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Clinical characteristics and outcomes of invasive *Lomentospora prolificans* infections: Analysis of patients in the FungiScope® registry

Jeffrey D. Jenks[1,2] | Danila Seidel[3] | Oliver A. Cornely[3] | Sharon Chen[4] | Sebastiaan van Hal[5] | Carol Kauffman[6] | Marisa H. Miceli[6] | Melina Heinemann[7] | Martin Christner[8] | Alfredo Jover Sáenz[9] | Alexander Burchardt[10] | Björn Kemmerling[10] | Raoul Herbrecht[11] | Joerg Steinmann[12,13] | Shmuel Shoham[14] | Sandra Gräber[15] | Livio Pagano[16] | Dries Deeren[17] | Monica A. Slavin[18] | Martin Hoenigl[1,2,19]

[1]Department of Medicine, University of California San Diego, San Diego, CA, USA

[2]Clinical and Translational Fungal Research Group, University of California San Diego, San Diego, CA, USA

[3]Department I of Internal Medicine, ECMM Excellence Centre of Medical Mycology, CECAD-Excellence Cluster on Cellular Stress Responses in Aging-Associated Diseases, University Hospital Cologne, Cologne, Germany

[4]Sydney Medical School, Centre for Infectious Diseases and Microbiology, Westmead Hospital, The University of Sydney, Camperdown, New South Wales, Australia

[5]Department of Microbiology and Infectious Diseases, Royal Prince Alfred Hospital, Sydney, New South Wales, Australia

[6]Department of Medicine, University of Michigan, Ann Arbor, MI, USA

[7]Department of Medicine, University Medical Center Hamburg-Eppendorf, Hamburg, Germany

[8]Department of Medical Microbiology, Virology and Hygiene, University Medical Center Hamburg-Eppendorf, Hamburg, Germany

[9]Territorial Unit of Nosocomial Infection and antibiotic policy (TUNI), University Hospital Arnau de Vilanova, Lleida, Spain

[10]Department of Hematology, Hospital of Justus Liebig University, Giessen, Germany

[11]Department of Oncology and Hematology, Strasbourg University Hospital, Strasbourg, France

Summary

Objectives: Invasive fungal infections caused by *Lomentospora prolificans* are associated with very high mortality rates and can be challenging to treat given pan-drug resistance to available antifungal agents. The objective of this study was to describe the clinical presentation and outcomes in a cohort of patients with invasive *L prolificans* infections.

Methods: We performed a retrospective review of medical records of patients with invasive *L prolificans* infection in the FungiScope® registry of rare invasive fungal infections. Patients diagnosed between 01 January 2008 and 09 September 2019 were included in for analysis.

Results: The analysis included 41 patients with invasive *L prolificans* infection from eight different countries. Haematological/oncological malignancies were the most frequent underlying disease (66%), disseminated infection was frequent (61%), and the lung was the most commonly involved organ (44%). Most infections (59%) were breakthrough infections. Progression/deterioration/treatment failure was observed in 23/40 (58%) of patients receiving antifungal therapy. In total, 21/41 (51%) patients, and 77% of patients with underlying haematological/oncological malignancy, had a fatal outcome attributed to invasive fungal infection. Combination antifungal therapy was frequent (24/40) and associated with improved survival. In particular, treatment regimens including terbinafine were significantly associated with higher treatment success at final assessment (P = .012), with a positive trend observed for treatment regimens that included voriconazole (P = .054).

Conclusions: *Lomentospora prolificans* infections were associated with mortality rates of 77% and above in patients with underlying haematological/oncological malignancies and those with disseminated infections. While combination therapy is

[12]Institute of Clinical Hygiene, Medical Microbiology and Infectiology, Klinikum Nürnberg, Paracelsus Medical University, Nuremberg, Germany

[13]Institute of Medical Microbiology, University Hospital Essen, University of Duisburg-Essen, Essen, Germany

[14]Johns Hopkins University School of Medicine, Baltimore, MD, USA

[15]Institute of Medical Microbiology and Epidemiology of Infectious Diseases, University Hospital Leipzig, Leipzig, Germany

[16]Department of Hematology, Fondazione Policlinico A. Gemelli – IRCCS, Università Cattolica del Sacro Cuore, Rome, Italy

[17]Department of Hematology, AZ Delta, Roeselare, Belgium

[18]Department of Infectious Diseases, Peter MacCallum Cancer Centre, National Centre for Infections in Cancer, Melbourne, Vic., Australia

[19]Department of Medicine, ECMM Excellence Centre of Medical Mycology, Medical University of Graz, Graz, Austria

Correspondence
Martin Hoenigl, MD, Ass. Prof., Division of Infectious Diseases and Global Public Health, University of California San Diego, 200 West Arbor Drive #8208, San Diego, CA 92103.
Email: hoeniglmartin@gmail.com

Jeffrey D. Jenks, MD, MPH, Ass. Prof., Department of Medicine, University of California San Diego, 330 Lewis St, Suite 301, San Diego, CA 92103.
Email: jjenks@ucsd.edu

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the preferred option for now, the hope lies with novel antifungals currently under development.

KEYWORDS
clinical presentation, fungal infections, *Lomentospora prolificans*, outcomes, treatment

1 | INTRODUCTION

Lomentospora prolificans are filamentous fungi commonly found in soil and polluted waters and are increasingly recognised as a cause of serious invasive fungal infections (IFIs) in Australia, California and the southern USA, and Europe.[1-8] *L prolificans* is the causative agent in 1.6% and 0.9% of infections after haematopoetic stem cell transplant and solid organ transplantation (SOT) in the United States, respectively.[9] Risk factors for these infections vary but include underlying haematological malignancy, SOT, trauma including burns, poorly controlled diabetes mellitus and other conditions leading to immunodeficiency.[4,9] Mortality rates of up to 90% are associated with these infections.[10] Treatment of invasive infections is challenging as *L prolificans* isolates are often pan-drug resistant, with elevated minimum inhibitory concentrations (MICs) against all available antifungal agents.[2,4,11-15] More than 10 years ago, two relatively large studies reported that voriconazole was associated with survival rates between 44% and 66%[16-18] and voriconazole was deemed the treatment of choice for invasive *L prolificans* infections.[18-21] This is supported by a recent review of patients published after

2000 in which overall mortality was lower in patients who received voriconazole compared to treatment with other antifungal agents.[10] Although voriconazole is considered the drug of choice, combination therapy, particularly with voriconazole plus terbinafine, is also frequently used to combat these infections.[4,10,20] The objective of this study was to describe the clinical presentation and outcomes in a cohort of 41 patients with invasive *L prolificans* infections occurring between 2008 and 2019 that were documented in the FungiScope® Registry.[22]

2 | METHODS

A retrospective review of medical records of all patients with IFIs caused by *L prolificans* in FungiScope® diagnosed between 01 January 2008 and 09 September 2019 was performed. FungiScope® is a registry of rare IFIs and is currently active in 84 countries.[22] All proven and probable infections based on the European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group and the National Institute of Allergy and Infectious Diseases Mycoses Study Group (EORTC/MSG) criteria were included in this analysis.[23] Of the 41 patients included, 20 originated from the Mycoses Study Group International Prospective Study of Phaeohyphomycosis,[24] five had been published in a case-series in 2018,[4] and a total of six were included in a previous review of *Scedosporium* and *Lomentospora* infections.[10] Results of the superiority of antifungal combination therapy in this study cohort has been published elsewhere.[25]

Breakthrough infections were classified according to recent MSG/European Confederation of Medical Mycology (ECMM) criteria.[26] Treatment success was defined as stable disease/partial response or complete response, while treatment failure was defined as deterioration/progression or failure of antifungal therapy at final assessment.[27] Infections were determined to be disseminated if *L prolificans* was isolated from blood or two non-contiguous anatomic sites. IFI-related mortality was defined as death due to IFI as determined by the FungiScope® registry investigator(s).

Statistical analyses used IBM SPSS Statistics v26 (IBM Corp.). Age and treatment durations were presented as median and interquartile range (IQR) in days. Treatment regimens were compared between those with treatment success vs treatment failure, 28-day overall survival vs mortality, and those with vs without IFI-attributed mortality using two-sided Fisher's exact test. The study protocol and all study-related procedures were approved by the University of California San Diego (UCSD), CA, USA Institutional Review Board (IRB) (Project #181119).

3 | RESULTS

Forty-one patients with invasive *L prolificans* infection (36 proven, 5 probable) from 8 different countries were documented in FungiScope® registry, including patients from Australia (n = 17), the United States (n = 11, including 8 from the University of California San Diego), Germany (n = 8), and five other countries with one case each. Description of each case including underlying risk factor(s), age, source of isolate, MIC's, antifungal treatment, adjunctive therapy (eg surgery), survival *t* 28 days and outcomes are described (Table S1). The majority of patients (66%; 27/41) were diagnosed in 2014 or later. Median age of patients was 65 years (IQR 48-69). Haematological/oncological malignancies were the most frequent underlying diseases and observed in 27 (66%) of patients. Disseminated infection was detected in 25 (61%) of patients, 19 (46%) had growth of *L prolificans* in blood culture, and the lung (18 patients; 44%) was the most frequently involved organ. Patient characteristics and outcomes are summarised in Table 1.

Most patients (24/41, 59%) were classified as breakthrough infections, of which nine (38%) occurred during posaconazole prophylaxis (8 suspension, 1 tablet formulation), six (25%) during voriconazole prophylaxis, five (21%) during fluconazole prophylaxis and one each during prophylaxis with liposomal amphotericin B (LAmB), micafungin and during empiric antifungal treatment with combination LAmB + posaconazole and LAmB + micafungin. While there was no significant association between breakthrough infection and antifungal treatment response, a trend was observed towards higher IFI-attributed mortality in those with breakthrough infection ($P = .061$).

Overall, treatment failure occurred in 23/40 infections receiving antifungal therapy (58%), and both 28-day overall mortality and overall death attributable to *L prolificans* infection were observed in 51% of patients (21/41) each. Treatment failure (84% and 81%) and IFI-attributed mortality (80% and 77%, respectively) were highest among patients with disseminated infection and those with underlying haematological/oncological malignancy.

Nineteen patients were treated with a terbinafine containing regimen (Table 1); most patients (18/19) received terbinafine in combination with other antifungals, the most frequent combination with voriconazole + terbinafine (16 of 18). Compared to other antifungal regimens, treatment with terbinafine (vast majority used dosages of 250 mg daily or 250 mg twice daily) was significantly associated with higher treatment success overall at final assessment ($P = .012$), with a positive trend also observed for treatment regimens that included voriconazole (n = 31; including 16 who received voriconazole + terbinafine combination; $P = .054$). Treatment containing LAmB (n = 15; 11/15 combination therapy) was associated with both treatment failure (4/4 with monotherapy and 8/11 with combination therapy failed treatment; $P = .046$) and higher IFI-attributed mortality ($P = .043$). Among those who received treatment with voriconazole but without terbinafine, 6/15 (40%) responded to treatment, which was slightly lower than the 44% (11/25) treatment response observed for other treatments. Only seven patients received voriconazole monotherapy (median 22 days, IQR 3-47 days); of those, 4/7 (57%) had treatment failure with IFI-attributed mortality within 28 days of diagnosis, while 3/7 (43%) survived. Better outcomes were observed in those with combination antifungal therapy, and specifically, those receiving voriconazole + terbinafine combination therapy are described in detail elsewhere.[25]

TABLE 1 Demographic and clinical characteristics of the study cohort

	Study cohort (n = 41)
Female sex	16 (39%)
Age (median, interquartile range)	65 (48-69)
Country case occurred	
Australia	17 (41%)
United States	11 (27%)
Germany	8 (20%)
Other[a]	5 (12%)
Underlying diseases/main risk factors	
Haematological/oncological malignancies	27 (66%)
Trauma/surgery	6 (15%)
Solid organ transplantation	3 (7%)
Other[b]	5 (12%)
Intensive care unit	6 (15%)
Site(s) of infection	
Disseminated infection	25 (61%)
Growth in blood culture	19 (46%)
Lung	18 (44%)
Eye	9 (22%)
Skin/deep soft tissue	5 (12%)
Bone	4 (10%)
Brain/central nervous system	5 (12%)
Breakthrough infection	24 (59%)
Antifungal treatment[c]	
Voriconazole ± other antifungals	31/40 (78%)
Terbinafine ± other antifungals	19/40 (48%)
LAmB ± other antifungals	15/40 (38%)
Antifungal combination therapy (vs monotherapy)	24/40 (60%)
Combination voriconazole + terbinafine ± other antifungals	16/40 (40%)
Surgery	7 (18%)
Outcomes[d]	
Progression, deterioration, or failure of antifungal treatment	23/40 (58%)
28-d overall mortality	21 (51%)
Death attributable to *Lomentospora prolificans* infection	21 (51%)

[a]Countries include: Belgium, France, Italy, the Netherlands and Spain (each one case)

[b]Other includes Burn, chronic granulomatous disease, chronic pulmonary disease, chronic cardiovascular disease/obesity and contact lenses.

[c]Those who survived received antifungal treatment for a median of 181 d (IQR 47-332 d).

[d]Final response assessment was conducted at a median of 241 d (IQR 84-335) after diagnosis in those who survived and median 13 d (IQR 4-35 d) after IFI diagnosis in the deceased (ie final assessment on the day of death).

Seven patients underwent surgical treatment (Table 1), which was significantly associated with higher 28-day survival rates (P = .045; 3/4 of those receiving surgery for eye infections and 2/3 receiving other surgery survived).

4 | DISCUSSION

We analysed clinical characteristics, antifungal treatment and outcome of 41 patients with invasive *L prolificans* infections in the United States, Australia and Europe. Haematological/oncological malignancies were the most frequently observed underlying disease (66%), disseminated infection was frequent (61%), the lung was the most frequently involved organ (44%), and most patients (59%) were classified as breakthrough infections. These findings further confirm another recent large survey of *L prolificans* infections, in which 63% had underlying haematological/oncological malignancy, 59% disseminated infection, and lung was the most frequently involved organ (39%) as well.[10] Overall, 28-day mortality rates were high with more than 50% failing antifungal treatment, similar to previous studies.[1,3,10,17] Mortality rates were highest in patients with underlying haematological/oncological malignancies, with more than 80% failing antifungal treatment, and in those with disseminated infection, with 84% failing treatment.

In vitro synergism has been demonstrated for combination antifungal therapy with terbinafine + itraconazole against Mucorales,[28] terbinafine + voriconazole against *Fusarium* spp[29] and terbinafine + voriconazole against *L prolificans*,[30-32] and it was suggested almost 20 years ago that combination therapy with an azole plus terbinafine may be a treatment option for these infections.[33] However, the benefit of terbinafine-based regimens was not significant in the recent review of 56 published cases of invasive lomentosporiosis (including 5 more recent cases that were also included in this study), where voriconazole-based regimens were superior but significance was not reached in the subgroups of combination treatment.[10] Previous in vitro studies have shown that while some *L prolificans* isolates are susceptible to voriconazole,[34] the majority have high MICs to all antifungal agents, including voriconazole, which may correlate with treatment failure with voriconazole monotherapy.[35] Clinical studies have demonstrated the superiority of voriconazole-based treatment regimens for *L prolificans* infections compared to LAmB-based regimens,[1,16] a finding that was confirmed in our study. Furthermore, recently published data from our cohort[25] showed the highest treatment success with voriconazole when used in combination with another antifungal agent. Importantly, 39% of patients in our cohort had *L prolificans* breakthrough infections occurring under triazole prophylaxis/empirical therapy, with more than a third occurring during voriconazole prophylaxis, further evidence that voriconazole alone may be insufficient to prevent or treat infections caused by *L prolificans*. This study shows for the first time that terbinafine-based regimens were significantly associated with treatment success and survival and that the treatment response rate using voriconazole in combination with terbinafine was twice that

of other antifungal regimens. Our study also showed a significant survival benefit in those receiving surgery, which was also recently shown in children with invasive *Scedosporium* and Lomentospora infections who underwent surgery and received voriconazole.[8] Importantly, the majority of infections in this analysis occurred in 2014 and later, with outcomes likely influenced by potential changes in the epidemiology of lomentosporiosis associated with the rise of mould active antifungal prophylaxis and advances in treatment of haematological/oncological malignancies. As a result, patients who develop lomentosporiosis today may be more immunosuppressed than those who developed the infection 20 years ago, a theory that is supported by the fact that high mortality rates remained mostly unchanged despite the introduction of newer and better tolerated antifungals.[4,16]

In conclusion, *L prolificans* infections are associated with high mortality, particularly in patients with underlying haematological/oncological malignancies and those with disseminated infection. While combination therapy shows some success in lowering persistently high mortality rates, hope lies on novel antifungals that are currently being developed, specifically F901318 (Olorofim; F2G), which shows excellent activity against *L prolificans*[36] and which is currently being evaluated in a Phase 2b open-label study (NCT03583164). Until novel drugs are available, our findings suggest that voriconazole or terbinafine-based regimens, particularly voriconazole + terbinafine combination therapy, could be the preferred choice for the treatment of invasive *L prolificans* infections.

CONFLICT OF INTEREST

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AUTHOR CONTRIBUTIONS

Jenks JD, Hoenigl M, Seidel D and Cornely O conceived the idea for this study. Seidel D compiled the data for analysis. Hoenigl M and Jenks JD analysed the data. Cornely O, Chen S, Hoenigl M, Jenks JD, Kauffman C, Miceli M, Heinemann M, Christner M, Sáenz A, Burchardt A, Kemmerling B, Herbrecht R, Steinmann J, Shoham S, Gräber S, Pagano L, Van Hal S, Deeren D and Slavin M contributed cases to the FungiScope® registry that were analysed for this manuscript. All authors contributed to the writing, revision and finalisation of this manuscript.

ORCID

Jeffrey D. Jenks https://orcid.org/0000-0001-6632-9587
Oliver A. Cornely https://orcid.org/0000-0001-9599-3137
Marisa H. Miceli https://orcid.org/0000-0002-3175-0512
Martin Hoenigl https://orcid.org/0000-0002-1653-2824

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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