REVIEW ARTICLE

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Rhodotorula species infections in humans: A systematic review

Petros Ioannou [iD] | Rodanthi Vamvoukaki | George Samonis [iD]

Department of Internal Medicine & Infectious Diseases, University Hospital of Heraklion, Heraklion, Greece

Correspondence
Petros Ioannou, Department of Internal Medicine & Infectious Diseases, University Hospital of Heraklion, Heraklion, Greece.
Email: p.ioannou@med.uoc.gr

Summary

Background: Fungal infections by *Rhodotorula* species are increasingly reported in the literature and consist of bloodstream infections, especially in patients with central venous catheters (CVC), as well as central nervous system (CNS), ocular and other less frequent infections.

Objectives: The aim of this systematic review was to record and evaluate all available evidence regarding infections by *Rhodotorula* species.

Methods: Systematic review of PubMed (through 9 August 2017) for studies providing epidemiological, clinical, microbiological, as well as treatment data and outcomes of *Rhodotorula* species infections.

Results: A total of 111 studies, containing data of 248 patients, were eventually included in the analysis. The most common *Rhodotorula* infections were those of bloodstream, CNS and ocular infections, as well as peritoneal dialysis-associated peritonitis. Epidemiology of each type of infection was different, with the bloodstream ones being more common in patients with malignancy and CVCs, while those of the CNS were more common in patients with AIDS. Mortality was variable being higher in CNS infections. Amphotericin B remains the most common agent used for treatment, irrespectively of the infection site.

Conclusions: This systematic review thoroughly describes fungal infections by *Rhodotorula* species and provides information on their epidemiology, clinical picture, microbiology, treatment and outcomes.

KEYWORDS
fungaemia, fungal infection, keratitis, meningitis, peritonitis, *Rhodotorula*

1 | INTRODUCTION

Rhodotorula belongs to the phylum *Basidiomycota* and forms spherical-to-ellipsoidal budding yeast as well as rudimentary hyphae and small capsules.[1] It is widely distributed in the environment and is also found in the normal flora of the human gastrointestinal, respiratory and genital system as well as in the moist areas of the skin.[2] Even though it had been considered non-pathogenic, in the last decades there is growing evidence that it can be important human pathogen, especially in immunocompromised hosts, causing a variety of different infections, such as fungaemia, meningitis, peritoneal dialysis-associated peritonitis and keratitis.[3,4]

The purpose of this study was to systemically review all published cases of *Rhodotorula* infections in the literature and describe the epidemiology, microbiology, treatment and outcomes of these infections in humans.

2 | METHODS

2.1 | Data search

For this review, we adopted the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines.[5] Eligible studies were identified through search of PubMed/MEDLINE

with the following text-word: Rhodot*[tw]. Day of last search was 9 August 2017.

2.2 | Study selection

Studies were included in analysis if they met the following criteria: (a) published in English; and (b) reporting data on patients' clinical characteristics, microbiology, treatment and outcomes. From the analysis were excluded studies with the following criteria: (a) secondary research papers (eg, reviews), editorials and papers not reporting results on primary research; (b) studies not in humans; (c) studies on colonisation but not infection by *Rhodotorula*; and (d) studies not in English. Two investigators (PI and RV) using

Abstrackr[6] independently reviewed the titles and abstracts of the resulting references, and then, they retrieved and rescreened the full-text publications of potentially relevant articles. Study selection was based on consensus. Reference lists of included studies were searched for relevant articles.

2.3 | Endpoints

The study endpoint was to record the type of *Rhodotorula* spp. infections included in the literature as well as the patient characteristics for different type of infections, the microbiological data on *Rhodotorula* spp. infections and their treatment and outcomes.
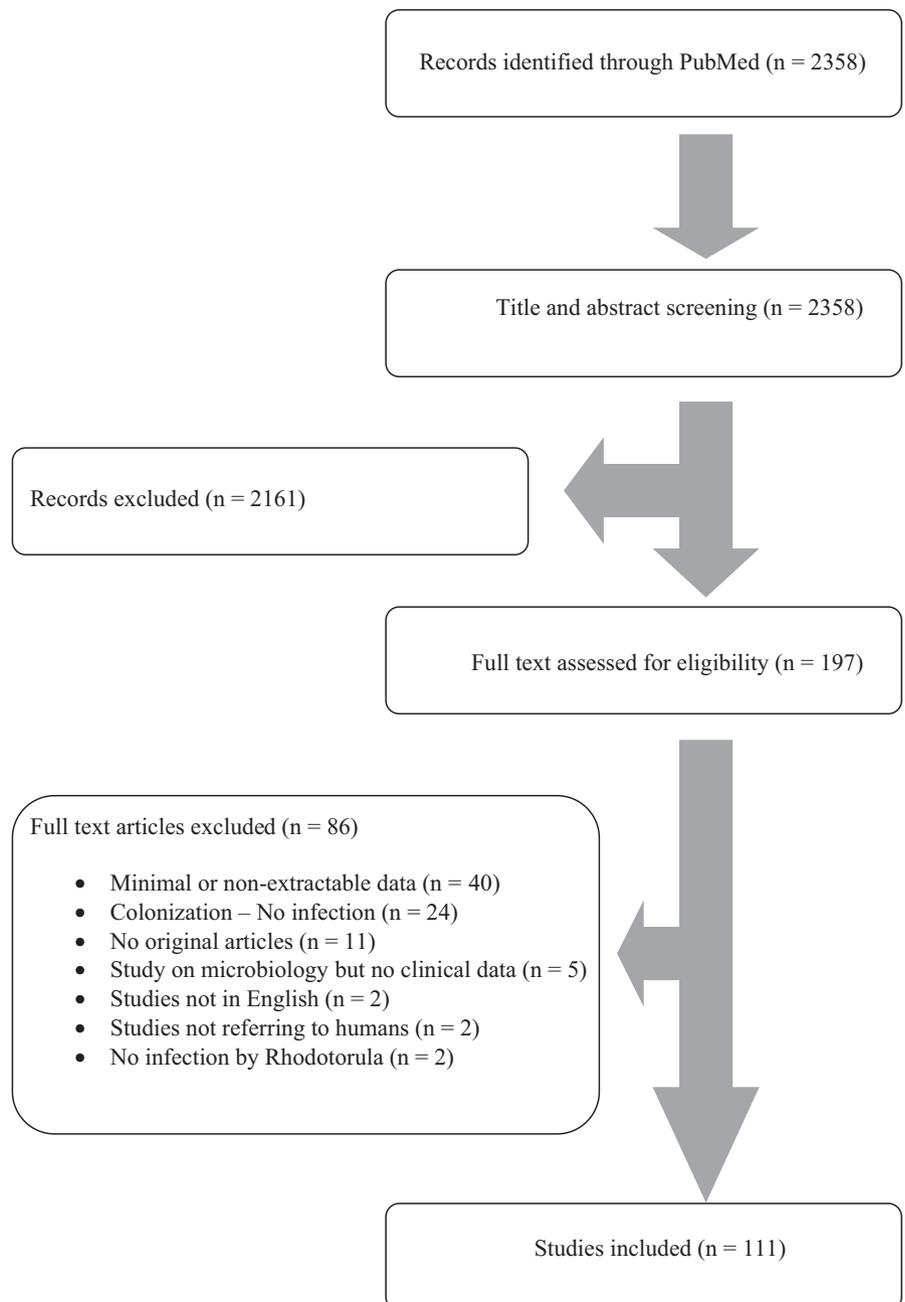
Records identified through PubMed (n = 2358)

Title and abstract screening (n = 2358)

Records excluded (n = 2161)

Full text assessed for eligibility (n = 197)

Full text articles excluded (n = 86)

- Minimal or non-extractable data (n = 40)
- Colonization – No infection (n = 24)
- No original articles (n = 11)
- Study on microbiology but no clinical data (n = 5)
- Studies not in English (n = 2)
- Studies not referring to humans (n = 2)
- No infection by Rhodotorula (n = 2)

Studies included (n = 111)

FIGURE 1 PRISMA flow diagram

2.4 | Data extraction and definitions

Data from each eligible study were extracted by two investigators (PI and RV). The extracted data included study type, year of publication and country; patient demographic data (age and gender); patient's relevant medical history (diagnosis of cancer, autoimmune disease or chronic kidney disease on peritoneal dialysis); infection data and microbiology (predisposing conditions, such as the presence of a central venous catheter (CVC) or neutropenia—infection site, isolated fungal strains, the presence of complications); treatment administered for the fungal infection; and outcomes (ie, cure or death). Relation of death to the index infection was reported according to the study authors. The complications recorded included any organ dysfunction or clinical deterioration that was considered by the authors to be related to the *Rhodotorula* spp. infection.

3 | RESULTS

3.1 | Literature search

A total of 2358 articles from PubMed were screened. After reviewing the titles and abstracts, 197 articles were selected for full-text review. From them, 86 were excluded: 40 had minimal or no extractable data on outcomes, 24 had data only on colonisation by *Rhodotorula* spp., 16 were not clinical (basic research, reviews or studies only on microbiological data and susceptibility testing only), 2 were not in English, 2 did not involve humans, and another 2 did not involve *Rhodotorula* spp. infection. No additional studies were found by hand-screening of the included articles' references. Finally, 111 met the criteria.[7-117] Additional information was kindly provided by the corresponding author of one study.[35] The review process is graphically presented in Figure 1.

3.2 | Included studies' characteristics

The 111 studies finally included in the present analysis involved a total of 248 patients with 37 of studies conducted in Asia, 35 in Europe, 30 in North America, 6 in South America, 2 in Africa and 1 in Oceania. The final sum included 90 case reports, 10 retrospective, 6 prospective observational studies and 5 case series.

3.3 | Epidemiology, microbiology, treatment and outcomes of *Rhodotorula* spp. infections

The patients' age ranged from neonates to 78 years, with a mean age of 35.7 years; 65.4% were male. The commonest infections were fungaemias in 61.7% (153 patients), central nervous system (CNS) infection in 21.4% (53 patients), ocular infections in 5.6% (14 patients) and peritoneal dialysis-associated peritonitis in 4% (10 patients). The *Rhodotorula* strains reported were *R. mucilaginosa* in 68.6% (170 cases), *R. glutinis* in 11.7% (29 cases), *R. minuta* in 3.2% (8 cases) and *R. marina* in 0.4% (1 case), but in 16.1% (40 cases), species were not reported. The commonest antifungals used were amphotericin B in

71.2% [151 out of 212 cases with available data (w.a.d.)], fluconazole in 25.5% (54 cases), 5-flucytosine in 8% (17 cases), itraconazole in 5.2% (11 cases), voriconazole in 4.7% (10 cases) and ketoconazole in 3.8% (8 cases), while in 9% (19 cases), no antifungal was used. When antifungal treatment was administered, antifungal combination for the treatment of *Rhodotorula* infection was used in 12.3% (26 out of 212 cases). Clinical cure was achieved in 82.9% of cases (155 out of 187 patients w.a.d.), and overall mortality was 17.3% (30 out of 173 patients w.a.d.), but the mortality attributed directly to the *Rhodotorula* infection was 12.1% (21 patients).

3.4 | Fungaemias

Among the 111 *Rhodotorula* infections studies, 54 (48.6%) reported fungaemias, accounting for 153 patients out of 248 (61.7%) in total.[7-60] Among patients with fungaemia, 62.8% were male (76 out of 121 cases w.a.d.) with mean age 33.5 years. Patients with malignancy represented 68.4% (104 out of 152 fungaemias w.a.d.), while haematologic malignancies accounted for 67.1% (55 out of 82 cases with malignancy w.a.d.). When data were provided, 74.1% of patients (40 out of 54 malignancy cases w.a.d.) were receiving chemotherapy at the time of *Rhodotorula* isolation, while 22.3% (23 out of 103 fungaemias w.a.d.) were bone marrow precursor cell or solid organ transplant recipients, namely bone marrow precursor cell transplant recipients in 78.3% (18 out of the 23 cases transplant cases), kidney recipients in 13.4% (3 out of the 23) and liver and lung recipients in 4.35% (1 out of the 23) each. Furthermore, 8.2% (8 out of 97 fungaemias w.a.d.) were recovering from surgery, 4.9% of patients (6 out of 122 fungaemias w.a.d.) were AIDS patients, and 3.8% (5 out of 132 fungaemias w.a.d.) had an autoimmune disease. Importantly, 81.6% (120 out of 147 fungaemias w.a.d.) had a CVC, 29.2% (33 out of 113 fungaemias w.a.d.) had neutropenia, and 34.7% (17 out of 49 fungaemias w.a.d.) were on parenteral nutrition. Interestingly, 28.7% (29 out of 101 fungaemias w.a.d.) had received antifungal prophylaxis, most commonly fluconazole in 72.4% (21 out of 29 cases with prophylaxis) and amphotericin B in 10.3% (3 out of 29 cases). In 4.6% (7 out of 153 fungaemias w.a.d.), a concomitant diagnosis of infective endocarditis (IE) was made. The strains reported were *R. mucilaginosa* in 65.4% (100 out of 153 fungaemias w.a.d.), *R. glutinis* in 12.4% (19 out of 153), *R. minuta* in 2% (3 out of 153), but in 20.3% (31 out of 153), species were not reported. Complications occurred in 79.4% (81 out of 102 fungaemias w.a.d.), with sepsis being the commonest (77.4%; 72 out of 93 fungaemias w.a.d.), while 28.9% (11 out of 38 fungaemias w.a.d.) developed organ dysfunction and 16.1% (5 out of 31 fungaemias w.a.d.) developed shock. For fungaemia treatment, amphotericin B was used in 65.4% (83 out of 127 fungaemias w.a.d.), fluconazole in 15.7% (20 out of 127), 5-flucytosine in 6.3% (8 out of 127), voriconazole in 3.9% (5 out of 127), caspofungin in 2.4% (3 out of 127), ketoconazole and miconazole in 1.6% (2 out of 127 each), while 17.3% (22 out of 127) did not receive treatment. When antifungal treatment was administered, antifungal combination for the treatment of *Rhodotorula* fungaemias was used in 8.7% (11 out of 127). When present, CVC was removed in 74.2% (89 out

of 120 cases with CVC and available data), and in 12.4% of them (11 out of 89 patients with CVC removed), no antifungals were given. Interestingly, 50% of patients that did not receive any antifungal had a CVC removed (11 out of 22). Among the 72 patients w.a.d., the median duration of treatment was 14 days, with a minimum of 3 and a maximum of 90, while 1 patient received long-term treatment due to refusal of CVC removal. Clinical cure was achieved in 83.2% (109 out of 131 fungaemias w.a.d.). Overall mortality was 13.2% (20 out of 151 fungaemias w.a.d.), but the mortality attributed directly to the *Rhodotorula* infection was 9.3% (14 out of 151 fungaemias w.a.d.). Univariate analysis revealed that recent surgery before the occurrence of *Rhodotorula* fungaemia was associated with an increased risk of overall mortality, since among the patients with a *Rhodotorula* fungaemia, 3.1% of the survivors were recovering from surgery, while 20% among those who died were recovering from surgery (*P* = 0.0113). Characteristics of patients with *Rhodotorula* fungaemias are shown in Table 1.

3.5 | CNS infections

Among the 111 *Rhodotorula* infections studies, 18 (16.2%) reported CNS infections, accounting for 53 patients out of 248 (21.4%) in total.[58-75] Of them, 68% were male (17 out of 25 cases w.a.d.) with a mean age was 33.8 years. Importantly, 66% of patients (35 out of 53 w.a.d.) were HIV-positive, while among them, 91.4% (32 out of 35) had AIDS. Interestingly, 7.5% (4 out of 53 cases w.a.d.) did not have any known predisposing factors for developing a CNS *Rhodotorula* infection. The *Rhodotorula* strains reported were *R. mucilaginosa* in 88.7% (44 out of 53 cases w.a.d.) and *R. glutinis* in 9.4% (5 out of 53), while in 1.9% (1 out of 53), the species was not reported. Amphotericin B was used in 93% (40 out of 43 cases w.a.d.), fluconazole in 69.8% (30 out of 43), 5-flucytosine in 9.3% (4 out of 43), itraconazole in 4.7% (2 out of 43) and miconazole in 2.3% (1 out of 43). When antifungal treatment was administered, antifungal combination for the treatment of *Rhodotorula* CNS infections was used in 7% (3 out of 43 cases). Among the 12 patients w.a.d., the median duration of treatment was 22 days, with a minimum of 14 and a maximum of 180. Clinical cure was achieved in 58.9% (10 out of 17 patients with CNS infection and available data) and overall mortality in 41.1% (7 out of 17), with all deaths attributed directly to the *Rhodotorula* infection. No parameter from the ones mentioned above was shown to be associated with higher overall mortality, when univariate statistical analysis was performed. Characteristics of patients with *Rhodotorula* CNS infection are shown in Table 2.

3.6 | Ocular infections

Among the 111 studies, 14 (12.6%) reported *Rhodotorula* ocular infections, accounting for 14 patients out of 248 in total (5.6%) with a mean age of 42.1 years.[76-89] Among them, 78.6% were male (11 out of 14). Cases consisted of keratitis in 50% (7 out of 14), endophthalmitis in 35.7% (5 out of 14), scleritis in 7.1% (1 out of 14) and dacryocystitis along with keratitis in 7.1% (1 out of 14). All keratitis

TABLE 1 Characteristics of patients with *Rhodotorula* species fungaemias

Characteristic	Value
Male, n (%)	76 out of 121 (62.8%)
Age, mean (±SD) in years	33.5 (21.2)
Medical history	
Active malignancy, n (%)	104 out of 152 (68.4%)
Haematologic malignancy (among patients with malignancy), n (%)	55 out of 82 (67.1%)
Solid malignancy (among patients with malignancy), n (%)	27 out of 82 (32.9%)
Malignancy on chemotherapy, n (%)	40 out of 54 (74.1%)
Bone marrow precursor cell or solid organ transplant recipients, n (%)	23 out of 103 (22.3%)
Post-surgery, n (%)	8 out of 97 (8.2%)
HIV positive, n (%)	6 out of 122 (4.9%)
AIDS, n (%)	6 out of 122 (4.9%)
Autoimmune syndrome, n (%)	5 out of 132 (3.8%)
Central venous catheter, n (%)	120 out of 147 (81.6%)
Previous antibiotic use, n (%)	50 out of 79 (63.3%)
Parenteral nutrition, n (%)	17 out of 49 (34.7%)
Neutropenia, n (%)	33 out of 113 (29.2%)
Patients on antifungal prophylaxis, n (%)	29 out of 101 (28.7%)
Type of antifungal prophylaxis	
Fluconazole, n (%)	21 out of 29 (72.4%)
Amphotericin B, n (%)	3 out of 29 (10.3%)
Micafungin, n (%)	2 out of 29 (6.9%)
Ketoconazole, n (%)	1 out of 29 (3.5%)
Posaconazole, n (%)	1 out of 29 (3.5%)
Anidulafungin, n (%)	1 out of 29 (3.5%)
Voriconazole, n (%)	1 out of 29 (3.5%)
***Rhodotorula* species**	
R. mucilaginosa, n (%)	100 out of 153 (65.4%)
Rhodotorula spp. (species unknown), n (%)	31 out of 153 (20.3%)
R. glutinis, n (%)	19 out of 153 (12.4%)
R. minuta, n (%)	3 out of 153 (2%)
Patients with sepsis, n (%)	72 out of 93 (77.4%)
Patients with organ dysfunction, n (%)	11 out of 38 (28.9%)
Patients with shock, n (%)	5 out of 31 (16.1%)
Treatment of *Rhodotorula* fungaemias	
Amphotericin B, n (%)	83 out of 127 (65.4%)
Fluconazole, n (%)	20 out of 127 (15.7%)
Flucytosine, n (%)	8 out of 127 (6.3%)
Voriconazole, n (%)	5 out of 127 (3.9%)
Caspofungin, n (%)	3 out of 127 (2.4%)

(Continues)

TABLE 1 (Continued)

	Value
Miconazole, n (%)	2 out of 127 (1.6%)
Ketoconazole, n (%)	2 out of 127 (1.6%)
No antifungals, n (%)	25 out of 127 (17.3%)
Antifungal combination used	11 out of 127 (8.7%)
Central venous catheter removal, n (%)	89 out of 120 (74.2%)
Duration of treatment, median (IQR) in days	14 (13.4-21)
Outcome	
Clinical cure, n (%)	109 out of 131 (83.2%)
Deaths due to the infection, n (%)	14 out of 151 (9.3%)
Deaths overall, n (%)	20 out of 151 (13.2%)

Values show cases among patients with available data.
AIDS, acquired immunodeficiency syndrome; HIV, human immunodeficiency virus; IQR, intraquartile range; SD, standard deviation.

and scleritis cases were preceded by trauma or surgery (9 out of 9). In 80% of the endophthalmitis cases (4 out of 5), patients were intravenous drug users, while in 20% (1 patient), endophthalmitis was preceded by surgery. The *Rhodotorula* strains reported were *R. mucilaginosa* in 35.7% (5 out of 14), *R. glutinis* in 14.3% (2 out of 14) and *R. minuta* in 14.3% (2 out of 14), while in 35.7% (5 out of 14), species were not reported. Amphotericin B was used in 85.7% (12 out of 14), voriconazole in 14.3% (2 out of 14), and 5-flucytosine, posaconazole, itraconazole and miconazole in 7.1% (1 out of 14 cases) each. Antifungal combination for the treatment of *Rhodotorula* ocular infections was used in 35.7% (5 out of 14). Among the 8 patients w.a.d., the median duration of treatment was 30 days, with a minimum of 14 and a maximum of 90. Among the reported cases, 84.6% (11 out of 13 patients w.a.d.) also had surgical treatment. Clinical cure was achieved in 84.6% (11 out of 13 patients w.a.d.), and no patient died, but 84.6% (11 out of 13) eventually had reduced visual acuity or blindness. Characteristics of patients with *Rhodotorula* ocular infections are shown in Table 3.

3.7 | Peritoneal dialysis-associated peritonitis

Among the 111 studies, 8 (7.2%) reported peritoneal dialysis-associated *Rhodotorula* peritonitis, accounting for 10 patients out of 248 in total (4%) with a mean age of 41.6 years.[90-97] Of them, 70% were male (7 out of 10). The strains reported were *R. mucilaginosa* in 80% (8 out of 10) and *R. glutinis* and *R. minuta* in 10% (1 case) each. Amphotericin B was used in 80% (8 out of 10), fluconazole in 30% (3 out of 10), and 5-flucytosine and ketoconazole in 20% (2 out of 10) each. Antifungal combination for the treatment of *Rhodotorula* peritoneal dialysis-associated peritonitis was used in 20% (2 out of 10 cases). The dialysis catheter was removed in 70% (7 out of 10). Among the 8 patients w.a.d., the median duration of treatment was 22 days, with a minimum of 1 and a maximum of 70. Clinical cure was achieved in 100% (10 patients). There was one death (10%; 1 out of

TABLE 2 Characteristics of patients with *Rhodotorula* species central nervous infections

	Value
Characteristic	
Male, n (%)	17 out of 25 (68%)
Age, mean (±SD) in years	33.8 (14.5)
Medical history	
HIV positive, n (%)	35 out of 53 (66%)
AIDS (among HIV-positive patients), n (%)	32 out of 35 (91.4%)
Active malignancy, n (%)	3 out of 25 (12%)
Haematologic malignancy (among patients with malignancy), n (%)	2 out of 3 (66.7%)
Solid malignancy (among patients with malignancy), n (%)	1 out of 3 (33.3%)
Autoimmune syndrome, n (%)	2 out of 25 (8%)
No known predisposing factors, n (%)	4 out of 53 (7.5%)
Rhodotorula species	
R. mucilaginosa, n (%)	47 out of 53 (88.7%)
R. glutinis, n (%)	5 out of 53 (9.4%)
Rhodotorula spp. (species unknown), n (%)	1 out of 53 (1.9%)
Treatment of *Rhodotorula* CNS infections	
Amphotericin B, n (%)	40 out of 43 (93%)
Fluconazole, n (%)	30 out of 43 (69.8%)
Flucytosine, n (%)	4 out of 43 (9.3%)
Itraconazole, n (%)	2 out of 43 (4.7%)
Miconazole, n (%)	1 out of 43 (2.3%)
No antifungals, n (%)	0 out of 43 (0%)
Antifungal combination used	3 out of 43 (7%)
Duration of treatment, median (IQR) in days	22 (15.25-63.75)
Outcome	
Clinical cure, n (%)	10 out of 17 (58.9%)
Deaths due to the infection, n (%)	7 out of 17 (41.1%)
Deaths overall, n (%)	7 out of 17 (41.1%)

Values show cases among patients with available data.
AIDS, acquired immunodeficiency syndrome; CNS, central nervous system; HIV, human immunodeficiency virus; IQR, intraquartile range; SD, standard deviation.

10 patients) that could not be attributed to the *Rhodotorula* infection. Eventually, 62.5% (5 out of 8 patients w.a.d.) failed peritoneal dialysis and changed modality of renal replacement therapy. Characteristics of patients with *Rhodotorula* peritoneal dialysis-associated peritonitis are shown in Table 4.

3.8 | Endocarditis

Among the 111 studies on *Rhodotorula* infections, 9 (8.1%) reported endocarditis, accounting for 9 patients out of 248 (3.6%) in total.[9,16,24,33,39,41,59,101,104] Among them, 66.7% were male (6 out of 9) with a mean age of 41.3 years. Fungaemia was present in 77.8% (7 out

TABLE 3 Characteristics of patients with *Rhodotorula* species ocular infections

	Value
Characteristic	
Male, n (%)	11 out of 14 (78.6%)
Age, mean (±SD) in years	42.1 (18.7)
Medical history	
HIV positive, n (%)	2 out of 14 (14.3%)
AIDS (among HIV-positive patients), n (%)	2 out of 2 (100%)
Active malignancy, n (%)	0 out of 14 (0%)
Autoimmune syndrome, n (%)	0 out of 14 (0%)
Type of ocular infection	
Keratitis, n (%)	7 out of 14 (50%)
Endophthalmitis, n (%)	5 out of 14 (35.7%)
Scleritis, n (%)	1 out of 14 (7.1%)
Dacryocystitis & keratitis, n (%)	1 out of 14 (7.1%)
Rhodotorula species	
R. mucilaginosa, n (%)	5 out of 14 (35.7%)
Rhodotorula spp. (species unknown), n (%)	5 out of 14 (35.7%)
R. glutinis, n (%)	2 out of 14 (14.3%)
R. minuta, n (%)	2 out of 14 (14.3%)
Treatment of *Rhodotorula* ocular infections	
Amphotericin B, n (%)	12 out of 14 (85.7%)
Ketoconazole, n (%)	2 out of 14 (14.3%)
Voriconazole, n (%)	2 out of 14 (14.3%)
Itraconazole, n (%)	1 out of 14 (7.1%)
Posaconazole, n (%)	1 out of 14 (7.1%)
Miconazole, n (%)	1 out of 14 (7.1%)
Flucytosine, n (%)	1 out of 14 (7.1%)
No antifungals, n (%)	0 out of 14 (0%)
Antifungal combination used	5 out of 14 (35.7%)
Surgical management, n (%)	11 out of 13 (84.6%)
Duration of treatment, median (IQR) in days	30 (17.5-75)
Outcome	
Clinical cure, n (%)	11 out of 13 (84.6%)
Complicated by reduced visual acuity, n (%)	11 out of 13 (84.6%)
Deaths overall, n (%)	0 out of 14 (0%)

Values show cases among patients with available data.
AIDS, acquired immunodeficiency syndrome; HIV, human immunodeficiency virus; IQR, intraquartile range; SD, standard deviation.

of 9 cases), while in the cases of the other 2 patients, *Rhodotorula* species grew from a heart valve and a cardiac bioprosthetic material. The strains reported were *R. mucilaginosa* in 44.4% (4 out of 9) and *R. glutinis* in 11.1% (1 out of 9), while in 44.4% (4 out of 9), species were not reported. Amphotericin B was used in 66.7% (6 out of 9), 5-flucytosine in 22.2% (2 out of 9) and fluconazole, voriconazole and itraconazole in 11.1% (1 out of 9) each, while antifungal treatment was not administrated in 22.2% (2 out of 9). Surgery was

TABLE 4 Characteristics of patients with *Rhodotorula* species peritoneal dialysis-associated peritonitis

	Value
Characteristic	
Male, n (%)	7 out of 10 (70%)
Age, mean (±SD) in years	41.6 (20.1)
Medical history	
HIV positive, n (%)	1 out of 10 (0%)
AIDS (among HIV-positive patients), n (%)	0 out of 1 (0%)
Autoimmune syndrome, n (%)	1 out of 10 (10%)
Active malignancy, n (%)	0 out of 10 (0%)
Rhodotorula species	
R. mucilaginosa, n (%)	8 out of 10 (80%)
R. glutinis, n (%)	1 out of 10 (10%)
R. minuta, n (%)	1 out of 10 (10%)
Patients with sepsis, n (%)	1 out of 5 (20%)
Treatment of *Rhodotorula* ocular infections	
Amphotericin B, n (%)	8 out of 10 (80%)
Fluconazole, n (%)	3 out of 10 (30%)
Ketoconazole, n (%)	2 out of 10 (20%)
Flucytosine, n (%)	2 out of 10 (20%)
No antifungals, n (%)	0 out of 10 (0%)
Antifungal combination used	2 out of 10 (20%)
Removal of peritoneal dialysis catheter, n (%)	7 out of 10 (70%)
Duration of treatment, median (IQR) in days	22 (14-57.75)
Outcome	
Clinical cure, n (%)	10 out of 10 (100%)
Changed modality of renal replacement therapy, n (%)	5 out of 8 (62.5)
Deaths due to the infection, n (%)	0 out of 10 (0%)
Deaths overall, n (%)	1 out of 10 (10%)

Values show cases among patients with available data.
AIDS, acquired immunodeficiency syndrome; HIV, human immunodeficiency virus; IQR, intraquartile range; SD, standard deviation.

performed in 22.2% (2 out of 9) cases. Among the 6 patients w.a.d., the median duration of treatment was 6 weeks, with a minimum of 4 and a maximum of 12 weeks, while 1 patient continued on voriconazole indefinitely. Combination treatment has been given to 22.2% (2 out of 9 patients). Clinical cure was achieved in 77.8% (7 patients). There were two deaths (22.2%; 2 out of 9 patients), with only one directly attributed to the *Rhodotorula* infection. Characteristics of patients with *Rhodotorula* endocarditis are shown in Table 5.

3.9 | Miscellaneous infections

Less frequent *Rhodotorula* species infections included skin infections in 2% (5 out of 248), bone and joint infections in 1.6% (4 out of 248), lower respiratory tract infections and onychomycosis in

TABLE 5 Characteristics of patients with *Rhodotorula* species infective endocarditis

	Value
Characteristic	
Male, n (%)	6 out of 9 (66.7%)
Age, mean (±SD) in years	41.3 (19.5)
Medical history	
Haematologic malignancy, n (%)	1 out of 9 (11.1%)
Organ transplantation, n (%)	1 out of 9 (11.1%)
HIV positive, n (%)	0 out of 9 (0%)
Central venous catheter	3 out of 9 (33.3%)
Evidence of fungaemia	7 out of 9 (77.8%)
Rhodotorula species	
R. mucilaginosa, n (%)	4 out of 9 (44.4%)
Rhodotorula spp. (species unknown), n (%)	4 out of 9 (44.4%)
R. glutinis, n (%)	1 out of 9 (11.1%)
Treatment of *Rhodotorula* endocarditis	
Amphotericin B, n (%)	6 out of 9 (66.7%)
Flucytosine, n (%)	2 out of 9 (22.2%)
Fluconazole, n (%)	1 out of 9 (11.1%)
Voriconazole, n (%)	1 out of 9 (11.1%)
Itraconazole, n (%)	1 out of 9 (11.1%)
No antifungals, n (%)	2 out of 9 (22.2%)
Surgery (cardiac valve replacement), n (%)	2 out of 9 (22.2%)
Duration of treatment, median (IQR) in weeks	6 (4-8)
Outcome	
Clinical cure, n (%)	7 out of 9 (77.8%)
Deaths due to the infection, n (%)	1 out of 9 (11.1%)
Deaths overall, n (%)	2 out of 9 (22.2%)

Values show cases among patients with available data.
HIV, human immunodeficiency virus; IQR, intraquartile range; SD, standard deviation.

1.2% (3 out of 248) each, liver and intra-abdominal infections in 0.8% (2 out of 248) each, and pelvic infection, urinary tract infection, non-peritoneal dialysis-associated peritonitis, supraclavicular lymphadenitis and infected mouth ulcer in 0.4% (1 out of 248) each.

4 | DISCUSSION

During the last decades, several emerging fungi have been described causing invasive diseases in immunocompromised patients.[118] Besides *Candida* spp., many other fungi have emerged as potential pathogens in such patients.[119] This systematic review provides thorough information on epidemiology, clinical characteristics, treatment and outcomes of *Rhodotorula* species infections. Fungaemias, CNS infections, ocular infections and peritoneal dialysis-associated peritonitis were the most common, while very different predisposing factors have been identified for each of them.

Fungaemia, being the commonest *Rhodotorula* species infection reported in the literature, affects mostly young people. The presence of CVC, malignancy on chemotherapy and/or previous chemotherapy, recent antimicrobial treatment, total parenteral nutrition, neutropenia, bone marrow precursor cell or solid organ transplantation, recent surgery and AIDS were highly prevalent in patients with *Rhodotorula* fungaemia, implicating these factors as important risks, as reported previously.[3] It is of note that these factors have been repeatedly identified to predispose to other invasive mycoses as well.[120-122] When univariate statistical analysis was performed, only recent surgery before the occurrence of *Rhodotorula* fungaemia was associated with an increased risk of overall mortality. However, multivariate analysis could not be performed with the present data, since there are many missing values.

Interestingly, this review has revealed that almost 30% of the study's patients who were on antifungal prophylaxis developed *Rhodotorula* fungaemia. This could be explained since in most cases the prophylactic agent was fluconazole, while *Rhodotorula* should be actually considered intrinsically resistant to this drug.[123-125] For treatment of *Rhodotorula* fungaemia, amphotericin B was the commonest antifungal regimen used, and CVC, whenever present, was usually removed. Mortality has reached 10%, being not that high, as compared to that caused by *Candida* species fungaemia.[122]

Rhodotorula species CNS infections were the second most common in the literature. AIDS, malignancy on chemotherapy and autoimmune diseases were the commonest underlying conditions, while, surprisingly, 7.5% of patients did not have an obvious predisposing factor. Importantly, patients with an HIV infection, who represented 2 out of 3 patients with *Rhodotorula* species CNS infections, are known to be prone to Cryptococcal meningitis.[126,127] Hence, differential diagnosis between Cryptococcal and *Rhodotorula* meningitis can be crucial, given that *Rhodotorula* is resistant to fluconazole, an antifungal commonly used in the case of Cryptococcal infection.[123-126] However, there are no guidelines on the treatment of *Rhodotorula* meningitis, probably due to the rarity of this infection. Thus, it is not surprising that the present review revealed that the commonest antifungals used for treatment of *Rhodotorula* CNS infection were not only amphotericin B, but also 5-flucytosine and fluconazole—antifungals used for Cryptococcal meningitis. Mortality has reached 40%, being similar to—or even higher than—the mortality of Cryptococcal meningitis.[128] This finding underlines the need to recognise *Rhodotorula* meningitis as a potentially lethal CNS infection; therefore, development of guidelines on the appropriate management of this disease is of utmost importance.

Rhodotorula species ocular infections represent mainly cases of keratitis. However, it must be underlined that almost 1 out of 3 ocular infections were endophthalmitis, and 3 out of 4 occurred in intravenous drug users. This finding is in accordance with the literature, since fungal endophthalmitis is an increasingly recognised condition in intravenous drug users, immunocompromised individuals and in otherwise healthy individuals after eye surgery.[129] Importantly, even though no patient with ocular infection died, vision loss or markedly reduced visual acuity was a common complication of these

infections; this is in line with the literature, where fungal keratitis has been shown to be associated with poor visual outcome, not necessarily due to the infection itself, but mainly to its complications.[130,131] However, it has to be noticed that *Rhodotorula* is quite an uncommon organism for ocular infections.[129-131]

As with ocular infections, peritoneal dialysis-associated peritonitis due to *Rhodotorula* species is an uncommon infection. The present review has revealed that mortality was not high and treatment was successful in all cases. However, more than half of the patients eventually failed peritoneal dialysis and had to change the modality of renal replacement therapy. Indeed, fungal peritonitis is associated with high risk of progression to sclerosing peritonitis due to peritoneal inflammation.[132-134]

The present systematic review has certain limitations that should be acknowledged. First of all, it mostly consists of case reports and case series. This implies that the results should be read cautiously, as case reports are descriptions of unusual presentations, while the usual ones may be underrepresented in a systematic review consisting of such studies. However, the present methodology was the only reliable way to study systematically *Rhodotorula* infections. If case reports, case series and studies describing less than 4 patients were excluded, as other investigators have done,[135] there would be only 8 studies left for inclusion with less than half of the patients being currently analysed.[28,29,32,44,46,50,60,73] However, even in that case, the review would be biased, since only fungaemias and CNS infections would have been reported. On the other hand, since *Rhodotorula* infections are quite rare, one would expect this study to be representative enough, including all possible clinical presentations. Hence, all well-described and informative cases reliably demonstrating the nature of the disease have been included in the analysis.

In conclusion, the epidemiology, clinical characteristics, microbiology, treatment and outcome of the *Rhodotorula* spp. infections with important clinical implications have been presented. Physicians caring for patients at risk should become familiar with these infections, since they carry considerable mortality and the causative organism has different antifungal resistance patterns than other commonly encountered yeast.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

ORCID

Petros Ioannou (iD) http://orcid.org/0000-0003-1082-5674

George Samonis (iD) http://orcid.org/0000-0001-5857-9703

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