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11 **Clinical Characteristics and Outcomes of invasive *Lomentospora prolificans* Infections:**
12 **Analysis of Patients in the FungiScope® Registry**

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78 **Abstract**

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

83

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

87

88 **Results:** The analysis included 41 patients with invasive *L. prolificans* infection from eight different
89 countries. Haematological/oncological malignancies were the most frequent underlying disease
90 (66%), disseminated infection was frequent (61%), and the lung was the most commonly involved
91 organ (44%). Most infections (59%) were breakthrough infections.
92 Progression/deterioration/treatment failure was observed in 23/40 (58%) of patients receiving

93 antifungal therapy. In total, 21/41 (51%) patients, and 77% of patients with underlying
94 haematological/oncological malignancy, had a fatal outcome attributed to invasive fungal infection.
95 Combination antifungal therapy was frequent (24/40) and associated with improved survival. In
96 particular, treatment regimens including terbinafine were significantly associated with higher
97 treatment success at final assessment ($p=0.012$), with a positive trend observed for treatment
98 regimens that included voriconazole ($p=0.054$).

99

100 **Conclusions:** *L. prolificans* infections were associated with mortality rates of 77% and above in
101 patients with underlying haematological/oncological malignancies and those with disseminated
102 infections. While combination therapy is the preferred option for now, the hope lies with novel
103 antifungals currently under development.

104 **Introduction**

105 *Lomentospora prolificans* are filamentous fungi commonly found in soil and polluted
106 waters and are increasingly recognized as a cause of serious invasive fungal infections (IFIs) in
107 Australia, California and the southern USA, and Europe ¹⁻⁸. *L. prolificans* is the causative agent
108 in 1.6% and 0.9% of infections after haematopoietic stem cell transplant and solid organ
109 transplantation (SOT) in the United States, respectively ⁹. Risk factors for these infections vary
110 but include underlying haematological malignancy, SOT, trauma including burns, poorly
111 controlled diabetes mellitus, and other conditions leading to immunodeficiency ^{4,9}. Mortality rates
112 of up to 90% are associated with these infections ¹⁰. Treatment of invasive infections is
113 challenging as *L. prolificans* isolates are often pan-drug resistant, with elevated minimum
114 inhibitory concentrations (MICs) against all available antifungal agents ^{2,4,11-15}. More than 10
115 years ago, two relatively large studies reported that voriconazole was associated with survival
116 rates between 44% and 66% ¹⁶⁻¹⁸ and voriconazole was deemed the treatment of choice for
117 invasive *L. prolificans* infections ¹⁸⁻²¹. This is supported by a recent review of patients published
118 after 2000 in which overall mortality was lower in patients who received voriconazole compared
119 to treatment with other antifungal agents ¹⁰. Although voriconazole is considered the drug of
120 choice, combination therapy, particularly with voriconazole plus terbinafine, is also frequently
121 used to combat these infections ^{4,10,20}. The objective of this study was to describe the clinical
122 presentation and outcomes in a cohort of 41 patients with invasive *L. prolificans* infections
123 occurring between 2008 and 2019 that were documented in the FungiScope® Registry ²².

124

125 **Methods**

126 A retrospective review of medical records of all patients with IFIs caused by *L. prolificans*
127 in FungiScope® diagnosed between 01/01/2008 – 09/09/2019 was performed. FungiScope® is a
128 registry of rare IFIs and is currently active in 84 countries²². All proven and probable infections
129 based on the European Organization for Research and Treatment of Cancer/Invasive Fungal
130 Infections Cooperative Group and the National Institute of Allergy and Infectious Diseases
131 Mycoses Study Group (EORTC/MSG) criteria were included in this analysis²³. Of the 41
132 patients included, 20 originated from the Mycoses Study Group International Prospective Study
133 of Phaeohyphomycosis²⁴, five had been published in a case-series in 2018⁴, and a total of six
134 were included in a previous review of *Scedosporium* and *Lomentospora* infections¹⁰. Results of
135 the superiority of antifungal combination therapy in this study cohort has been published
136 elsewhere²⁵.

137 Breakthrough infections were classified according to recent MSG/European
138 Confederation of Medical Mycology (ECMM) criteria²⁶. Treatment success was defined as
139 stable disease/partial response or complete response, while treatment failure was defined as
140 deterioration/progression or failure of antifungal therapy at final assessment²⁷. Infections were
141 determined to be disseminated if *L. prolificans* was isolated from blood or two non-contiguous
142 anatomic sites. IFI-related mortality was defined as death due to IFI as determined by the
143 FungiScope® registry investigator(s).

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

151 **Results**

152 Forty-one patients with invasive *L. prolificans* infection (36 proven, 5 probable) from 8
153 different countries were documented in FungiScope® registry, including patients from Australia
154 (n=17), the United States (n=11, including 8 from the University of California San Diego),
155 Germany (n=8), and five other countries with one case each. Description of each case including
156 underlying risk factor(s), age, source of isolate, MIC's, antifungal treatment, adjunctive therapy
157 (e.g. surgery), survival t 28 days, and outcomes are described (**Supplemental Table**). The
158 majority of patients (66%; 27/41) were diagnosed in 2014 or later. Median age of patients was
159 65 years (IQR 48 – 69). Haematological/oncological malignancies were the most frequent

160 underlying diseases and observed in 27 (66%) of patients. Disseminated infection was detected
161 in 25 (61%) of patients, 19 (46%) had growth of *L. prolificans* in blood culture, and the lung (18
162 patients; 44%) was the most frequently involved organ. Patient characteristics and outcomes
163 are summarized in **Table 1**.

164 Most patients (24/41, 59%) were classified as breakthrough infections, of which nine
165 (38%) occurred during posaconazole prophylaxis (8 suspension, 1 tablet formulation), six (25%)
166 during voriconazole prophylaxis, five (21%) during fluconazole prophylaxis, and one each during
167 prophylaxis with liposomal amphotericin B (LAmB), micafungin, and during empiric antifungal
168 treatment with combination LAmB + posaconazole and LAmB + micafungin. While there was no
169 significant association between breakthrough infection and antifungal treatment response, a
170 trend was observed towards higher IFI-attributed mortality in those with breakthrough infection
171 ($p=0.061$).

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

177 Nineteen patients were treated with a terbinafine containing regimen (Table 1); Most
178 patients (18 /19) received terbinafine in combination with other antifungals, the most frequent
179 combination with voriconazole + terbinafine (16 of 18). Compared to other antifungal regimens,
180 treatment with terbinafine (vast majority used dosages of 250 mg daily or 250 mg twice daily)
181 was significantly associated with higher treatment success overall at final assessment
182 ($p=0.012$), with a positive trend also observed for treatment regimens that included voriconazole
183 ($n=31$; including 16 who received voriconazole + terbinafine combination; $p=0.054$). Treatment
184 containing LAmB ($n=15$; 11/15 combination therapy) was associated with both treatment failure
185 (4/4 with monotherapy and 8/11 with combination therapy failed treatment; $p=0.046$) and higher
186 IFI-attributed mortality ($p=0.043$). Among those who received treatment with voriconazole but
187 without terbinafine, 6/15 (40%) responded to treatment, which was slightly lower than the 44%
188 (11/25) treatment response observed for other treatments. Only seven patients received
189 voriconazole monotherapy (median 22 days, IQR 3-47 days); of those, 4/7 (57%) had treatment
190 failure with IFI-attributed mortality within 28 days of diagnosis, while 3/7 (43%) survived. Better
191 outcomes was observed in those with combination antifungal therapy, and specifically those
192 receiving voriconazole + terbinafine combination therapy are described in detail elsewhere ²⁸.

193 Seven patients underwent surgical treatment (Table 1), which was significantly
194 associated with higher 28-day survival rates ($p=0.045$; 3/4 of those receiving surgery for eye
195 infections and 2/3 receiving other surgery survived).

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203 Discussion

204 We analysed clinical characteristics, antifungal treatment and outcome of 41 patients
205 with invasive *L. prolificans* infections in the United States, Australia and Europe.
206 Haematological/oncological malignancies were the most frequently observed underlying disease
207 (66%), disseminated infection was frequent (61%), the lung was the most frequently involved
208 organ (44%), and most patients (59%) were classified as breakthrough infections. These
209 findings further confirm another recent large survey of *L. prolificans* infections, in which 63% had
210 underlying haematological/oncological malignancy, 59% disseminated infection, and lung was
211 the most frequently involved organ (39%) as well ¹⁰. Overall, 28-day mortality rates were high
212 with more than 50% failing antifungal treatment, similar to previous studies ^{1,3,10,17}. Mortality
213 rates were highest in patients with underlying hematologic/oncologic malignancies, with more
214 than 80% failing antifungal treatment, and in those with disseminated infection, with 84% failing
215 treatment.

216 *In vitro* synergism has been demonstrated for combination antifungal therapy with
217 terbinafine + itraconazole against Mucorales ²⁹, terbinafine + voriconazole against *Fusarium* spp
218 ³⁰, and terbinafine + voriconazole against *L. prolificans* ³¹⁻³³, and it was suggested almost twenty
219 years ago that combination therapy with an azole plus terbinafine may be a treatment option for
220 these infections ³⁴. However, the benefit of terbinafine-based regimens was not significant in the
221 recent review of 56 published cases of invasive lomentosporiosis (including 5 more recent
222 cases that were also included in this study), where voriconazole-based regimens were superior
223 but significance was not reached in the subgroups of combination treatment ¹⁰. Previous *in vitro*
224 studies have shown that while some *L. prolificans* isolates are susceptible to voriconazole ³⁵, the
225 majority have high MICs to all antifungal agents, including voriconazole, which may correlate
226 with treatment failure with voriconazole monotherapy ³⁶. Clinical studies have demonstrated the

227 superiority of voriconazole-based treatment regimens for *L. prolificans* infections compared to
228 LAmB-based regimens ^{1,16}, a finding that was confirmed in our study. Furthermore, recently
229 published data from our cohort ²⁸ showed the highest treatment success with voriconazole when
230 used in combination with another antifungal agent. Importantly, 39% of patients in our cohort
231 had *L. prolificans* breakthrough infections occurring under triazole prophylaxis/empirical therapy,
232 with more than a third occurring during voriconazole prophylaxis, further evidence that
233 voriconazole alone may be insufficient to prevent or treat infections caused by *L. prolificans*.
234 This study shows for the first time that terbinafine-based regimens were significantly associated
235 with treatment success and survival, and that the treatment response rate using voriconazole in
236 combination with terbinafine was twice that of other antifungal regimens. Our study also showed
237 a significant survival benefit in those receiving surgery, which was also recently shown in
238 children with invasive *Scedosporium* and *Lomentospora* infections who underwent surgery and
239 received voriconazole ⁸. Importantly, the majority of infections in this analysis occurred in 2014
240 and later, with outcomes likely influenced by potential changes in the epidemiology of
241 lomentosporiosis associated with the rise of mould active antifungal prophylaxis and advances
242 in treatment of haematological/oncological malignancies. As a result, patients who develop
243 lomentosporiosis today may be more immunosuppressed than those who developed the
244 infection 20 years ago, a theory that is supported by the fact that high mortality rates remained
245 mostly unchanged despite the introduction of newer and better tolerated antifungals ^{4,16}.

246 In conclusion, *L. prolificans* infections are associated with high mortality, particularly in
247 patients with underlying haematological/oncological malignancies and those with disseminated
248 infection. While combination therapy shows some success in lowering persistently high mortality
249 rates, hope lies on novel antifungals that are currently being developed, specifically F901318
250 (Olorofim; F2G, Manchester, U.K.), which shows excellent activity against *L. prolificans* ³⁷ and
251 which is currently being evaluated in a Phase 2b open-label study (NCT03583164). Until novel
252 drugs are available, our findings suggest that voriconazole or terbinafine-based regimens,
253 particularly voriconazole + terbinafine combination therapy, could be the preferred choice for the
254 treatment of invasive *L. prolificans* infections.

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261

262 **Author Contributions:**

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

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271 **Conflicts of Interest:**

272 OAC has received research grants from Actelion, Amplyx, Astellas, Basilea, Cidara, Da
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278 Tetrphase, Vical, and received lecture honoraria from Astellas, Basilea, Gilead, Grupo
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280 SC has received grant funding from Merck, Astellas, and Gilead and serves or has served on
281 advisory boards for Merck, Gilead, Pfizer and F2G

282 SVH has received grant funding from Merck, Astellas, and Gilead.

283 CK serves on a Data Safety Monitoring Board for Cidara Therapeutics.

284 MHM received grant funding from Astellas, Scynexis and Mayne Pharmaceutical as well as
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292 Merck, Gilead, Pfizer, Jazz, Cidara

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412 **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	
<i>Australia</i>	17 (41%)
<i>United States</i>	11 (27%)
<i>Germany</i>	8 (20%)
<i>Other[#]</i>	5 (12%)
Underlying Diseases/Main Risk Factors	
<i>Hematological/Oncological Malignancies</i>	27 (66%)
<i>Trauma/Surgery</i>	6 (15%)
<i>Solid Organ Transplantation</i>	3 (7%)
<i>Other[§]</i>	5 (12%)
<i>Intensive Care Unit</i>	6 (15%)
Site(s) of Infection	
<i>Disseminated infection</i>	25 (61%)
<i>Growth in Blood Culture</i>	19 (46%)
<i>Lung</i>	18 (44%)
<i>Eye</i>	9 (22%)
<i>Skin / Deep Soft Tissue</i>	5 (12%)
<i>Bone</i>	4 (10%)
<i>Brain / Central Nervous System</i>	5 (12%)
Breakthrough Infection	24 (59%)
Antifungal Treatment*	
<i>Voriconazole +/- other antifungals</i>	31/40 (78%)
<i>Terbinafine +/- other antifungals</i>	19/40 (48%)
<i>LAmB +/- other antifungals</i>	15/40 (38%)
<i>Antifungal Combination Therapy (versus Monotherapy)</i>	24/40 (60%)
<i>Combination Voriconazole + Terbinafine +/- other antifungals</i>	16/40 (40%)
Surgery	7 (18%)
Outcomes‡	
<i>Progression, Deterioration, or Failure of</i>	23/40 (58%)

<i>Antifungal Treatment</i>	
<i>28-day Overall Mortality</i>	21 (51%)
<i>Death attributable to L. prolificans infection</i>	21 (51%)

413 * Those who survived received antifungal treatment for a median of 181 days (IQR 47-332
414 days).

415 # Countries include: Belgium, France, Italy, The Netherlands and Spain (each one case)

416 \$ Other includes Burn, chronic granulomatous disease, chronic pulmonary disease, chronic
417 cardiovascular disease/obesity and contact lenses.

418 ¥ Final response assessment was conducted at a median of 241 days (IQR 84-335) after
419 diagnosis in those who survived and median 13 days (IQR 4-35 days) after IFI diagnosis in the
420 deceased (i.e. final assessment on the day of death).

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