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Characterization and outcome of invasive infections due to *Paecilomyces variotii*: analysis of patients from the FungiScope® registry and literature reports

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Objectives: To provide a basis for clinical management decisions in *Paecilomyces variotii* infection.

Methods: Unpublished cases of invasive *P. variotii* infection from the FungiScope® registry and all cases reported in the literature were analysed.

Results: We identified 59 cases with *P. variotii* infection. Main baseline factors were presence of indwelling devices in 29 cases (49.2%), particularly peritoneal catheters (33.9%) and prosthetic heart valves (10.2%), haematological or oncological diseases in 19 (32.2%), major surgery in 11 (18.6%), and diabetes mellitus in 10 cases (16.9%). The most prevalent infection sites were peritoneum ($n = 20$, 33.3%) and lungs ($n = 16$, 27.1%). Pain and fever were frequent ($n = 35$, 59.3% and $n = 33$, 55.9%, respectively). Diagnosis was established by culture in 58 cases (98.3%). *P. variotii* caused breakthrough infection in 8 patients. Systemic antifungals were given in 52 patients (88.1%). Amphotericin B was administered in 39, itraconazole in 15, and posaconazole in 8 patients. Clinical isolates were frequently resistant to voriconazole, whereas the above-mentioned antifungals showed good *in vitro* activity. Infections of the blood and CNS caused high mortality. Overall mortality was 28.8% and death was attributed to *P. variotii* in 10 cases.

Conclusions: *P. variotii* causes life-threatening infections, especially in immunocompromised and critically ill patients with indwelling devices. Patients undergoing peritoneal dialysis are at particular risk. Multidisciplinary management is paramount, including molecular techniques for diagnosis and treatment with efficacious systemic antifungals. Amphotericin B, itraconazole and posaconazole are regarded as treatments of choice. Combination with flucytosine may be considered. Surgical debridement and removal of indwelling devices facilitate favourable outcome.

Introduction

Paecilomyces spp. are filamentous and thermo-tolerant fungi that are ubiquitously found in soil, decomposing organic material, food products and house dust.[1,2] They were often considered as contaminants when isolated clinically, but are recently increasingly recognized to cause invasive infections, primarily in immunocompromised patients or those with indwelling material.[3] However, immunocompetent individuals can also be affected.[3,4]

The majority of these infections is caused by the *Paecilomyces variotii* species complex, comprising *P. brunneolus, P. dactylethromorphus, P. divaricatus, P. formosus*, and *P. variotii sensu stricto.*[5] *P. variotii* is the asexual state of *Byssochlamys spectabilis.*[1]

Until 2011, *P. variotii* and *P. lilacinus* were considered the most prevalent agents of human infection in the *Paecilomyces* genus.[4] However, in the last decade, phylogenetic analysis of the 18S ribosomal RNA gene revealed that these species are not related.[6] *Paecilomyces* spp. belong to the Family *Aspergillaceae* (Order *Eurotiales*), close to *Aspergillus, Penicillium* and related genera, whereas *P. lilacinus* has been transferred to the new Family *Ophiocordycipitaceae* (Order *Hypocreales*).[6] For *P. lilacinus*, a new genus name, *Purpureocillium*, has been proposed.[5,6] Available *in vitro* susceptibility data suggest major differences in species-dependent MIC ranges, with voriconazole demonstrating generally good *in vitro* activity and amphotericin B having poor activity against *P. lilacinum.*[1,7,8] making prompt and accurate species identification vital.

P. variotii can affect various organ systems and has been reported to cause bloodstream infections, CNS infections, osteomyelitis, peritonitis, pneumonia, skin and soft-tissue infections, among others.[1,3,8–14] In addition, *P. variotii* has been associated with severe, often vision-threatening, endophthalmitis.[15] Symptoms of infection appear to be non-specific and may be difficult to distinguish from other fungal infections.[3] Infections with *P. variotii* are generally rare.[14] However, larger numbers of cases were observed during outbreaks, e.g. after earthquakes.[9]

Hence, there are several challenges in diagnosing and treating these emerging infections. Owing to the low number 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 registered in FungiScope® and cases reported in the literature, in order to identify baseline factors, establish demographic knowledge and provide a basis for diagnostic and therapeutic decisions for *Paecilomyces*-associated infections.

Methods

FungiScope® (www.fungiscope.net) is an international web-based registry for rare and emerging invasive fungal infections (IFI) (www.clinicaltrials.gov, NCT 01731353). The methodology has been described elsewhere.[16] FungiScope® is approved by the Institutional Review Board and Ethics Committee of the University Hospital Cologne, Germany (Study ID: 05–102). A dataset of *Paecilomyces* spp. patient cases was extracted from the registry and included in the analysis (Figure 1).

Additionally, a literature search was performed in PubMed® and Web of Science (Clarivate Analytics, USA) for all reported cases of invasive *Paecilomyces* infections from database inception to 31 July 2020. The predefined search filters '(*Paecilomyces**) AND ((invasive OR disseminated OR infection) AND (case OR patient OR report))' yielded 358 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 such as keratitis, 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 *P. lilacinus* infection, as this fungus was recently transferred to the new genus *Purpureocillium.*[6] For the same reason, we excluded cases of *Paecilomyces* spp. with identification only to the genus level. Additionally, two cases caused by *Metarhizium marquandii* (formerly *Paecilomyces marquandii*) and *Cordyceps javanica* (formerly *Paecilomyces javanicus*) were excluded.

Every report was reviewed for patient demographics, underlying conditions and immunosuppression as predisposing factors for IFI, clinical signs and symptoms at diagnosis, site of infection and diagnostic and therapeutic procedures. If available, radiological results suggesting IFI, mycological

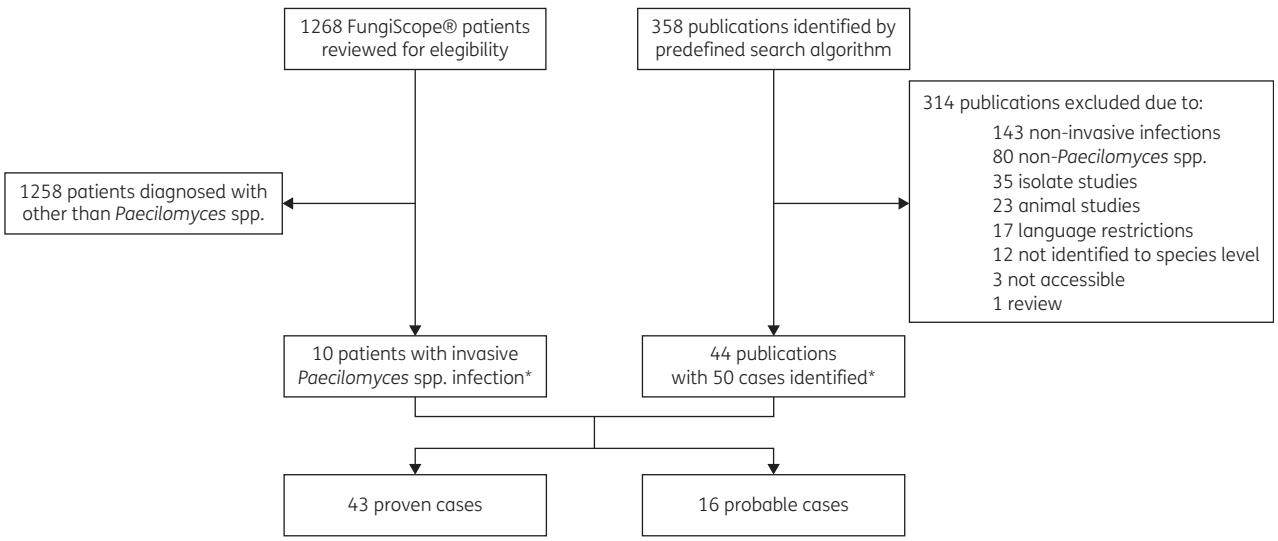

Figure 1. Enrolment and study flow chart. *One case was reported both in FungiScope® and the literature.

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 day 90 after diagnosis and mortality attributed to the infection were documented. Follow-up period was defined from day of diagnosis to last patient contact.

Proven or probable IFI were included following the revised 2019 EORTC/MSG criteria.[17] Dissemination was defined as either infection at two or more non-contiguous body sites or bloodstream infection with at least one positive blood culture. Breakthrough IFI (BT-IFI) was defined as *Paecilomyces* infection occurring during exposure to any antifungal agent.[18]

Statistical analysis was performed with the Statistical Package for the Social Sciences (SPSS) (version 25.0, IBM, USA). Patient characteristics from categorical variables were summarized employing frequencies and percentages, while median and IQR were used for continuous variables. Categorical data were compared using Fisher's exact test. A P value ≤ 0.05 was set as statistically significant.

Results

Fifty-nine cases of *Paecilomyces* infection reported in the FungiScope® registry ($n = 9$, 15.3%) and the literature ($n = 49$, 83.1%) were included in our study (Table S1, available as Supplementary data at *JAC* Online). One case was both published and registered in FungiScope®.[19]

Cases were reported from 22 countries worldwide with the highest number of cases from the United States ($n = 15$, 25.4%), five cases each (8.5%) from Australia and India, and four each (6.8%) from China and Turkey (Figure 2). Cases were diagnosed between 1967 and 2020. All infections were caused by *P. variotii*. Coinfections with other fungal pathogens were present in two cases (3.4%) (Table 1). Additional identification of bacterial pathogens was reported in eight cases (13.6%), of which two were detected at other body sites than *P. variotii* (Table S2), and *P. variotii* was considered the main causative agent in all cases.

Predisposing factors

The most frequent predisposing factor was presence of indwelling devices ($n = 29/59$, 49.2%), with 33.9% being peritoneal catheters ($n = 20/59$), and 10.2% prosthetic heart valve infections ($n = 6/59$). Haematological and oncological diseases ($n = 19/59$, 32.2%) were the second most prevalent baseline factor. Major surgery and diabetes mellitus were also frequent with 11 (18.6%) and 10 cases (16.9%), respectively. Only two patients (3.4%) lacked factors predisposing for IFI (Table 1).

Site of infection

The peritoneum was the most prevalent site of infection ($n = 20/59$, 33.3%), followed by the lungs ($n = 16/59$, 27.1%). Other frequent sites of infection were deep soft-tissue ($n = 7/59$, 11.9%), bloodstream ($n = 6/59$, 10.2%), and heart valve ($n = 6/59$, 10.2). Disseminated disease occurred in 14 patients (23.7%), adjacent organs were affected in 5 patients (8.5%) (Table 1, Table S2).

Signs and symptoms

Fever at the time of diagnosis of the IFI was frequently reported ($n = 33/59$, 55.9%). Clinical symptoms were mostly associated with the anatomic region involved, such as pain at the site of infection ($n = 35/59$, 59.3%), dyspnoea ($n = 14/59$, 23.7%), gastrointestinal symptoms ($n = 11/59$, 18.6%), and cough ($n = 10/59$, 16.9%) (Table 2, Table S3).

Diagnostics

Imaging procedures supported diagnosis in 25 cases (42.4%). Chest CT ($n = 10/59$, 16.9%) and chest radiograph ($n = 5/59$, 8.5%) were predominantly performed, followed by paranasal sinus CT and echocardiography ($n = 4/59$, 6.8%, each). In chest CT, nodular

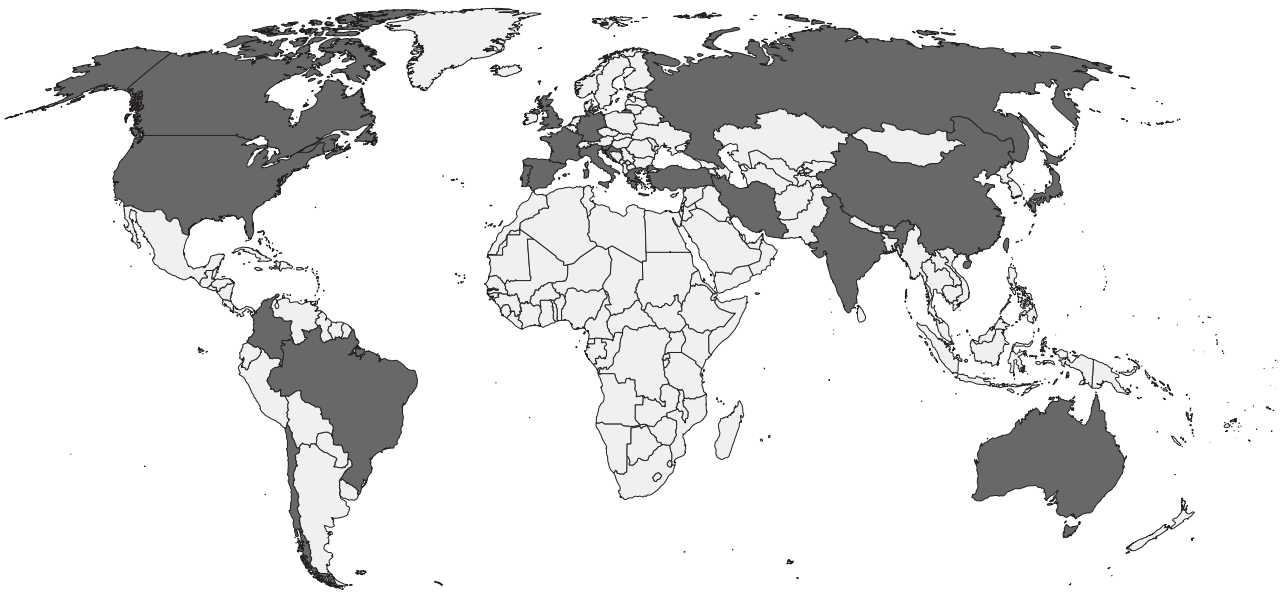

Figure 2. Countries where *Paecilomyces variotii* infections have been reported. Fifteen cases were reported from the United States, five cases each from Australia and India, four each from China and Turkey, three each from Chile and Spain, two each from Canada, France, Germany, Greece and Russia, and one each from Brazil, Colombia, Croatia, Iran, Italy, Japan, Portugal, Slovenia, Taiwan and the United Kingdom.

Table 1. Patient characteristics

Characteristic	Total (*N* = 59)		Deaths in the respective cohort (*N*, %)		Mortality (*N* = 59)
EORTC					
Proven	43	72.9%	11	25.6%	18.6%
Probable	16	27.1%	6	37.5%	10.2%
Age, years, median (IQR)	52 (25–61)				
Sex					
Female	26	44.1%	9	34.6%	15.3%
Mixed infection					
Aspergillus fumigatus and *A. niger*, lung	1	1.7%	1	100.0%	1.7%
Aspergillus spp., lung	1	1.7%	0	–	–
Underlying condition[a]					
Haematological/oncological disease[b]	19	32.2%	7	36.8%	11.9%
Acute leukaemia	5	8.5%	2	40.0%	3.4%
Breast cancer	2	3.4%	2	100.0%	3.4%
Chronic granulomatous disease	4	6.8%	0	–	–
Non-Hodgkin lymphoma	3	5.1%	1	33.3%	1.7%
Allogeneic HSCT[c]	7	11.9%	3	42.9%	5.1%
Autologous HSCT[c]	3	5.1%	2	66.7%	3.4%
GVHD	2	3.4%	2	100.0%	3.4%
Neutropenia	9	15.3%	4	44.4%	6.8%
Major surgery	11	18.6%	4	36.4%	6.8%
Trauma	1	1.7%	0	–	–
SOT[d]	3	5.1%	1	33.3%	1.7%
Diabetes mellitus	10	16.9%	4	40.0%	6.8%
Steroid treatment	5	8.5%	3	60.0%	5.1%
Chronic lung disease	4	6.8%	4	100.0%	6.8%
Chronic renal disease (peritoneal dialysis)	19	32.2%	3	15.8%	5.1%
Indwelling devices[a,e]					
Central venous catheter	2	3.4%	0	–	–
Peritoneal catheter	20	33.9%	3	15.0%	5.1%
Prosthetic valve	6	10.2%	4	66.7%	6.8%
Other baseline factors[f]	3	5.1%	1	33.3%	1.7%
No baseline factor identified	2	3.4%	0	–	–
Organ involvement[a]					
Blood	6	10.2%	3	50.0%	5.1%
Bone and joints	5	8.5%	0	–	–
CNS	3	5.1%	3	100.0%	5.1%
Deep tissue	7	11.9%	2	28.6%	3.4%
Heart	6	10.2%	4	66.7%	6.8%
Kidney	5	8.5%	2	40.0%	3.4%
Liver	2	3.4%	2	100.0%	3.4%
Lung	16	27.1%	6	37.5%	10.2%
Peritoneum	20	33.9%	3	15.0%	5.1%
Sinuses	3	5.1%	1	33.3%	1.7%
Skin	3	5.1%	1	33.3%	1.7%
Spleen	4	6.8%	3	75.0%	5.1%
Vessels	2	3.4%	2	100.0%	3.4%
Other sites[g]	3	5.1%	2	66.6%	3.4%

Continued

Table 1. *Continued*

Characteristic	Total (*N* = 59)		Deaths in the respective cohort (*N*, %)		Mortality (*N* = 59)
Dissemination					
Adjacent organs	5	8.5%	1	20.0%	1.7%
Disseminated	14	23.7%	5	35.7%	8.5%
Not disseminated	39	66.1%	9	23.1%	15.3%

ALL, acute lymphoblastic leukaemia; AML, acute myeloid leukaemia; GVHD, graft-versus-host disease; HSCT, haematopoietic stem cell transplantation; MDS, myelodysplastic syndrome; SOT, solid organ transplantation.
[a]Data may be superadditive.
[b]Each one case reported with β-thalassaemia major, chronic leukaemia, hairy cell leukaemia, myelodysplastic syndrome, multiple myeloma.
[c]One case received both autologous and allogenic transplantation.
[d]Lung (*n* = 2) and liver (*n* = 1) transplant.
[e]Each one ureteral stent and ventriculoperitoneal shunt.
[f]Other baseline factors include lung resection, multiple episodes of lung and liver abscesses of unknown aetiology, malnutrition (*n* = 1, each).
[g]Other sites include intestine, ear and pancreas (*n* = 1, each).

infiltrates and ground-glass opacifications were common findings. Definitive diagnosis was established via fungal culture in all cases except one, which had an unreported diagnostic procedure (98.3%)(Table 2, Table S4).

Antifungal susceptibility

In vitro antifungal susceptibility was evaluated for 20 clinical isolates by different methods (Table 2). In 11 isolates, the method was not reported.

Amphotericin B demonstrated generally good *in vitro* activity in susceptibility testing against *P. variotii*, however, variable results were obtained by CLSI microdilution method (Table 2). Itraconazole and posaconazole showed good *in vitro* activity by any of the methods used. The same was observed for flucytosine. High MICs were shown for caspofungin and voriconazole, particularly when evaluated with Etest and EUCAST microdilution method. No susceptibility testing was performed for isavuconazole.

Treatment and outcome

Nine patients (15.3%) had received antifungal prophylaxis prior to the diagnosis of invasive *Paecilomyces* infection, with eight patients developing BT-IFI (13.6%). One case did not fulfil the pharmacokinetic parameters classifying BT-IFI.[18] Prophylaxis was administered due to underlying haematological disease or after lung solid organ transplantation. In the majority of patients (*n* = 52/59, 88.1%), systemic antifungal therapy was administered, mainly with single (*n* = 23/52, 44.2%) or sequential monotherapy (*n* = 18/52, 34.6%). Antifungal combination therapies have been described in individual cases (*n* = 11/52, 21.2%) (Table 3) and with lower mortality rates than with monotherapy (*n* = 1/11 versus *n* = 12/41, *P* = 0.253, Tables S5 and S6).

Amphotericin B was most frequently used (*n* = 39/52, 75.0%). Mortality in this group was 28.2%. Azoles were given in 59.6% of cases (*n* = 31/52) with a 22.6% mortality rate. Echinocandins were used in five cases (9.6%) with no death reported. Flucytosine was combined with fluconazole or itraconazole in three cases (5.8%) with favourable outcome (Table 3).

The systemic administration of a specific antifungal class was not associated with a significant decrease in mortality (amphotericin B, *P* = 0.475; triazoles, *P* = 1.000; echinocandins, *P* = 0.314) (Table S6).

Median duration of systemic antifungal therapy was 35 days (IQR 18–91). Surgical interventions for IFI were performed in 15 patients (25.4%) with good treatment response reported in most (*n* = 12/15, 80.0%). Removal of vascular or intraperitoneal catheters was performed in all but one patient (*n* = 21/22, 95.5%; Table 3). In patients where removal of indwelling devices was reported the mortality rate was lower compared with patients with preserved devices (*n* = 4/25 and *n* = 2/3, respectively; *P* = 0.107; Table S6).

All-cause mortality was 28.8% (*n* = 17/59). One patient was lost to follow-up with unknown outcome. In BT-IFI, the mortality rate did not significantly differ from non-BT-IFI cases (*P* = 0.690; Table S6). In 10 cases, death was attributed to IFI (58.8%; Table 3).

No deaths were seen in patients with bone or joint infection (*n* = 0/5). Peritoneal infection also had a comparably low mortality rate of 15.0% (*n* = 3/20), while CNS and bloodstream infections/endocarditis had a remarkably high mortality (*n* = 3/3 and *n* = 7/12, respectively). Mortality in disseminated disease was higher than in cases with single organ involvement or adjacent organs (*P* = 0.161) (Table 3; Table S6).

Death occurred within 42 days after diagnosis in 13 of 17 cases (76.5%) and within 90 days in 15 cases (88.2%). Autopsy was performed on five patients (29.4%). Median duration from diagnosis to last follow-up day was 58 days (IQR 19–180) (Table 3).

Discussion

Previously considered a contaminant, *P. variotii* has been identified as the cause of an increasing number of infections in both immunocompromised and immunocompetent hosts. Here, we present the largest analysis addressing management and outcome of invasive *P. variotii* infections to date by identifying 59 cases in FungiScope® and the literature.

Table 2. Diagnostic procedures and susceptibility testing

Characteristic	*N*	Percentage of total
Signs and symptoms of infection[a]		
Bleeding	2	3.4%
Cough	10	16.9%
Dyspnoea	14	23.7%
Erythema	4	6.8%
Fever	33	55.9%
Gastrointestinal symptoms	11	18.6%
Haemoptysis	2	3.4%
Neurological signs	8	13.6%
Pain	35	59.3%
Tachypnoea	2	3.4%
Other signs and symptoms[b]	14	23.7%
Imaging procedures[a]		
CT head	1	1.7%
CT paranasal sinuses	4	6.8%
CT thorax	10	16.9%
MRI head	1	1.7%
Ultrasound heart	4	6.8%
X-ray thorax	5	8.5%
Mycological evidence[a]		
Culture	58	98.3%
Histology	5	8.5%
Microscopy	4	6.8%
Susceptibility testing		
CLSI microdilution	4	6.8%
Etest	2	3.4%
EUCAST microdilution	3	5.1%
Macrodilution method	1	1.7%
Unknown	11	16.9%
MIC (mg/L) by CLSI microdilution, median (IQR)		
Amphotericin B		1.5 (0.6-2.0)
Caspofungin		1.0 (1.0-8.0)
Fluconazole		10.0 (4.0-72.0)
Flucytosine		0.5 (0.5-0.5)
Itraconazole		0.8 (0.3-1.5)
Ketoconazole		2.0 (2.0-2.0)
Miconazole		32.0 (32.0-32.0)
Posaconazole		0.1 (0.1-0.1)
Terbinafine		1.0 (1.0-1.0)
Voriconazole		1.0 (1.0-1.0)
MIC (mg/L) by concentration gradient diffusion assay, median (IQR)		
Amphotericin B		0.02 (0.01-0.03)
Caspofungin		8.5 (1.0-16.0)
Itraconazole		0.4 (0.1-0.6)
Posaconazole		0.03 (0.03-0.03)
Voriconazole		4.8 (1.5-8.0)
MIC (mg/L) by EUCAST microdilution, median (IQR)		
Amphotericin B		0.1 (0.03-0.5)
Anidulafungin		0.001 (0.001-0.001)
Caspofungin		1.1 (0.1-2.0)
Flucytosine		0.1 (0.1-0.1)

Continued

Table 2. *Continued*

Characteristic	*N*	Percentage of total
Itraconazole		0.05 (0.03-0.1)
Posaconazole		0.03 (0.03-0.03)
Voriconazole		1.0 (0.3-8.0)

MRI, magnetic resonance imaging.
[a]Data may be superadditive.
[b]Other signs and symptoms included haematuria ($n = 3$), malaise ($n = 3$), nasal congestion ($n = 1$), otorrhoea ($n = 1$), rhinorrhoea ($n = 1$), signs of heart failure ($n = 2$), and weight loss ($n = 3$).

Symptoms of *P. variotii* infection are often non-specific.[3] A multidisciplinary approach seems indispensable to diagnose this infection in at-risk patients. Our analysis shows that imaging techniques have mainly been used to detect pulmonary infections, and to a lesser extent for detection of heart and sinus involvement. Clinical isolation by direct specimen sampling from the affected sites represents the most important diagnostic measure.[3]

There is potential for misidentification as other fungal pathogens.[1] Knowledge of phylogenetic relationships and identification to species level is crucial to allow conclusions on susceptibility and clinical outcome. Additionally, the morphology of other fungi such as *Hamigera* spp. or *Rasamsonia* spp. poses a challenge for correct identification.[5,20] Molecular diagnostic approaches facilitate definitive identification, e.g. by small subunit ribosomal sequence analysis or proteomic profiling via matrix-assisted laser desorption-ionization mass spectrometry.[1,3,5]

Notably, we identified no case from the African continent (Figure 2). The geographical distribution of *P. variotii* infections seems unlikely to be affected by limited diagnostic resources, as most cases were diagnosed by culture. A reporting bias can be suspected, as *P. variotii* was isolated from non-clinical samples in African countries.[21] However, infections caused by *Paecilomyces* mainly affect patients with severe chronic conditions who are less present in healthcare settings with limited resources.[22]

In vitro activity is difficult to correlate with clinical efficacy in *Paecilomyces* spp. infections. Clinical breakpoints have not been established and susceptibility is largely extrapolated from MIC values and breakpoints of related fungi.[3] We detected low amphotericin B MICs, as has been reported in other studies.[1] Mortality during treatment with amphotericin B was higher than with azoles. However, this is likely to be biased, as amphotericin B may have been used predominantly in critically ill patients. Itraconazole and posaconazole have good *in vitro* activity against *P. variotii* isolates. In our analysis, the mortality rate was high in patients treated with posaconazole, however, with a small sample size. Conversely, high MIC values of voriconazole suggest low clinical efficacy.[1] Nonetheless, successful treatment with voriconazole was achieved in five patients. Combination therapies yielded high survival rates although infrequently used. Thus, it is not possible to draw firm conclusions on synergistic effects. A combination of active azoles or amphotericin B with flucytosine appears reasonable considering the good *in vitro* activity of flucytosine and the favourable outcome in cases reporting a combination therapy. However, the adverse effects of flucytosine, particularly bone marrow suppression, must be taken into account in the decision-making process.

Susceptibility data are scant for newer antifungal agents such as isavuconazole and no *Paecilomyces*-associated infection treated with isavuconazole has been reported to date. Interestingly, the new orally available β-glucan synthase inhibitor ibrexafungerp was shown to be highly active against *P. variotii in vitro*.[23] It is currently being evaluated in clinical trials and may offer new treatment options in the future. Surgery and removal of indwelling devices facilitated favourable outcome in our dataset and should be considered whenever possible.

Unexpectedly, we observed *P. variotii* as a frequent cause of fungal peritonitis. IFI is a serious complication in peritoneal dialysis, causing 1%–15% of peritonitis episodes.[24] *Candida* spp. is most prevalent with approximately 75%, but mould infections, particularly *Aspergillus* spp., are occasionally reported.[25] Reported mortality rates range from 20% to 40%.[25,26] Our analysis demonstrates a comparably low mortality of 15%. As for other peritoneal dialysis-associated infections, dialysis catheters should be removed in persistent peritonitis.[27] However, catheter preservation and intraperitoneal administration of fluconazole was performed in one case with favourable outcome. The intraperitoneal administration of antifungal drugs, particularly amphotericin B and fluconazole, is sporadically reported in the treatment of peritonitis caused by filamentous fungi and may support cure. The use of intraperitoneal amphotericin B is, however, limited by the occurrence of chemical peritonitis and abdominal pain.[28]

As with most analyses of rare infections, our study has certain limitations. There is a potential selection bias in case reports and registry data. Patients receiving higher quality of care and successfully treated cases are more likely to be enrolled, implying that the overall mortality in this analysis may be lower than in an unselected population.[29] Review of the literature was complicated by frequent microbiological identification only to genus level and recent taxonomic changes of *Paecilomyces* species. Complete information for analysis was not always retrievable from the original reports and some authors could not provide missing information. Owing to various standards in mycological diagnostics and considering that most of the *P. variotii* isolates were identified based on culture with subjective observation of morphological characteristics, there may be an unknown rate of misidentification.

In conclusion, *P. variotii* is an emerging fungal pathogen representing a threat for patients with inherited or acquired immunodeficiency. Patients with indwelling catheters are at particular risk. Infections may present as primary or BT-IFI. High virulence

Table 3. Antifungal treatment and outcome

			Deaths		
Characteristic	*n*	%	*n*	Proportion of respective cohort	Proportion all cases (*n* = 59)
Prophylactic agent	9	15.3%	3	33.3%	5.1%
Amphotericin B	5	8.5%	2	40.0%	3.4%
Caspofungin	1	1.7%	1	100.0%	1.7%
Fluconazole	1	1.7%	0	–	–
Itraconazole	2	3.4%	0	–	–
Voriconazole	1	1.7%	0	–	–
Breakthrough IFI	8	13.6%	3	37.5%	5.1%
Systemic antifungal therapy[a]	52	88.1%	12	23.1%	20.3%
Amphotericin B	39	66.1%	11	28.2%	18.6%
Triazoles	31	52.5%	7	22.6%	11.9%
Fluconazole	7	11.9%	1	14.3%	1.7%
Itraconazole	15	25.4%	2	13.3%	3.4%
Posaconazole	8	13.6%	4	50.0%	6.8%
Voriconazole	6	10.2%	1	16.7%	1.7%
Echinocandins	5	8.5%	0	–	–
Anidulafungin	1	1.7%	0	–	–
Caspofungin	4	6.8%	0	–	–
Other antifungal agent	8	13.6%	1	12.5%	1.7%
Flucytosine	3	5.1%	0	–	–
Ketoconazole	5	8.5%	1	20.0%	1.7%
Treatment days, median (IQR)				35 (28-91)	
Non-systemic therapy	2	3.4%	1	50.0%	1.7%
Local amphotericin B	1	1.7%	1	100.0%	1.7%
Local fluconazole	1	1.7%	0	–	–
G-CSF	3	5.1%	1	33.3%	1.7%
Granulocyte infusion	1	1.7%	0	–	–
Treatment sequence					
Combination single	3	5.1%	0	–	–
Combination sequential	2	3.4%	0	–	–
Monotherapy + combination	6	10.2%	1	16.7%	1.7%
Monotherapy single	23	39.0%	5	21.7%	8.5%
Monotherapy sequential	18	30.5%	6	33.3%	10.2%
No treatment	5	8.5%	4	80.0%	6.8%
Combinations					
Amphotericin B plus azole	7	11.9%	1	14.3%	1.7%
Amphotericin B plus echinocandin	3	5.1%	0	–	–
Azoles plus other antifungal agent	3	5.1%	0	–	–
Antifungal surgery	15	25.4%	3	20.0%	5.1%
Removal of indwelling devices					
Catheter removal	21	35.6%	3	14.3%	5.1%
Prosthesis replacement	4	6.8%	2	50.0%	3.4%
Removal Double J stent	1	1.7%	0	–	–
Ventriculoperitoneal shunt removal	1	1.7%	1	100.0%	1.7%
Overall mortality					
Deaths			17		28.8%
Unknown			1		1.7%
Death attributed to IFI			10	58.8%	16.9%
Autopsy			5	29.4%	8.5%
Death before or on day 42			14	82.4%	23.7%

Continued

Table 3. *Continued*

Characteristic	*n*	%	Deaths		
			n	Proportion of respective cohort	Proportion all cases (*n* = 59)
Death before or on day 90			16	94.1%	27.1%
Date of death unknown			1	5.9%	1.7%
Observation time (days), median (IQR)	58 (19–180)				

G-CSF, granulocyte-colony stimulating factor; IFI, invasive fungal infection.
[a]Data may be superadditive.

and less predictable susceptibility patterns urge for prompt pathogen identification to the species level. Cultural and molecular techniques are paramount for accurate diagnosis. Treatment is challenging due to resistance to some antifungals and the lack of clinical breakpoints. The dilemma is clearly reflected by the high mortality rates. Amphotericin B, itraconazole and posaconazole show the most favourable *in vitro* susceptibility patterns and may constitute the best treatment options. This is in line with the guidance for optimal treatment of rare mould infections upcoming by the European Confederation of Medical Mycology (ECMM) Guideline programme (in press) but needs confirmation in a larger and more homogeneous cohort. Broader knowledge on emerging IFI should be acquired, and international registries such as FungiScope® provide a valuable source of comprehensive data, particularly for rare pathogens.

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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. JSG 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. I.F.R., L.H., M.H., N.K., L.L.S., J.M., J. Steinmann and M.S. contributed cases to the FungiScope® registry and revised and approved the final manuscript. 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 are available as Supplementary data at *JAC* Online.

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