











Invasive *Trichoderma* spp. infections: clinical presentation and outcome of cases from the literature and the FungiScope® registry

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Background: *Trichoderma* spp. are filamentous fungi causing invasive fungal diseases in patients with haematological malignancies and in peritoneal dialysis patients.

Objectives: To analyse clinical presentation, predisposing factors, treatment and outcome of *Trichoderma* infections.

Methods: A systematic literature review was conducted for published cases of invasive *Trichoderma* infection in PubMed until December 2021 and by reviewing the included studies' references. Cases from the FungiScope® registry were added to a combined analysis.

Results: We identified 50 invasive infections due to *Trichoderma* species, including 11 in the FungiScope® registry. The main underlying conditions were haematological malignancies in 19 and continuous ambulatory peritoneal dialysis (CAPD) in 10 cases. The most prevalent infection sites were lung (42%) and peritoneum (22%). Systemic antifungal therapy was administered in 42 cases (84%), mostly amphotericin B ($n=27$, lipid-based formulation 13/27) and voriconazole in 15 cases (30%). Surgical interventions were performed in 13 cases (26%). Overall mortality was 48% ($n=24$) and highest for allogeneic HSCT and solid organ transplantation (SOT) recipients [80% (4/5) and 77% (7/9), respectively]. In patients treated with amphotericin B, voriconazole and caspofungin, mortality was 55% (15/27), 46% (7/15) and 28% (2/7), respectively. Three out of four patients treated with a combination therapy of voriconazole and caspofungin survived.

Conclusions: Despite treatment with antifungal therapies and surgery, invasive *Trichoderma* infections are life-threatening complications in immunocompromised patients, especially after HSCT and SOT. In addition, *Trichoderma* spp. mainly affect the lungs in patients with haematological malignancies and the peritoneum in CAPD patients.

Introduction

Filamentous fungi, such as *Aspergillus*, *Fusarium*, *Penicillium* and *Trichoderma* species, are found worldwide, commonly in soil and water habitats, and are known to produce mycotoxins.¹ They can be found in rotten biological material, where they accelerate degradation of organic material.² *Trichoderma* is effective against common soil-borne pathogens and is thus used as a commercial biopesticide.³ As opposed to *Aspergillus*, *Fusarium* and *Penicillium* that cause severe infections in a broad variety of patients, *Trichoderma* has long been considered non-pathogenic in humans, but localized and disseminated infections in immunocompromised and immunocompetent patients have been reported worldwide.⁴ *Trichoderma longibrachiatum* is the most commonly reported species associated with invasive fungal infections (IFI), followed by *Trichoderma atroviride*, *Trichoderma bissettii*, *Trichoderma citrinoviride*, *Trichoderma harzianum*, *Trichoderma koningii*, *Trichoderma pseudokoningii* and *Trichoderma viride*.⁵⁻⁷

Trichoderma species cause a variety of clinical manifestations, such as invasive pulmonary infection, peritonitis, CNS infection, endocarditis, fungaemia and disseminated disease affecting distant organs, especially in patients with haematological malignancies and those undergoing continuous ambulatory peritoneal dialysis (CAPD).⁸⁻¹⁰ The tissue morphology of *Trichoderma* species is characterized by the presence of hyaline septate hyphae, similar to *Aspergillus* spp. and other agents of hyalohyphomycosis.^{4,11} Thus, culture and molecular approaches are necessary for diagnosis.⁴ Except for echinocandins and voriconazole, *Trichoderma* isolates show relatively high MICs *in vitro* of other antifungal drugs.^{12,13} The associated mortality rate is reported to be as high as 53%.¹⁴ Currently, there are no evidence-based guidelines for the clinical management of invasive *Trichoderma* infections.

In this study, we conducted a comprehensive analysis from the FungiScope[®] registry and the literature to identify clinical presentation, predisposing factors, treatment, outcome and effective therapeutic options of invasive *Trichoderma* infections.

Methods

We collected cases from the medical literature (PubMed) and FungiScope[®], a global registry for invasive fungal infections (IFI) (www.clinicaltrials.gov NCT 01731353).¹⁵ The PubMed database was searched for all reported cases of *Trichoderma* infections from database inception to 31 December 2021 using the search term (*Trichoderma**) AND ((invasive OR disseminated OR infection) AND (case OR patient OR report)). References of articles were reviewed to identify additional studies (Figure 1). Authors of the studies were contacted to obtain further data. FungiScope[®] was approved by the local institutional review board and ethics committee of the University of Cologne, Germany (Study ID: 05-102).

For each case, clinical data were collected: underlying conditions, symptoms and clinical signs, site(s) of infection, imaging findings, mycological evidence, antifungal treatment, antifungal susceptibility and clinical response and outcome. Mortality on days 42 and 90 after diagnosis of IFI and initiation of targeted therapy was documented. In addition, mortality attributed to the infection was noted. The follow-up period was defined as time from diagnosis of *Trichoderma* infection to last day of contact or death.

Invasive *Trichoderma* infection was classified as proven or probable according to the revised criteria of the European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group and the National Institute of Allergy and Infectious Diseases Mycoses Study Group (EORTC/MSG).¹⁶ Disseminated disease was defined as a disease in two or more non-contiguous organs or bloodstream infection, while disease in adjacent organs was defined as IFI manifestation in two or more adjacent organs.

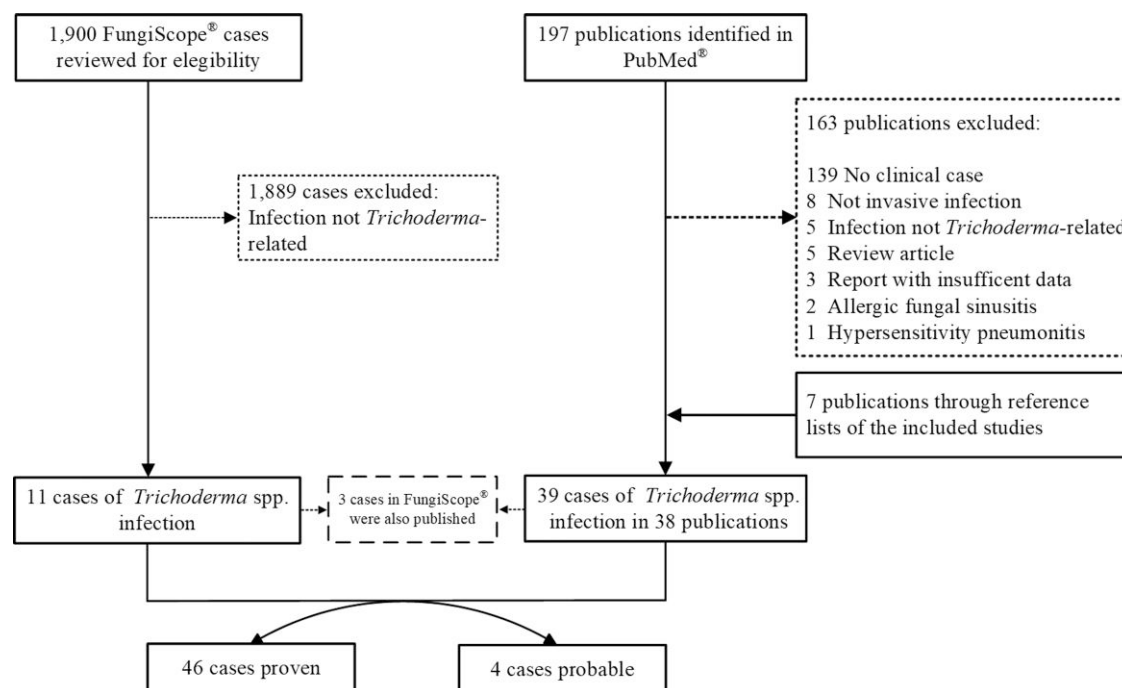


Figure 1. Enrolment and study flow chart.

Table 1. Patient characteristics

Characteristic	n	Percentage of total	Death in the respective cohort		Mortality (N=50)
			n	%	
Age (years), median (IQR)		45 (27–62)			
Sex (female/male) ^a	17/32	34%/64%	8/16	47%/50%	16%/32%
Mixed infection ^b	4	8%	2	50%	4%
Underlying conditions and risk factors ^c					
haematological/oncological diseases ^d	19	38%	9	47%	18%
chemotherapy ^e	13	26%	5	38%	10%
corticosteroids	19	38%	12	63%	24%
neutropenia ^f	14	28%	5	35%	10%
immunosuppressive drugs ^g	12	24%	9	75%	18%
biological immune response modulators ^h	4	8%	3	75%	6%
allogeneic HSCT	5	10%	4	80%	8%
graft-versus-host disease	3	6%	2	66%	4%
autologous HSCT	1	2%	0	-	-
SOT ⁱ	9	18%	7	77%	14%
broad-spectrum antibiotic use	11	22%	7	63%	14%
intraperitoneal catheter	11	22%	7	63%	14%
CAPD ^j	10	20%	6	60%	12%
central venous catheter	9	18%	4	44%	8%
surgery	6	12%	3	50%	6%
diabetes mellitus	5	10%	3	60%	6%
ICU treatment	4	8%	2	50%	4%
parenteral nutrition	4	8%	0	-	-
other ^k	15	30%	8	53%	16%
Organ involvement ^c					
lung	21	42%	11	52%	22%
peritoneum	11	22%	7	63%	14%
CNS	8	16%	5	62%	10%
heart	7	14%	3	42%	6%
blood	5	10%	1	20%	2%
liver	5	10%	4	80%	8%
gastrointestinal tract	4	8%	4	100%	8%
paranasal sinuses	4	8%	1	25%	2%
skin	4	8%	4	100%	8%
other organs ^l	5	10%	4	80%	8%
disseminated	12	24%	8	66%	16%
adjacent organs	3	6%	2	66%	4%

^aOne unknown.

^b*Absidia corymbifera* (disseminated infection), *Aspergillus niger* (lung) and *Cunninghamella bertholletiae* (lung) and *Fusarium* spp. (lung) (n=1, each).

^cUnderlying conditions and risk factors, and organ involvement are super-additive.

^dHaematological/oncological diseases include ALL (n=6), AML (n=5), non-Hodgkin lymphoma (n=2), aplastic anaemia (n=2) and multiple myeloma, lung cancer, medulloblastoma and neuroblastoma (n=1, each).

^eChemotherapy includes cytotoxic antineoplastic agents.

^fAuthors reported neutropenia without further details.

^gDrugs used for prevention and treatment of allograft rejection after organ transplantation and graft-versus-host disease in HSCT: tacrolimus (n=8), cyclosporine A (n=4), mycophenolate mofetil (n=3), azathioprine (n=2), sirolimus (n=1) and methotrexate (n=1).

^hBiological immune response modulators include alemtuzumab (n=1), infliximab (n=1), eculizumab and rituximab (n=1) and anti-thymocyte globulin (n=1).

ⁱLiver (n=5), kidney (n=1), lung (n=2) and liver and bowel (n=1).

^jUnderlying conditions: diabetic nephropathy (n=4), chronic kidney disease of unknown aetiology (n=2) and amyloidosis, focal segmental glomerulosclerosis, IgA nephropathy and unclassified systemic vasculitis (n=1, each).

^kOther risk factors are super-additive and include oral mucositis and HIV/AIDS (n=2, each), amyloidosis, arthritis, cardiac implantable electronic device, chronic *Aspergillus fumigatus* colonization, chronic liver disease, Crohn's disease, complex cyanotic heart disease, contaminated IV fluid, cystic fibrosis, dilated hypertensive cardiomyopathy, extracorporeal membrane oxygenation, functional asplenia, ileostomy, gastrointestinal mucositis, lymphopenia, nephrotic syndrome, peritoneal catheter, prosthetic heart valve, Sjogren-Larsson syndrome, sternal wound infection and trauma (n=1, each) and no reported risk factor (n=2).

^lOther organ involvements include deep soft tissue and pericardium (n=2, each), diaphragm and liver capsule (n=1), intraabdominal dissemination (n=1), kidney (n=1), lower limb and spleen (n=1) and pretracheal abscesses (n=1).

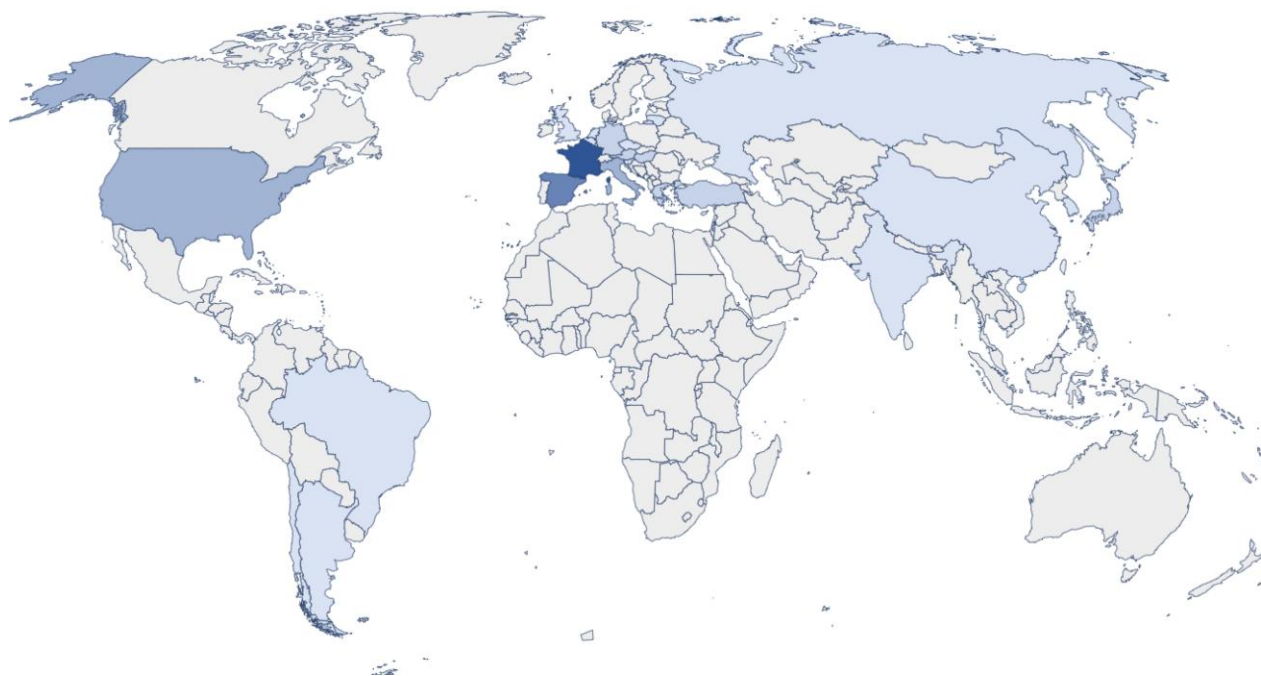


Figure 2. Geographical distribution of invasive *Trichoderma* infections. Cases were reported from France ($n=10$), Spain ($n=7$), Italy and the USA ($n=4$, each), Austria, Germany, Greece, Hungary, Japan and Turkey ($n=2$, each) and Argentina, Belgium, Brazil, Chile, China, the Czech Republic, India, Korea, Lithuania, the Netherlands, Russia, Slovenia and the UK ($n=1$, each). This figure appears in colour in the online version of JAC and in black and white in the print version of JAC.

Statistical analyses were performed using SPSS v25 (IBM, Chicago, IL, USA). Frequencies and percentages were used to summarize categorical data and median, range and IQR for continuous variables. Categorical variables were compared using χ^2 test and Fisher's exact test. A P value ≤ 0.05 was considered statistically significant.

Results

Fifty cases of invasive *Trichoderma* infection were identified in the published literature ($n=42$) and in FungiScope® ($n=11$, 3 of which had been previously published).^{6,17,18} Forty-six (92%) infections were proven and four (8%) probable (Figure 1). The median age at diagnosis was 45 years (range 3–82, IQR 27–62) and most patients were male (64%, $n=32$) (Table 1). Cases diagnosed between 1970 and 2021 were reported from 23 countries, most after 2000 (37/50, 74%) (Figure 2).

Haematological malignancy was the most common underlying condition ($n=19$, 38%), followed by CAPD ($n=10$, 20%) and solid organ transplantation (SOT) ($n=9$, 18%). Further predisposing factors were corticosteroid treatment ($n=19$, 38%), neutropenia ($n=14$, 28%), chemotherapy ($n=13$, 26%), immunosuppressive therapy ($n=12$, 24%) and broad-spectrum antibiotic use ($n=11$, 22%). One patient was infected via contaminated IV infusion of glucose-saline [Table 1 and Table S1 (available as [Supplementary data](#) at JAC Online)].

Lung and peritoneum were the organs most frequently affected [$n=21$ (42%) and $n=11$ (22%), respectively]. Other frequently affected organs were CNS ($n=8$, 16%) and liver ($n=5$, 10%). Lung involvement was particularly prevalent in patients

with malignancy ($n=15/19$, 79%) ($P<0.001$). In addition, dissemination and adjacent organ involvement occurred in 12 (24%) and 3 (6%) cases, respectively (Table 1 and Table S1).

Fever ($n=29$, 58%) and pain in the infected body site ($n=22$, 44%) were the most frequently reported clinical symptoms. The symptoms were primarily associated with the affected regions, such as abdominal pain ($n=11$, 22%) in patients with peritonitis, endocarditis or liver infection, headache ($n=7$, 14%) in patients with sinusitis or CNS infection, and cough ($n=6$, 12%) in patients with lung infection. In addition, eight patients (16%) presented with clouding of the peritoneal fluid (Table 2).

Imaging procedures were performed in 62% ($n=31$) of the patients, most frequently chest CT ($n=16$, 32%). Pulmonary nodular infiltration was reported in 68% of patients with chest CT (11/16) and pulmonary halo sign and/or pulmonary air crescent/cavity in 38% (6/16) of these patients. Other frequent imaging procedures were head CT ($n=6$) and echocardiography ($n=4$) with abnormal findings (Table 2). Culture and/or molecular techniques were used to identify *Trichoderma* species in most cases [$n=49$ (98%) and $n=24$ (48%), respectively] (Table 2 and Table S1). In addition, positive galactomannan [serum ($n=2$) and bronchoalveolar lavage ($n=1$)] and serum β -D-glucan were reported for three and two patients, respectively.

Infections were caused by eight different *Trichoderma* species, with *T. longibrachiatum* being the most frequently reported ($n=24$, 48%), followed by *T. harzianum* ($n=4$, 8%), *T. koningii* and *T. viride* ($n=3$, 6%, each), *T. atroviride* and *T. pseudokoningii* ($n=2$, 4%, each) and *T. bissettii* and *T. citrinoviride* ($n=1$, 2%, each). Identification to the species level was not done for 10

Table 2. Clinical signs and symptoms, and diagnostic procedures^a; N = 50

Characteristic	n	Percentage of total
Signs and symptoms of infection		
fever	29	58%
pain of the area of involvement ^b	22	44%
pulmonary symptoms ^c	12	24%
clouding of the peritoneal fluid	8	16%
neurological symptoms/signs	8	16%
diarrhoea	4	8%
soft tissue oedema/swelling	4	8%
skin or mucosal ulcerations	3	6%
other ^d	9	18%
Imaging procedures		
CT ^e	24	48%
echocardiography	4	8%
abdominal ultrasound	3	6%
bronchoscopy	3	6%
MRI head	3	6%
X-ray thorax	3	6%
other ^f	3	6%
Mycological evidence		
culture	49	98%
molecular procedures ^g	24	48%
histology	17	34%
microscopy	11	22%

^aData are super-additive.

^bAbdominal pain (n = 11), headache (n = 7; 1 with facial pain and 1 with abdominal pain in addition), chest pain (n = 2) and flank, gingiva and lower limb pain (n = 1, each).

^cCough (n = 6), dyspnoea (n = 4), respiratory failure (n = 1), chest pain (n = 2) and haemoptysis and tachypnoea (n = 1, each).

^dErythema and decreasing bowel sound (n = 2, each) and chills, decreased appetite, exanthema, excessive salivation, retrobulbar pressure, purulent discharge and vomiting (n = 1, each).

^eChest (n = 16), head (n = 6), abdomen (n = 4) and paranasal sinuses (n = 2).

^fNasal endoscopy (n = 2) and X-ray abdomen (n = 1).

^gSequencing (n = 20), diagnostic PCR (n = 4) and MALDI-TOF MS, DNA fingerprinting and random amplified polymorphic DNA (RAPD) analysis (n = 1, each).

isolates (20%). Coinfection with other moulds was reported for four patients (Table 1 and Table S1).

Ten patients (20%) received antifungal prophylaxis before the diagnosis of invasive *Trichoderma* infection, fluconazole being used in most (6/10). Systemic antifungal therapy was administered in 42 patients (84%). Amphotericin B was the most commonly used antifungal drug (n = 27, 54%; lipid-based amphotericin B in 13/27, 48%), followed by voriconazole (n = 15, 30%) and caspofungin (n = 7, 14%). Twelve patients (24%) received combined antifungal therapy, six with a combination of amphotericin B plus a triazole and four with caspofungin plus voriconazole. Systemic antifungal treatment and surgery was used in nine cases (18%). Four patients were treated only surgically (8%). Central venous catheters (n = 3) and intraperitoneal

Table 3. Treatment and outcome

Characteristic	n	Percentage of total	Deaths	
			n	proportion of respective cohort
Treatment strategy ^a				
systemic antifungal therapy	42	84%	22	52%
plus surgery	9	18%	5	55%
surgery only	4	8%	0	-
intraperitoneal catheter removal	10	20%	6	60%
CVC removal	3	6%	0	-
other ^b	4	8%	2	50%
Primary antifungal prophylaxis	10	20%	8	80%
Secondary antifungal prophylaxis	2	4%	0	-
G-CSF	5	10%	3	60%
Granulocyte infusion	2	4%	2	100%
Monotherapy				
amphotericin B	27	54%	15	55%
lipid-based formulation of amphotericin B	13	26%	7	53%
voriconazole	15	30%	7	46%
caspofungin	7	14%	2	28%
fluconazole	6	12%	5	83%
itraconazole	5	10%	4	80%
ketoconazole	3	6%	2	66%
flucytosine	2	4%	2	100%
anidulafungin	1	2%	1	100%
isavuconazole	1	2%	1	100%
miconazole	1	2%	0	-
Combination therapy				
amphotericin B plus azole	6	12%	4	66%
caspofungin plus voriconazole	4	8%	1	25%
amphotericin B plus flucytosine	2	4%	2	100%
Treatment days overall, median (IQR)	38 (22–58)			
Treatment days of patients alive, median (IQR)	60 (28–67)			
Overall mortality, deaths ^c	24	48%		
death attributable to IFI	16	32%		
Observation time (days), median (IQR)	41 (17–173)			
Observation time of patients alive (days), median (IQR)	105 (27–365)			

CVC, central venous catheter; G-CSF, granulocyte colony-stimulating factor.

^aData are super-additive.

^bNo therapy (n = 2) and no information and cardiac implantable electronic device removal (n = 1, each).

^cOne unknown.

catheters (n = 10) or cardiac implantable electronic devices (n = 1) were removed in 14 cases (28%) after diagnosis of IFI and

Table 4. Antifungal susceptibility testing of *Trichoderma* clinical isolates

Antifungal drug	Microdilution method (MIC, mg/L)		Etest [®] method (MIC, mg/L)	
	number of isolates tested	median (IQR)	number of isolates tested	median (IQR)
Amphotericin B	13	1.0 (0.5–2.0)	6	2.0 (1.5–2.0)
Anidulafungin	1	0.12	3	0.015 (0.015–16)
Caspofungin	4	0.5 (0.5–0.87)	7	0.09 (0.05–0.24)
Fluconazole	9	64 (20.5–96)	3	256 (256–256)
Flucytosine	7	64 (32–256)	1	6
Itraconazole	12	8 (1.25–16)	6	32 (1–32)
Ketoconazole	3	1 (0.51–4.5)	-	-
Micafungin	1	0.06	3	0.016 (0.012–1.0)
Miconazole	4	0.17 (0.04–6)	-	-
Posaconazole	1	0.03	4	32 (12.5–32)
Terbinafine	1	0.03	-	-
Voriconazole	9	1 (0.5–2)	7	0.25 (0.22–0.5)

5 patients (10%) received granulocyte colony-stimulating factor before diagnosis of IFI. Two patients did not receive any treatment for IFI and for one patient the case report did not provide information on therapeutic measures (Table 3 and Table S1).

Antifungal susceptibility test results for clinical isolates are presented in Table 4 and Table S2. Antifungal susceptibility results were reported for clinical isolates of 34 (68%) cases, with MIC values reported for 30 of 34 cases. In four cases, authors reported whether the causative *Trichoderma* species were susceptible to antifungal drugs, but did not provide MIC values. The microdilution method was used for most isolates (14/34, 41%) and Etest[®] for seven isolates (20%); for nine (26%) the method was not reported. MICs of antifungals varied depending on the species and method used. *Trichoderma* isolates showed variable MICs of amphotericin B according to the microdilution method and Etest[®], with a median value of 1.0 mg/L (IQR 0.5–2.0) and 2.0 mg/L (IQR 1.5–2.0), respectively. Echinocandins had low MICs for *Trichoderma* species and caspofungin was the sole antifungal that had low MICs for all isolates (range 0.047–1.0 mg/L). However, *T. bissettii* ($n=1$) had a high MIC of anidulafungin (>32 mg/L). Among the triazoles, voriconazole had the lowest MICs using the microdilution method and Etest[®], with a median of 1.0 mg/L (IQR 0.5–2) and 0.25 mg/L (IQR 0.22–0.5), respectively. Nevertheless, voriconazole showed poor *in vitro* activity against *T. atroviride* ($n=1$, MIC=8 mg/L) and *T. citrinoviride* ($n=1$, MIC=4 mg/L). Overall, fluconazole had the highest MIC values for most isolates [13/16 (81%) had an MIC >16 mg/L].

The median follow-up was 41 days (IQR 17–173 days). All-cause mortality was 48% ($n=24$), 42 day mortality was 38% ($n=19$) and 90 day mortality was 40% ($n=20$) (Table 3). Mortality was highest in patients who underwent allogeneic HSCT and SOT [80% (4/5) and 77% (7/9), respectively]. Besides, mortality was high in patients who received primary antifungal prophylaxis (8/10, 80%) and immunosuppressive therapy (9/12, 75%). Mortality in patients with disseminated infection was higher compared with patients with single organ involvement or adjacent organ involvement [8/12 (66%) versus 16/37 (43%), respectively] ($P=0.16$). In patients with peritoneal involvement without disseminated disease, mortality was 63% (7/11). In

addition, monotherapy and combination therapy resulted in similar survival rates [14/30 (47%) and 6/12 (50%), respectively] ($P=0.84$). The mortality was lower in patients treated with caspofungin (2/7, 28%) and voriconazole (7/15, 46%) than in patients treated with other triazoles (11/15, 73%) and amphotericin B (15/27, 55%). In patients treated with voriconazole combined with caspofungin and an azole combined with amphotericin B, mortality rates were 25% (1/4) and 66% (4/6), respectively. Mortality in patients who underwent surgery was lower than the overall mortality (5/13, 38%) ($P=0.61$). Autopsy was performed in eight patients; in three, diagnosis of *Trichoderma* infection was established post-mortem.

Discussion

Although IFI caused by *Trichoderma* is rare, our study shows that these infections have been increasingly reported since 2000 compared with previous years, especially in patients with haematological malignancies.^{4,5} If this is due to increasing awareness among treating physicians, improved diagnostics or the emergence of more resistant fungal species due to the broad use of antifungal prophylaxis is difficult to determine, but it is likely a combination of these. However, guidance to diagnose and treat *Trichoderma* infections has not been published yet. To the best of our knowledge, this study presents the most extensive analysis on the management of invasive *Trichoderma* infection to date.

The first invasive human infection caused by *Trichoderma* species was described in a patient accidentally administered contaminated IV fluid.¹⁹ Immunocompromised patients and patients undergoing CAPD were at high risk of invasive *Trichoderma* infections.⁵ In our study, invasive infections caused by *Trichoderma* species were most frequently reported in immunosuppressed patients. Also, previous use of broad-spectrum antibiotics and indwelling devices or catheters are other frequently reported predisposing factors.⁴

Invasive *Trichoderma* infections often affect the lung, peritoneum and CNS. Lungs are the primary site of invasive *Trichoderma* infections in patients with malignancies. Clinical symptoms were non-specific, but might help to pinpoint the affected organ as

most reported symptoms were in context with the site of involvement. Fever was the most common symptom regardless of the infected body site. Our analysis shows that pulmonary nodular infiltration and less frequently pulmonary halo sign, air crescent and cavitation are frequent findings in patients with *Trichoderma* lung infection, which are also common findings in pulmonary infections caused by other fungi.²⁰ In addition, galactomannan assay and serum β -D-glucan may be positive, which may be mistakenly interpreted as invasive aspergillosis.^{21,22} Furthermore, *Trichoderma* species share similar morphology with other hyalohyphomycoses in tissue sections.^{4,11} Clinical, radiological and histopathological similarities of *Trichoderma* infections with other IFI present a diagnostic challenge for physicians. Therefore, it is crucial to apply culture and molecular diagnostic approaches for definitive diagnosis and susceptibility testing of antifungal drugs to make an informed treatment decision.

Guidelines recommend a triazole or a lipid formulation of amphotericin B for primary treatment of rare mould infections.²³ A proper analysis to confirm if these recommendations apply to *Trichoderma* infections as well was not possible using our case collection, due to the heterogeneity of risk groups, the variety of treatment regimens applied to these patients and, in addition, the lack of observation time in 28% of cases. Keeping in mind these limitations, in our patient population all-cause mortality was higher in those treated with amphotericin B and triazoles, except for voriconazole. Besides, these drugs generally show high MIC values for *Trichoderma* species. Eight of the 15 patients treated with voriconazole survived, of which 6 had respective MIC <1 mg/L (one unknown). Two cases with an MIC value ≥ 1 mg/L received caspofungin in addition to voriconazole.^{1,5} Echinocandins show good *in vitro* activity against *Trichoderma* species. However, it has been reported that anidulafungin showed poor *in vitro* activity against *T. bissettii*.⁶ Caspofungin on the other hand was used successfully in few patients, in line with the assessed *in vitro* activity of caspofungin against the respective isolates. Nevertheless, it is difficult to correlate clinical response to antifungal drugs based on their *in vitro* activity due to the limited number of cases with available information and the lack of clinical breakpoint values of antifungals for *Trichoderma*.

According to our analysis, caspofungin has a low MIC for *Trichoderma* species. A disadvantage of echinocandins might be that these drugs are fungistatic rather than fungicidal compared with amphotericin B and voriconazole against filamentous fungi.²⁴ Successful treatment of invasive pulmonary *Trichoderma* infection in patients with underlying malignancies using combination therapy of voriconazole and caspofungin has been reported.^{1,5,22} To validate these findings and to determine whether caspofungin might be a suitable option for treatment of *Trichoderma* infections, a larger patient population representative of the major risk groups is needed. Antifungal susceptibility differs between *Trichoderma* species. Thus, species-level identification and antifungal susceptibility testing are recommended to guide treatment decisions. Surgical interventions for treatment of *Trichoderma* infections have been associated with improved outcome and should be considered if the disease pattern and patient conditions allow it. Successful treatments of liver or paranasal sinus infections have been reported.^{4,17} Early catheter

removal might be a successful therapeutic intervention when the portal of entrance has been determined as such, e.g. in dialysis patients, as described in a patient with a successful treatment course who received neither systemic antifungal drugs nor surgical treatment.²⁵

Mortality in patients with invasive *Trichoderma* infections remains high despite continuously improving medical approaches.¹⁴ Outcome was particularly worse in patients undergoing HSCT or SOT, patient populations with a general high mortality rate.²⁶ Furthermore, mortality was high in those patients who developed *Trichoderma* infection during antifungal prophylaxis with amphotericin B or a triazole, although MICs of these drugs were high for most isolates tested. This may be due to the fact that more severely ill patients are more likely to receive antifungal prophylaxis, under the rationale of increased risk of developing infection. *Trichoderma*-associated peritonitis was associated with high mortality, similar to reports of peritonitis related to fungi other than *Trichoderma*.²⁷⁻²⁹

Several limitations of this study do not allow for a comprehensive and confirmatory analysis on effective therapeutic strategies, which are urgently needed to improve patient outcome. Results must be interpreted with caution, as our population includes cases from the FungiScope[®] registry as well as the literature, which may or may not introduce a bias towards reports of cases diagnosed in settings where healthcare facilities are well equipped combined with high awareness and specialized knowledge of fungal infections as well as the availability of resources to provide research results through publication. The majority of patients included in this study were reported from Europe and none from Africa, which supports our notion. Incomplete data for several published cases further limited possible analyses, which for example concerned survival probability due to missing data on observation time. A correlation between *in vitro* activity of antifungal drugs against *Trichoderma* and clinical efficacy could not be assessed. Clinical breakpoints of antifungal drugs for *Trichoderma* species are not determined yet; also, susceptibility data were only available for a limited number of clinical isolates derived using different methods and varying activity of antifungal drugs was reported for the same *Trichoderma* species.^{8,9} Effective therapeutic strategies could not be identified in this study due to the heterogeneity of patients not only by means of reported risk factors but also with respect to diagnosis of the infection, affected organs, dissemination status and treatment strategies used.

In conclusion, invasive infections due to *Trichoderma* species are rare and mortality is high. Since clinical, radiological and histological findings of invasive infections caused by *Trichoderma* are similar to those of other moulds, it is crucial to use culture and molecular methods for their definitive diagnosis. Moreover, susceptibility testing should be performed, despite clinical breakpoints not being available, as *in vitro* activity may predict clinical response. Voriconazole may be a treatment option for *Trichoderma* infections where species-level identification and *in vitro* susceptibility tests suggest activity against the pathogen. In addition, according to our presented data, caspofungin might be considered for treatment if amphotericin B and triazoles show no efficacy against *Trichoderma* species *in vitro* or disease progression is noted during adequate therapy. Studies including larger datasets that allow for analysis of more homogeneous

patient populations are needed to identify predictors for survival and eventually improve patient outcome for invasive *Trichoderma* infections.

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Author contributions

E.S. conceived the study idea and performed literature research. E.S., J.S. and D.S. analysed and interpreted data, drafted the manuscript, created tables and figures, and revised and approved the final manuscript. J.S., J.S.-G., P.K., O.A.C. and D.S. maintained the FungiScope[®] registry and enrolled and validated cases. J.S.-G., P.K. and O.A.C. interpreted data and revised and approved the final manuscript. O.A.C. initiated and leads FungiScope[®]. I.F.-R., L.K., E.M., B.W., C.L.-F., Z.R., N.K., S.C., A.J.K. and H.W. contributed cases to the FungiScope[®] registry, interpreted data and revised and approved the final manuscript.

Supplementary data

Tables S1 and S2 are available as [Supplementary data](#) at JAC Online.

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