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# Risk factors and mortality in invasive *Rasamsonia* spp. infection: Analysis of cases in the FungiScope<sup>®</sup> registry and from the literature

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## Summary

**Background:** The new *Rasamsonia* spp. complex can develop invasive infection in immunosuppression or chronic pulmonary disease. It has potential to be misidentified as other genera due to morphological similarities. Nowadays, there is a gap of knowledge on this fungi.

**Objectives:** To provide knowledge base of risk factors and therapeutic decisions in invasive *Rasamsonia* spp. complex infection.

**Patients/Methods:** Cases of invasive infection due to *Rasamsonia* spp. (formerly *Geosmithia/Penicillium* spp.) from FungiScope<sup>®</sup> registry and all reported cases from a literature were included.

**Results:** We identified 23 invasive infections due to *Rasamsonia* spp., six (26.1%) in the FungiScope<sup>®</sup> registry. Main risk factors were chronic granulomatous disease (n = 12, 52.2%), immunosuppressive treatment (n = 10, 43.5%), haematopoietic stem cell transplantation (n = 7, 30.4%), graft-versus-host disease and major surgery (n = 4, 17.4%, each). Predominantly affected organs were the lungs (n = 21, 91.3%), disease disseminated in seven cases (30.4%). Fungal misidentification occurred in 47.8% (n = 11), and sequencing was used in 69.6% of the patients (n = 16) to diagnose. Breakthrough infection occurred in 13 patients (56.5%). All patients received anti-fungal treatment, mostly posaconazole (n = 11), caspofungin (n = 10) or voriconazole (n = 9). Combination therapy was administered in 13 patients (56.5%). Susceptibility testing showed high minimum inhibitory concentrations for azoles and amphotericin B, but not for echinocandins. No preferable treatment influencing favourable outcome was identified. Overall mortality was 39% (n = 9).

**Conclusion:** *Rasamsonia* spp. are emerging fungi causing life-threatening infections, especially in immunocompromised and critically ill patients. Mortality is high.

Jannik Stemler and Jon Salmanton-García contributed equally to this work.

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Treatment is challenging and clinicians dealing with this patient population should become aware of this infection constituting a medical emergency.

#### KEYWORDS

chronic granulomatous disease, filamentous fungi, *Geosmithia*, immunosuppression, invasive fungal infections, misidentification, *Rasamsonia*, registry

## 1 | INTRODUCTION

The *Rasamsonia* spp. complex comprises filamentous fungi causing pneumonia and occasionally disseminated disease in immunocompromised patients.<sup>1,2</sup> Taxonomy introduced *Rasamsonia* spp. as a genus of the family *Trichocomaceae* only in 2011.<sup>3</sup> It harbours eleven thermotolerant and thermophilic species, and former synonyms of the genus are *Geosmithia*, *Penicillium* and *Talaromyces*.<sup>3-7</sup> There is potential for misidentification due to morphological similarities, for example as *Paecilomyces* spp.<sup>8</sup>

Typical hosts present with chronic lung diseases such as cystic fibrosis (CF) or with chronic granulomatous disease (CGD), but a wide range of immunosuppressed patients may be affected.<sup>2,9-12</sup> Colonization precedes infection for an undetermined period, and coinfection with bacterial or other fungal pathogens may hamper diagnosis.<sup>13-15</sup> Along with imaging procedures, morphological, proteomic and genomic analyses have been used for diagnostics.<sup>16</sup> Heterogeneous susceptibility profiles may necessitate prolonged treatment, sometimes in combination of more than one drug, and surgery. Antifungals from all approved classes have been used.<sup>4,9,17</sup> Currently, there is no reliable treatment guideline. Although rigorous treatment is essential, most physicians are inexperienced as with any ultra-rare disease.

Therefore, we conducted a combined analysis of cases registered in FungiScope® and cases reported in the literature to provide a knowledge base for therapeutic decisions and to identify risk factors for *Rasamsonia* spp. infection and its predictors of mortality.

## 2 | METHODS

FungiScope® (www.fungiscope.net) is a web-based registry which collects cases of rare invasive fungal diseases worldwide (www.

clinicaltrials.gov, NCT 01731353). Its methodology is described elsewhere.<sup>18</sup> FungiScope® was approved by the local Institutional Review Board and Ethics Committee of the University Hospital Cologne, Germany (Study ID: 05-102). Data of *Rasamsonia* spp. cases were extracted from the database for analysis.

PubMed database was searched for case reports and case series in all available languages since database inception until September 2019. The predefined search algorithm “(*Rasamsonia*\* OR *Geosmithia*\*) AND ((invasive OR disseminated OR infection) AND (case OR patient OR report))” yielded 23 results. Publications were selected for further evaluation by screening of title and abstracts. Reference lists were checked for other suitable studies, and one additional case was identified in a review. Authors of publications were contacted in order to obtain additional data (Figure 1). Reported cases between 2010 and 2019 were included for analysis. We decided to exclude cases of *Paecilomyces* spp. infection before 2010, when this fungus was related to *Rasamsonia* spp., due to its potential for misidentification.

Every report was reviewed for patient demographics, underlying diseases and risk factors for invasive fungal infection (IFI), misidentification of fungal pathogen, *Rasamsonia* spp. involved, clinical signs and symptoms at time of diagnosis of IFI, site of infection, imaging procedures, mycological evidence leading to diagnosis of IFI, susceptibility testing, minimum inhibitory concentrations (MICs), antifungal prophylaxis and antifungal and surgical treatment of IFI. Mortality on day 42 and day 90, and attributable mortality were documented. Observation time was defined from day of diagnosis to last patient contact.

Proven or probable IFI was included in accordance with 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) definitions.<sup>19</sup> One case from FungiScope® and one case from the

literature could not be classified accordingly.<sup>20</sup> Both patients had CF and therefore did not meet host criteria, while clinical symptoms and mycological evidence were present. Of note, the FungiScope® patient recently underwent lung transplantation and fulfils criteria for probable IFI of the International Society for Heart and Lung Transplantation (ISHLT).<sup>21</sup> In the recently revised EORTC/MSG criteria, solid organ transplantation is included as host factor and classifies the case as probable IFI.<sup>22</sup> Similarly, specialists consider seven criteria for “highly probable” invasive pulmonary fungal infection in CF patients of which the literature case fulfils at least five.<sup>23</sup> Subsequently, both cases were included as probable in our analysis.

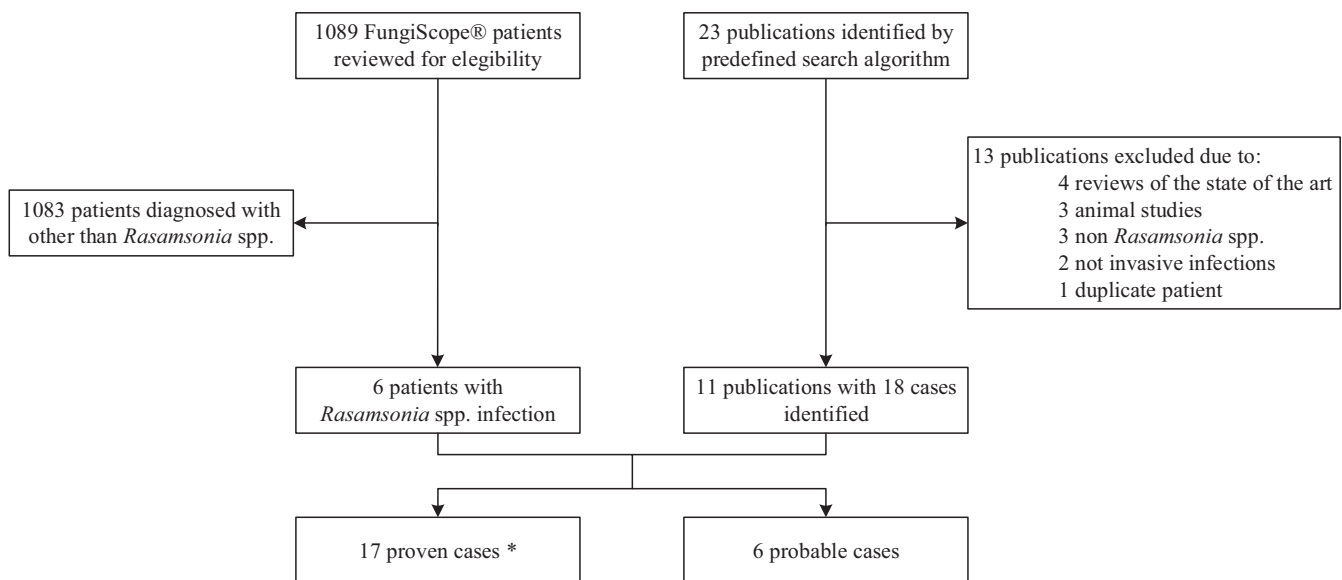
Disseminated infection was defined as disease at two or more non-contiguous sites and classified separately from infection at adjacent organs. Breakthrough invasive fungal infection (BT-IFI) was defined as onset of *Rasamsonia* spp. infection occurring during ongoing exposure to antifungals, following European Confederation of Medical Mycology and Mycoses Study Group Education and Research Consortium definitions.<sup>24</sup>

Statistical analysis used SPSS software version 25 (IBM). Patient characteristics from categorical variables were summarized

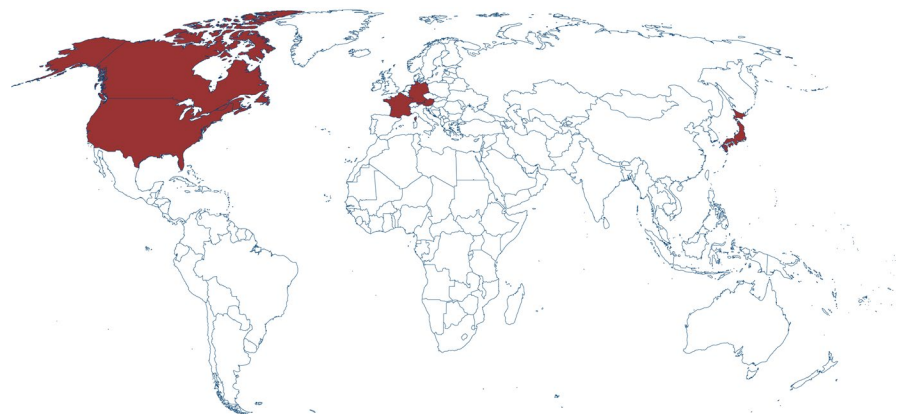
employing frequencies and percentages, while median and interquartile range (IQR) were used in continuous variables. Categorical data were compared using Fisher's exact test. A *P* value  $\leq .05$  was set as statistically significant.

### 3 | RESULTS

Twenty-three cases with confirmed invasive *Rasamsonia* spp. infection from the FungiScope® registry (*n* = 6, 26.1%), and the literature (*n* = 18, 73.9%) were enrolled.<sup>2,11,12,15,16,20,25-29</sup> One of the FungiScope® cases (4.3%) was published previously<sup>29</sup> (Figure 1). One case report was excluded since it closely resembled a patient history published elsewhere.<sup>30</sup> Eligible cases were reported from six countries: Canada (*n* = 7, 30.4%), United States (*n* = 5, 21.7%), France, Germany (*n* = 4, 17.4%, each), Japan (*n* = 2, 8.7%) and Austria (*n* = 1, 4.3%) (Figure 2). All cases were diagnosed between 2005 and 2018. A total of 17 cases (73.9%) were classified as proven IFI and six (26.1%) as probable. Median age at diagnosis was 25 years (IQR: 16–52), and patients were mostly male (*n* = 17; 73.9%) (Table 1, Table S1).



**FIGURE 1** Enrolment and study flow chart. \*1 case was reported both in FungiScope® and the literature<sup>29</sup>



**FIGURE 2** Geographical distribution of invasive *Rasamsonia* spp. infections. Canada (*n* = 7), United States (*n* = 5), France, Germany (*n* = 4, each), Japan (*n* = 2) and Austria (*n* = 1)

*Rasamsonia argillacea* was the most frequently detected pathogen ( $n = 19$ , 82.6%), followed by *Rasamsonia piperina* ( $n = 3$ , 13.0%) and *Rasamsonia aegroticola* ( $n = 1$ , 4.3%). Before diagnosis of *Rasamsonia* spp. infection, misidentification of fungal species occurred in 11 cases (47.8%) to *Penicillium* and *Paecilomyces* spp., mostly identified as *Paecilomyces variotii* ( $n = 5$ , 21.7%). Coinfection with at least one other fungal pathogen was present in six cases (26.1%) (Table 1, Table S1).

Haematological diseases were the most common risk factor for IFI in 19 patients (82.6%), of which 12 (52.2%) had CGD. Further risk factors were immunosuppressive medication ( $n = 10$ , 43.5%), previous allogeneic haematopoietic stem cell transplantation (HSCT) ( $n = 7$ , 30.4%), graft-versus-host disease (GvHD) ( $n = 4$ , 17.4%) and major surgery ( $n = 4$ , 17.4%). There were three CF patients (13.0%) of which two underwent lung transplantation prior to diagnosis (Table 1, Table S2).

The lung was the most often affected organ ( $n = 21$ , 91.3%). Other sites of infection were bones/joints ( $n = 4$ , 17.4%) and central nervous system ( $n = 3$ , 13%). Disseminated disease or involvement of adjacent organs was confirmed in seven (30.4%) and four patients (17.4%), respectively (Table 1, Table S3).

Dyspnoea and cough were the most frequent clinical signs reported ( $n = 10$ , 43.5% and  $n = 9$ , 39.1% respectively), followed by fever ( $n = 6$ , 26.1%) and haemoptysis ( $n = 4$ , 17.4%). Imaging techniques were used to support diagnosis in 20 cases (82.6%), predominantly chest computed tomography ( $n = 18$ , 78.2%). Final diagnosis via culture-based methods was done in four (17.4%) but had to be established via molecular techniques in 16 patients (69.6%). These were performed by sequencing of the internal transcribed spacer or  $\beta$ -tubulin regions ( $n = 12$ , 52.2% and  $n = 2$ , 8.7%, respectively). Information on sequencing method used was missing in two cases (8.7%). Information on identification was missing in three patients (13.0%) (Table 2, Table S4).

Antifungal susceptibility test was performed in 19 cases (78.2%), 17 (73.9%) of which provided MIC values. In six cases (26.1%), Clinical and Laboratory Standards Institute (CLSI) methodology was used. Susceptibility tests revealed particularly wide MIC ranges for most triazoles tested, 0.5 to  $>32$   $\mu\text{g}/\text{mL}$  for voriconazole ( $n = 15$ ) and 0.25 to  $>16$   $\mu\text{g}/\text{mL}$  for posaconazole ( $n = 13$ ). For amphotericin B, MICs varied between 1 and 8  $\mu\text{g}/\text{mL}$ , whereas for echinocandins they ranged from  $\leq 0.015$  to 0.5  $\mu\text{g}/\text{mL}$  (Tables 2 and 3).

Twenty patients (87%) had received treatment or prophylaxis with an antifungal agent prior to diagnosis of *Rasamsonia* infection. Thirteen patients (56.5%) developed BT-IFI. All patients received treatment for *Rasamsonia* spp. infection: triazoles in 17 patients (73.9%), of which posaconazole in 11 (47.8%) and voriconazole in nine patients (39.1%). Three patients (13.0%) received both posaconazole and voriconazole. Echinocandins were given to 16 (69.6%) and amphotericin B to nine patients (39.1%). Thirteen patients (56.5%) received combination therapy. Median treatment duration was 85 days (IQR: 42-240). Surgical procedures for IFI treatment were performed in nine cases (39.1%) (Table 4, Table S5).

There was no statistically significant effect on mortality of disseminated infection ( $P = 1.00$ ), previous species misidentification ( $P = .68$ ) or selected antifungal drug class (amphotericin B,  $P = .64$ ; azoles and echinocandins,  $P = 1.00$ ). No statistical significance was detected when comparing mortality by breakthrough infection ( $P = .67$ ). Overall mortality was 39.1% ( $n = 9$ ), 42-day mortality was 13% ( $n = 3$ ), 90-day was 26% ( $n = 6$ ), and mortality attributed to *Rasamsonia* spp. in four patients (17.4%). In patients with proven IFI mortality was 47% and with probable IFI 17% ( $P = .17$ ) (Table 4, Tables S6 and S7).

## 4 | DISCUSSION

*Rasamsonia* infections are very rare diseases. Identifying 23 cases only in FungiScope® and literature, we still present the largest analysis addressing risk factors and mortality of invasive *Rasamsonia* spp. infection.

X-linked inheritance pattern of CGD, the most frequent at-risk population explains male predominance of 74% in our analysis.<sup>31</sup> HSCT and GvHD as well as CF were additional risk factors. Previous reports identified CF as most frequent underlying condition, but that may apply for colonization only.<sup>1</sup>

In CF patients, it is challenging to classify fungal disease according to EORTC/MSG criteria.<sup>19</sup> These patients are not necessarily immunosuppressed, and CF is not defined as host factor discarding "possible" and "probable" IFI. Patients lacking histologically proven IFI cannot be classified accordingly despite showing clinical signs and mycological evidence. Fungal pathogens are usually considered chronic colonizers in this population and more frequent bacterial infections may lead clinicians to neglect the clinical relevance of fungi. However, colonization with *Rasamsonia* spp. can precede infection and is associated with clinical deterioration.<sup>9,14</sup> In this analysis, we classified two patients as probable applying the ISHLT and the newly revised EORTC/MSG criteria and the recently proposed criteria for invasive pulmonary fungal infections in CF patients by Schwarz et al.<sup>21-23</sup>

*Rasamsonia* spp. infection happens to be an oligosymptomatic disease. Clinical presentation varies widely depending on infected body site. There are no specific signs or symptoms as with many invasive fungal diseases. Hence, there is need for a multidisciplinary approach to diagnose this infection in at-risk patients including imaging, a broad set of molecular microbiological methods and histology.

The misleading morphological pattern of *Rasamsonia* spp. suggestive of other fungi, especially *Paecilomyces* spp., challenges timely diagnosis and treatment. Hence, these infections might be underdiagnosed. *Paecilomyces* spp. usually causes keratitis, but may be detected in lungs, bones, blood, paranasal sinuses and soft tissue. It can affect both immunocompromised and immunocompetent hosts and is mainly observed in CGD.<sup>32</sup> Although *Paecilomyces* spp. infections show a different clinical pattern, the misidentification rate makes us hypothesize that *Rasamsonia* spp. has played

TABLE 1 Patients' characteristics

	n	%
Patient source <sup>a</sup>		
FungiScope <sup>®</sup>	6	26.1
Publication	18	73.9
Country		
Austria	1	4.3
Canada	7	30.4
France	4	17.4
Germany <sup>b</sup>	4	17.4
Japan	2	8.7
United States	5	21.7
EORTC		
Proven/probable	17/6	73.9/26.1
Age, median (IQR)	25 (16-52)	
Sex		
Female	5	21.7
Male	17	73.9
UNK	1	4.3
Pathogen		
<i>Rasamsonia aegroticola</i>	1	4.3
<i>Rasamsonia argillacea</i>	19	82.6
<i>Rasamsonia piperina</i>	3	13.0
Prior misidentification		
<i>Paecilomyces</i> spp. <sup>c</sup>	7	30.4
<i>Penicillium</i> spp./ <i>Paecilomyces</i> spp.	2	8.7
<i>Penicillium</i> spp.	2	8.7
Coinfection and infection site		
<i>Aspergillus fumigatus</i>	3	13.0
Lung	2	8.6
Muscular abscess	1	4.3
<i>Lichtheimia ramosa</i> , lung	2	8.7
<i>Aspergillus nidulans</i> , lung	1	4.3
<i>Candida albicans</i> , lung	1	4.3
Underlying condition <sup>d</sup>		
Haematological disease	19	82.6
Malignancy <sup>e</sup>	7	30.4
Chronic granulomatous disease	12	52.2
Immunosuppressive treatment	10	43.5
HSCT	7	30.4
GvHD	4	17.4
Major surgery	4	17.4
Neutropenia	3	13.0
Cystic fibrosis	3	13.0
ICU stay	3	13.0
Inflammatory bowel disease	3	13.0
Recurrent pneumonia	3	13.0

(Continues)

TABLE 1 (Continued)

	n	%
Other risk factors <sup>f</sup>	5	21.7
Organ involvement <sup>d</sup>		
Single organ	12	52.2
Disseminated	7	30.4
Adjacent organs	4	17.4
Lungs	21	91.3
Bones/Joints	4	17.4
CNS	3	13.0
Other sites <sup>g</sup>	7	30.4

Abbreviations: CNS, central nervous system; EORTC, European Organization for Research and Treatment of Cancer (EORTC) and the National Institute of Allergy and Infectious Diseases Mycoses Study Group (MSG) definitions for invasive fungal infections; GvHD, Graft-versus-Host Disease; HSCT, haematological stem cell transplantation; ICU, intensive care unit; IQR, interquartile range; UNK, unknown.

<sup>a</sup>One case (4.3%) from FungiScope<sup>®</sup> case was already published.

<sup>b</sup>One case (4.3%) from Germany had a first *Rasamsonia argillacea* episode and experienced reinfection later.

<sup>c</sup>*Paecilomyces variotii* (n = 5).

<sup>d</sup>Underlying conditions and organ involvement might be superadditive.

<sup>e</sup>Malignancies included acute myeloid leukaemia, primary myelofibrosis (n = 2, each), acute lymphoblastic leukaemia, myelodysplastic syndrome and non-stated malignancy (n = 1, each).

<sup>f</sup>Other risk factors include underweight or malnutrition (n = 3), central venous catheter, diabetes mellitus, lung transplantation, previous invasive fungal infection (n = 2, each), cardiovascular disease, environmental mould exposure and pancreatic insufficiency (n = 1, each).

<sup>g</sup>Other sites of infections include blood, deep tissue, digestive system and heart (n = 2, each), eye, paranasal sinuses, skin, Lymph node, kidney, thyroid and vessels (n = 1, each).

a role before its first detection. This portrays the importance of adequate molecular diagnostic measures.<sup>33</sup> Identification to species level in order to establish diagnosis is inevitable. Nonetheless, in our analysis misidentification was not a significant predictor of mortality.

The geographical distribution of *Rasamsonia* spp. seems to be marked by availability of resources in diagnostics.<sup>20</sup> Reporting bias can be suspected considering that only certain laboratories regularly perform PCR sequencing from fungal cultures. Additionally, infections due to *Rasamsonia* spp. affect critically ill patients with severe underlying diseases who in lower resource healthcare settings might not present as such.

Susceptibility testing in our patient sample revealed particularly high MICs for most azoles (itraconazole, posaconazole and voriconazole), whereas echinocandins showed a more favourable pattern. This is in accordance with published in vitro data of clinical *Rasamsonia* spp. isolates.<sup>14</sup> However, exact methodology (such as CLSI or EUCAST) was not available in all cases.

In our analysis, MIC values and selected antifungals did not impact patient outcome. When recovering a mould from a clinical

specimen in a symptomatic patient, guidelines recommend first-line treatment with an azole.<sup>34</sup> Considering susceptibility patterns and non-availability of epidemiologic cut-off values (ECVs),

**TABLE 2** Diagnostics procedures and susceptibility test results

	n	%
Signs and symptoms <sup>a</sup>		
Dyspnoea	10	43.5
Cough	9	39.1
Fever	6	26.1
Haemoptysis	4	17.4
Neurological signs	2	8.7
Other <sup>b</sup>	3	13.0
Imaging procedures <sup>a</sup>		
MRI	4	17.4
CT	19	82.6
Head	1	4.3
Chest	18	78.3
X ray, chest	3	13.0
Mycological evidence <sup>a</sup>		
Molecular		
PCR <sup>c</sup>	15	65.2
ITS	12	52.2
β-tubulin	2	8.7
UNK	2	8.7
UNK	1	4.3
Morphological		
Culture	4	17.4
UNK	2	8.7
UNK	3	13.0
MICs, median (IQR) <sup>d,e</sup>		
Amphotericin B	1.5 (1-5)	
Anidulafungin <sup>e</sup>	0.03 (NA)	
Caspofungin	0.25 (0.14-0.5)	
Micafungin	4.5 (0.63-8)	
Itraconazole	0.02 (0.02-0.05)	
Posaconazole	1.5 (0.44-5)	
Voriconazole	8 (6.25-10)	
Terbinafine	0.19 (0.13-NA)	

Abbreviations: CLSI, Clinical and Laboratory Standards Institute; CT, computed tomography; ITS, internal transcribed spacer; MIC, minimum inhibitory concentration; MRI, magnetic resonance imaging; NA, not applicable; NA, not available; PCR, polymerase chain reaction; IQR, interquartile range; UNK, unknown.

<sup>a</sup>Signs and symptoms, imaging procedures and mycological evidence might be superadditive.

<sup>b</sup>Other signs include erythema, pain, mild respiratory signs, night sweats and weight loss (n = 1, each).

<sup>c</sup>In one patient (4.3%) both ITS and β-tubulin were performed.

<sup>d</sup>Results are provided only regarding the results of the 6 patients with confirmed CLSI procedure.

<sup>e</sup>Anidulafungin was only tested in one patient (4.3%).

appropriate decision of antifungal treatment and evaluation of response remain challenging in *Rasamsonia* spp. infections. Physicians might consider novel agents like isavuconazole, yet in vitro data showed reduced activity against *Rasamsonia* spp. isolates.<sup>17</sup> Future treatment agents, such as olorofim, may be promising. To date, no antifungal is available that shows promising results in vivo. If surgical resection is feasible, it may be considered. Therefore, a multidisciplinary approach for the therapeutic management should be endeavoured.

Breakthrough invasive fungal infection occurred in more than half of the cases. However, its mortality did not differ significantly from mortality in non-BT-IFI. The large proportion of patients who had received an antifungal before the infection suggests this as another predisposing factor. At the same time, this questions effective prophylaxis for *Rasamsonia* spp. infection. Overall mortality of 40% was similar to reported mortality rates of mucormycosis.<sup>35</sup> Of note, the mortality rate of *Paecilomyces* spp. infections has been reported much lower, but including cutaneous and eye infections.<sup>36</sup>

Limitations of our work are manifold. First, sample size was small and reporting bias cannot be quantified. Second, complete information for analysis was not always retrievable from the original case reports and some authors were unable to provide further information. Definition of IFI according to EORTC/MSG criteria was difficult as described. The pathogenic role of *Rasamsonia* spp. in CF patients can be disputed, and consensus criteria to define IFI in this population are needed. When authors publish case reports, they should provide a full dataset of the patient's history and course of disease. Otherwise, retrievable information for researchers and clinicians is low. International registries such as FungiScope<sup>®</sup> allow the full collection of clinical information on symptoms, diagnostics, susceptibility and treatment.

In conclusion, *Rasamsonia* spp. is an emerging IFI pathogen representing a threat for patients with inherited immunodeficiencies and iatrogenic immunosuppression. Infections may present as primary or BT-IFI. Multidisciplinary management including molecular techniques and treatment including surgery may be needed. Treatment is challenging due to in vitro resistance to many antifungals and lack of ECVs. Echinocandins show the most favourable in vitro pattern so far and might be the best treatment. Further investigations on larger cohorts of patients with invasive *Rasamsonia* spp. infections could elucidate survival benefits and management strategies. Broader knowledge on rare IFIs should be acquired, and international registries are a valuable resource to do so.

## CONFLICT OF INTEREST

JS declares no conflict of interest. JS-G declares no conflict of interest. DS declares no conflict of interest. BA has received grants from Leadiant, other from Astellas, other from Scynexis, from Shire, from F2G, from UpToDate outside the submitted work. HB declares no conflict of interest. MH has received grant funding from Gilead. RH has received grants and personal fees from Gilead, grants and personal fees from Pfizer, personal fees from Astellas, personal fees from Basilea, personal fees from MSD, personal

TABLE 3 Antifungal minimum inhibitory concentration (MIC) of *Rasamsonia* spp. samples

Case	Country	Year	Pathogen	Method	AMB	ANI	CAS	MIC	FLUCO	ITR	POS	VOR	FLUCY	TER
1	United States	2016	<i>Rasamsonia aegroticola</i>	UNK	2			≤0.015		2	1	>16		
2	Canada	2005	<i>Rasamsonia argillacea</i>	UNK	2					1				
3	Canada	2006	<i>Rasamsonia argillacea</i>	UNK	8					4	4	>8		
5	Canada	2007	<i>Rasamsonia argillacea</i>	UNK	2		≤0.03				0.5	>8		
6	France	2007	<i>Rasamsonia argillacea</i>	CLSI	1		0.25	0.015		8	4	>16		
7	Austria	2010	<i>Rasamsonia argillacea</i>	UNK	1				>256	>32	0.25	0.5		
8	Canada	2010	<i>Rasamsonia argillacea</i>	UNK	4		0.5	≤0.015			2	>16		
9	Canada	2010	<i>Rasamsonia argillacea</i>	UNK	4		0.5	≤0.015		>16	4			
10	France	2010	<i>Rasamsonia argillacea</i>	CLSI	4	0.03	0.5	0.06		1	0.25	1		0.25
11	France	2011	<i>Rasamsonia argillacea</i>	CLSI	8	0.03	0.25	0.03		8	2	≥8		0.125
12	France	2011	<i>Rasamsonia argillacea</i>	Etest	3		0.032			4	8	32		
14	United States	2011	<i>Rasamsonia argillacea</i>	CLSI	1		0.5	≤0.015		0.5	0.5	>16		
17	Germany	2017	<i>Rasamsonia argillacea</i>	UNK	2		0.06			>32				
19	United States	Unknown	<i>Rasamsonia argillacea</i>	CLSI	2						>16	>16		
20	United States	Unknown	<i>Rasamsonia argillacea</i>	CLSI	1		0.03				1	16		
21	Japan	2015	<i>Rasamsonia piperina</i>	UNK	1			0.5		≤0.015		>8		
22	Japan	2018	<i>Rasamsonia piperina</i>	UNK	2			<0.015		0.5		>8	<0.12	

Note: Data are given in µg/mL.

Abbreviations: AMB, amphotericin B; ANI, anidulafungin; CAS, caspofungin; CLSI, Clinical and Laboratory Standards Institute; FLUCO, fluconazole; FLUCY, flucytosine; ITR, itraconazole; MIC, micafungin; POS, posaconazole; TER, terbinafine; VOR, voriconazole; UNK, unknown.



**TABLE 4** Antifungal treatment and outcome

	n	%	Deaths	
Prophylaxis/previous IFI treatment <sup>a</sup>	20	87.0	8/20	40.0%
Amphotericin B	3	13.0	2/3	66.7%
Echinocandin	3	13.0	2/3	66.7%
Azole	19	82.6	7/19	36.8%
Breakthrough IFI	13	56.5	6/13	46.2%
Antifungal therapy <sup>a</sup>	23	100.0	9/23	39.1%
Amphotericin B	9	39.1	4/9	44.4%
Echinocandin	16	69.6	6/16	37.5%
Anidulafungin	2	8.7	1/2	50.0%
Caspofungin	10	43.5	4/10	40.0%
Micafungin	7	30.4	2/7	28.6%
Azole	17	73.9	6/17	35.3%
Itraconazole	2	8.7	1/2	50.0%
Posaconazole	11	47.8	2/11	18.2%
Voriconazole	9	39.1	4/9	44.4%
Other	3	13.0	1/3	33.3%
Flucytosine	2	8.7	1/2	50.0%
Terbinafine	2	8.7	1/2	50.0%
Combined therapy	13	56.5	5/13	38.5%
Amphotericin B + Azole	2	8.7	0/2	0.0%
Amphotericin B + Azole + Echinocandin	3	13.0	2/3	66.7%
Amphotericin B + Echinocandin <sup>b</sup>	4	17.4	2/4	50.0%
Azole + Echinocandin <sup>c</sup>	9	39.1	3/9	33.3%
Treatment sequence				
Monotherapy	5	21.7	2/5	40.0%
Monotherapy sequential	5	21.7	2/5	40.0%
Monotherapy + combination	5	21.7	3/5	60.0%
Combination single	3	13.0	1/3	33.3%
Combination sequential	5	21.7	1/5	20.0%
Treatment days, median (IQR)	85 (44-245)			
Surgery	9	39.1	3/9	33.3%
Overall mortality	9	39.1		
Death attributable to IFI				
Yes	4	17.4		
No	2	8.7		
UNK	3	13.0		
Autopsy	2	8.7		
Death on/before day 42	3	13.0		
Death on/before day 90	3	13.0		
Observation time (days), median (IQR)	95 (30-198)			

Abbreviations: IFI, invasive fungal infection; IQR, interquartile range; UNK, unknown.

<sup>a</sup>Antifungal administered in prophylaxis/previous IFI treatment and in antifungal therapy might be superadditive.

<sup>b</sup>One patient (4.3%) combined first with flucytosine and then with terbinafine.



<sup>c</sup>One patient (4.3%) combined with terbinafine.

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#### AUTHORS CONTRIBUTIONS

JS conceived the study idea, designed the study, performed literature research, analysed and interpreted data, created the manuscript, created tables and figures, revised and approved the final manuscript. JSG performed literature research, analysed and interpreted data, created the manuscript, created tables and figures, revised and approved the final manuscript. DS interpreted data, created figures, revised and approved the final manuscript. BA contributed data on published cases and revised and approved the final manuscript. HB contributed cases to the FungiScope<sup>®</sup> registry and revised and approved the final manuscript. MH contributed cases to the FungiScope<sup>®</sup> registry and revised and approved the final manuscript. RH contributed cases to the FungiScope<sup>®</sup> registry and revised and approved the final manuscript. LM contributed cases to the FungiScope<sup>®</sup> registry and revised and approved the final manuscript. AM contributed cases to the FungiScope<sup>®</sup> registry and revised and approved the final manuscript. SCM interpreted data, revised and approved the final manuscript. ES performed literature research and revised and approved the final manuscript. MZ performed literature research and revised and approved the final manuscript. PK interpreted data, revised and approved the final manuscript. OAC conceived and leads FungiScope<sup>®</sup>, contributed cases to the FungiScope<sup>®</sup> registry, interpreted data, revised and approved the final manuscript.

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## SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

TableS1-S7

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