cases with successful treatment outcome noted only in the patient with sinusitis [71]. TDM of voriconazole and posaconazole were reported only in eight [35, 43, 47, 53, 74–76, 78] and three [81] cases, respectively.

Several surgical interventions had been used, depending on the site of *Scedosporium* infection, in addition to antifungal therapies to improve clinical outcomes. These included repeated arthroscopic [45], skin with or without phlebectomy [47, 83], vertebral [35] or sinus debridement [43, 71], skin graft or reconstruction [47], trans-atrial approach [75], wound or abscess drainage [43, 76], valve replacement and excision of vegetation [53], aortic replacement [35], mediastinoscopy [43] or mediastinal exploration [29], breast implant removal or decortication [43], enucleation [43], vitrectomy [46, 77], and cleansing bronchoscopies [81]. Fifteen of the 20 patients (75.0%) with disseminated *Scedosporium* infections died [27, 29, 40, 41, 43, 53, 54, 75–79], nine were IFD-related mortality; the time to death ranged from day 6 to 18 months post-IFD diagnosis or day 29 to 31 months post-lung Tx. Six of the 11 patients (54.5%) with pulmonary scedosporiosis died [27, 29, 36, 40, 81]; half were attributable to IFD. All patients who had scedosporiosis limited to bone, sinus, or skin involvement survived, with either complete or significant clinical improvement.

The recent global clinical practice guideline has strongly recommended voriconazole monotherapy as first-line treatment with TDM [85•]. The guideline group moderately supports the use of voriconazole-based combination therapy (with LAmB, ABLC, echinocandins, or terbinafine) as alternative. Isavuconazole, posaconazole, or itraconazole monotherapy is marginally recommended as second-line treatment. A combination of voriconazole and echinocandins, or posaconazole monotherapy is recommended as salvage therapy. Likewise, the group advises against ABLC or LAmB monotherapy for the treatment of *Scedosporium* infection. The guideline group marginally supports surgical interventions for scedosporiosis. Treatment should be continued, generally for weeks to months, until resolution of signs and symptoms of scedosporiosis.

Observational Studies in Lung, Liver-Lung, and Heart-Lung Tx Recipients with Lometosporiosis and/or Scedosporiosis

While several large observational studies on lomentosporiosis and/or scedosporiosis were published in recent years [39, 86, 87, 88••], the majority did not include lung Tx recipients nor perform further analysis of the lung Tx cohort, likely due to the small numbers of lung Tx recipients included. For instance, only 15 out of the 264 patients included in the study by Seidel et al. [39••] were LTx recipients; 11 with scedosporiosis and 4 with lomentosporiosis. The reported median (IQR) time to *Scedosporium* infection was 82 (26–461) days post-lung Tx. CNS and disseminated scedoporiosis were associated with higher mortality in SOT recipients (with 37.9% receiving either a renal or lung Tx) [39••]. A population-based surveillance study in Australia [32] reported that 36.0% of the LTx recipients with positive cultures of *S. aurantiacum* or *S. apiospermum* had proven scedosporiosis; however, lung Tx, CF and chronic lung disease were not predisposing factors for *Scedosporium* infection but for isolation of *Scedosporium* spp. in the respiratory samples. Caston et al. [89] reported that one-third of the 27 patients with positive respiratory cultures of *S. apiospermum* had proven ($n = 3$) or probable ($n = 6$) invasive pulmonary infection; among these patients, four were lung Tx recipients. This study also noted that patients with invasive pulmonary scedosporiosis had a higher rejection rate, a longer time to acquiring IFD post-Tx, a higher lymphocyte count, and received previous prophylaxis with aerosolised AmB or intravenous AmB, in comparison to those with invasive aspergillosis [89].

Three retrospective, single-centre studies [28, 31, 90•] describing the clinical characteristics and treatment outcomes of *S/L* infections among lung Tx recipients, with and without other solid organ Tx, were published from 2001 to 2020 (Table 2). A 24-year Australian study by Vazirani et al. [90•] recently reported 19 invasive *S/L* infections among the lung Tx cohort; median (IQR) time to IFD was 748 (369, 4870) days post-lung Tx. Posaconazole, with or without terbinafine, was the most commonly used antifungal(s) for IFD, with a median (IQR) treatment duration of 326 (159, 648) days. This study also revealed that the survival rate at 24-year post-lung Tx among those with positive respiratory cultures of *S/L* was not statistically different from the rest of the lung Tx cohort. Similar observation was noted among those who had *S/L* colonisation prior to lung Tx.

In the work of Parize et al. [28], only one lomentosporiosis affecting lung and pleura was documented among 14 CF patients following lung and or liver Tx and was treated with a combination of voriconazole, terbinafine and caspofungin. The patient, however, died at day 56 post-Tx. Nine had *Scedosporium* spp. or *L. prolificans* colonisation prior to Tx while 13 had *Scedosporium* spp. and/or *L. prolificans* colonisation post-Tx. Voriconazole was the most commonly used antifungal prophylaxis pre- or post-Tx. In another Australian study by Tamm et al. [31], one had scedosporiosis alone, four had scedosporiosis with *L. prolificans* co-infection, and two had *Aspergillus* spp. co-infection. All were pulmonary infections treated with itraconazole and fluconazole; none died due to disseminated scedosporiosis. The time to infection and death ranged from 9 to 58 months post-lung Tx and 3 to 35 months post-IFD, respectively.

Table 2 Summary of lomentosporiosis and scedosporiosis in lung transplant recipients (observational studies)

Author (year)	Study design/study period/place	*N*; patient population (primary underlying condition before LTx); Age	Initial immunosuppressive agents/induction therapy	*Scedo/LoPro* colonisation Pre-LTx	*Scedo/LoPro* colonisation post-LTx	Fungus spp. for IFD	Time to first isolate of *Scedo/LoPro*
LTx or HLTx patient cohort							
Vazirani et al. (2020) [90•]	Retrospective, single-centre/24 years/Australia	30; double LTx (*n* = 26), single LTx (*n* = 3), HLTx (*n* = 1); COPD, CLAD redo (*n* = 7, 23.3% each); median (IQR): 61 (48, 67) years old	Cyclosporine/-Tacrolimus/Everolimus/Azathioprine/MMF/Prednisolone	*n* = 6	NR	*L. prolificans* (*n* = 12); *S. apiospermum* (*n* = 7)	Median (IQR): 748 (369, 4870) days post-LTx
Parize et al. (2017) [28]	Retrospective, single-centre/15 years/France	14; double LTx (*n* = 12) alone, Liver + LTx (*n* = 2); CF (*n* = 14, 100.0%); median (range): 20 (10–37) years old	Cyclosporine/-Tacrolimus/MMF/steroids; anti-thymocyte globulin (*n* = 9), basiliximab (*n* = 4)	*n* = 9; *P. boydii* (*n* = 2); *S. apiospermum* complex (*n* = 5); *S. aurantiacum* (*n* = 1); *L. prolificans* (*n* = 1)	*n* = 13; *P. boydii* (*n* = 2); *S. apiospermum* complex (*n* = 6); *S. apiospermum* (*n* = 1); *S. aurantiacum* (*n* = 1); *L. prolificans* (*n* = 2); *L. prolificans* + *S. apiospermum* (*n* = 1)	*L. prolificans* (*n* = 1)	NR
Tamm et al. (2001) [31]	Retrospective, single-centre/14 years/Australia	7; double LTx (*n* = 2), single LTx (*n* = 1), HLTx (*n* = 4); Emphysema (*n* = 3, 42.9%); mean* (range): 40.6 (22–52) years old	Cyclosporine/-Azathioprine/-Prednisolone; Anti-thymocyte globulin	NR	NR	*S. apiospermum* (*n* = 1); *LoPro* + *S. apiospermum* (*n* = 4); *S. apiospermum* + *Aspergillus* spp. (*n* = 2)	Mean* (range): 21 (9–58) months post-Tx

Author (year)	Site(s) of isolate for *Scedo/LoPro* or clinical manifestation(s)	Initial antifungal prophylaxis received before IFD	Antifungal maintenance therapy	Surgical intervention	Other	Outcome
LTx or HLTx patient cohort						
Vazirani et al. (2020) [90•]	Lung	NR	POSA TERBI (*n* = 6); VORI + TERBI (*n* = 2); ISAVU + TERBI (*n* = 2); others received monotherapy	NR	TDM VORI or POSA	Survival rate at 24-year post-LTx of those with positive cultures of *Scedo/LoPro* was not statistically different to the remainder of LTx cohort

Table 2 (continued)

Parize et al. (2017) [28]	Lung, pleuritis	Pre-LTx: VORI (n = 7); POSA (n = 1); ITRA (n = 1) Post-LTx: VORI (n = 11); POSA (n = 2); ITRA (n = 1)	VORI + TERBI + CASPO	NR	TDM VORI or POSA	Died with IFD at day 56 post-LTx (n = 1); died due to other reasons (n = 6)
Tamm et al. (2001) [31]	Lung	ITRA (n = 5); no antifungal agent prescribed (n = 2)	ITRA + FLUCO (n = 7)	Multiple stent insertions (n = 1)	NR	Died (n = 4); time to death (range) 3–35 months post-IFD diagnosis

AmB amphotericin B, *CASPO* caspofungin, *CF* cystic fibrosis, *CLAD* chronic lung allograft dysfunction, *COPD* chronic obstructive pulmonary disease, *FLUCO* fluconazole, *IFD* invasive fungal disease, *ISAVU* isavuconazole, *ITRA* itraconazole, *IV* intravenous, *HLTx* heart-lung transplant, *LoPro Lomentospora prolificans*, *LTx* lung transplant, *MMF* mycophenolate mofetil, *NR* not reported, *POSA* posaconazole, *Scedo Scedosporium*, *TDM* therapeutic drug monitoring, *TERBI* terbinafine, *VORI* voriconazole. CLAD redo refers to LTx recipients whose initial LTx was complicated by CLAD and underwent second LTx

Challenges and Future Recommendations for the Diagnosis and Management of S/L Infections in Lung Tx Recipients

The number of reported *S/L* infections remains low among lung Tx recipients over the last decade. Given the rare occurrence of these fungal infections in the lung Tx cohort, conducting a randomised controlled trial to establish clinical evidence for diagnosis and management of lomentosporiosis and scedosporiosis is not feasible. Furthermore, the few large, observational studies of lomentosporiosis and/or scedosporiosis did not provide in-depth analysis or findings for this patient cohort. Therefore, it is important to establish prospective clinical registries or online databases specifically tailored for lung Tx recipients with these rare mould infections to refine treatment strategies, which could lead to improvements in disease management and clinical outcomes.

Timely identification and diagnosis of lomentosporiosis and scedosporiosis remain difficult. The lack of reliable biomarkers poses challenges in confirming the diagnosis of *S/L* infections. A uniform approach to the type and frequency of surveillance sampling to identify *S/L* colonisation prior to lung Tx and the type of culture media used to optimise detection of *S/L* spp., is warranted before embarking on prospective cohort studies in the lung Tx setting.

Scedosporiosis is commonly disseminated in lung Tx recipients while a variety of clinical manifestations of lomentosporiosis have been noted. In lung Tx and other settings, disseminated lomentosporiosis and scedosporiosis were associated with poor prognosis and high mortality rate, in-part due to the limited treatment options available. Hence, the efficacy of new candidates in the antifungal pipeline such as olorofim, auranofin, or fosmanogepix, for the treatment of *S/L* infection is well-anticipated. To date, voriconazole is the drug of choice against lomentosporiosis and scedosporiosis, often being used with or without terbinafine, respectively. The use of voriconaole TDM was limited in this review despite the highly variable inter-individual pharmacokinetic profile of voriconazole and the known drug-drug interactions between voriconazole and immunosuppressive agents that are commonly used in the lung Tx setting. With a view to optimising the use of voriconazole, TDM for voriconazole is essential especially among the CF lung Tx recipients as voriconazole levels are often undetectable in these patients [91]. Studies investigating the effectiveness of non-drug therapies such as surgical interventions for management of *S/L* infections in the lung Tx setting remain scant.

There are several limitations of this review. We included only those published in the English literature. Given the limited information available in each reported case, we cannot verify all included cases against the proven/ probable IFD criteria, as defined by the European Organisation for Treatment of Cancer/Mycoses Study Group (EORTC/MSG) [92] or by the ISHLT [93].

Conclusions

Whilst infections caused by *S/L* remain rare in the lung Tx cohort, they are associated with high mortality, especially in the setting of disseminated disease. This review highlights the need to standardise surveillance and culture procedure for *S/L* in the LTx setting as well as to develop better diagnostic tools and antifungal agents to optimise the management of lomentosporiosis and scedosporiosis. Larger, prospective cohort studies tailored to this patient cohort are warranted.

Declarations

Conflict of Interest BR received travel grants for conferences from Pfizer, Gilead, Shionogi, Merck/MSD, and speaker's fees from Merck/MSD, Gilead, Pfizer, IQone. SC-AC has received untied educational grants from MSD Australia, F2G and speaker's fees from Gilead Sciences Inc., and sits on the Antifungal Advisory Boards of MSD Australia, Gilead Sciences Inc., and F2G. DCMK has received grants from MSD and F2G. MAS has received grants from Merck, F2G and Gilead Sciences Inc. and speaker's fees from Pfizer and Gilead Sciences Inc., and sits on a data review committee for Roche. Other author: none to declare.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- • Of importance
- •• Of major importance

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