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**Methods:** Unpublished cases of invasive *P. lilacinum* infection from the FungiScope® registry and all cases reported in the literature were analysed.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 improvements 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 sinusits, peritonitis, and pneumonia.\(^3,12-16\)

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 hyalohyphomyces.\(^17\) 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\(^6\) 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\(^6\) (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\(^6\) is approved by
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. 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.

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            | 3                                     | 15.8% 17.8%        |
| Proven        | 85            | 18                                    | 84.2% 21.2%        |
| Age, years, median (IQR) | 53 (31–64) |                                       |                    |
| Sex           |               |                                       |                    |
| Female        | 38            | 9                                     | 37.6% 8.9%         |
| Male          | 62            | 12                                    | 61.4% 11.9%        |
| Unknown       | 1             | –                                     | 1.0%               |
| Mixed infection |             |                                       |                    |
| Alternaria alternata, skin | 1 | –                                     | 1.0%               |
| Alternaria infectoria, skin | 1 | –                                     | 1.0%               |
| Arthographis kairae, lung | 1 | –                                     | 1.0%               |
| Aspergillus flavus + Penicillium spp., lung | 1 | –                                     | 1.0%               |
| Aspergillus niger, lung | 1 | –                                     | 1.0%               |
| Aspergillus terreus, Aspergillus flavus, Penicillium spp., Fusarium spp., lung | 1 | –                                     | 1.0%               |
| Cunninghamella bertholletiae + Aspergillus aliaceus, lung | 1 | –                                     | 1.0%               |
| Fusarium spp., skin | 1 | –                                     | 1.0%               |
| **Underlying conditions** |               |                                       |                    |
| Haematological/oncological disease | 31            | 8                                     | 30.7% 7.9%         |
| Acute leukaemia | 10            | 2                                     | 9.9% 2.0%          |
| Solid tumours | 8             | 2                                     | 7.9% 2.0%          |
| Lymphoma      | 7             | 1                                     | 6.9% 1.0%          |
| Autoimmune haemolytic anaemia | 2 | –                                     | 1.0%               |
| Chronic granulomatous disease | 2 | –                                     | 2.0%               |
| Hypogammaglobulinaemia | 1 | –                                     | 1.0%               |
| Immune thrombocytopenic purpura | 1 | –                                     | 1.0%               |
| HCT           |               |                                       |                    |
| Allogenic     | 3             | 1                                     | 3.0% 1.0%          |
| Autologous    | 3             | –                                     | 3.0%               |
| GVHD          | 3             | 2                                     | 3.0% 2.0%          |
| Solid organ transplant | 26 | 4                                     | 25.7% 4.0%        |
| Heart         | 3             | 1                                     | 3.0% 1.0%          |
| Kidney        | 10            | 2                                     | 9.9% 2.0%          |
| Kidney + liver | 2             | –                                     | 2.0%               |
| Liver         | 2             | 1                                     | 2.0% 1.0%          |
| Lung          | 9             | 2                                     | 8.9% 2.0%          |
| Chronic lung disease | 9 | 3                                     | 8.9% 3.0%        |
| Chronic renal disease | 10 | 2                                     | 9.9% 2.0%        |
| Diabetes mellitus | 19 | 4                                     | 18.8% 4.0%     |
| HIV           | 4             | 3                                     | 4.0% 3.0%          |
| Dialysis      |               |                                       |                    |
| Haemodialysis | 3             | –                                     | 3.0%               |
| Peritoneal dialysis | 3 | –                                     | 3.0%               |
| Long-term immunosuppression | 7 | –                                     | 6.9%               |
| Neutropenia   | 14            | 4                                     | 13.9% 4.0%        |
| Major surgery | 6             | 1                                     | 5.9% 1.0%          |
| Steroid treatment | 27 | 6                                     | 26.7% 5.9%     |
| Trauma        | 5             | –                                     | 5.0%               |
| No baseline factor | 11            | –                                     | 10.9%             |
| Indwelling devices |            |                                       |                    |

Continued
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)].

**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                 |
| Blood | 18 | 17.8% | 6 | 33.3% | 5.9% |
| Bone and joints | 6 | 5.9% | 1 | 16.7% | 1.0% |
| Deep tissue | 24 | 23.8% | 3 | 12.5% | 3.0% |
| 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.

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).

Including five non-specified cases, three cases with acute myeloid leukaemia and two cases with biphenotypic leukaemia.

Including two cases of osteosarcoma and one case each with breast cancer, neuroblastoma, pancreatic cancer, retinoblastoma, rhabdomyosarcoma, testicular cancer.

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.

Other organ involvements include eye (n = 2), kidney (n = 2), and vessels (n = 1).

**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 para-nasal 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 cavitory 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  | 7.8% |
| 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.

aOther 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 fulfill 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 ≤ 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. 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).

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
contribute to the emergence of mycoses other than Aspergillus and Mucorales. 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. 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. 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. 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. Both typical phialides with ellipsoidal or fusiform conidia or atypical, elongated and Acremonium-like conidiophores with cylindrical conidia are described. Detection of adventitious sporulation may facilitate an initial presumptive identification through careful histological examination. Molecular diagnostic approaches, such as small subunit ribosomal sequence analysis or proteomic profiling via MALDI-TOF/MS, may facilitate more definitive identification. 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. 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 (0.05–0.5)   |
| 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                            | 4.0 (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.
### Table 4. Antifungal treatment and outcome

| Characteristic                                | n   | %   | Deaths (n) | Proportion of deaths (%) |
|-----------------------------------------------|-----|-----|------------|--------------------------|
|                                               |     |     |            | 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 + Azaoles                      | 11  | 10.9% | 4          | 36.4%                    | 4.0%                       |
| Amphotericin B + Other                        | 4   | 4.0%  | 2          | 50.0%                    | 2.0%                       |
| Azaoles + Echinocandins                        | 8   | 7.9%  | –          | –                        | –                           |
| Azaoles + 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
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 FungiScopeV provide a valuable method of pooling broader knowledge on rare and emerging pathogens.

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Table 4. Continued

| Characteristic | n  | %   | Deaths (n) in the respective cohort | Proportion of deaths (%) overall cases (n = 101) |
|---------------|----|-----|-----------------------------------|---------------------------------------------|
| Autopsy       |    |     |                                   |                                             |
| Yes           | 2  | 2.0%| 2 of 2 (100%)                     |                                             |
| No            | 15 | 14.9%| 15 of 15 (100%)                   |                                             |
| Unknown       | 5  | 5.0%| 5 of 5 (100%)                     |                                             |
| Death before or on day 42 | 9  | 8.9%| 9 of 9 (100%)                     |                                             |
| Death before or on day 90 | 10 | 9.9%| 10 of 10 (100%)                   |                                             |
| Death after day 90 | 5  | 5.0%| 5 of 5 (100%)                     |                                             |
| Date of death unknown | 7  | 6.9%| 7 of 7 (100%)                     |                                             |
| Observation time (days), median (IQR) | 120 | (42–366) | 120 of 120 (100%)               | (42–366)                                    |

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

Data may be superadditive.

Transparency declarations
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Author contributions
R.S. conceived the study idea, enrolled cases, performed literature research, analysed and interpreted data, and 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.

References
1. Hoenigl M, Salmanton-Garcia J, Walsh TJ et al. Global guideline for the diagnosis and management of rare mold infections: an initiative of the European Confederation of Medical Mycology in cooperation with the International Society for Human and Animal Mycology and American Society for Microbiology. Lancet Infect Dis 2021; in press. 10.1016/S1473-3099(20)30784-2.
2. Luangso-Ard J, Houbraken J, van Doorn T. JAC Emerging Fungal Infection Registry. Mycoses 2017; 60: 508–16.
3. Donnelly JP, Chen SC, Kauffman CA et al. Revision and update of the consensus definitions of invasive fungal disease from the European Organization for Research and Treatment of Cancer and the Mycoses Study Group Education and Research Consortium. Clin Infect Dis 2020; 71: 1367–76.
4. Cornely OA, Hoenigl M, Lass-Flörl C et al. Defining breakthrough invasive fungal infection-Position paper of the mycoses study group education and research consortium and the European Confederation of Medical Mycology. Mycoses 2019; 62: 716–9.

10.1093/jac/dkaa039/6143532