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Invasive infections with *Purpureocillium lilacinum*: clinical characteristics and outcome of 101 cases from FungiScope® and the literature

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Objectives: To provide a basis for clinical management decisions in *Purpureocillium lilacinum* infection.

Methods: Unpublished cases of invasive *P. lilacinum* infection from the FungiScope® registry and all cases reported in the literature were analysed.

Results: We identified 101 cases with invasive *P. lilacinum* infection. Main predisposing factors were haematological and oncological diseases in 31 cases (30.7%), steroid treatment in 27 cases (26.7%), solid organ transplant in 26 cases (25.7%), and diabetes mellitus in 19 cases (18.8%). The most prevalent infection sites were skin ($n = 37/101$, 36.6%) and lungs ($n = 26/101$, 25.7%). Dissemination occurred in 22 cases (21.8%). Pain and fever were the most frequent symptoms ($n = 40/101$, 39.6% and $n = 34/101$, 33.7%, respectively). Diagnosis was established by culture in 98 cases (97.0%). *P. lilacinum* caused breakthrough infection in 10 patients (9.9%). Clinical isolates were frequently resistant to amphotericin B, whereas posaconazole and voriconazole showed good *in vitro* activity. Susceptibility to echinocandins varied considerably. Systemic antifungal treatment was administered in 90 patients (89.1%). Frequently employed antifungals were voriconazole in 51 (56.7%) and itraconazole in 26 patients (28.9%). Amphotericin B treatment was significantly associated with high

mortality rates ($n = 13/33$, 39.4%, $P = <0.001$). Overall mortality was 21.8% ($n = 22/101$) and death was attributed to *P. lilacinum* infection in 45.5% ($n = 10/22$).

Conclusions: *P. lilacinum* mainly presents as soft-tissue, pulmonary or disseminated infection in immunocompromised patients. Owing to intrinsic resistance, accurate species identification and susceptibility testing are vital. Outcome is better in patients treated with triazoles compared with amphotericin B formulations.

Introduction

With increasing numbers of immunosuppressed patients at risk for opportunistic infections, the selective pressure caused by widespread antifungal use, and improvement in diagnostics, mycoses caused by filamentous fungi other than *Aspergillus* or Mucorales are on the rise.[1] *Purpureocillium lilacinum*, formerly known as *Paecilomyces lilacinus*,[2] is increasingly reported to cause opportunistic infections in immunocompetent and immunocompromised individuals, affecting different organ systems with potential to cause systemic disease.

P. lilacinum is a saprobic, hyaline hyphomycete with a ubiquitous environmental distribution, and can be detected in soil samples and decaying material worldwide. It has been found in hospital water supply systems as well as water streams in the Middle East,[3,4] likely as a consequence of its agricultural use as a biological control agent for plant-parasitic nematodes.[5] Outbreaks of infections related to sterilized sodium bicarbonate solution and skin lotions have been reported, as this fungus is potentially resistant to sterilization processes.[6,7]

P. lilacinum causes a variety of clinical manifestations in immunocompetent and immunocompromised individuals, ranging from superficial mycoses to life-threatening systemic infections.[8,9] *P. lilacinum* has a tropism for ocular structures, thus, the most frequently reported clinical manifestations in humans are eye infections such as keratomycosis in contact lens wearers, after intra-ocular lens implantation or ocular trauma.[10,11] However, *Purpureocillium* is increasingly recognized as an aetiological agent of invasive fungal infections (IFI), such as bloodstream infections, bursitis, endocarditis, invasive sinusitis, peritonitis, and pneumonia.[9,12–16]

Infections with *P. lilacinum* possess several diagnostic and therapeutic challenges as their tissue morphology is nearly indistinguishable from that of *Aspergillus* spp. and other agents of hyalohyphomycosis.[17] Additionally, until 2011 *P. lilacinum* was considered to belong to the genus *Paecilomyces* spp., as they share morphological similarities.[2] However, based on phylogenetic analysis and partial 18S ribosomal RNA gene sequencing, a nomenclature shift has been proposed and *P. lilacinum* has been transferred to the new family *Ophiocordycipitaceae* (Order *Hypocreales*) as a new genus *Purpureocillium*.[2] The accurate identification to species level is crucial as *Paecilomyces* and *Purpureocillium* spp. show major differences in MICs of antifungal agents.[11]

Current knowledge on infections with *Purpureocillium* spp. is mainly based on case reports and small case series. Due to the paucity of reported cases and the lack of clinical trials, the optimal strategy for disease management has not yet been defined. Therefore, we have conducted a combined analysis of cases of invasive *Purpureocillium* infection entered in the FungiScope® registry and cases reported in the literature to identify baseline factors, establish demographic knowledge, and provide a basis for diagnostic and therapeutic decisions.

Methods

FungiScope® (www.fungiscope.net) is an international web-based registry for rare and emerging IFI (www.clinicaltrials.gov, NCT 01731353). The methodology has been described elsewhere.[18] FungiScope® is approved by

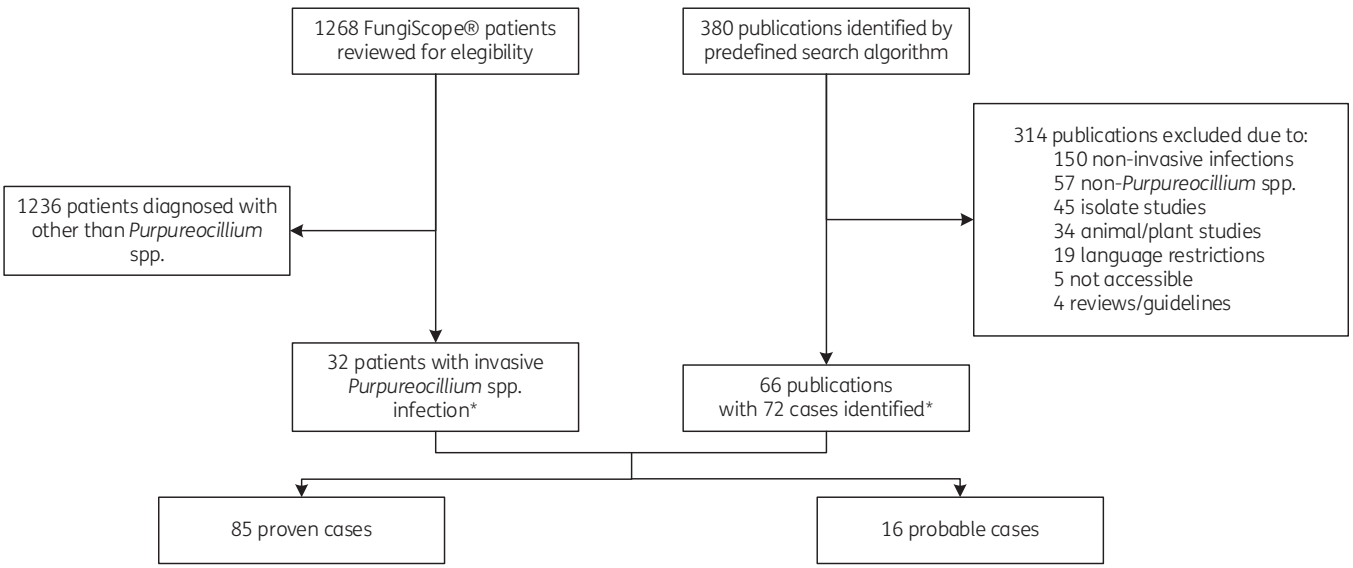

Figure 1. Enrolment and study flow chart. *Three cases were reported both in FungiScope® and the literature.[15,16,21]

the Institutional Review Board and Ethics Committee of the University Hospital Cologne, Germany (Study ID: 05–102). A dataset of *Purpureocillium* spp. cases was extracted from the registry and records were retrospectively reviewed (Figure 1).

Additionally, a literature search was performed in PubMed® and Web of Science (Clarivate Analytics, USA) for all reported cases of invasive *Purpureocillium* infections since database inception until 31 August 2020. The predefined search filters '(*Paecilomyces**) OR (*Purpureocillium**) AND ((invasive OR disseminated OR infection) AND (case OR patient OR report))' yielded 380 results. Publications in English, French, German, Spanish, and Turkish were selected based on title and abstract for further evaluation. Reference lists of articles were screened for other suitable studies and authors were contacted to obtain additional data. Cases with colonization, superficial infections, non-systemic eye infections, microbiological studies on isolates and non-human infections were excluded (Figure 1). Small case series were included to allow complete data reporting. We excluded cases of *Paecilomyces* spp. identified only to the genus level and *Paecilomyces* other than *P. lilacinus*.

Each report was reviewed for patient demographics, underlying conditions and immunosuppression as predisposing factors for IFI, signs and symptoms at diagnosis, infection site and diagnostic and therapeutic procedures. If available, radiological results suggesting IFI, mycological evidence, susceptibility testing and MIC, antifungals used for prophylaxis and treatment as well as surgical treatment of IFI were documented. Mortality on day 42 and 90 after diagnosis, and mortality attributed to the infection were documented. The follow-up period was defined as being from day of diagnosis to last patient contact.

Proven or probable IFI were included, following the revised 2019 EORTC/MSG criteria.[19] Dissemination was defined as either infection at two or more non-contiguous anatomical sites or bloodstream infection with at least one positive blood culture. Breakthrough IFI (BT-IFI) was defined as *Purpureocillium* infection occurring during exposure to any systemic antifungal agent.[20]

Statistical analysis was performed with the Statistical Package for the Social Sciences (SPSS) version 25 (IBM, USA). Patient characteristics from categorical variables were summarized employing frequencies and percentages, while median and IQR were used in continuous variables. Categorical data were compared using Fisher's exact test. A P value ≤ 0.05 was set as statistically significant.

Results

In our study, 101 cases of *Purpureocillium* infection reported in the FungiScope® registry ($n = 32$, 31.7%) and the literature ($n = 69$, 68.3%) were included (Table S1). Three cases have been both published and registered in the FungiScope® registry and were only included once in the analysis.[15,16,21]

A total of 85 cases (84.2%) were classified as proven and 16 (15.8%) as probable IFI. Median age at diagnosis was 53 years (IQR 31–64), and patients were mostly male ($n = 62$; 61.4%).

Cases were reported from 26 countries worldwide with the highest number of cases from the United States ($n = 31$, 30.7%) (Figure 2). Cases were diagnosed between 1974 and 2020. All infections were caused by *P. lilacinum*. Coinfection with at least one other fungal pathogen was present in eight cases (7.9%) (Table 1).

Predisposing factors

The most frequent predisposing factors were haematological and oncological diseases ($n = 31/101$, 30.7%), with 9.9% being acute leukaemia ($n = 10/101$), and 7.9% solid tumours ($n = 8/101$). Steroid treatment was second most prevalent predisposing factor ($n = 27/101$, 26.7%). Solid organ transplantation (SOT) and diabetes mellitus were also frequent with 26 (25.7%) and 19

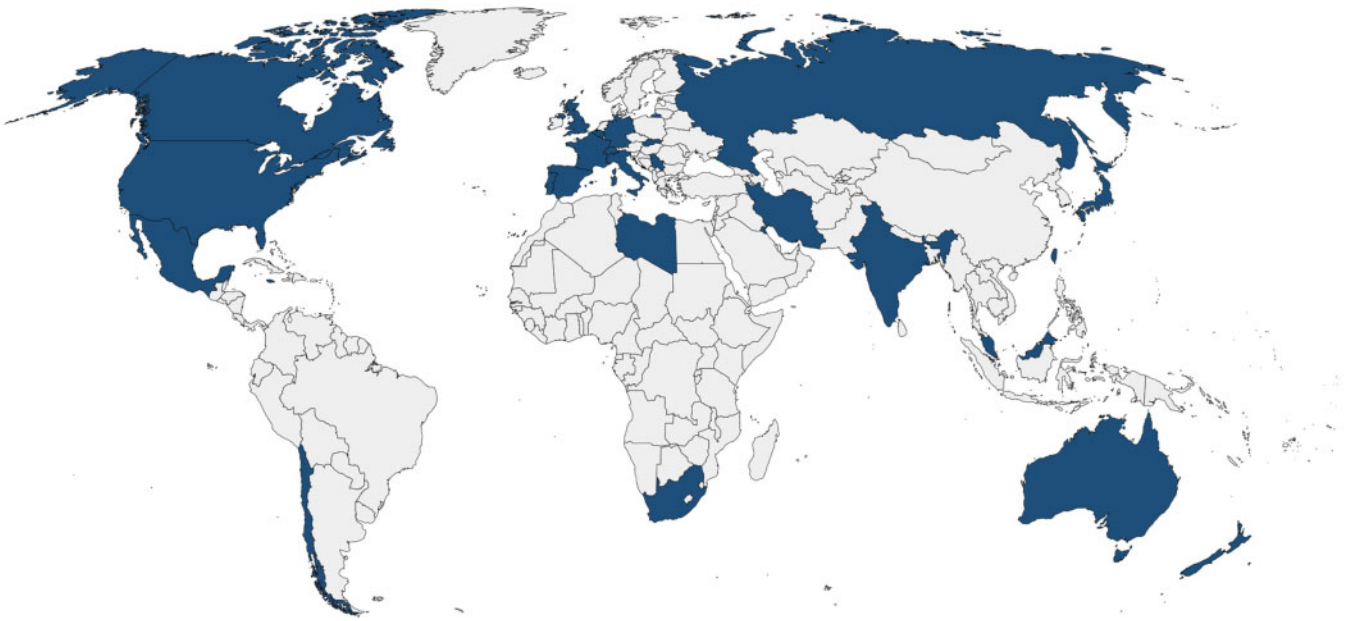

Figure 2. Countries where *Purpureocillium lilacinum* infections have been reported. Thirty-one cases were reported from the United States, thirteen from Spain, eight from India, five from Slovakia, four each from France, Japan, and Taiwan, three each from Canada and Germany, two each from Belgium, Iran, Malaysia, New Zealand, Portugal, Russia, Serbia, Switzerland, and United Kingdom, and one case each was reported from Australia, Chile, Italy, Jamaica, Kuwait, Libya, Mexico, and South Africa. This figure appears in colour in the online version of *JAC* and in black and white in the print version of *JAC*.

Table 1. Patient characteristics

Characteristic	Total ($n = 101$)		Deaths in the respective cohort, *n* (%)		Mortality ($n = 101$)
EORTC/MSG					
Probable	16	15.8%	3		
Proven	85	84.2%	18	21.2%	17.8%
Age, years, median (IQR)	53	(31–64)			
Sex					
Female	38	37.6%	9	23.7%	8.9%
Male	62	61.4%	12	19.4%	11.9%
Unknown	1	1.0%	–	–	–
Mixed infection	8	7.9%	3	37.5	3.0%
Alternaria alternata, skin	1	1.0%	–	–	–
Alternaria infectoria, skin	1	1.0%	1	100.0%	1.0%
Arthrographis kalrae, lung	1	1.0%	–	–	–
Aspergillus flavus + *Penicillium* spp., lung	1	1.0%	1	100.0%	1.0%
Aspergillus niger, lung	1	1.0%	–	–	–
Aspergillus terreus, Aspergillus flavus, Penicillium spp., *Fusarium* spp., lung	1	1.0%	–	–	–
Cunninghamella bertholletiae + *Aspergillus alliaceus*, lung	1	1.0%	–	–	–
Fusarium spp., skin	1	1.0%	1	100.0%	1.0%
Underlying conditions[a]					
Haematological/oncological disease	31	30.7%	8	25.8%	7.9%
Acute leukaemia[b]	10	9.9%	2	20.0%	2.0%
Solid tumours[c]	8	7.9%	2	25.0%	2.0%
Lymphoma[d]	7	6.9%	1	14.3%	1.0%
Autoimmune haemolytic anaemia	2	1.0%	1	50.0%	1.0%
Chronic granulomatous disease	2	2.0%	1	50.0%	1.0%
Hypogammaglobulinaemia	1	1.0%	–	–	–
Immune thrombocytopenic purpura	1	1.0%	1	100.0%	1.0%
HSCT					
Allogenic	3	3.0%	1	33.3%	1.0%
Autologous	3	3.0%	–	–	–
GvHD	3	3.0%	2	66.7%	2.0%
Solid organ transplant	26	25.7%	4	15.4%	4.0%
Heart	3	3.0%	1	33.3%	1.0%
Kidney	10	9.9%	–	–	–
Kidney + liver	2	2.0%	–	–	–
Liver	2	2.0%	1	50.0%	1.0%
Lung	9	8.9%	2	22.2%	2.0%
Chronic lung disease	9	8.9%	3	33.3%	3.0%
Chronic renal disease	10	9.9%	2	20.0%	2.0%
Diabetes mellitus	19	18.8%	4	21.1%	4.0%
HIV	4	4.0%	3	75.0%	3.0%
Dialysis					
Haemodialysis	3	3.0%	–	–	–
Peritoneal dialysis	3	3.0%	–	–	–
Long-term immunosuppression	7	6.9%	1	14.3%	1.0%
Neutropenia	14	13.9%	4	28.6%	4.0%
Major surgery	6	5.9%	1	16.7%	1.0%
Steroid treatment	27	26.7%	6	22.2%	5.9%
Trauma	5	5.0%	–	–	–
No baseline factor	11	10.9%	–	–	–
Indwelling devices					

Continued

Table 1. *Continued*

Characteristic	Total ($n = 101$)		Deaths in the respective cohort, n (%)		Mortality ($n = 101$)
Bronchial stent	3	3.0%	–	–	–
Central venous catheter	10	9.9%	–	–	–
Prosthetic aortic valve	3	3.0%	3	100.0%	3.0%
Organ involvement[e]					
Blood	18	17.8%	6	33.3%	5.9%
Bone and joints	6	5.9%	1	16.7%	1.0%
Central nervous system	5	5.0%	1	20.0%	1.0%
Deep tissue	24	23.8%	3	12.5%	3.0%
Heart	5	5.0%	4	80.0%	4.0%
Lung	26	25.7%	4	15.4%	4.0%
Peritoneum	4	4.0%	1	25.0%	1.0%
Sinuses	13	12.9%	1	7.7%	1.0%
Skin	37	36.6%	6	16.2%	5.9%
Dissemination					
Adjacent organs	15	14.9%	1	6.7%	1.0%
Disseminated	22	21.8%	7	31.8%	6.9%
Not disseminated	64	63.4%	13	20.3%	12.9%

Abbreviations: EORTC/MSG, European Organization for Research and Treatment of Cancer and the Mycoses Study Group Education and Research Consortium; GvHD, graft-versus-host disease; HSCT, haematopoietic stem cell transplantation; MDS, myelodysplastic syndrome; SOT, solid organ transplantation.
Data may be superadditive.
[a]Other underlying conditions included hepatitis C ($n = 3$), rheumatoid arthritis ($n = 2$), acute SOT rejection and PTLD ($n = 1$), chronic hepatitis B ($n = 1$), chronic lung allograft dysfunction ($n = 1$), chronic persisting hepatitis of unknown aetiology ($n = 1$), Guillain-Barré Syndrome ($n = 1$), and Sweet's syndrome ($n = 1$).
[b]Including five non-specified cases, three cases with acute myeloid leukaemia and two cases with biphenotypic leukaemia.
[c]Including two cases of osteosarcoma and one case each with breast cancer, neuroblastoma, pancreatic cancer, retinoblastoma, rhabdomyosarcoma, testicular cancer.
[d]Including four cases with chronic lymphocytic leukaemia, one case with non-Hodgkin lymphoma, one case with not further specified lymphoma, and one case with multiple myeloma.
[e]Other organ involvements include eye ($n = 2$), kidney ($n = 2$), and vessels ($n = 1$).

cases (18.8%), respectively. Only 11 patients (10.9%) lacked predisposing factors for IFI [Table 1 and Table S1 (available as Supplementary data at *JAC* Online)].

Site of infection

Skin was the most common site involved ($n = 37/101$, 36.6%), followed by infections of the lung ($n = 26/101$, 25.7%). Other frequent sites of infection were deep soft tissue ($n = 24/101$, 23.8%), bloodstream ($n = 18/101$, 17.8%), and sinuses ($n = 13/101$, 12.9%). Disseminated disease occurred in 22 patients (21.8%), adjacent organs were affected in 15 patients (14.9%) (Table 1, Table S2).

Signs of infection

Pain at the site of infection was frequently reported ($n = 40/101$, 39.6%). Fever at the time of diagnosis of the IFI was also a common clinical sign ($n = 34/101$, 33.7%). Other symptoms were mostly associated with the anatomic region involved, such as erythema of the skin ($n = 29/101$, 28.7%), dyspnoea ($n = 12/101$, 11.9%), neurological symptoms ($n = 10/101$, 9.9%), or skin nodules ($n = 10$, 9.9%) (Table 2). Cutaneous and sub-cutaneous infections had a wide range of clinical manifestation, from oedema, erythematous papules and nodules, vesicles or necrotic ulcerous lesions, to soft-tissue infection (Table 2, Table S3). One patient presented with the rare manifestation of sporotrichoid lymphocutaneous infection (Figure S1a).

Diagnostics

Imaging procedures supported diagnosis in 46 cases (45.5%). Chest computed tomography (CT) ($n = 20/101$, 19.8%) and paranasal sinus CT ($n = 8/101$, 7.9%) were predominantly performed, followed by CNS imaging (CT or MRI in $n = 8/101$, 7.9%; Figure S1b) and chest radiograph ($n = 7/101$, 6.9%). In chest CT, nodular infiltrates and cavitary lesions were common findings ($n = 8/20$ and $n = 5/20$, respectively). Definitive diagnosis was established via fungal culture in 98 cases (97.0%) and via histopathological examination in 29 cases (28.7%) (Table 2, Table S4). Fungal colonies present white at first, then mostly becoming purple to violaceous (Figure 3a and b and Figure S2a–c). Microscopic examination reveals typical phialides with ellipsoidal or fusiform conidia (Figure 3c–e and Figure S2d–i). Histopathological examination of infected tissue may show adventitious sporulation (Figure 3f).

Table 2. Clinical signs and symptoms and diagnostic procedures

Characteristic	*n*	%
Signs and symptoms of infection		
Cough	8	7.9%
Dyspnoea	12	11.9%
Erythema	29	28.7%
Fever	34	33.7%
Gastrointestinal symptoms	3	3.0%
Nasal obstruction/sinus tenderness	8	7.9%
Neurological signs	10	9.9%
Pain	40	39.6%
Skin nodules	10	9.9%
Skin oedema/swelling	6	5.9%
Skin ulcerations	6	5.9%
Tachypnoea	3	3.0%
Weight loss	4	4.0%
Other signs and symptoms[a]	14	13.9%
Imaging procedures		
CT head	5	5.0%
CT paranasal sinuses	8	7.9%
CT thorax	20	19.8%
MRI head	3	3.0%
Ultrasound heart	3	3.0%
X-ray thorax	7	6.9%
Mycological evidence		
Culture	98	97.0%
Histology	29	28.7%
Microscopy	10	9.9%
PCR	6	5.9%

Data may be superadditive.
[a]Other signs and symptoms included bleeding ($n = 2$), chills ($n = 2$), hypotension ($n = 2$), adynamia ($n = 1$) diastolic murmur ($n = 1$), epistaxis ($n = 1$), hepatomegaly ($n = 1$), jaundice ($n = 1$), night sweat ($n = 1$), paralysis of the left oculomotor nerve ($n = 1$), and proptosis of the left eye ($n = 1$).

This phenomenon involves the production of reproductive structures similar to those observed *in vitro*, i.e. phialides and conidia.

Antifungal susceptibility

In *vitro* antifungal susceptibility was evaluated for 30 clinical isolates by different methods (Table 3). In 13 isolates, methodology was not reported, therefore, MIC data for these isolates were not collated. In the remaining isolates, amphotericin B (AmB), fluconazole, flucytosine, and itraconazole were least active *in vitro* in susceptibility testing against *P. lilacinum* with any of the reported methods. Posaconazole and voriconazole had the lowest MIC. All tested echinocandins showed contrasting data with variable *in vitro* activity against *P. lilacinum*. Susceptibility testing for isavuconazole was not performed (Table 3).

Treatment and outcome

Twelve patients (11.9%) had received antifungal prophylaxis before the diagnosis of IFI with one patient solely receiving AmB by inhalation. Ten patients developed BT-IFI (9.9%) (Table 4, Table S5). One case did not fulfil the pharmacokinetic parameters classifying BT-IFI.[20] Prophylaxis was administered due to underlying haematological or oncological disease or after SOT.

In the majority of patients ($n = 90/101$, 89.1%), systemic antifungal therapy was administered, mainly with single ($n = 36/101$, 35.6%) or sequential monotherapy ($n = 29/101$, 28.7%). Monotherapy followed by combination therapy has been described in 23 cases (22.8%) (Table 4). The combination of AmB with an azole antifungal was mostly used ($n = 11/25$, 44.0%). Monotherapy and combination therapy resulted in comparable mortality rates ($n = 12/65$, 18.5% versus $n = 5/25$, 20.0%, $P = 1.00$).

Triazoles were administered in 78 cases ($n = 78/90$, 86.7%), predominantly voriconazole ($n = 51/90$, 56.7%) and itraconazole ($n = 26/90$, 28.9%). Mortality in this group was 17.9% ($n = 14/78$). AmB was given in 33 cases ($n = 33/90$) with 39.4% mortality rate. Echinocandins were used in twelve cases (13.3%) with one death reported (Table 4). The administration of AmB was associated with a significant increase in mortality compared with systemic treatment without amphotericin B (AmB $P \leq 0.001$) (Table S6). Median duration of systemic antifungal therapy was 60 days (IQR 26–180). Surgery was performed in 34 patients (33.7%) with a mortality rate of 20.6% ($P = 0.612$) (Table S6).

All-cause mortality was 21.8% ($n = 22/101$). In BT-IFI, mortality rate did not significantly differ from non-BT-IFI cases ($P = 0.295$; Table S6). Autopsy was performed on two patients (9.1%) and results were reported in one case. The autopsy revealed positive blood culture and infiltration of both kidneys in a patient with initial skin eruptions during aplasia, following protracted disease course and haematogenous dissemination.[6] To examine disease-specific mortality in cases without autopsy results, death was attributed to *P. lilacinum* infection by the treating physicians and by the authors, respectively. In ten cases (45.5%) death was attributed to IFI (Table 4).

Skin and deep soft tissue infection had a low mortality with 16.2% ($n = 6/37$) and 12.5% ($n = 3/24$), respectively. Mortality of lung infections was also comparably low ($n = 4/26$, 15.4%). The highest mortality was found in cases with bloodstream and heart involvement ($n = 6/18$, 33.3% and $n = 4/5$, 80.0%, respectively). Mortality in disseminated disease was numerically higher than in cases with single organ involvement or adjacent organs, but the difference did not reach statistical significance ($P = 0.216$) (Table 4, Table S6).

Death occurred within 42 days after diagnosis in 9 of 22 cases (40.9%) and within 90 days after diagnosis in 10 cases (45.5%). Median duration from diagnosis to last follow up day was 120 days (IQR 42–366) (Table 4).

Discussion

Previously considered a contaminant, *P. lilacinum* has increasingly been recognized as a cause of infection in both immunocompromised and immunocompetent hosts. Here, we present the largest analysis addressing management and outcome of invasive *P. lilacinum* infections by identifying 101 cases in the global FungiScope® registry and the literature.

Purpureocillium infections have a cosmopolitan distribution and cases in this analysis have been reported from six continents (Figure 2). The widespread use of antifungals is considered to

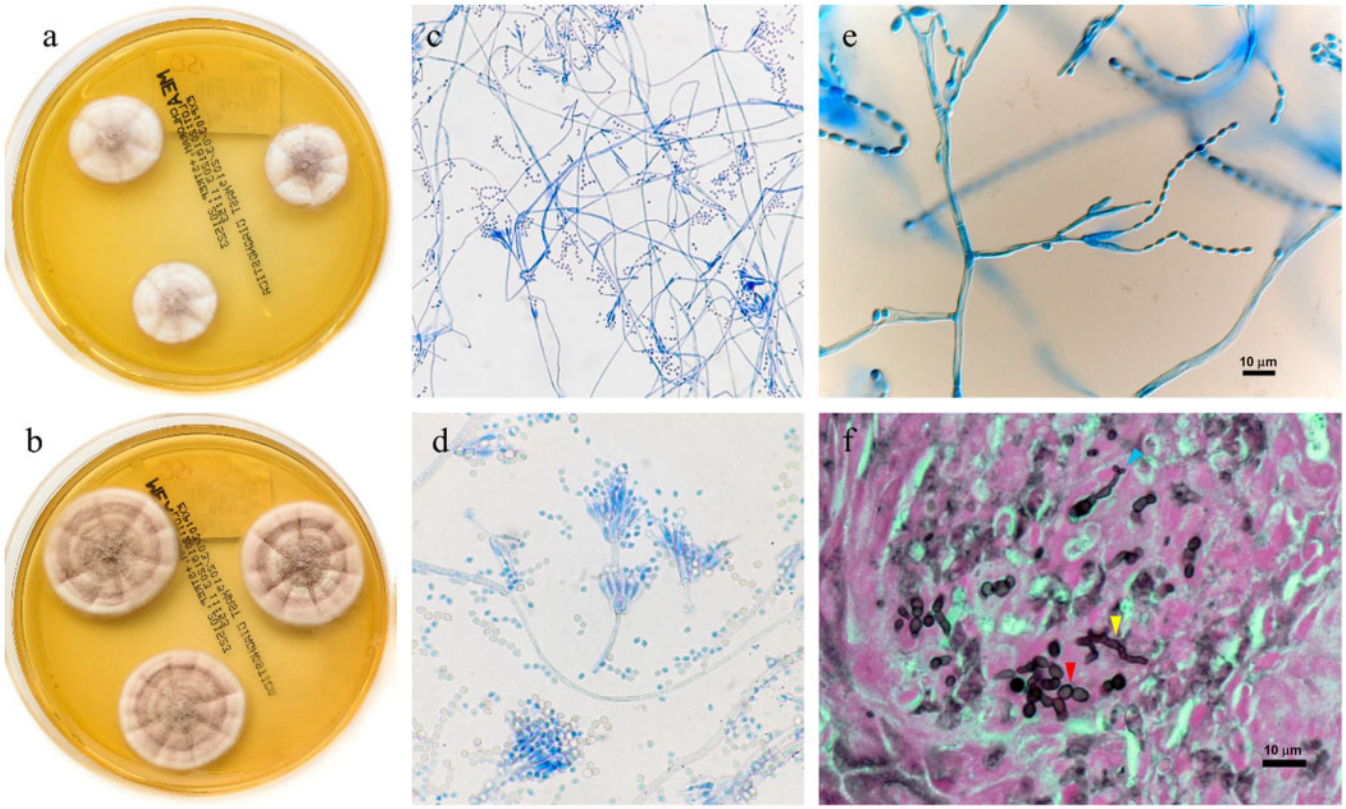

Figure 3. Macroscopic, microscopic and histopathological presentation of *Purpureocillium lilacinum*. (a and b) Malt extract agar plate incubated at 26°C showing white to lilac colonies of *P. lilacinum* after 5 days and 7 days of culture. (c and d) Lactophenol cotton blue staining. Typical phialides with a distinct neck bearing conidia. Conidia are ellipsoidal to fusiform with a smooth wall. Magnification: ×400 and ×1000. (e) Lactophenol cotton blue staining. *P. lilacinum* isolate showing elongated phialides producing chains of lemon-shaped conidia. Magnification ×600. (f) Histopathological examination (Grocott stain) reveals three different aspects of *P. lilacinum* growing within infected tissue: globose yeast-like structures (red arrowhead), septate hyphae (yellow arrowhead) and conidia that arise from the apical orifice of a phialide (blue arrowhead). Magnification ×600. Images (a–d) courtesy of Jörg Steinmann and images (e–f) courtesy of René Pelletier.

contribute to the emergence of mycoses others than *Aspergillus* and Mucorales.[1] In our analysis, BT-IFI were observed in 10% of cases. As reported for other emerging moulds, severe immunosuppression caused by haematological disease and treatment, steroid treatment or SOT is the main predisposing factor for *Purpureocillium* infections.[1] Route of entry is frequently through either direct inoculation of the skin or through respiratory inhalation, as reflected in the main infection sites.

The fungus escapes local immune defences and can migrate via the lymph flow, as illustrated by the reported lymphocutaneous infection (Figure S1a). Indeed, *P. lilacinum* conidia have been shown to infect macrophages and dendritic cells, demonstrating the ability of *P. lilacinum* to invade human phagocytic cells, thus facilitating dissemination.[22] Additionally, the phenomenon of adventitious sporulation is associated with an increased rate of positive blood cultures, explaining higher rates of dissemination in contrast to fungi without adventitious sporulation, e.g. *Aspergillus* species.[23] In our analysis, dissemination occurred in 22% of cases.

Symptoms of *P. lilacinum* infection are mainly non-specific and difficult to distinguish from other fungal infections. A multimodal approach comprising radiology, microbiology and histopathology is required for diagnosis. In this analysis, radiological imaging was commonly utilized to detect pulmonary infections, and also contributed to detection of sinus and CNS involvement to a lesser extent. Clinical isolation by direct specimen sampling from the affected sites represents the most important diagnostic measure. Accordingly, diagnosis was mainly confirmed by culture and histological examination. Notably, this carries the risk of misidentification, as *P. lilacinum* resembles other mould infections on cytological and histological examination.[24] Both typical phialides with ellipsoidal or fusiform conidia or atypical, elongated and *Acremonium*-like conidiophores with cylindrical conidia are described.[2] Detection of adventitious sporulation may facilitate an initial presumptive identification through careful histological examination.[23] Molecular diagnostic approaches, such as small subunit ribosomal sequence analysis or proteomic profiling via MALDI-TOF/MS, may facilitate more definitive identification.[25] Routine identification of emerging moulds in the clinical laboratory will ultimately improve our knowledge of their clinical epidemiology and antifungal susceptibility patterns.

Treatment of rare mould infections is challenging as they may exhibit decreased susceptibility or are even intrinsically resistant to whole classes of antifungals. This is clearly reflected in the high mortality rates reported for many of the less common moulds.[1] It is therefore highly relevant to obtain prompt and accurate species identification to tailor clinical management. Consistent with other

Table 3. Susceptibility testing

Characteristic	*n*	%
Susceptibility testing		
CLSI microdilution	6	5.9%
Concentration gradient diffusion assay (Etest)	5	5.0%
EUCAST microdilution	2	2.0%
Macrodilution method	2	2.0%
Sensititre™ YeastOne™	2	2.0%
Unknown	13	12.9%
Median MIC (mg/L)		
By CLSI microdilution (IQR)		
Amphotericin B	16.0 (8.0–32.0)	
Anidulafungin	0.03 (0.03–0.03)	
Caspofungin	0.1 (0.03–0.1)	
Micafungin	0.03 (0.03–16.0)	
Fluconazole	24.0 (12.0–144.0)	
Itraconazole	16.5 (1.0–32.0)	
Posaconazole	0.1 (0.1–0.1)	
Voriconazole	0.6 (0.3–1.0)	
Flucytosine	128.0 (128.0–128.0)	
By concentration gradient diffusion assay (IQR)		
Amphotericin B	32.0 (32.0–32.0)	
Caspofungin	6.0 (2.3–20.0)	
Itraconazole	32.0 (8.0–32.0)	
Posaconazole	0.4 (0.2–0.5)	
Voriconazole	0.1 (0.05–0.2)	
By EUCAST microdilution (IQR)		
Amphotericin B	36.0 (8.0–64.0)	
Anidulafungin	64.0 (64.0–64.0)	
Caspofungin	4.5 (1.0–8.0)	
Micafungin	36.0 (8.0–64.0)	
Fluconazole	256.0 (256.0–256.0)	
Itraconazole	24.0 (16.0–32.0)	
Posaconazole	0.6 (0.3–1.0)	
Voriconazole	0.4 (0.3–0.5)	
Flucytosine	128.0 (128.0–128.0)	
By macrodilution method (IQR)		
Amphotericin B	32.0 (32.0–32.0)	
Fluconazole	128.0 (128.0–128.0)	
Itraconazole	8.5 (1.0–16.0)	
Ketoconazole	1.0 (1.0–1.0)	
Miconazole	0.5 (0.5–0.5)	
Flucytosine	128.0 (128.0–128.0)	
By Sensititre™ YeastOne™ (IQR)		
Amphotericin B	16.0 (16.0–16.0)	
Anidulafungin	16.0 (16.0–16.0)	
Caspofungin	40.0 (16.0–64.0)	
Fluconazole	128.0 (128.0–128.0)	
Itraconazole	16.5 (1.0–32.0)	
Posaconazole	0.5 (0.5–0.5)	
Voriconazole	0.3 (0.2–0.5)	
Flucytosine	32.0 (32.0–32.0)	

Abbreviations: CLSI, Clinical and Laboratory Standards Institute; EUCAST, European Committee on Antimicrobial Susceptibility Testing.

reported susceptibility profiles, AmB was least active against *P. lilacinum* isolates.[26] *In vitro* activity is difficult to correlate with clinical efficacy in *P. lilacinum* infections, as clinical breakpoints have not been established. However, in line with the antifungal susceptibility profile, we demonstrated a significantly higher mortality in cases where AmB was used for treatment. Based on susceptibility profile and clinical outcome in this cohort, voriconazole and posaconazole may constitute the most favourable treatment options. However, it is important to keep in mind that intraspecies variability in strains of *P. lilacinum* exhibiting *in vitro* and *in vivo* resistance to voriconazole has also been reported, caused by an as-yet unknown mechanism of drug resistance.[27] Susceptibility testing for triazoles is therefore required. Interestingly, itraconazole showed high MIC values in *in vitro* susceptibility testing but was the second most commonly employed antifungal agent, with mortality rates similar to cases prescribed voriconazole. For isavuconazole, susceptibility data and clinical experience are scant. In this cohort, two cases were treated with isavuconazole with favourable outcome. In all tested echinocandins, the antifungal susceptibility varied considerably in our analysis, consistent with observations from other studies.[26]

Several novel antifungal compounds are currently under investigation in clinical trials and may offer new treatment options in future. Interestingly, *P. lilacinum* exhibited *in vitro* resistance to the new orally available β-glucan synthase inhibitor ibrexafungerp whereas the drug is highly active against *P. variotii*.[28] In contrast, manogepix, the active moiety of fosmanogepix, targeting the glycosylphosphatidylinositol anchor synthesis pathway, showed the greatest activity against clinical isolates of *P. lilacinum* among all antifungals tested.[29] For olorofim, targeting an enzyme of the pyrimidine biosynthesis pathway, no *in vitro* efficacy was observed in two *P. lilacinum* clinical isolates, whereas MICs for *P. variotii* were low.[30] Owing to these different susceptibility profiles, it will remain highly relevant to obtain accurate species identification and antifungal susceptibility testing.

As with most analyses of rare pathogens, our study has certain limitations. There is a potential patient selection bias in registry data and case reports, which biases the cohort toward a group receiving higher quality of care and having better outcome.[31] Thus, the overall mortality in this analysis may be underestimated. Review of the literature was complicated by frequent identification only to genus level and recent taxonomical changes of *Purpureocillium* spp. There may be an unknown rate of misidentification, considering that most isolates were diagnosed based on culture and histological examination. The impact of non-culture-based methods is not well-studied and diagnostic procedures have not been standardized for the vast majority of rare moulds. Furthermore, our findings were naturally limited by the data available to us for analysis. In addition, the patient cohort was heterogeneous, and the size of our cohort did not allow for subgroup analysis, a major limitation in retrospective studies of rare diseases.[32]

In conclusion, *P. lilacinum* is an emerging fungus representing a life-threatening pathogen for patients with immunodeficiency. Infections may present as BT-IFI or primary with non-specific symptoms and imaging findings. Thus, culture and molecular techniques are paramount for accurate diagnosis. Intrinsic resistances urge for prompt pathogen identification to the species level

Table 4. Antifungal treatment and outcome

				Proportion of deaths (%)	
Characteristic	*n*	%	Deaths (*n*)	in the respective cohort	over all cases (*n* = 101)
Prophylactic agent	12	11.9%	1	8.3%	1.0%
Amphotericin, inhalation	2	2.0%	–	–	–
Anidulafungin	1	1.0%	1	100.0%	1.0%
Fluconazole	7	6.9%	–	–	–
Itraconazole	2	2.0%	–	–	–
Liposomal amphotericin	1	1.0%	–	–	–
Breakthrough IFI	10	9.9%	1	9.1%	1.0%
Systemic antifungal therapy	90	89.1%	17	18.9%	16.8%
Amphotericin B	33	32.7%	13	39.4%	12.9%
Triazoles	78	77.2%	14	17.9%	13.9%
Fluconazole	11	10.9%	–	–	–
Isavuconazole	2	2.0%	–	–	–
Itraconazole	26	25.7%	5	19.2%	5.0%
Posaconazole	12	11.9%	3	25.0%	3.0%
Voriconazole	51	50.5%	10	19.6%	9.9%
Echinocandins	12	11.9%	1	8.3%	1.0%
Caspofungin	8	7.9%	1	12.5%	1.0%
Micafungin	4	4.0%	–	–	–
Other antifungals	20	19.8%	3	15.0%	3.0%
Griseofulvin	4	4.0%	–	–	–
Ketoconazole	8	7.9%	–	–	–
Miconazole	2	2.0%	1	50.0%	1.0%
Terbinafine	5	5.0%	–	–	–
Flucytosine	4	4.0%	2	50.0%	2.0%
Therapy days, median (IQR)	60	(26–180)			
Non-systemic antifungal therapy					
Topical amphotericin B	5	5.0%			
Topical nystatin	2	2.0%			
Topical voriconazole	1	1.0%			
G-CSF	4	4.0%	3	75.0%	3.0%
Treatment sequence					
Combination single	2	2.0%	–	–	–
Monotherapy + Combination	23	22.8%	5	21.7%	5.0%
Monotherapy sequential	29	28.7%	7	24.1%	6.9%
Monotherapy single	36	35.6%	5	13.9%	5.0%
No treatment	10	9.9%	5	50.0%	5.0%
Combinations					
Amphotericin B + Azoles	11	10.9%	4	36.4%	4.0%
Amphotericin B + Other	4	4.0%	2	50.0%	2.0%
Azoles + Echinocandins	8	7.9%	–	–	–
Azoles + Other	4	4.0%	–	–	–
Other + Other	1	1.0%	–	–	–
Surgical treatment	35	33.7%	8	22.9%	7.9%
Removal of indwelling devices					
CVC removal	10	9.9%	–	–	–
Bronchial prosthesis removal	1	1.0%	–	–	–
Valve replacement	2	2.0%	2	100.0%	2.0%
Overall mortality	22	21.8%			
Deaths attributed to IFI	10	9.9%			
Non-attributable	8	7.9%			
Unknown	4	4.0%			

Continued

Table 4. *Continued*

Characteristic	*n*	%	Deaths (*n*)	Proportion of deaths (%) in the respective cohort	Proportion of deaths (%) over all cases (*n* = 101)
Autopsy					
Yes	2	2.0%			
No	15	14.9%			
Unknown	5	5.0%			
Death before or on day 42	9	8.9%			
Death before or on day 90	10	9.9%			
Death after day 90	5	5.0%			
Date of death unknown	7	6.9%			
Observation time (days), median (IQR)	120	(42–366)			

Abbreviations: G-CSF, granulocyte-colony stimulating factor; IFI, invasive fungal infection.
Data may be superadditive.

and challenge successful treatment. The lack of clinical breakpoints aggravates the situation. MIC results should be interpreted carefully and in conjunction with multiple factors that affect antifungal activity *in vivo*.[33] Our analysis revealed that voriconazole and posaconazole exhibit the most favourable *in vitro* susceptibility and may constitute the best treatment options, while the administration of AmB was associated with higher mortality rates. These observations require confirmation, ideally in a larger and more homogeneous cohort. Owing to the rarity of IFI and the diversity of patient populations at risk, the field still lacks high-quality evidence in several critical areas that affect patient management. Optimization of the complex multidisciplinary management of those infections has the potential to improve prognosis. International registries such as FungiScope® provide a valuable method of pooling broader knowledge on rare and emerging pathogens.

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Transparency declarations

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Author contributions

R.S. conceived the study idea, enrolled cases, performed literature research, analysed and interpreted data, drafted the manuscript, created tables and figures, revised and approved the final manuscript. J.S.G. enrolled cases, performed literature search, analysed and interpreted data, created tables and figures, revised and approved the final manuscript. E.S. and X.M. performed literature research and revised and approved the final manuscript. Z.R., C.R.A.P., I.F.R., A.B., G.D., A.J.K. and A.J.M. contributed cases to the FungiScope® registry and revised and approved the final manuscript. R.P., J. Steinmann and G.R.T. have contributed cases and provided image files and descriptions. D.S. manages FungiScope®, enrolled cases, interpreted data, revised and approved the final manuscript. O.A.C. conceived and leads FungiScope®, contributed cases to the FungiScope® registry, interpreted data, revised and approved the final manuscript. J. Stemler conceived the study idea, performed literature research, analysed and interpreted data, revised and approved the final manuscript.

Supplementary data

Tables S1 to S6 and Figures S1 and S2 are available as Supplementary data at *JAC* Online.

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