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MAJOR ARTICLE

Invasive *Scedosporium* and *Lomentospora prolificans* Infections in Australia: A Multicenter Retrospective Cohort Study

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Background. Management of *Scedosporium/Lomentospora prolificans* infections remains challenging. We described predisposing factors, clinical manifestations, and outcomes of these rare mold infections, including predictors of early (1-month) and late (18-month) all-cause mortality and treatment failure.

Methods. We conducted a retrospective Australian-based observational study of proven/probable *Scedosporium/L prolificans* infections from 2005 to 2021. Data on patient comorbidities, predisposing factors, clinical manifestations, treatment, and outcomes up to 18 months were collected. Treatment responses and death causality were adjudicated. Subgroup analyses, multivariable Cox regression, and logistic regression were performed.

Results. Of 61 infection episodes, 37 (60.7%) were attributable to *L prolificans*. Forty-five of 61 (73.8%) were proven invasive fungal diseases (IFDs), and 29 of 61 (47.5%) were disseminated. Prolonged neutropenia and receipt of immunosuppressant agents were documented in 27 of 61 (44.3%) and 49 of 61 (80.3%) episodes, respectively. Voriconazole/terbinafine was administered in 30 of 31 (96.8%) *L prolificans* infections, and voriconazole alone was prescribed for 15 of 24 (62.5%) *Scedosporium* spp infections. Adjunctive surgery was performed in 27 of 61 (44.3%) episodes. Median time to death post–IFD diagnosis was 9.0 days, and only 22 of 61 (36.1%) attained treatment success at 18 months. Those who survived beyond 28 days of antifungal therapy were less immunosuppressed with fewer disseminated infections (both $P < .001$). Disseminated infection and hematopoietic stem cell transplant were associated with increased early and late mortality rates. Adjunctive surgery was associated with lower early and late mortality rates by 84.0% and 72.0%, respectively, and decreased odds of 1-month treatment failure by 87.0%.

Conclusions. Outcomes associated with *Scedosporium/L prolificans* infections is poor, particularly with *L prolificans* infections or in the highly immunosuppressed population.

Keywords. lomentosporiosis; outcomes; scedosporiosis; survivors; treatment response.

Difficult-to-treat *Scedosporium* spp and *Lomentospora prolificans* infections mostly affect patients with hematological malignancy (HM), hematopoietic stem cell transplant (HSCT), or solid organ transplant (SOT). Prognosis is poor as these fungi have innate resistance to many, if not all, common antifungal agents [1, 2]. In addition to increased mortality (63.3%), *Scedosporium/L prolificans* infections are associated with prolonged hospital stay and excess cost [3].

The advent of novel antifungal agents, with improved in vitro and in vivo activity against *Scedosporium* spp and *L prolificans*, offers promise [4–7]; however, optimal use of these novel agents remains to be determined. Understanding the infection characteristics of patients who survive beyond 28 days of antifungal therapy can assist patient management. However, none of the few large observational studies [8–12] have evaluated treatment responses of *Scedosporium/L prolificans* infections beyond 1 year. Conducting a randomized controlled trial to establish evidence for treating *Scedosporium/L prolificans*

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infections remains challenging given the low case numbers and heterogeneity of patient populations. This study characterized the predisposing factors, clinical manifestations, and outcomes of *Scedosporium/L prolificans* infections, particularly in those who survived beyond 28 days of antifungal therapy. The predictors of early and late all-cause mortality and of treatment failure at 1 month following antifungal therapy were determined.

METHODS

A retrospective, 6-center, observational study of proven/probable *Scedosporium/L prolificans* infections diagnosed between January 2005 and April 2021 was conducted in Australia. Episodes of infection were identified from pathology (microbiology and histopathology) information systems at each hospital. Fungi were identified using standard morphological and phenotypic methods, and species were assigned by matrix-assisted laser desorption/ionization–time of flight mass spectrometry and/or sequencing of the fungal internal transcribed spacer regions [13]. Clinical data were retrieved from medical and pharmacy records.

Each infection episode was reviewed by an expert panel of 3 infectious diseases physicians for study inclusion. Episodes with incomplete medical and pharmacy records where follow-up data were not available, episodes considered to be colonized, or involving patients who had participated in the open-label phase 2b olorofim study (NCT03583164) were excluded. Data collected included patient demographics, underlying conditions, site of infection, causative fungus (*Scedosporium* spp, *L prolificans*), fungal copathogens, predisposing factors in the past 30–90 days, antifungal treatment, adjunctive therapies, survival status, and overall treatment response at the time-points of 1, 3, 6, 9, 12, 15, and 18 months. Follow-up was for 18 months or until death or loss to follow-up. Ethics approval was obtained for all hospitals (HREC/63020/PMCC).

Definitions

Definitions for proven/probable invasive fungal disease (IFD) were described according to the updated European Organisation for Research and Treatment of Cancer/Mycoses Study Group Education and Research Consortium (EORTC/MSGERC) [14], with modification for immunocompetent patients where host-specific criteria were not required for classification of probable IFD [15]. For cardiothoracic transplant recipients, proven/probable IFD was assigned according to International Society of Heart and Lung Transplantation definitions [16]. Infection was disseminated if blood cultures were positive or where ≥2 noncontiguous sites were involved. Day of IFD diagnosis was the day of collection of the clinical specimen yielding *Scedosporium/L prolificans*. The expert panel adjudicated cause of death [17] and antifungal treatment response up to 18 months according to the EORTC/MSGERC categories [18] (Supplementary Table 1).

Statistical Analyses

All analyses were performed using SPSS 28.0 software (IBM Corporation). Analysis was undertaken for all episodes of infection and then stratified into the following subgroups for analyses: (1) causative pathogen (*Scedosporium* spp, *L prolificans*); (2) survival beyond 28 days of antifungal therapy (survivor, nonsurvivor); and (3) immunosuppression level (high [eg, HM/HSCT], moderate [eg, SOT, immunosuppressed for reasons other than HM/HSCT and SOT], or low/no [eg, minor/no medical condition]). A χ^2 or Fisher exact test was used to compare categorical variables and Wilcoxon rank-sum or Kruskal-Wallis test for continuous variables. Cumulative survival rate post–IFD diagnosis was estimated using the Kaplan-Meier method. Heat maps were generated using Microsoft Word 2016 software to depict overall treatment response of each infection episode. Univariable and multivariable Cox proportional hazard regression analyses were performed for early (1-month) and late (18-month) mortality. The predictors of 1-month treatment failure were determined using multivariate logistic regression. The significance level was set at $P < .05$.

RESULTS

Overall Analysis

Sixty-seven episodes of proven/probable of *Scedosporium/L prolificans* infections were identified in 65 patients. Five episodes were in the open-label phase 2b olorofim study and data for 1 were incomplete; hence, 61 episodes (60 patients) were evaluable (Table 1), of which 57 (93.4%) were managed as inpatients. The median patient age was 59.0 years and 63.9% of episodes were in males. Common underlying conditions were HM (62.3%), HSCT (27.9%), and diabetes mellitus (26.2%). Receipt of immunosuppressive therapies (80.3%) and prolonged neutropenia (44.3%) were the main predisposing factors. Forty-five of 61 (73.8%) episodes were proven IFD, of which 29 (47.5%) were disseminated. *Lomentospora prolificans* accounted for 60.7% of episodes (n = 37). Of the 24 episodes of *Scedosporium* spp infections, 20 were due to *Scedosporium apiospermum* complex and the remainder were *Scedosporium aurantiacum*.

Only 55 episodes of infection received targeted antifungals as 6 deaths occurred prior to the IFD diagnosis. Adjunctive surgery was performed in 27 of 61 episodes (44.3%), with debridement the most common 17 of 61 episodes (27.9%) (Supplementary Table 2). Deaths occurred in 29 episodes at 1-month follow-up; 26 were due to *Scedosporium/L prolificans* infections (89.7%), translating into an IFD-attributable mortality of 42.6%. Median time to death post–IFD diagnosis was 9.0 (range, 0.0–433.0) days. Treatment success at 18 months was 36.1% (22 episodes).

Table 1. Clinical and Infection Characteristics of All Episodes of Infections (N = 61)

Variable	Overall (N = 61)[a]	Stratified by Causative Fungal Pathogen			Stratified by Survival Status Beyond 28 d of Antifungal Therapy		
		Lomentospora prolificans (n = 37)	*Scedosporium* spp[b] (n = 24)	*P* Value[c]	Survivor (n = 34)	Nonsurvivor (n = 27)	*P* Value[d]
Age, y, median (range)	59.0 (21.0–91.0)	59.0 (21.0–75.0)	60.0 (23.0–91.0)	.154	59.5 (23.0–91.0)	59.0 (21.0–75.0)	.299
Male sex	39 (63.9)	27 (73.0)	12 (50.0)	.068	19 (55.9)	20 (74.1)	.142
Primary diagnosis[e,f]							
HM/disorder[g]	38 (62.3)	30 (81.1)	8 (33.3)	<.001	12 (35.3)	26 (96.3)	<.001
Leukemia	26 (42.6)	22 (59.5)	4 (16.7)	.001	8 (23.5)	18 (66.7)	<.001
HSCT	17 (27.9)	13 (35.1)	4 (16.7)	.116	5 (14.7)	12 (44.4)	.010
Allogeneic	14 (23.0)	11 (29.7)	3 (12.5)	.118	4 (11.8)	10 (37.0)	.020
Autologous	3 (4.9)	2 (5.4)	1 (4.2)	1.000	1 (2.9)	2 (7.4)	.579
SOT	9 (14.8)	3 (8.1)	6 (25.0)	.136	8 (23.5)	1 (3.7)	.036
Renal transplant	5 (8.2)	0	5 (20.8)	.007	5 (14.7)	0	.060
Cardiothoracic transplant[h]	4 (6.6)	3 (8.1)	1 (4.2)	1.000	3 (8.8)	1 (3.7)	.623
Immunosuppressed[i]	2 (3.3)	0	2 (8.3)	.151	2 (5.9)	0	.498
Other malignancy	1 (1.6)	1 (2.7)	0	1.000	1 (2.9)	0	1.000
Other comorbidities[e,j]							
Diabetes	16 (26.2)	7 (18.9)	9 (37.5)	.107	11 (32.4)	5 (18.5)	.222
Chronic renal disease	8 (13.1)	1 (2.7)	7 (29.2)	.005	7 (20.6)	1 (3.7)	.066
Chronic lung disease	4 (6.6)	3 (8.1)	1 (4.2)	1.000	2 (5.9)	2 (7.4)	1.000
Chronic liver disease	2 (3.3)	0	2 (8.3)	.151	2 (5.9)	0	.498
Predisposing factors[e,k]							
Baseline neutropenia[l]	30 (49.2)	26 (70.3)	4 (16.7)	<.001	5 (14.7)	25 (92.6)	<.001
Duration of neutropenia, d, median (range)[l]	23.5 (1.0–174.0)	24.0 (1.0–174.0)	18.5 (13.0–43.0)	.659	20.0 (13.0–43.0)	24.0 (1.0–174.0)	.957
Prolonged neutropenia[m]	27 (44.3)	23 (62.2)	4 (16.7)	<.001	5 (14.7)	22 (81.5)	<.001
Trauma/open injury	2 (3.3)	0	2 (8.3)	.151	2 (5.9)	0	.498
Surgery	9 (14.8)	5 (13.5)	4 (16.7)	.729	6 (17.6)	3 (11.1)	.718
Receipt of immunosuppressive agents[e,k]	49 (80.3)	34 (91.9)	15 (62.5)	.008	22 (64.7)	27 (100.0)	<.001
Prolonged corticosteroid use[n]	14 (23.0)	8 (21.6)	6 (25.0)	1.000	5 (14.7)	9 (33.3)	.251
Chemotherapy	26 (42.6)	22 (59.5)	4 (16.7)	.001	7 (20.6)	19 (70.4)	<.001
Calcineurin inhibitors	20 (32.8)	12 (32.4)	8 (33.3)	.942	10 (29.4)	10 (37.0)	.529
Monoclonal antibodies	6 (9.8)	2 (5.4)	4 (16.7)	.200	4 (11.8)	2 (7.4)	.685
Protein kinase inhibitors	3 (4.9)	3 (8.1)	0	.272	1 (2.9)	2 (7.4)	.579
Site of infection[e,o]							
Disseminated infection	29 (47.5)	27 (73.0)	2 (8.3)	<.001	6 (17.6)	23 (85.2)	<.001
Blood	23 (37.7)	23 (62.2)	0	<.001	1 (2.9)	22 (81.5)	<.001
CNS	13 (21.3)	11 (29.7)	2 (8.3)	.046	3 (8.8)	10 (37.0)	.008
Lung	38 (62.3)	29 (78.4)	9 (37.5)	.001	14 (41.2)	24 (88.9)	<.001
Skin/soft tissue infections	14 (23.0)	5 (13.5)	9 (37.5)	.030	10 (29.4)	4 (14.8)	.178
Other proven/probable IFD[e,p]	7 (11.5)	6 (16.2)	1 (4.2)	.229	2 (5.9)	5 (18.5)	.224

Data are presented as No. (%) unless otherwise indicated.

Abbreviations: CNS, central nervous system; HM, hematological malignancy; HSCT, hematopoietic stem cell transplant; IFD, invasive fungal disease; SOT, solid organ transplant.

[a]One patient had 3 episodes of infection, in which the second episode of infection was excluded due to incomplete records.

[b]*Scedosporium apiospermum* complex (n = 20) and *Scedosporium aurantiacum* (n = 4).

[c]*P* value denotes comparison analyses (Pearson χ^2 or Fisher exact test or Wilcoxon rank-sum test) between the subgroups of causative fungal pathogen.

[d]*P* value denotes comparison analyses (Pearson χ^2 or Fisher exact test or Wilcoxon rank-sum test) between the subgroups of survivors and nonsurvivors.

[e]Some may have >1 encounter; not mutually exclusive.

[f]No known host or risk factors for IFD (n = 11).

[g]Other HM/disorders included lymphoma, multiple myeloma, aplastic anemia, and myelodysplastic syndrome (n = 3 each). No significant *P* values for all comparison analyses.

[h]Cardiothoracic transplant included lung (n = 2), heart (n = 1), and heart-lung (n = 1) transplant. No significant *P* values for all comparison analyses.

[i]Other immunosuppressed included microscopic polyarteritis and antiphospholipid syndrome (n = 1 each).

[j]Diabetes or chronic renal/lung/liver disease as comorbidities.

[k]Thirty days prior to IFD diagnosis except for the receipt of immunosuppressive agents (90 days prior) and systemic corticosteroids (60 days prior).

[l]Missing data: n = 1.

[m]Defined as absolute neutrophil count <500 cells/μL for >10 days.

[n]Defined as the use of ≥0.3 mg/kg corticosteroids for ≥3 weeks in the past 60 days); missing data: n = 4.

[o]Other sites of infection (eg, heart, kidneys, gastrointestinal, liver, spleen, spine, bone, joint, wound, eye, ear, nasal/sinus, vessels, catheter/prosthetic materials, glands) have relatively small sample size (n < 7) and no significant differences were found between the subgroups stratified by causative fungal pathogen or survival status beyond 28 days of antifungal therapy (*P* > .05). Sites of infection (eg, kidneys, bone) had small sample size (n < 7), but significant differences were found between the subgroups of survivors and nonsurvivors (*P* < .05).

[p]Aspergillosis (n = 4), candidemia (n = 3), or mucormycosis (n = 1).

Subgroup Analyses

Causative Pathogen

Infection episodes due to *Scedosporium* spp were more common in patients with renal transplant ($P = .007$) and chronic renal disease ($P = .005$), whereas *L prolificans* infection was more common in patients with leukemia ($P = .001$) (Table 1). Prolonged neutropenia ($P < .001$), receipt of concomitant immunosuppressant therapy ($P = .008$), and chemotherapy ($P = .001$) were associated with *L prolificans* infections, as were disseminated infections ($P < .001$), involving blood ($P < .001$), lung ($P = .001$), and the central nervous system (CNS) ($P = .046$) (Table 1). Gastrointestinal tract, adrenal/thyroid, heart, kidney, liver, and spleen involvement only occurred in disseminated *L prolificans* infections while 2 disseminated *Scedosporium* spp infections involved the CNS, lung, spine, skin/soft tissue, and large vessels (eg, aortic graft). *Scedosporium* spp were more likely to affect skin/soft tissue ($P = .030$; Table 1). For *L prolificans* infections, voriconazole/terbinafine combination therapy was administered in 30 of 31 episodes (96.8%), while voriconazole monotherapy was prescribed in 15 of 24 (62.5%) *Scedosporium* spp infections. The median duration of antifungal treatment was shorter for *L prolificans*, compared with *Scedosporium* spp infections (median, 10.5 [range, 1.0–585.0] days vs 156.0 [range, 8.0–585.0] days; $P < .001$) as the majority of those with *L prolificans* infections were dead at 1 month (n = 26/37 [70.3%]). Adjunctive surgery was more common in *Scedosporium* spp infections (18/24 [75.0%] vs 9/37 [24.3%]; $P < .001$).

A lower survival rate was noted in *L prolificans* infections (Figure 1*A*) where the median time to death post–IFD diagnosis was 6.0 (range, 0.0–433.0) days, shorter than those with *Scedosporium* spp infections (median, 62.5 [range, 9.0–264.0] days; $P < .001$). Only 5 *L prolificans* infections (n = 5/37 [13.5%]) were treated successfully at 1 month and 18 months. At 18-month follow-up, 2 had stable *L prolificans* infections, 14 had progression, and 16 had indeterminate responses; of these, 29 died and 3 were lost to follow-up (Figure 2*A* and 2*B*). More *Scedosporium* spp infections (n = 9/24 [37.5%]) were deemed to have treatment success at 1 month. At 18-month follow-up, 17 attained treatment success (n = 17/24 [70.8%]), 1 had stable *Scedosporium* spp infection, 5 had progression, and 1 had indeterminate response; of these, 8 died and 1 was lost to follow-up (Figure 3).

Survival Following 28 Days of Antifungal Therapy

Compared with episodes involving nonsurvivors, survivors were less immunosuppressed, with lower proportions of HSCT ($P = .010$), HM, prolonged neutropenia, and chemotherapy (all $P < .001$) (Table 1). There were more *Scedosporium* spp infections among survivors (n = 23/34 [67.6%]) compared with nonsurvivors (n = 1/27 [3.7%]) ($P < .001$). A smaller proportion of survivors had disseminated infections ($P < .001$; Table 1). Antifungal treatment duration (median, 166.0 [range, 32.0–585.0] days vs 5.0 [range, 1.0–18.0] days) and time to death post–IFD diagnosis (median, 131.0 [range, 34.0–433.0] days vs 6.0 [range, 0.0–24.0] days) were longer among survivors than nonsurvivors (both $P < .001$). A higher proportion of the survivors (n = 25/34 [73.5%]) received adjunctive surgery compared with nonsurvivors (n = 2/27 [7.4%]) ($P < .001$). All nonsurvivors failed treatment, whereas 58.8% (n = 20/34) of the survivors had treatment failure at 1-month follow-up ($P < .001$; Figures 2 and 3).

Degree of Immunosuppression

Compared with those not considered highly immunosuppressed (Supplementary Table 3), prolonged neutropenia and immunosuppressive treatments were more common in infection episodes affecting highly immunosuppressed patients (both $P < .001$). Most infections in the highly immunosuppressed subgroup were disseminated ($P < .001$), with *L prolificans* more frequently isolated (n = 30/38 [78.9%]) ($P < .001$). The duration of antifungal treatment was shorter (median, 10.5 [range, 1.0–585.0] days) in the highly immunosuppressed subgroup ($P < .001$), and the survival rate was reduced ($P < .001$) (Figure 1*B*), with a median time to death post–IFD diagnosis of 7.0 (range, 0.0–433.0) days. Up to 82% of the highly immunosuppressed subgroup failed treatment by 1-month follow-up (n = 31/38) (Figures 2 and 3). All of those with low/no immunosuppression received adjunctive surgery.

Predictors of Mortality and Treatment Failure

Disseminated infection and HSCT were associated with 6.87 times (hazard ratio [HR], 6.87 [95% confidence interval {CI}, 2.63–17.96]) and 2.17 times (HR, 2.17 [95% CI, 1.01–4.66]) the rate of 1-month mortality adjusting for adjunctive surgery (Table 2). Receipt of adjunctive surgery was associated with an 84.0% reduction (HR, 0.16 [95% CI, .05–.48]) in the rate of 1-month mortality following *Scedosporium/L prolificans* infections, adjusting for disseminated infection and HSCT. The same predictors were observed for 18-month mortality when adjusted for causative pathogen (Table 2). Receipt of adjunctive surgery was associated with an 87.0% reduction (odds ratio, 0.13 [95% CI, .02–.77]) in the odds of treatment failure by 1-month follow-up, adjusting for disseminated infection, HM, and causative pathogen (Supplementary Table 4).

DISCUSSION

Both *Scedosporium* spp and *L prolificans* infections are associated with high morbidity and mortality [9, 10, 19–21]. Including only proven/probable infections, we found substantive differences in the clinical manifestations, patient risk populations, and outcomes for these 2 fungal pathogen groups. While differences in the epidemiology and features of *Scedosporium/L prolificans* infections are appreciated [9, 10], regional and even institutional-specific data are essential to

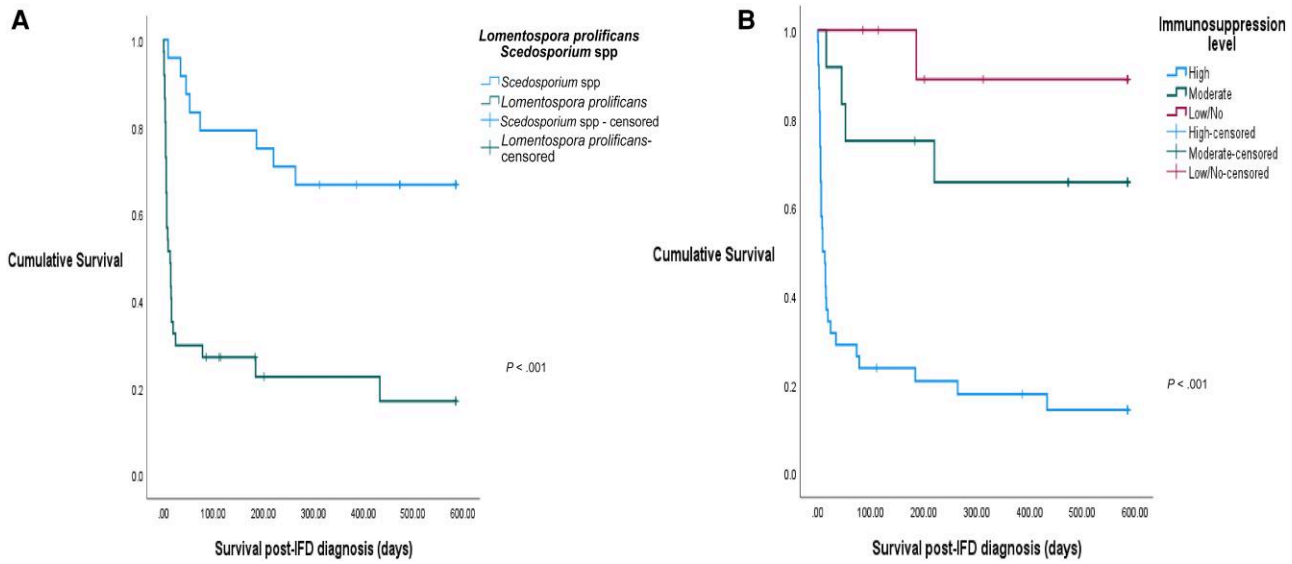

Figure 1. Survival curves stratified by causative fungal pathogen (*A*) and immunosuppression level (*B*). Abbreviation: IFD, invasive fungal disease.

inform timely management decisions. For the first time, our study provided a longitudinal view of adjudicated treatment response of each infection episode at regular intervals (ie, 1, 3, 6, 9, 12, 15, and 18 months). These data, in addition to those comparing the survivor and nonsurvivor subgroups, are keys to guide optimal use of both current and newer antifungals.

Notably, the predominance of *L prolificans* over *Scedosporium* spp infections in our study contrasts with surveys performed elsewhere [10–12]. This is due at least in part to geographical differences in species distribution, which may depend on local environmental (eg, soil pH) or climatic conditions [1, 22, 23], further consolidating the results of an earlier Australian study [24]. Interestingly, organ involvement outside the CNS and lung was reported only in disseminated *L prolificans* infections. Disseminated scedosporiosis has been described [10, 25], but our study observed more localized and indolent skin/soft tissue infections with *Scedosporium* spp. While distinct clinical presentations between *S apiospermum* and *Scedosporium boydii* were reported in a large French observational study [12], we are unable to confirm this as the different species within the *S apiospermum* complex were not further differentiated given the retrospective nature of our study. The finding that *L prolificans* infections are often disseminated with a propensity to affect the lungs and CNS emphasizes the need for urgent investigation for infection elsewhere, as fungemia progresses rapidly [8–12, 26]. Expedited collection of blood cultures/tissue specimens, adoption of molecular techniques [13], and multisystem imaging are essential to timely identify disseminated infections. Siderophores may also have an emerging role as an early diagnostic biomarker in IFD [27], which merits future investigations.

Importantly, we have shown that the clinical manifestations, predisposing factors, treatment modalities, and outcomes of the survivors differed significantly from the nonsurvivors, and these have not been extensively studied before. Appreciation of these characteristics and outcomes of patients who survived beyond 28 days of antifungal therapy provides insights on identifying optimal time of initiation and treatment duration of antifungal agents. The survivor subgroup was less immunosuppressed and had lower proportions of HM/HSCT patients with prolonged neutropenia and receipt of immunosuppressive agents, particularly chemotherapy. This could explain the predominance of *Scedosporium* spp infections, with relatively lower numbers of disseminated disease with blood, CNS, or lung involvements as well as lower mortality and failure rates observed in the survivors. We also noted that up to 74.0% of the survivors had adjunctive surgery, with a longer median time to death of 131.0 days post–IFD diagnosis reported, consistent with previous observations that adjunctive surgery confers improved survival [9, 11, 19]. Indeed, for the first time, we have demonstrated that adjunctive surgery was associated with a decreased odds of treatment failure at 1-month follow-up.

Our study has provided insights that stratifying patients according to degree of immunosuppression is useful for clinical management and predicting survival. The poor outcomes observed in infections among the most immunosuppressed subgroup (HM/HSCT patients), combined with the fact that *L prolificans* was the main causative species, highlights the critical need for early detection/diagnosis of these subgroups of infections. We observed greater mortality in the highly immunosuppressed and *L prolificans* subgroups where HSCT and disseminated infection were predictors of both

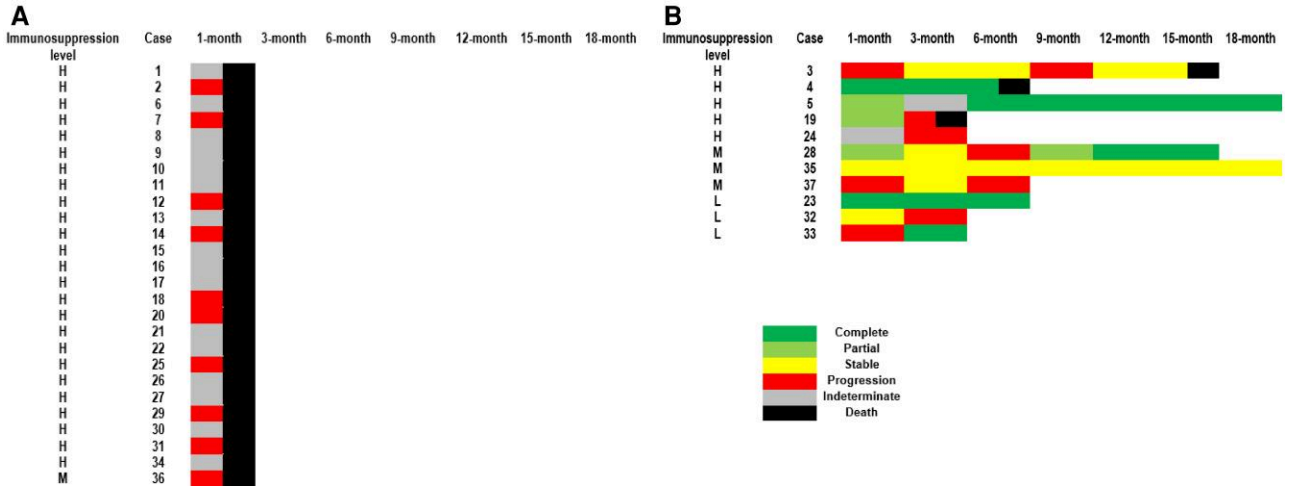

Figure 2. Heat maps depicting overall treatment response up to 18-month follow-up after initiation of antifungal treatment for the nonsurvivor subgroup with *Lomentospora prolificans* infection (n = 26; *A*) and the survivor subgroup with *L prolificans* infection (n = 11; *B*). Cases 24, 32, and 37 were lost to follow-up. A cutoff of ±1.5 months around each follow-up time point was used to allow for the fact that follow-up visits may not be conducted at exactly each time point given the retrospective study design. Immunosuppression level: high (H; eg, hematological malignancy [HM], hematopoietic stem cell transplant [HSCT]); moderate (M; eg, solid organ transplant [SOT], immunosuppressed for reasons other than HM/HSCT and SOT); or low/no (L; eg, minor/no medical condition).

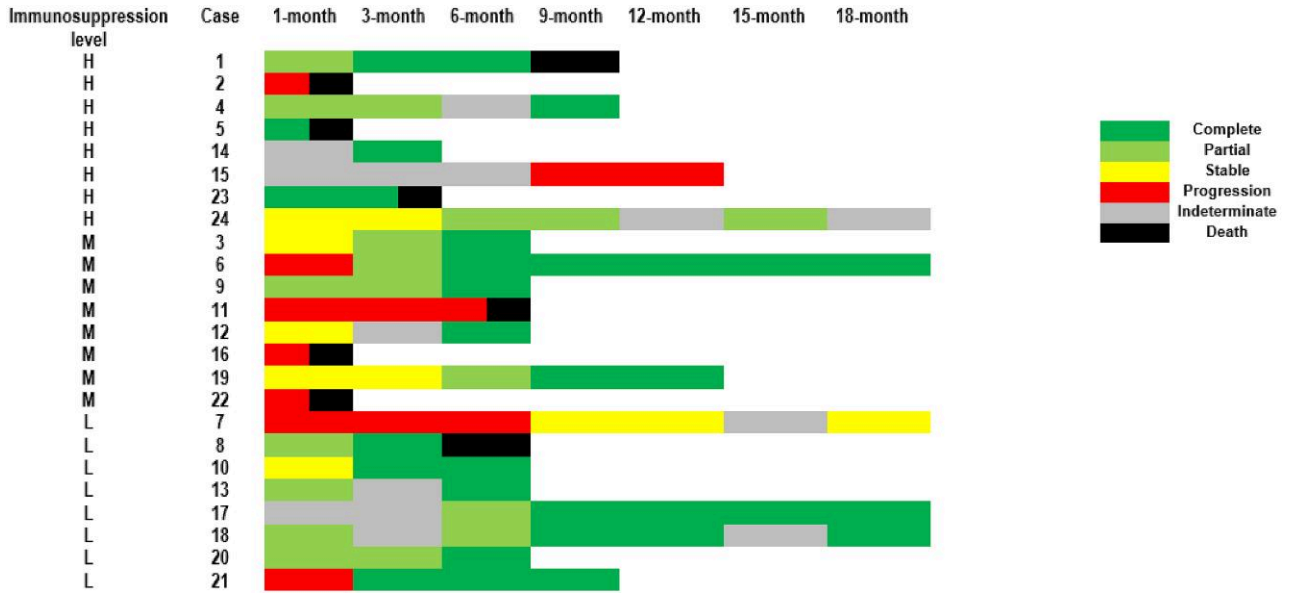

Figure 3. Heat maps depicting overall treatment response up to 18-month follow-up after initiation of antifungal treatment for those with *Scedosporium* spp infections (n = 24). Case 15 was lost to follow-up. A cutoff of ±1.5 months around each follow-up time point was used to allow for the fact that follow-up visits may not be conducted at exactly each time point given the retrospective study design. Only case 2 did not survive beyond 28 days of antifungal therapy. Immunosuppression level: high (H; eg, hematological malignancy [HM], hematopoietic stem cell transplant [HSCT]); moderate (M; eg, solid organ transplant [SOT], immunosuppressed for reasons other than HM/HSCT and SOT); or low/no (L; eg, minor/no medical condition).

early and late mortality (Table 2). Disseminated infection with fungemia, CNS involvement, and HM are associated with increased mortality in *Scedosporium/L prolificans* infections [9, 10, 12, 19–21]. Apart from host immunosuppression, site of infection, and delayed diagnosis, these fatal outcomes are in part due to limited treatment options. Currently available antifungal agents exhibit high minimum inhibitory concentrations against *L prolificans* in particular [2, 10, 28]. Hence, there is an unmet need for novel antifungal agents that have excellent activity against these fungi.

Table 2. Predictors of 1-Month (Early) and 18-Month (Late) All-Cause Mortality Following Diagnosis of Invasive *Scedosporium* and *Lomentospora prolificans* Infections

	1-mo (Early)						18-mo (Late)					
	Univariable Analysis			Multivariable Analysis			Univariable Analysis			Multivariable Analysis		
Characteristic	HR	(95% CI)	*P* Value	HR	(95% CI)	*P* Value	HR	(95% CI)	*P* Value	HR	(95% CI)	*P* Value
Age	0.98	(.96–1.00)	.117	…	…		0.99	(.97–1.01)	.339	…	…	
Male sex	1.51	(.69–3.32)	.306	…	…		1.50	(.75–3.00)	.247	…	…	
Year of infection[a]	0.76	(.31–1.86)	.546	…	…		0.86	(.38–1.96)	.716	…	…	
Underlying condition/risk factors												
HM	14.11	(3.33–59.73)	<.001	…	…		8.02	(3.09–20.81)	<.001	…	…	
HSCT	0.56	(.39–.81)	.002	2.17	(1.01–4.66)	.046	2.85	(1.47–5.53)	.002	2.03	(1.01–4.10)	.047
SOT	0.31	(.07–1.31)	.111	…	…		0.34	(.11–1.12)	.077	…	…	
Prolonged neutropenia	10.15	(4.05–25.43)	<.001	…	…		8.39	(3.99–17.63)	<.001	…	…	
Trauma	0.05	(.00–128.65)	.448	…	…		0.05	(.00–29.07)	.348	…	…	
Surgery	0.55	(.17–1.81)	.321	…	…		0.37	(.12–1.22)	.103	…	…	
Prolonged corticosteroid use	1.11	(.53–2.36)	.780	…	…		1.39	(.67–2.88)	.383	…	…	
Cancer chemotherapy	5.08	(2.29–11.27)	<.001	…	…		4.57	(2.31–9.06)	<.001	…	…	
Calcineurin inhibitors	1.30	(.62–2.76)	.490	…	…		1.02	(.51–2.02)	.965	…	…	
Monoclonal antibodies	1.16	(.35–3.83)	.810	…	…		1.26	(.44–3.55)	.668	…	…	
Protein kinase inhibitors	1.91	(.45–8.04)	.378	…	…		1.44	(.35–6.00)	.616	…	…	
Site of infection/coinfection												
Disseminated infection	8.38	(3.36–20.90)	<.001	6.87	(2.63–17.96)	<.001	6.52	(3.14–13.56)	<.001	5.11	(2.13–12.29)	<.001
Blood	18.27	(7.22–46.19)	<.001	…	…		17.80	(7.54–41.99)	<.001	…	…	
CNS	2.68	(1.24–5.80)	.012	…	…		2.44	(1.20–5.00)	.014	…	…	
Lung	8.26	(2.49–27.42)	<.001	…	…		4.56	(1.99–10.45)	<.001	…	…	
Other proven/probable IFD	2.17	(.83–5.69)	.116	…	…		2.05	(.85–4.92)	.109	…	…	
Receipt of treatment												
Combination antifungal therapy	1.44	(.63–3.25)	.386	…	…		1.26	(.63–2.51)	.518	…	…	
Adjunctive surgery	0.11	(.04–.31)	<.001	0.16	(.05–.48)	.001	0.20	(.09–.42)	<.001	0.28	(.12–.67)	.004
Causative fungal pathogen												
Lomentospora prolificans	9.59	(2.88–31.93)	<.001	…	…		5.15	(2.30–11.53)	<.001	1.90	(.70–5.15)	.208
Scedosporium spp	0.10	(.03–.35)	<.001	…	…		0.19	(.09–.44)	<.001	…	…	

Cox regression model: One variable from each category/domain (ie, underlying condition/risk factor, site of infection, receipt of treatment, causative fungal pathogen) in the univariable analysis was chosen based on either the narrower CI or clinical grounds. The number of variables included in each adjusted model was based on a minimum of 10 outcomes per explanatory variable to avoid overfitting.

Abbreviations: CI, confidence interval; CNS, central nervous system; HM, hematological malignancy; HR, hazard ratio; HSCT, hematopoietic stem cell transplant; IFD, invasive fungal disease; SOT, solid organ transplant.

[a]Category of year of infection (ie, 2005–2010 vs 2011–2021).

A key finding of our study is the higher rate of treatment failure in *L prolificans* infections compared with those caused by *Scedosporium* spp. The higher proportion of HM/HSCT patients with disseminated infections in the *L prolificans* subgroup is 1 likely explanation. While Jenks et al [9] reported that treatment failure rates were the highest in *L prolificans* cases with HM (81.0%) or with disseminated infections (84.0%), they defined those with stable disease as treatment success, in contrast with our approach guided by the EORTC/MSGERC [18]. The EORTC/MSGERC criteria may have limitations in classifying treatment response for certain *Scedosporium/L prolificans* infections, which tend to be chronic or slowly progressive (eg, osteomyelitis, sinusitis). Recent viewpoints have highlighted that stable disease may signal early control of IFDs awaiting immune recovery in immunocompromised hosts and is a reasonable therapeutic goal in the real-world setting [29]. Combined voriconazole/terbinafine therapy has been associated with improved survival and treatment success for *L prolificans* infections [8, 9, 28]; however, we did not observe this in our study. The majority of lomentosporiosis cases were treated with voriconazole/terbinafine for a median of only 10.5 days and died by 1 month (Figure 2), questioning the effectiveness of such therapy. Conversely, we noted that most *Scedosporium* spp infections responded to treatment

between 3 and 6 months of follow-up (Figure 3), suggesting that prolonged antifungal therapy of at least 6 months may be warranted. This is pertinent as the recommendation regarding optimal treatment duration for scedosporiosis is not well-established [30].

This study of adult patients has several limitations, including its retrospective design that included a relatively smaller proportion of SOT recipients. As this study encompassed only 6 tertiary hospitals, the findings may not be generalizable elsewhere; however, all of these hospitals delivered care to patients with *Scedosporium/L prolificans* infections in a similar manner, with broad adherence to national management guidelines [31]. This study may have been underpowered to detect a difference where one might exist given the low case numbers that are commonly seen in studies of rare IFDs. Finally, analysis of *Scedosporium* spp infections was not further stratified to species level, and thus we were unable to determine if fungal species (eg, *S aurantiacum, S boydii*) within this group influenced outcomes.

Managing *Scedosporium/L prolificans* infections remains challenging given their complex clinical setting. We highlight the pressing need for better therapies, particularly for HM/HSCT patients or those with *L prolificans* infections. Our clinical data support the notion that stable disease may represent a successful response with these infections. In the less immunosuppressed or survivor subgroup, we noted that prolonged therapy of currently available antifungal agents is required, with slow responses and late failures observed. For new antifungal agents yet to be marketed, these granular data regarding differences in outcomes of *Scedosporium/L prolificans* infections and the impact of immunosuppression provide useful information for comparative effectiveness studies.

Supplementary Data

Supplementary materials are available at *Open Forum Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

Author contributions. Study conceptualization and design: C. F. N., S. C.-A. C., D. C. M. K., and M. A. S. Data collection: C. F. N., S. C.-A. C., K. H., and Q. A, N. Adjudication of treatment outcomes: S. C.-A. C., A. C., and M. A. S. Provision of patients: S. C.-A. C., A. C., D. M., J. A. T., and M. A. S. Data analysis: C. F. N. with statistical advice from T. S. Drafted the manuscript: C. F. N. All authors reviewed and agreed to the final version of the manuscript.

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Patient consent. This study was approved by the Peter MacCallum Cancer Centre Human Research Ethics Committee under a national mutual acceptance scheme with a patient waiver of consent given the noninterventional, retrospective nature of the study design (HREC/63020/PMCC).

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