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Needles in a haystack: Extremely rare invasive fungal infections reported in FungiScope®—Global Registry for Emerging Fungal Infections

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Objectives: Emerging invasive fungal infections (IFI) have become a notable challenge. Apart from the more frequently described fusariosis, lomentosporiosis, mucormycosis, scedosporiosis, and certain dematiaceae or yeasts, little is known about extremely rare IFI.
Methods: Extremely rare IFI collected in the FungiScope® registry were grouped as *Dematiaceae, Hypocreales, Saccharomycetales, Eurotiales, Dermatomycetes, Agaricales*, and *Mucorales*.
Results: Between 2003 and June 2019, 186 extremely rare IFI were documented in FungiScope®. *Dematiaceae* (35.5%), *Hypocreales* (23.1%), *Mucorales* (11.8%), and *Saccharomycetales* (11.3%) caused most IFI. Most patients had an underlying malignancy (38.7%) with acute leukemia accounting for 50% of cancers. Dissemination was observed in 26.9% of the patients. Complete or partial clinical response rate was 68.3%, being highest in *Eurotiales* (82.4%) and in *Agaricales* (80.0%). Overall mortality rate was 29.3%, ranging from 11.8% in *Eurotiales* to 50.0% in *Mucorales*.
Conclusions: Physicians are confronted with a complex variety of fungal pathogens, for which treatment recommendations are lacking and successful outcome might be incidental. Through an international consortium of physicians and scientists, these cases of extremely rare IFI can be collected to further investigate their epidemiology and eventually identify effective treatment regimens.

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Introduction

Managing invasive fungal infections (IFI) remain a major challenge, particularly in cancer, solid organ transplanted (SOT), and long-term immunosuppressed patients, but also in trauma or diabetes.[1–5] *Aspergillus* spp. *Candida* spp., *Cryptococcus* spp., *Pneumocystis* spp. and endemic fungi cause the vast majority of IFI.[1,5,6] Emerging fungi include Mucorales, *Fusarium* spp., *Lomentospora* spp., *Scedosporium* spp., dematiaceae or yeasts (e.g. *Geotrichum* spp., *Rhodotorula* spp., *Saprochaete* spp. or *Trichosporon* spp.), with IFI incidences ranging from 0.2 to 0.4 per 100,000 inpatients.[5] Guidelines provide recommendations on the clinical management of IFI.[7–10] However, IFI caused by extremely rare fungi lack a detailed characterization.

Since 2003, the FungiScope® registry collects emerging IFI cases retrospectively.[11] Periodically, subsets are published providing an overview on IFI epidemiology and clinical features, namely dematiaceae,[12] *Fusarium* spp.,[13,14] *Geotrichum* spp. and *Saprochaete* spp.,[15] Mucorales,[16–18] *Rasamsonia* spp.[19] or *Scedosporium* spp. and *Lomentospora* spp.[20–23] However, most rare IFI remain unshared with the scientific community.

Herewith we summarize extremely rare IFI documented in the FungiScope® registry, emphasizing the spectrum of pathogens in patients at risk for such infections.

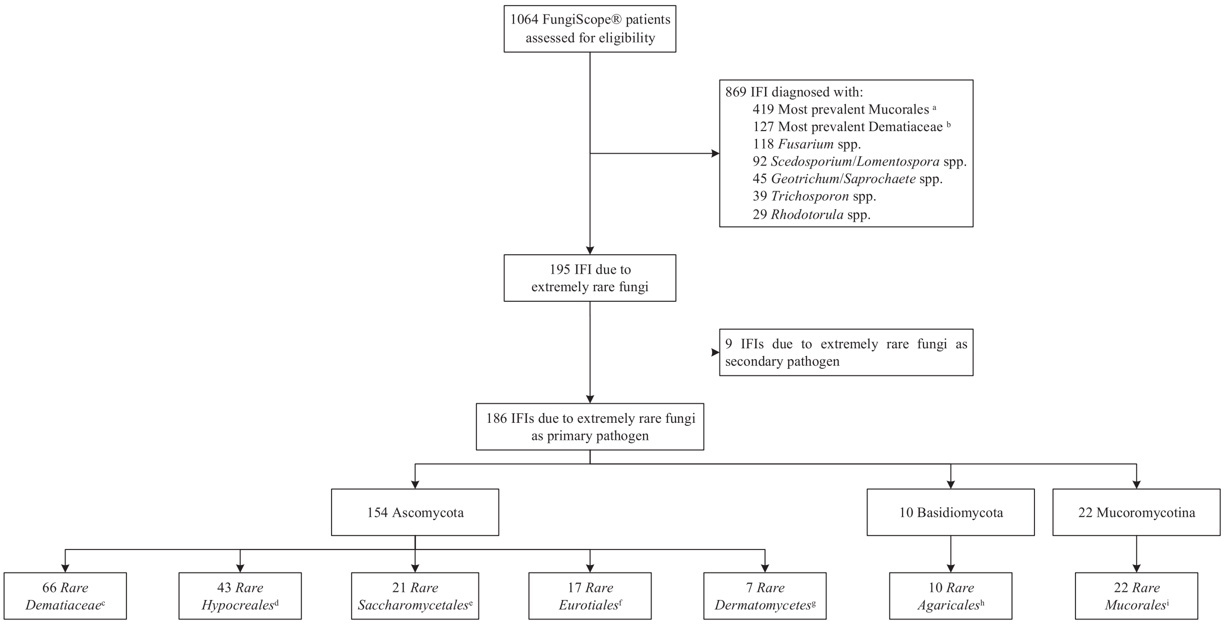

Fig. 1. Enrolment and study flow-chart of extremely rare invasive infections reported in FungiScope®. [a] Most prevalent Mucorales species include *Absidia* spp., *Lichtheimia* spp., *Mucor* spp., *Rhizomucor* spp., and *Rhizopus* spp. [b] Most prevalent dematiaceae species include *Alternaria* spp., *Cladophialophora* spp., *Cladosporium* spp., *Curvularia* spp., *Exophiala* spp., *Exserohilum* spp., *Fonsecaea* spp., *Ramichloridium* spp., and *Rhinocladiella* spp. [c] Therty-two *Rare Dematiaceae* patients have been previously described in other publications stated in Table S1. [d] Four *Rare Hypocreales* patients have been previously described in other publications stated in Table S1. [e] Four *Rare Saccharomycetales* patients have been previously described in other publications stated in Table S1. [f] Eight *Rare Eurotiales* patients have been previously described in other publications stated in Table S1. [g] Three *Rare Dermatomycetes* patients have been previously described in other publications stated in Table S1. [h] One *Rare Agaricales* patients have been previously described in other publications stated in Table S1. [i] Seventeen *Rare Mucorales* patients have been previously described in other publications stated in Table S1.

Methods

Setting

To date, 1066 probable or proven IFI have been documented in the ongoing FungiScope® registry (www.ClinicalTrials.gov, NCT 01731353), approved by the local Ethics Committee of the University of Cologne (Study ID: 05-102).[11] Anonymized data include sociodemographics, causative fungi, risk factors, diagnostics, treatment and outcome were collected via an online questionnaire (www.clinicalsurveys.net).

IFI caused by fungi that were unreported or scarcely reported in the literature and for which no data on incidence is available to our knowledge were selected for this overview. This excluded (I) some dematiaceae[8,12,24] (*Alternaria* spp., *Cladophialophora* spp., *Cladosporium* spp., *Curvularia* spp., *Exophiala* spp., *Exserohilum* spp., *Fonsecaea* spp., *Ramichloridium* spp. and *Rhinocladiella* spp.), (II) *Fusarium* spp.,[10,13,14] (III) Mucorales[5,9,16–18] (*Absidia* spp., *Lichtheimia* spp., *Mucor* spp., *Rhizomucor* spp., and *Rhizopus* spp.), (IV) *Lomentospora* spp. and *Scedosporium* spp.[10] and (V) certain yeasts[7] (*Geotrichum* spp.,[15,25] *Rhodotorula* spp.[15], *Rhodotorula Saprochaete* spp.,[26] and *Trichosporon* spp.[25]).

Eligible cases were assorted into three groups based on their taxonomy: (I) Ascomycota, with the subgroups *Dematiaceae, Hypocreales, Saccharomycetales, Eurotiales* and *Dermatomycetes*, (II) Basidiomycota, with the subgroup *Agaricales*, and (III) Mucoromycotina, with the subgroup *Mucorales*. (Fig. 1, Table 1, Table S1).

Infections were categorized as *Proven* or *Probable* according to the European Organization for Research and Treatment of Cancer/Mycoses Study Group (EORTC/MSG) definitions.[27] IFI with microbiological diagnosis based on a positive polymerase chain reaction (PCR) only, that otherwise fulfilled the EORTC/MSG criteria were categorized as *Probable (PCR)*. Patients with reported imaging procedures and mycological evidences from non-sterile sites suggesting IFI, but without an adequate host factor defined by the current EORTC/MSG criteria[27] were classified as *Other*, permitting the characterization based on their clinical relevance.

Dissemination, was defined as positive blood cultures and/or at least two non-contiguous body sites were affected. Breakthrough IFI (BT-IFI) was defined when the onset of a new IFI occurred during exposure to an antifungal.[28] Observation time was set as the time between the diagnosis day and the day of last contact with the patient. Response to treatment was outlined following pre-established criteria.[29] Complete and partial response were assessed as favorable, while stable disease and disease progression were considered to be an unfavorable clinical response (Table S2). Unless otherwise specified, deaths are presented by all-cause mortality rates.

Statistical analysis

Categorical data were displayed by frequencies and percentages, while continuous variables by median and interquartile range (IQR). Mortality was analyzed using Kaplan-Meier survival plots. Comparative analyses were not performed considering the heterogeneity of causative pathogens. SPSS v25.0 was employed for statistical analyses (SPSS, IBM Corp., Chicago, IL, United States).

Results

Between January 2003 and June 2019, 186 rare IFI, diagnosed between 1997 and 2019, were documented in FungiScope®. Most cases were from India ($n = 30$, 16.1%), the United States ($n = 24$, 12.9%), Spain ($n = 21$, 11.3%), and Germany ($n = 19$, 10.2%) (Fig. 2, Table S3). IFI were caused by (I) *Ascomycota* ($n = 154$, 82.8%) with the subgroups *Dematiaceae* ($n = 66$, 35.5%), *Hypocreales* ($n = 43$, 23.1%), *Saccharomycetales* ($n = 21$, 11.3%), *Eurotiales* ($n = 17$, 9.1%), and *Dermatomycetes* ($n = 7$, 3.8%), (II) *Agaricales* ($n = 10$, 5.4%), and (III) *Mucorales* ($n = 22$, 11.8%). Most infections were *proven* ($n = 147$, 79.0%), after a positive culture from a sterile site, mainly blood,

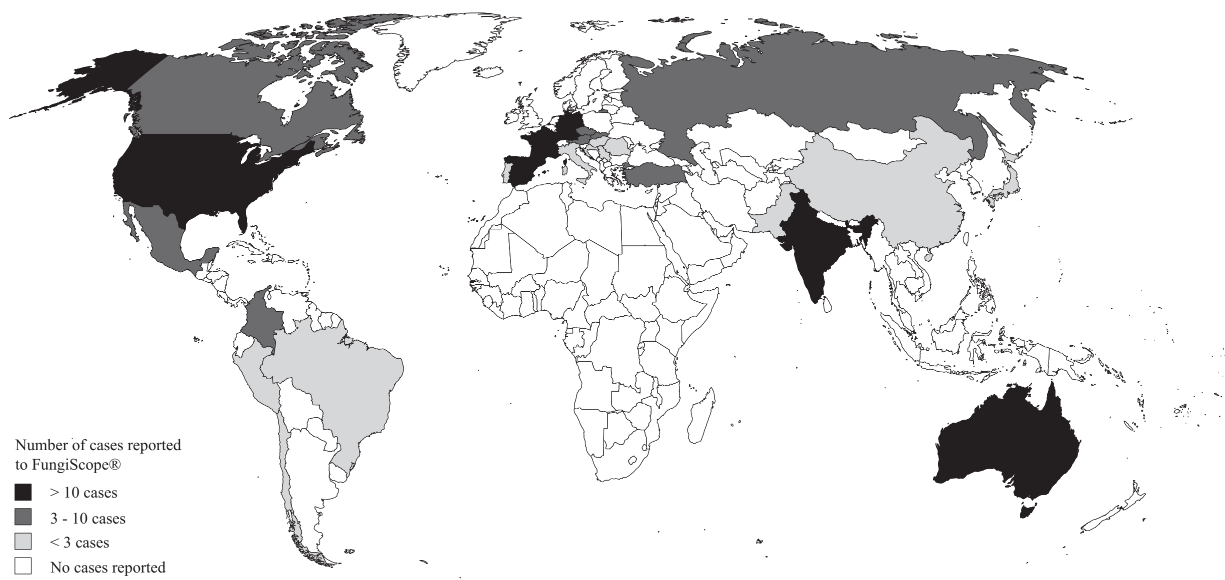

Fig. 2. Geographical distribution of extremely rare invasive infections reported in FungiScope®. India ($n = 30$), United States ($n = 24$), Spain ($n = 21$), Germany ($n = 19$), France ($n = 12$), Australia ($n = 11$), Russia, Canada ($n = 9$, each), Austria, Czech Republic ($n = 6$, each), Colombia, Mexico, Slovakia, and Turkey ($n = 5$, each), Martinique – French West Indies ($n = 4$), China, Italy, and Romania ($n = 2$, each), and Brazil, Chile, Croatia, Hungary, Japan, Pakistan, Peru, Portugal, and Serbia ($n = 1$, each).

fluids, or organ tissue. post-mortem diagnosis was done in five patients (2.7%) (Table 1, Table S1). The male/female ratio was 1.7:1. The vast majority were adults ($n = 165$, 88.7%; median age: 51 [IQR: 35–64] years). Overall, malignancies ($n = 72$, 38.7%), corticosteroid administration ($n = 56$, 30.1%) and SOT ($n = 27$, 14.5%) were the most prevalent risk factors. Chronic diseases ($n = 57$, 30.6%), mostly renal ($n = 29$, 50.9%), and diabetes ($n = 38$, 20.4%), were also frequent (Table 2, Table S1). The most commonly affected sites were lungs ($n = 61$, 32.8%), soft tissue ($n = 49$, 26.3%), blood ($n = 31$, 16.7%), paranasal sinuses ($n = 25$, 13.4%), and skin ($n = 20$, 11.8%). Fifty patients (26.9%) showed dissemination (Table 3, Table S1). The majority of IFI ($n = 161$, 86.6%) were treated with systemic antifungal drugs, 80 (43.0%) patients had surgery in addition. Twelve patients (6.5%) underwent surgery only. Overall mortality was 29.6% (55/186 deaths) (Table 4, Table S1, Fig. 3).

Ascomycota

Dematiaceae

Sixty-six phaeohyphomycoses (35.5%) were diagnosed, caused by *Medicopsis* spp., *Microascus* spp., *Phaeoacremonium* spp., *Scopulariopsis* spp., or *Verruconis* spp. ($n = 5$, 7.6% each) (Table 1). The male/female ratio was 1.6:1. Chronic diseases ($n = 26$, 39.4%), SOT ($n = 18$, 27.3%), malignancy ($n = 13$, 19.7%) and trauma ($n = 10$, 15.2%) were the most prevalent risk factors. For 23 patients (34.8%) corticosteroid use before IFI was reported. Diabetes was common ($n = 17$, 25.8%). For eight patients (12.1%) no risk factor was reported. Infections affected soft tissue ($n = 25$, 37.9%), skin ($n = 17$, 25.8%), lung ($n = 14$, 21.2%), paranasal sinuses ($n = 10$, 15.2%), and CNS ($n = 9$, 13.6%). Dissemination occurred in 10 patients (15.2%), two (20.0%) with fungemia (Table 2, Table S1). Eight patients (12.1%) had BT-IFI after a median of 63 (IQR 34–155) days of prophylaxis, four while receiving voriconazole. Fifty-six patients (84.8%) received antifungals for a median of 84 (IQR 42–210) days, mainly single or sequential monotherapies ($n = 41$, 62.1%). Most were treated with triazoles ($n = 52$, 92.3%, mainly voriconazole [$n = 28$, 53.8%] or itraconazole [$n = 15$, 28.8%]), and 15 patients (26.8%) received a combination with at least one other antifungal, mainly amphotericin B ($n = 8$, 44.4%). Thirty-four cases (51.5%) underwent surgery (Table 3, Table S1). At day 42, 26 patients (39.4%) had favorable response and additional 14 (21.2%) were already discharged alive, one under progression refusing further treatment. Overall favorable response was reported for 45 patients (68.2%), stable disease for 8 patients (12.1%). Mortality at day 42 was 7.6% (5/66 deaths) and 21.2% ($n = 14$) overall (Table 4, Table S1, Fig. 3).

Hypocreales

Forty-three patients (23.1%) had IFI caused mainly due to *Purpureocillium lilacinum* ($n = 17$, 39.5%) or *Acremonium* spp. ($n = 12$, 27.9%) (Table 1). The male/female ratio was 1.4:1. Malignancies ($n = 20$, 46.5%, eight solid tumors [40.0%]) and foreign bodies ($n = 10$, 23.3%, mostly central vascular catheter [CVC] [$n = 8$, 80.0%]), were the main predisposing factors. Neutropenia ($n = 11$, 25.6%), corticosteroid administration ($n = 10$, 23.3%) and intensive care unit (ICU) stay ($n = 7$, 16.3%) were additional factors. Ten patients (23.3%) had diabetes. Four patients (9.3%) did not report a risk factor. Lung ($n = 16$, 37.2%), blood ($n = 11$, 25.6%), eyes ($n = 8$, 18.6%) and paranasal sinuses ($n = 7$, 16.3%) were the most common infection sites. Fourteen patients (32.6%) had dissemination, 11 (78.6%) with fungemia (Table 2, Table S1). Eleven patients (25.6%) had BT-IFI after a median of 41 (IQR: 30–76) days of prophylaxis, six with fluconazole. Thirty-three patients (76.7%) received antifungals for a median of 58 (IQR: 34–146) days, with triazoles ($n = 29$, 87.9%), mainly voriconazole ($n = 24$, 82.8% of triazoles), or amphotericin B ($n = 21$, 63.6%), mainly deoxycholate or liposomal ($n = 8$, 38.1%, each). Twelve patients (36.3%) received triazoles combined with amphotericin B. Fifteen patients (34.9%) had surgery (Table 3, Table S1). Favorable response at day 42 was observed in 12 (27.9%), and additional 11 patients (25.6%) were discharged alive by that time, one with progressive IFI. The overall favorable response was 67.4% ($n = 29$). Mortality at day 42 was 27.9% (12/43 deaths), and overall 30.2% (13/43 deaths) (Table 4, Table S1, Fig. 3).

Saccharomycetales

Twenty-one (11.3%) IFI were caused mainly due to *Saccharomyces cerevisiae* ($n = 12$, 57.1%) (Table 1), with a male/female ratio of 4.25:1. Malignancies ($n = 11$, 52.4%, six solid tumors [54.5%]), chronic diseases ($n = 11$, 52.4%) and placement of foreign bodies ($n = 11$, 52.4%; [CVC $n = 10$, 90.9%]), were the most prevalent risk factors. Five patients (23.8%) were treated in the ICU. Blood ($n = 16$,

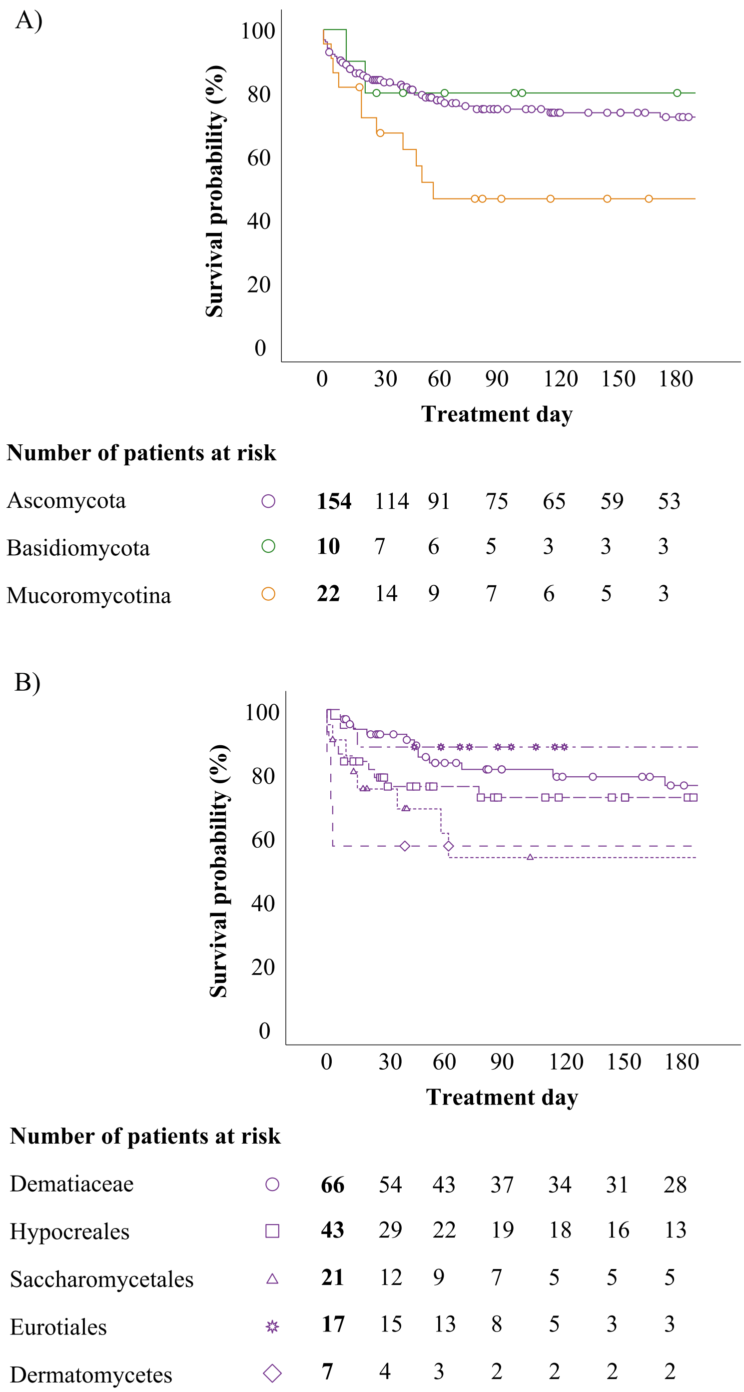

Fig. 3. Probability of survival with extremely rare invasive infections reported in FungiScope®. A) Rare Ascomycota ($n = 154$), Basidiomycota ($n = 10$) and Mucoromycotina ($n = 22$). Patients were censored on their last known survival status day, represented by open circles. B) *Rare Dematiaceae* ($n = 66$), *Hypocreales* ($n = 43$), *Saccharomycetales* ($n = 21$), *Eurotiales* ($n = 17$), and *Dermatomycetes* ($n = 7$). Patients were censored on their last known survival status day, represented by open circles (*Rare Dematiaceae*), open squares (*Rare Hypocreales*), open triangles (Rare Saccharomycetales), open stars (*Rare Eurotiales*) and open diamonds (*Rare Dermatomycetes*).

76.2%) and entry site of foreign body ($n = 7$, 33.3%) were the most frequent infection sites (Table 2, Table S1). Three patients (14.3%) had BT-IFI after a median of 13 (IQR: 11–168) days of prophylaxis. Seventeen patients (81.0%) received antifungals, all single or sequential monotherapy for a median of 24 (IQR: 16–39) days. Triazoles were administered in 13 patients (76.5%), mainly fluconazole ($n = 9$, 69.2%), and echinocandins in eight (47.1%). Four patients (19.0%) underwent surgery, two (11.8%) in addition to antifungals. CVC was removed in seven patients (Table 3, Table S1). One patient (4.8%) had complete response and additional eight (38.1%) were discharged alive by day 42. Overall, 15 patients (71.4%) had favorable response. Mortality at day 42 was 33.3% (7/21 deaths) and overall 42.9% (8/21 deaths) (Table 4, Table S1, Fig. 3).

Eurotiales

Seventeen (9.1%) IFI, mainly due to *Paecilomyces* spp. ($n = 6$) and *Penicillium* spp. ($n = 5$) (Table 1) were diagnosed. The male/female ratio was 1.4:1. Corticosteroids were administered in 58.8% of them ($n = 10$). Half of the patients ($n = 9$) had malignancies (eight acute leukemia). Chronic diseases, neutropenia ($n = 7$, each) and

Table 1
Taxonomic overview and frequency of rare fungal pathogens.

Ascomycota	**154 (82.8)**
Rare Dematiaceae	**66 (35.5)**
Calosphaeriales	
Pleurostomataceae	
Pleurostoma ootheca	1 (1.5)
Pleurostoma richardsiae	1 (1.5)
Chaetothyriales	
Herpotrichiellaceae	
Phialophora verrucosa	1 (1.5)
Phialophora spp.	1 (1.5)
Dothideales	
Saccotheciaceae	
Aureobasidium proteae	1 (1.5)
Aureobasidium pullulans	3 (4.5)
Glomerellales	
Glomerellaceae	
Colletotrichum gloeosporioides	1 (1.5)
Incertae sedis	
Incertae sedis	
Acrophialophora fusispora	2 (3.0)
Nigrospora oryzae	2 (3.0)
Nigrospora spp.	1 (1.5)
Phialemoniopsis ocularis	1 (1.5)
Scytalidium thermophilum	1 (1.5)
Scytalidium spp.	2 (3.0)
Veronaea botryosa	1 (1.5)
Verruconis gallopava	5 (7.6)
Microascales	
Microascaceae	
Microascus brevicaulis	2 (3.0)
Microascus cirrosus	2 (3.0)
Microascus gracilis	1 (1.5)
Scopulariopsis spp.	4 (6.0)
Ophiostomatales	
Ophiostomataceae	
Pesotum piceae	1 (1.5)
Patellariales	
Patellariaceae	
Rhytidhysteron rufulum	2 (3.0)
Pleosporales	
Biatriosporaceae	
Nigrograna mackinnonii	1 (1.5)
Didymellaceae	
Didymella glomerata	1 (1.5)
Incertae sedis	
Medicopsis romeroi	5 (0.76)
Periconia tirupatiensis	1 (1.5)
Montagnulaceae	
Microsphaeropsis arundinis	2 (3.0)
Paraconiothyrium cyclothyrioides	1 (1.5)
Pleosporaceae	
Bipolaris spp.	3 (4.5)
Roussoellaceae	
Roussoella percutanea	1 (1.5)
Trematosphaeriaceae	
Trematosphaeria grisea	2 (3.0)
Sordariales	
Chaetomiaceae	
Amesia atrobrunnea	1 (1.5)
Chaetomium globosum	4 (6.0)
Thielavia subthermophila	1 (1.5)
Sordariaceae	
Chrysonilia spp.	1 (1.5)
Neurospora spp.	1 (1.5)
Togniniales	
Togniniaceae	
Phaeoacremonium parasiticum	1 (1.5)
Phaeoacremonium sphinctrophorum	1 (1.5)
Phaeoacremonium spp.	3 (4.5)
Rare Hypocreales	**43 (23.1)**
Hypocreales	
Clavicipitaceae	
Metarhizium robertsii	1 (2.3)

(*continued on next page*)

Table 1 (*continued*)

Cordycipitaceae	
Beauveria bassiana	2 (4.7)
Parengyodontium album	3 (7.0)
Hypocreaceae	
Trichoderma atroviride	1 (2.3)
Trichoderma harzianum	1 (2.3)
Trichoderma longibrachiatum	4 (9.3)
Trichoderma spp.	2 (4.7)
Incertae sedis	
Acremonium spp.	12 (27.9)
Ophiocordycipitaceae	
Purpureocillium lilacinum	17 (39.5)
Rare Saccharomycetales	**21 (11.3)**
Saccharomycetales	
Incertae sedis	
Kodamaea ohmeri	7 (33.3)
Saccharomycetaceae	
Saccharomyces cerevisiae	12 (57.1)
Wickerhamomycetaceae	
Wickerhamomyces anomalus	2 (9.5)
Rare Eurotiales	**17 (9.1)**
Eurotiales	
Aspergillaceae	
Paecilomyces variotii	5 (29.4)
Paecilomyces spp.	1 (5.9)
Penicillium chrysogenum	2 (11.8)
Penicillium solitum	1 (5.9)
Penicillium spp.	2 (11.8)
Rasamsonia argillacea	2 (11.8)
Talaromyces amestolkiae	1 (5.9)
Talaromyces stollii	1 (5.9)
Thermoascus crustaceus	2 (11.8)
Rare Dermatomycetes	**7 (3.8)**
Botryosphaeriales	
Botryosphaeriaceae	
Neofusicoccum mangiferae	1 (14.3)
Neoscytalidium dimidiatum	1 (14.3)
Neoscytalidium spp.	1 (14.3)
Incertae sedis	
Eremomycetaceae	
Arthrographis kalrae	1 (14.3)
Onygenales	
Onygenaceae	
Chrysosporium spp.	1 (14.3)
Arthrodermataceae	
Trichophyton mentagrophytes	1 (14.3)
Trichophyton rubrum	1 (14.3)
Basidiomycota	**10 (5.4)**
Rare Agaricales	**10 (5.4)**
Agaricales	
Psathyrellaceae	
Hormographiella aspergillata	5 (50.0)
Hormographiella spp.	1 (10.0)
Schizophyllaceae	
Schizophyllum commune	4 (40.0)
Mucoromycotina	**22 (11.8)**
Rare Mucorales	**22 (11.8)**
Mucorales	
Cunninghamellaceae	
Cunninghamella bertholletiae	7 (31.8)
Cunninghamella blakesleeana	1 (4.5)
Cunninghamella spp.	2 (9.1)
Saksenaeaceae	
Apophysomyces elegans	1 (4.5)
Apophysomyces variabilis	6 (27.3)
Saksenaea erythrospora	1 (4.5)
Saksenaea vasiformis	3 (13.6)
Syncephalastraceae	
Syncephalastrum racemosum	1 (4.5)

Data are n (%). *Incertae sedis* is a Latin term employed in taxonomy to describe *uncertain placement* of a certain taxon within the classification. In this table *Incertae sedis* has been used to express the uncertainty in terms of order and family of certain pathogens described.

Table 2
Patient characteristics by group of rare fungal pathogen.

	Ascomycota					Basidiomycota	Mucoromycotina
	Rare Dematiaceae (n = 66)	*Rare Hypocreales (n = 43)*	*Rare Saccharomycetales (n = 21)*	*Rare Eurotiales (n = 17)*	*Rare Dermatomycetes (n = 7)*	*Rare Agaricales (n = 10)*	*Rare Mucorales (n = 22)*
Sex *(Male)*	41 (62.1)	25 (58.1)	17 (81.0)	10 (58.8)	6 (85.7)	3 (30.0)	14 (63.6)
Year of infection, *[Range]*	[2000–2018]	[2003–2019]	[2003–2019]	[2006–2017]	[2006–2018]	[2007–2017]	[1997–2018]
Age at diagnosis, *median (IQR) [Range]*	51 (41 – 63) [14–92]	44 (18 – 63) [2–83]	64 (55 – 78) [0–84]	51 (21 – 61) [5–83]	45 (38 – 61) [17–71]	50 (38 – 53) [4–59]	46 (27 – 71) [10–80]
Underlying condition							
Hematological/Oncological malignancy	13 (19.7)	20 (46.5)	11 (52.4)	9 (52.9)	1 (14.3)	6 (60.0)	12 (54.5)
Acute leukemia	7 (53.8)	7 (35.0)	3 (27.2)	8 (88.9)	1 (100.0)	6 (100.0)	4 (33.3)
Chronic leukemia		1 (5.0)					1 (8.3)
Lymphom	2 (15.4)	1 (5.0)	1 (9.0)	1 (11.1)			1 (8.3)
Solid tumor[a]	2 (15.4)	8 (40.0)	6 (54.5)				2 (16.7)
Other[b]		1 (5.0)					1 (8.3)
Aplastic anemia		2 (10.0)					1 (8.3)
Myelodysplastic Syndrome	2 (15.4)		1 (9.0)				2 (16.7)
Treatment for malignancy							
Chemotherapy	8 (61.5)	15 (75.0)	6 (54.5)	8 (88.9)	1 (100.0)	6 (100.0)	9 (75.0)
HSCT – Allogeneic[c]	6 (46.2)	4 (20.0)	3 (27.2)	3 (33.3)	1 (100.0)	1 (16.7)	3 (25.0)
HSCT – Autologous		2 (10.0)		1 (11.1)			
Corticosteroids	23 (34.8)	10 (23.3)	1 (4.8)	10 (58.8)	2 (28.6)	4 (40.0)	6 (27.3)
Neutropenia	7 (10.6)	11 (25.6)	3 (14.3)	7 (41.2)	1 (14.3)	3 (30.0)	6 (27.3)
SOT[d]	18 (27.3)	5 (11.9)	1 (4.8)	2 (11.8)	1 (14.3)		
Trauma	10 (15.2)						5 (22.7)
Chronic disease	26 (39.4)	7 (16.3)	11 (52.4)	7 (41.2)	3 (42.9)	1 (10.0)	2 (9.1)
Chronic cardiovascular disease	3 (11.5)	1 (14.3)	4 (36.4)	2 (28.6)			
Chronic digestive disease[e]	3 (11.5)						
Chronic granulomatous disease							1 (50.0)
Chronic liver disease	3 (11.5)	1 (14.3)	3 (27.3)		1 (33.3)		
Chronic pulmonary disease	5 (19.2)	1 (14.3)	2 (18.2)	2 (28.6)	1 (33.3)	1 (100.0)	
Chronic renal disease	14 (53.8)	4 (57.1)	4 (36.4)	4 (57.1)	2 (66.7)		1 (50.0)
Diabetes mellitus	17 (25.8)	10 (23.3)	2 (9.5)	1 (5.9)	3 (42.9)	2 (20.0)	3 (13.6)
Treatment in ICU[f]	3 (4.5)	7 (16.3)	5 (23.8)	2 (11.8)	1 (14.3)	3 (30.0)	1 (4.5)
Medical	1 (33.3)	2 (28.6)	2 (40.0)	1 (50.0)	1 (100.0)	2 (66.7)	1 (100.0)
Neurosurgical	1 (33.3)	2 (28.6)				1 (33.3)	
Surgical	1 (33.3)		2 (40.0)	1 (50.0)			1 (100.0)
Unknown		1 (14.3)					
Other[g]		1 (14.3)	1 (20.0)				
Foreign body[h]	5 (7.6)	10 (23.3)	11 (52.4)	2 (11.8)			
Other risk factors[i]	17 (25.8)	14 (32.6)	9 (42.9)	6 (33.3)	3 (42.9)	2 (20.0)	4 (18.2)
No risk factor identified	8 (12.1)	4 (9.3)	1 (4.8)			1 (10.0)	1 (4.5)

(*continued on next page*)

Table 2 (*continued*)

	Ascomycota					Basidiomycota	Mucoromycotina
	Rare Dematiaceae (*n* = 66)	*Rare Hypocreales* (*n* = 43)	*Rare Saccharomycetales* (*n* = 21)	*Rare Eurotiales* (*n* = 17)	*Rare Dermatomycetes* (*n* = 7)	*Rare Agaricales* (*n* = 10)	*Rare Mucorales* (*n* = 22)
EORTC/MSG criteria							
Proven	55 (83.3)	37 (86.0)	20 (95.2)	7 (41.2)	6 (85.7)	6 (60.0)	16 (72.7)
Probable	10 (15.2)	4 (9.3)	1 (4.8)	8 (44.4)	1 (14.3)	2 (20.0)	5 (22.7)
Probable (PCR)	1 (1.5)			2 (11.1)		2 (20.0)	1 (4.5)
Other		2 (4.7)					
Site of infection							
Single organ	45 (68.2)	27 (61.9)	3 (14.3)	12 (70.6)	5 (71.4)	7 (70.0)	17 (77.3)
Adjacent organs	11 (16.7)	2 (4.8)	1 (4.8)	2 (11.8)	1 (14.3)	2 (20.0)	1 (4.5)
Dissemination [j]	10 (15.2)	14 (32.6)	17 (81.0)	3 (17.6)	1 (14.3)	1 (10.0)	4 (18.2)
Blood	2 (3.0)	11 (25.6)	16 (76.2)	1 (5.9)	1 (14.3)		
CNS [k]	9 (13.6)	4 (9.3)		1 (5. 9)	1 (14.3)	1 (10.0)	2 (9.1)
Eye	4 (6.1)	8 (18.6)	1 (4.8)	1 (5. 9)	2 (28.6)	1 (10.0)	
Paranasal sinuses	10 (15.2)	7 (16.3)			1 (14.3)	5 (50.0)	2 (9.1)
Lung	14 (21.2)	16 (37.2)	3 (14.3)	13 (76.5)	2 (28.6)	6 (60.0)	7 (31.8)
Soft tissue	25 (37.9)	5 (11.6)	1 (4.8)	1 (5. 9)	3 (42.9)	1 (10.0)	13 (59.1)
Skin	17 (25.8)	1 (2.3)	1 (4.8)				1 (4.5)
Bone	4 (6.1)	1 (2.3)				1 (10.0)	1 (4.5)
Joint	6 (9.1)		1 (4.8)	1 (5. 9)			
Digestive system [l]	1 (1.5)	2 (4.8)	3 (14.3)	1 (5. 9)			1 (4.5)
Peritoneum	2 (3.0)	2 (4.8)	1 (4.8)	2 (11.8)			
Foreign body [m]	1 (1.5)	3 (7.0)	7 (33.3)	1 (5. 9)			
Heart	2 (3.0)	4 (9.3)					
Other site of infection [n]	1 (1.5)	3 (7.0)			1 (14.3)		2 (9.1)

Data are n (%). IQR=interquartile range. Risk factors might be super-additive.

[a] Solid tumor includes Digestive system cancer (*n* = 4), Gastric cancer, Neuroblastoma, Osteosarcoma (*n* = 2, each), Breast cancer, Breast cancer with lung metastasis, Gallbladder cancer with liver metastasis, Medulloblastoma, Optic glioma, Prostate adenocarcinoma, Retinoblastoma and Skin cancer (*n* = 1, each).

[b] Other hematological/oncological malignancies includes Hemolytic anemia and Multiple myeloma (*n* = 1, each).

[c] HSCT=Hematopoietic Stem-Cell Transplantation.

[d] SOT=Solid Organ Transplantation, and includes Kidney (*n* = 15), Lung (*n* = 9), Liver (*n* = 4), Heart or Pancreas (*n* = 1, each).

[e] Chronic digestive disease includes Crohn's disease (*n* = 2) and Chronic reflux esophagitis with relapsing pneumonia due to microaspiration (*n* = 1).

[f] ICU=Intensive Care Unit.

[g] Other ICU includes Haematological ICU.

[h] Foreign body includes different type of catheters (*n* = 24) or prosthetic material (*n* = 5).

[i] Other risk factors include Infectious disease with bacteria or virus (*n* = 16), Major surgery (*n* = 10), Alcoholism (*n* = 8), Environment (construction, farming/gardening…) (*n* = 9), Contact lenses use/Smoker (*n* = 4), Burn, History of swelling or ulcers, Lymphopenia (*n* = 2, each), Acute respiratory distress syndrome, Aphakic bullous keratopathy, Dengue fever, Frequent right sided nasal block, Henoch-Schönlein purpura, Hypogammaglobulinemia on immunoglobulin replacement therapy, Intravenous drug abuse, Polypoid rhinosinusitis with polypectomy, Previous history of tuberculosis, Rapidly progressive glomerulonephritis (*n* = 1, each).

[j] Disseminated invasive fungal infection is defined as an infection with positive blood culture or at least two non-adjacent organs affected.

[k] CNS=Central Nervous System.

[l] Digestive system includes Liver, Gastrointestinal tract (*n* = 3, each), and Biliary tact, Spleen (*n* = 2, each).

[m] Foreign body includes different type of catheters (*n* = 15) or prosthetic material (*n* = 6).

[n] Other site of infection includes Vessels (*n* = 4), Thyroid (*n* = 3) and Kidney (*n* = 1).

Table 3
Administered antifungal therapy by group of rare fungal pathogens.

	Ascomycota					Basidiomycota	Mucoromycotina
	Rare Dematiaceae (n = 66)	*Rare Hypocreales (n = 43)*	*Rare Saccharomycetales (n = 21)*	*Rare Eurotiales (n = 17)*	*Rare Dermatomycetes (n = 7)*	*Rare Agaricales (n = 10)*	*Rare Mucorales (n = 22)*
Prophylaxis [a]	8 (12.1)	10 (23.3)	3 (14.3)	7 (41.2)	1 (14.3)	5 (50.0)	3 (13.6)
Amphotericin B	2 (25.0)	1 (10.0)					
Triazoles [b]	7 (87.5)	9 (90.0)	3 (100.0)	6 (85.7)		5 (100.0)	2 (66.6)
Echinocandins [c]	1 (12.5)	2 (20.0)		1 (14.3)	1 (100.0)	1 (20.0)	1 (33.3)
Length of prophylaxis in days	63 (34 – 155)	41 (30 – 76)	13 (11 – 168)	41 (5 – 69)	33 (33 – 33)	29 (20 – 39)	109 (59 – 9118)
Breakthrough IFI	8 (12.1)	11 (25.6)	3 (14.3)	7 (41.2)	1 (14.3)	5 (50.0)	3 (13.6)
Antifungal therapy	56 (84.8)	33 (76.7)	17 (81.0)	17 (100.0)	6 (85.7)	10 (100.0)	22 (100.0)
Amphotericin B	16 (28.6)	21 (63.6)	4 (23.5)	9 (52.9)	2 (33.3)	8 (80.0)	22 (100.0)
Deoxycholate	4 (25.0)	8 (38.1)		3 (33.3)	1 (50.0)	1 (12.5)	7 (31.8)
Lipid complex	3 (18.8)	5 (23.8)	1 (25.0)	2 (22.2)		2 (25.0)	
Liposomal	9 (56.3)	8 (38.1)	3 (75.0)	4 (44.4)	1 (50.0)	5 (62.5)	16 (72.7)
Echinocandins	9 (16.1)	12 (36.4)	8 (47.1)	8 (47.1)	1 (16.7)	3 (30.0)	4 (18.2)
Anidulafungin	1 (11.1)		1 (12.5)				1 (25.0)
Caspofungin	6 (66.7)	10 (83.3)	6 (75.0)	8 (100.0)	1 (100.0)	2 (66.7)	3 (75.0)
Micafungin	2 (22.2)	2 (16.7)	1 (12.5)			1 (33.3)	
Triazoles	52 (92.3)	29 (87.9)	13 (76.5)	14 (82.4)	5 (83.3)	8 (80.0)	14 (63.6)
Fluconazole	3 (5.8)	5 (17.2)	9 (69.2)	3 (21.4)	1 (20.0)		
Itraconazole	15 (28.8)	4 (13.8)		2 (14.3)	1 (20.0)	2 (25.0)	
Isavuconazole	3 (5.8)	2 (6.9)				1 (12.5)	2 (14.3)
Posaconazole	14 (26.9)	7 (24.1)	3 (23.1)	2 (14.3)	1 (20.0)	2 (25.0)	12 (85.7)
Voriconazole	28 (53.8)	24 (82.8)	2 (15.4)	12 (85.7)	2 (40.0)	3 (37.5)	4 (28.3)
Other antifungals	9 (16.1)		1 (5.9)	1 (5.9)			1 (4.5)
Flucytosine			1 (100.0)				
Ketoconazole	2 (22.2)						
Terbinafine	7 (77.8)			1 (100.0)			1 (100.0)
Length of therapy in days	84 (42 – 210)	58 (34 – 146)	24 (16 – 39)	49 (30 – 91)	63 (6 – 281)	83 (37 – 111)	51 (20 – 89)
Combination therapy							
Amphotericin B + Triazoles	7 (12.5)	11 (33.3)		1 (5.9)		3 (30.0)	9 (40.9)
Amphotericin B + Triazoles + Other [d]	1 (1.8)	1 (3.0)		1 (5.9)			2 (9.1)
Amphotericin B + Other [e]	2 (3.6)	1 (3.0)		3 (17.6)		2 (20.0)	1 (4.5)
Azoles	1 (1.8)			1 (5.9)			
Azoles + Other [f]	9 (16.1)	5 (15.2)		2 (11.8)		1 (10.0)	
Therapy sequence							
Single [g]	41 (73.2)	19 (57.6)	17 (100.0)	11 (64.7)	6 (100.0)	7 (70.0)	11 (50.0)
Combined [h]	3 (5.4)	3 (9.1)		2 (11.8)			3 (13.6)
Single + Combined [i]	5 (8.9)	14 (42.4)		3 (17.6)		2 (20.0)	4 (18.2)
Combined + Single [j]	8 (14.3)			1 (5.9)		1 (10.0)	4 (18.2)

(continued on next page)

Table 3 (*continued*)

	Ascomycota					Basidiomycota	Mucoromycotina
	Rare Dematiaceae (n=66)	*Rare Hypocreales (n=43)*	*Rare Saccharomycetales (n=21)*	*Rare Eurotiales (n=17)*	*Rare Dermatomycetes (n=7)*	*Rare Agaricales (n=10)*	*Rare Mucorales (n=22)*
Non-systemic antifungals	6 (9.1)	7 (16.3)		1 (5.9)	1 (14.3)	1 (10.0)	
Amphotericin B, inhaled		1 (14.3)				1 (100.0)	
Amphotericin B, topical	1 (16.7)	1 (14.3)		1 (100.0)			
Caspofungin, inhaled	1 (16.7)						
Fluconazole, topical		1 (14.3)		1 (100.0)			
Natamycin, topical	3 (50.0)	3 (42.9)			1 (100.00)		
Terbinafine, topical	1 (16.7)						
Voriconazole, inhaled		1 (14.3)					
Voriconazole, topical	1 (16.7)	3 (42.9)		1 (100.0)			
Surgery	34 (51.5)	15 (34.9)	4 (19.0)	4 (23.5)	2 (28.6)	7 (70.0)	14 (63.6)
Removal of central vascular catheter	4 (6.1)	7 (16.3)	7 (33.3)	2 (11.8)			
Other antifungal therapies [k]	2 (3.0)		1 (4.8)				2 (9.1)
No antifungal therapy	1 (1.5)	3 (7.0)			1 (14.3)		

Data are n (%). Days are median (interquartile range). Antifungals might be super-additive.

[a] IFI=Invasive fungal infection.

[b] Triazoles includes Fluconazole ($n=13$), Itraconazole ($n=3$), Posaconazole ($n=11$), and Voriconazole ($n=9$).

[c] Echinocandins includes Anidulafungin ($n=1$), Caspofungin ($n=5$) and Micafungin ($n=3$).

[d] Amphotericin $B+$Triazoles$+$Other includes amphotericin B combined with triazoles and with echinocandins or terbinafine or echinocandins and terbinafine.

[e] Amphotericin $B+$Other includes amphotericin B combined with echinocandins or flucytosine or echinocandins and terbinafine.

[f] Triazoles+ Other includes triazoles combined with another triazole or echinocandins or flucytosine or natamycin or terbinafine.

[g] Single therapy includes single monotherapy and single sequential therapy.

[h] Combined therapy includes combined monotherapy and combined sequential therapy.

[i] Single + Combined includes single monotherapy/sequential therapy first and combined monotherapy/sequential therapy second with or without other therapy later.

[j] Combined + single includes combined monotherapy/sequential therapy first and single monotherapy/sequential therapy second with or without other therapy later.

[k] Other antifungal therapies include Drainage of fluid collection, Hyperbaric oxygen therapy, Interferon gamma therapy, Reimplantation of joint and Rickham reservoir for cranial liposomal amphotericin B administration ($n=1$, each).

Table 4
Response to treatment and survival by group of rare fungal pathogen.

	Ascomycota					Basidiomycota	Mucoromycotina
	Rare Dematiaceae (*n* = *66*)	*Rare Hypocreales* (*n* = *43*)	*Rare Saccharomycetales* (*n* = *21*)	*Rare Eurotiales* (*n* = *17*)	*Rare Dermatomycetes* (*n* = *7*)	*Rare Agaricales* (*n* = *10*)	*Rare Mucorales* (*n* = *22*)
Day 42							
Favorable response [a]	26 (39.4)	12 (27.9)	1 (4.8)	8 (42.9)	3 (42.9)	5 (50.0)	8 (36.4)
Complete response	12 (18.2)	4 (9.3)	1 (4.8)	4 (23.5)	1 (14.3)	1 (10.0)	4 (18.2)
Partial response	14 (21.2)	8 (18.6)		4 (23.5)	2 (28.6)	4 (40.0)	4 (18.2)
Unfavorable response [b]	21 (31.8)	6 (14.0)	1 (4.8)	2 (11.8)		1 (10.0)	5 (22.7)
Stable disease	15 (22.7)	4 (9.3)	1 (4.8)	1 (5.9)		1 (10.0)	2 (9.1)
Progression	6 (9.1)	2 (4.7)		1 (5.9)			3 (13.6)
Not applicable [c]	5 (7.6)	12 (27.9)	7 (33.3)	2 (11.8)	3 (42.9)	2 (20.0)	7 (31.8)
Lost to follow up [d]	14 (21.2)	11 (25.6)	9 (42.9)	5 (29.4)	1 (14.3)	2 (20.0)	2 (9.1)
Unknown		2 (4.7)	3 (14.3)				
Day 84							
Favorable response [a]	24 (36.4)	9 (20.9)	1 (4.8)	4 (23.5)	2 (28.6)	3 (30.0)	6 (27.3)
Complete response	11 (16.7)	2 (4.7)		2 (11.8)		1 (10.0)	4 (18.2)
Partial response	13 (19.7)	7 (16.3)		2 (11.8)	2 (28.6)	2 (20.0)	2 (9.1)
Unfavorable response [b]	11 (16.7)	4 (9.3)		1 (5.9)			1 (4.5)
Stable disease	10 (15.2)	2 (4.7)					
Progression	1 (1.5)	2 (4.7)		1 (5.9)			1 (4.5)
Not applicable [c]	11 (16.7)	12 (27.9)	9 (42.9)	3 (17.6)	3 (42.9)	2 (20.0)	11 (50.0)
Lost to follow up [d]	20 ((30.3)	17 (39.5)	8 (38.1)	9 (52.9)	2 (28.6)	5 (50.0)	4 (18.2)
Final response							
Favorable response [a]	45 (68.2)	29 (67.4)	15 (71.4)	14 (82.4)	4 (57.1)	8 (80.0)	12 (54.5)
Complete response	39 (59.1)	24 (55.8)	12 (57.1)	14 (82.4)	1 (14.3)	6 (60.0)	11 (50.0)
Partial response	6 (9.1)	5 (11.6)	3 (14.3)		3 (42.9)	2 (20.0)	1 (4.5)
Unfavorable response [b]	21 (31.8)	14 (32.6)	6 (28.6)	3 (17.6)	3 (42.9)	2 (20.0)	10 (45.5)
Stable disease	8 (12.1)		1 (4.8)	1 (5.9)			1 (4.5)
Progression	13 (19.7)	14 (32.6)	5 (23.8)	2 (11.8)	3 (42.9)	2 (20.0)	9 (40.9)
Day of treatment end [e]	85 (31 – 210)	34 (16 – 106)	20 (14 – 37)	45 (30 – 84)	41 (2 – 275)	71 (28 – 101)	51 (20 – 108)
Observation time [f]	123 (47 – 246)	56 (22 – 200)	41 (14 – 299)	90 (60 – 125)	41 (2 – 276)	83 (28 – 187)	51 (20 – 120)
Survival							
Survived	52 (78.8)	29 (67.4)	12 (57.1)	15 (88.2)	4 (57.1)	7 (70.0)	11 (50.0)
Dead	14 (21.2)	13 (30.2)	9 (42.9)	2 (11.8)	3 (42.9)	3 (30.0)	11 (50.0)
Attributable to IFI [g]	8 (57.1)	7 (53.8)	4 (44.4)	1 (50.0)	2 (66.6)	2 (66.6)	8 (72.7)
Day of death	47 (14 – 71)	9 (1 – 31)	16 (10 – 60)	12 (7 – 16)	2 (0 – 3)	22 (12 – 267)	20 (5 – 49)

Data are n (%). Day of treatment end, Observation time and Day of death are provided as median days (interquartile range).

[a] Favorable response includes complete response and partial response, according to pre-established criteria[29].

[b] Unfavorable response includes Stable disease and Progression, according to pre-established criteria[29].

[c] Not applicable includes patients discharged dead from medical facilities before the respective time point.

[d] Lost to follow up includes patients discharged alive from medical facilities before the respective time point irrespective of treatment outcome without further follow up.

[e] Day of treatment end stands for the time span between diagnosis of IFI and final day of treatment.

[f] Observation time stands for the time span between diagnosis of IFI and last contact with the patient.

[g] IFI=Invasive fungal infection.

CVC placement ($n=2$) were further risk factors. Lung ($n=13$, 76.4%) and peritoneum ($n=2$, 11.8%) were the most frequent infection sites. Three patients had dissemination, none with fungemia (Table 2, Table S1). Seven IFI occurred during prophylaxis after a median of 41 (IQR: 5–69) days, in four while receiving posaconazole. All patients followed antifungal treatment for a median of 49 (IQR: 30–91) days, six as combination therapy. Triazoles ($n=14$), mostly voriconazole ($n=12$), and amphotericin B ($n=9$), mainly liposomal ($n=4$, 44.4%), were the most frequent antifungals. Four patients (23.5%) underwent surgery (Table 3, Table S1). Favorable response at day 42 was achieved in eight patients (42.9%) and overall in 14 (82.4%). Mortality was 11.8%, with both deaths occurring before day 42 (Table 4, Table S1, Fig. 3).

Dermatomycetes

Seven invasive dermatomycoses (3.8%) were diagnosed, including two by *Neoscytalidium* spp. and *Trichophyton* spp., each (Table 1). Six patients were male. Chronic disease, diabetes ($n=3$, each), corticosteroid administration and environmental factors ($n=2$, each) were relevant risk factors. Infection affected deep soft tissue ($n=3$), eyes or lungs ($n=2$, each) (Table 2, Table S1). Fungemia was reported for one case with lung infection. One patient had received micafungin prophylaxis for 33 days. Antifungals were administered in six patients for a median of 63 (IQR: 6–281) days. In two, paranasal sinus or soft tissue infection was surgically debrided (Table 3, Table S1). Favorable response was observed in four patients. Three patients died within 42 days (Table 4, Table S1, Fig. 3).

Basidiomycota

Agaricales

Ten IFI (5.4%) due to Agaricales were diagnosed, six caused by *Hormographiella* spp. (Table 1). The male/female ratio was 0.4:1. Six patients had acute leukemia. Three patients were treated in an ICU. For one patient no risk factor was reported. Patients had lung ($n=6$) or paranasal sinuses ($n=5$) infection. One patient had progressive disease from paranasal sinuses to the CNS (Table 2, Table S1). Five patients received antifungal prophylaxis for a median of 29 (IQR: 20–39) days, four with posaconazole. All patients received amphotericin B and/or triazoles for a median of 83 (IQR: 37–111) days, three as combination therapy. Seven patients underwent surgery (Table 3, Table S1). Day-42 favorable response was reported for five patients, overall for eight. Mortality at day 42 was 20.0% (2/10 deaths) and overall 30.0% (3/10 deaths) (Table 4, Table S1, Fig. 3).

Mucoromycotina

Mucorales

Twenty-two mucormycoses (11.8%), mainly caused by *Cunninghamella* spp. ($n=10$, 45.5%) and *Apophysomyces* spp. ($n=7$, 31.8%) (Table 1), were diagnosed. The male/female ratio was 1.8–:1. Malignancy was the main risk factor ($n=12$, 54.5%). Corticosteroid administration, neutropenia ($n=6$, 27.3%, each), and trauma ($n=5$, 22.7%) were also relevant risk factors. Diabetes and previous bacteremia were reported for three patients (13.6%) each. Most patients had soft tissue ($n=13$, 59.1%) or lung infection ($n=7$, 31.8%). Four patients reported dissemination (18.2%) (Table 2, Table S1). In three patients (13.6%) fungal infection occurred during prophylaxis after a median of 109 (IQR: 59–9118) days, in one with chronic granulomatous disease after 25 years with itraconazole. All patients received antifungals, for a median of 51 (IQR: 20–89) days. Amphotericin B ($n=22$, 100.0%), mainly liposomal ($n=16$, 72.7%) was administered in all, and triazoles in 14 patients (63.6%), mostly posaconazole ($n=12$, 85.7%). Fourteen cases (63.6%) underwent surgery (Table 3, Table S1). Favorable response was achieved for 10 patients (45.5%) within 42 days and overall for 12 (54.5%). Mortality at day 42 was 31.8% (7/22 deaths) and overall 50.0% (11/22 deaths) (Table 4, Table S1, Fig. 3).

Discussion

This study aimed to describe the epidemiology and characteristics of 186 extremely rare IFI documented in FungiScope®.

Most of these IFI occurred in male adults, as reported in previous studies.[2,5] Malignancies, together with long-term immunosuppression and chronic diseases, such as renal or cardiovascular, for which treatment may involve the placement of foreign bodies, predominated as risk factors, as repeatedly described in the literature.[5,12,24,30] Diabetes was a frequent underlying condition, which could be considered a predisposing factor in many cases. Almost 20% of the patients were from low and middle-income countries, where an underlying disease may often remain uncontrolled and thus, leaves the patient at higher risk for developing IFI.[5,12,24,30,31] Interestingly, three patients had infections due to *Beauveria bassiana* or *Metarhizium robertsii*, fungi commonly employed in entomopathogenic biocontrol. Although previous exposure to these products was not reported here, their role as a potential IFI risk factor should be considered, especially in rural areas.[32,33]

The major sites of infection described per group were similar to those reported IFI caused by more frequent fungi of similar taxonomy: soft tissue, skin, and lungs in the *Dematiaceae* group,[5,8,12,24] soft tissue and lungs in the *Dermatomycetes*[30] and *Mucorales* groups,[5,9,16,17] lungs and blood in the *Hypocreales* group,[10,13,14] lungs in the *Eurotiales* group[10,34] and *Hormographiella* spp. (*Agaricales* group),[35,36] paranasal sinuses in *Schizophyllum commune*-related cases (*Agaricales* group),[37] and blood in the *Saccharomycetales* group.[7,15,38] Since clinical presentation of extremely rare IFI is similar to more common IFI of the same phylogenetic lineage, for which more comprehensive data on epidemiology and successful clinical management is available, treatment regimens may also be applicable for the extremely rare cases.

BT-IFI ranged from 12.1% in *Dematiaceae* to 50.0% in *Agaricales* in this analysis, varying from those reported previously for *Dematiaceae* (12.1% in our analysis vs 36.0%),[39] *Saccharomycetales* (14.3% vs 52.2%),[15] *Agaricales* (50.0% vs 28.7%),[26] or *Mucorales* (13.6% vs 24.4%).[18] Rates are difficult to compare due to heterogeneity with respect to risk groups, fungal genera and potential differences in pathogenicity, and antifungal prophylactic regimen.

In our cases, triazoles and amphotericin B were the most used antifungal agents. In the ESCMID/ECMM guidelines, voriconazole and amphotericin B are recommended for treatment of phaeohyphomycoses[8] and *Fusarium* spp.[10], which might be extrapolated to *Dematiaceae* and *Hypocreales*-related infections, respectively. Triazoles and echinocandins were the most common antifungals in *Saccharomycetales*-related IFI of our analysis, which is recommended only for the treatment of certain infections caused by yeasts of this order.[7] Amphotericin B was the first-line treatment of choice in mucormycoses, some received salvage treatment with triazole, mostly posaconazole.[9] Whereas guidelines are available for diagnosis and clinical management of the above mentioned IFI, which physicians may apply to treat extremely rare IFI of similar taxonomy (e.g. Ascomycota yeasts, dematiaceae, Hypocreales, Mucorales), such are missing for *Eurotiales, Dermatomycetes*, and *Agaricales*. Only isolated cases have been reported, insufficient to permit informed treatment decision. *Eurotiales*-related infections were mainly treated with triazoles, with demonstrated in vitro activity against the endemic *Penicillium/Talaromyces marneffei* and other non-*marneffei* species,[40] or amphotericin B, which shows in vitro susceptibility against *Paecilomyces* spp.[10]. *Dermatomycetes* usually cause superficial skin infections and rarely IFI. As a matter of fact, only 70 invasive infections due to dermatomycetes have been reported until 2010, the first dating back to the year 1883, from which conclusions on effective therapy could not be drawn and personalized treatment has been recommended, considering the underlying conditions.[30] In *Agaricales*, as reported treatment strategies, both *Schizophyllum commune* and *Hormographiella* spp.-related infections were treated with amphotericin B or triazoles,[35–37] however, due to the few cases reported, there is a lack of specific treatment recommendation.

Patients with dissemination within the groups of *Dematiaceae, Hypocreales, Saccharomycetales, Eurotiales* and *Agaricales* had a higher survival rate compared to those in the *Mucorales* group, with a high pathogenicity profile.[41]

This study has certain limitations. First, likely not all cases from the participating centers have been diagnosed and included in FungiScope®, thus, true prevalence/incidence of such infections are not available. Second, certain pathogens might be overrepresented in the registry due to case collection tied to previous analyses, such as the *Dematiaceae* from a MSG study.[12] If excluded, the number of *Dematiaceae* cases would be similar in the Americas, Asia and Europe. Third, fewer cases in FungiScope® were from non-European countries, which is mainly attributed to logistic hurdles but also language barriers that may hamper the establishment of collaborations across continents. Despite these limitations, an international registry appears the most suitable method to collect a high number of IFI. Cases included in FungiScope® and selected for analysis are highly representative for IFI reported around the world, shown by similar distribution patterns, clinical presentation and treatment regimens.

Here, we present the largest series of extremely rare IFIs to date. Supported by collaborators from 83 countries, comprehensive data on these IFI could be compiled. FungiScope® is ongoing and further cases will be collected to provide a more comprehensive picture also on the most extremely rare of the emerging IFI in the future.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jinf.2020.08.015.

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