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ESCMID† and ECMM‡ joint clinical guidelines for the diagnosis and management of rare invasive yeast infections

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Abstract

The mortality associated with invasive fungal infections remains high with that involving rare yeast pathogens other than *Candida* being no exception. This is in part due to the severe underlying conditions typically predisposing patients to these healthcare-related infections (most often severe neutropenia in patients with haematological malignancies), and in part due to the often challenging intrinsic susceptibility pattern of the pathogens that potentially leads to delayed appropriate antifungal treatment. A panel of experts of the European Society of Clinical Microbiology and Infectious Diseases (ESCMID) Fungal Infection Study Group (EFISG) and the European Confederation of Medical Mycology (ECMM) undertook a data review and compiled guidelines for the diagnostic tests and procedures for detection and management of rare invasive yeast infections. The rare yeast pathogens were defined and limited to the following genera/species: *Cryptococcus adeliensis*, *Cryptococcus albidus*, *Cryptococcus curvatus*, *Cryptococcus flavescens*, *Cryptococcus laurentii* and *Cryptococcus uniguttulatus* (often published under the name *Filobasidium uniguttulatum*), *Malassezia furfur*, *Malassezia globosa*, *Malassezia pachydermatis* and *Malassezia restricta*, *Pseudozyma* spp., *Rhodotorula glutinis*, *Rhodotorula minuta* and *Rhodotorula mucilaginosa*, *Sporobolomyces* spp., *Trichosporon asahii*, *Trichosporon asteroides*, *Trichosporon dermatis*, *Trichosporon inkin*, *Trichosporon jirovecii*, *Trichosporon loubieri*, *Trichosporon mucoides* and *Trichosporon mycotoxinivorans* and ascomycetous ones: *Geotrichum candidum*, *Kodamaea ohmeri*, *Saccharomyces cerevisiae* (incl. *S. boulardii*) and *Saprochaete capitatae* (*Magnusiomyces* (*Blastoschizomyces*) *capitatus* formerly named *Trichosporon capitatum* or *Geotrichum* (*Dipodascus*) *capitatum*) and *Saprochaete clavata*. Recommendations about the microbiological investigation and detection of invasive infection were made and current knowledge on the most appropriate antifungal and supportive treatment was reviewed. In addition, remarks about antifungal susceptibility testing were made.

Keywords: Clinical guideline, *cryptococcus*, *Geotrichum*, *Kodamaea*, *Malassezia*, *Pseudozyma*, *Rhodotorula*, *Saccharomyces*, *Saprochaete*, *Sporobolomyces*, *Trichosporon*

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Introduction

In 2012 the first official European Society for Clinical Microbiology and Infectious Diseases (ESCMID) guideline on the diagnosis and treatment of a fungal infection was published [1–6]. Mucosal and invasive candidosis were covered and a comprehensive consensus guideline was developed with the participation of many experts from the ESCMID Fungal Infection Study Group (EFISG) representing many European countries. Before publication the recommendations were presented for discussion at a European Congress for Clinical Microbiology and Infectious Diseases (ECCMID) workshop and the subsequent manuscripts underwent peer-review before publication in the ESCMID journal, *Clinical Microbiology and Infection*.

Following the same rigorous procedure, EFISG continued the ESCMID guideline development process—this time in collaboration with the European Confederation of Medical Mycology (ECMM) and focusing on rare invasive fungal infections. The definition of such pathogens is somewhat pragmatic but yeasts other than *Candida*, mucorales, hyalohyphomycetous and dematiaceous fungi that are not common causes of invasive infections were included. This guideline presents the diagnostic and management guideline for 'rare invasive yeast infections' including several basidiomycetous yeasts: *Cryptococcus adeliensis*, *Cryptococcus albidus*, *Cryptococcus curvatus*, *Cryptococcus flavescens*, *Cryptococcus laurentii* and *Cryptococcus uniguttulatus* (often published under the name *Filobasidium uniguttulatum*), *Malassezia furfur*, *Malassezia globosa*, *Malassezia pachydermatis* and *Malassezia restricta*, *Pseudozyma* spp., *Rhodotorula glutinis*, *Rhodotorula minuta* and *Rhodotorula mucilaginosa*, *Sporobolomyces* spp., *Trichosporon asahii*, *Trichosporon asteroides*, *Trichosporon dermatis*, *Trichosporon inkin*, *Trichosporon jirovecii*, *Trichosporon loubieri*, *Trichosporon mucoides* and *Trichosporon mycotoxinivorans* and ascomycetous ones: *Geotrichum candidum*, *Kodamaea ohmeri*, *Saccharomyces cerevisiae* (incl. *S. boulardii*) and *Saprochaete capitatae* (*Magnusiomyces (Blastoschizomyces) capitatus* formerly named *Trichosporon capitatum* or *Geotrichum* (*Dipodascus*) *capitatum*) and *Saprochaete clavata*.

The selection of organisms has been based on the following criteria: (i) species were only included if they were documented as a cause of human invasive infections and (ii) rare *Candida* species were excluded because we anticipate that readers would probably refer to the ESCMID *Candida* guidelines rather than a rare invasive yeast infection guideline concerning species like *Candida palmioleophila* etc. although such species fulfil the term of being a rare cause of invasive infections. The species not considered being documented as cause of invasive human disease included *Cryptococcus albidosimilis*, *Cryptococcus diffluens*, *Cryptococcus humicola* and *Cryptococcus uzbekistanensis*, *Trichosporon* spp. others than those mentioned above, *Blastobotrys proliferans*, *Millerozyma farinosa*, *Ogataea polymorpha* and *Guehomyces pullulans*. Finally, the guideline was limited to true yeasts and hence the unicellular algae *Prototheca wickerhamii* and *Prototheca zopfii* var. *zopfii* were excluded although we realize they have been misidentified as yeasts on occasion.

For the uncommon *Candida* species we refer the reader to the general recommendations regarding diagnosis and treatment as described in the ESCMID *Candida* guideline [1–6]. However, as some of these species are characterized by unique intrinsic susceptibility patterns, which are not specifically addressed in the *Candida* guidelines, a table summarizing this information has been elaborated and included here (Table 1, [7–19]). This table also includes names used in the anamorphic and teleomorphic states, despite this distinction recently being made superfluous [20].

General recommendations regarding collection, transport and storage of clinical specimens, direct examination, isolation and identification procedures, which are valid for all yeast-associated human infections, can be found in appropriate textbooks (e.g. Barnett *et al.* [21]) and are not mentioned here. Only specific features regarding genus identifications for the specific yeasts discussed herein were considered. The methods to evaluate the quality of evidence and to reach consensus recommendations were described previously [1]. Strength of recommendations' quality of evidence was graded according to the criteria outlined in Table 2.

Rare Invasive Yeast Infections

It is important to underscore that the fungal organisms covered in this guideline are not rare *per se*. A number of the 'rare yeasts' are encountered as frequent colonizers of human skin, mucosal surfaces, in food items or in the environment. In the normal host, infections are typically limited to various superficial infections like pityriasis versicolor, white piedra and occasionally onychomycosis, the management of which are dealt with in dermatology guidelines [22–25]. However, in the immunosuppressed or otherwise compromised host, invasive infections may occur, some being related to the presence of a central venous catheter (CVC) and a few reported as nosocomial clusters that require molecular approaches to be properly documented. As predicted from their low pathogenicity, invasive infections are still reported at low numbers in severely immunocompromised hosts (Table 3) [26–30]. For example, these organisms together constituted 1.1% of the

TABLE 1. Summary of rare *Candida* species that have been associated with human infection (by anamorphic and teleomorphic name). Remarks that may be relevant in the clinical context are included. References are kept to a minimum as these species are not the topic of this guideline

Anamorphic state	Teleomorphic state	Specific comment relevant in clinical context
C. africana	Not described	Closely related to *C. albicans*. Intrinsic susceptibility pattern as for this species. Probably less pathogenic than *C. albicans* and almost exclusively found in female genital tract specimens [7]
C. auris	Not described	Related to *C. haemulonii*. Fluconazole MICs higher than for *C. albicans* [8]
C. bracarensis	Not described	Closely related to *C. glabrata*. Susceptibility pattern as for *C. glabrata* (azole MICs elevated compared with *C. albicans*) [9]
C. ciferrii	*Trichomonascus ciferrii*	Clinical significance uncertain. Inherent resistance to several antifungal compounds described [10]
C. dubliniensis	Not described	Closely related to *C. albicans*. Intrinsic susceptibility pattern as for this species. However, potential for acquired resistance to fluconazole appears to be greater than for *C. albicans* [11]
C. fabianii	*Cyberlindnera fabianii*	Clinical significance uncertain. Fluconazole MICs higher than for *C. albicans* [12]
C. famata	*Debaromyces hansenii*	This species has been reported as an infrequent cause of fungaemia. However, recent data questions if this species is actually human pathogenic (lack of growth at 37°C and no cases confirmed by sequencing [13]
C. guilliermondii	*Meyerozyma guilliermondii*	Closely related to *C. fermentati* and *C. palmioleophila*. High echinocandin and azole MICs [13]
C. haemulonii (incl. *C. duobushaemulonii*)	Not described	Emerging evidence suggests that it may be a human pathogen related to superficial infections and central venous catheter-related fungaemia, particularly in Brazil, the Caribbean and Asian regions. Elevated azole and amphotericin MICs are reported. Related to *C. auris* [14]
C. hellenica	*Zygoascus meyerae*	Fungaemia and respiratory infection has been reported. Decreased susceptibility to fluconazole, itraconazole, caspofungin, susceptible to voriconazole [15]
C. inconspicua	Not described	Closely related to *C. norvegensis*. Susceptibility pattern similar to *C. krusei* (intrinsically resistant to fluconazole) [16]
C. intermedia	Not described	Oropharyngeal colonizer, bloodstream infections, peritonitis. Susceptible to antifungal drugs except flucytosine [13]
C. kefyr	*Kluyveromyces marxianus*	No inherent resistance to antifungals described
C. lipolytica	*Yarrowia lipolytica*	Clinical significance uncertain. Fluconazole MICs higher than for *C. albicans*.
C. lusitaniae	*Clavispora lusitaniae*	Not a good target for amphotericin B even if MICs are in the susceptible range (≤1 mg/L) [17]
C. metapsilosis	Not described	Closely related to *C. parapsilosis*. Susceptibility pattern similar to this species (high echinocandin MICs) [18]
C. nivariensis	Not described	Closely related to *C. glabrata*. Susceptibility pattern as for *C. glabrata* (decreased susceptibility to azoles) [9]
C. norvegensis	*Pichia norvegensis*	Closely related to *C. inconspicua*. Susceptibility pattern similar to *C. krusei* (intrinsically resistant to fluconazole) [16]
C. orthopsilosis	Not described	Closely related to *C. parapsilosis*. Susceptibility pattern similar to this species (high echinocandin MICs) [18]
C. palmioleophila	Not described	Phenotypically related to *C. guilliermondii*. High azole MICs (but low echinocandin MICs in contrast to those for *C. guilliermondii*) [13]
C. pelliculosa	*Wickerhamomyces anomalus* (prev. *Pichia anomala*, *Hansenula anomala*)	Fluconazole MICs higher than for *C. albicans* [19]
C. pulcherrima	*Pichia kudriavzevii* (prev. *Metschnikowia pulcherrima*)	Clinical significance uncertain
C. rugosa	Not described	Fluconazole MICs higher than for *C. albicans* [19]
C. subhashii	Not described	Clinical significance uncertain
C. viswanathii	Not described	Clinical significance uncertain
C. zeylanoides	Not described	Clinical significance uncertain

TABLE 2. Strength of the EFISG and ECMM recommendation and quality of evidence

Strength of a recommendation (SoR)

Grade A	ESCMID and ECMM strongly support a recommendation for use
Grade B	ESCMID and ECMM moderately support a recommendation for use
Grade C	ESCMID and ECMM marginally support a recommendation for use
Grade D	ESCMID and ECMM support a recommendation against use

Quality of evidence (QoE)

Level I	Evidence from at least one properly designed randomized, controlled trial
Level II[a]	Evidence from at least one well-designed clinical trial, without randomization; from cohort or case–controlled analytical studies (preferably from more than one centre); from multiple time series; or from dramatic results of uncontrolled experiments
Level III	Evidence from opinions of respected authorities, based on clinical experience, descriptive case studies, or reports of expert committees

[a]Added index: $_r$: Meta-analysis or systematic review of randomized controlled trials. $_t$: Transferred evidence, that is, results from different patients' cohorts, or similar immune-status situation. $_h$: Comparator group is a historical control. $_u$: Uncontrolled trial. $_a$: Published abstract (presented at an international symposium or meeting).

almost 4000 fungaemia isolates in an 8-year national surveillance programme in Denmark [26,27]. In Paris, they represented 5.1% of the 3668 fungaemia isolates in a prospective surveillance programme from 2002 to 2012 (YEASTS Network, National Reference Centre for Invasive Mycoses and Antifungals, Paris, France (O. Lortholary, unpublished data), Table 3).

Saccharomyces cerevisiae is a biotechnologically highly important fungus with a broad use in the production of food and alcoholic beverages etc. Phylogenetically, the species is relatively closely related to *Candida glabrata* [31].

As most of these rare invasive yeast infections occur in the haematology and Intensive Care Unit (ICU) settings, clinicians should be aware that all of the responsible fungal species, presumably except *Saccharomyces* spp. and *Kodamaea ohmeri*, are regarded as intrinsically resistant to echinocandins. As a result of the rare nature of these pathogens, controlled prospective and comparative clinical trials are not feasible so solid data on treatment efficacy cannot be compiled. Moreover, clinical susceptibility breakpoints have not been established. Hence, management recommendations derive from clinical experience (cohort or case–controlled analytical studies, from multiple time series), pragmatic interpretations of susceptibility data and limited animal studies when available. Also because of their rare incidence, primary prophylaxis is not indicated unless specific local epidemiology suggests otherwise. As specific diagnostic surrogate markers have not been developed for these organisms (apart from the antigen test for *Cryptococcus* but mainly evaluated for *Cryptococcus*

TABLE 3. Summary of rare yeast isolates collected during the national surveillance programme in Denmark 2004–2011 and the surveillance programme in Paris hospitals, France October 2002–May 2012. Only unique isolates are included. For comparison and representing other parts of the world data from a US cancer centre, the Artemis study and a Brazilian study are included

	DK (national) [26,27]	Paris Hosp.[a]	US (cancer centre) [28]	Artemis study 1997–2007 [29]	Sao Paulo Brazil [30]
Fungaemia isolates (total)	3982	3668	3382	NA	1195
Rare yeasts other than *Candida*	44 (1.1%)	188 (5.1%)	94 (2.8%)	11,240	174 (14.5%)
Cryptococcus neoformans	13 (29.5%)	137 (72.8%)	NA	3,512 (31.2%)	79 (45.4%)
Cryptococcus spp.	1 (2.3%)	1 (0.5%)	NA	113 (1.0%)	NA
Geotrichum spp.	2 (4.5%)	19 (10.1%)	2 (5%)	NA	NA
Rhodotorula spp.	4 (9.1%)	5 (2.7%)	21 (51%)	462 (4.1%)	28 (16.1%)
Saccharomyces spp.[b]	22 (50.0%)	14 (7.4%)	8 (20%)	1,321 (11.8%)	NA
Trichosporon spp.	2 (4.5%)	11 (5.9%)	8 (20%)	1,196 (10.6%)	NA
Malassezia spp.	0	1	1 (2%)	NA	NA
Pichia anomala	0	NA	1 (2%)	28 (0.2%)	32 (18.4%)
Saprochaete capitata	0	NA	NA	109 (1.0%)	NA

NA, Not available.
[a]YEASTS Network, National Reference Centre for Invasive Mycoses and Antifungals, Paris, France (unpublished data).
[b]Taxonomically also a *Candida* species (*C. robusta*).

neoformans), blood culture remains an essential investigation for the detection of invasive infection and the general recommendations concerning volume and sampling frequency should be followed [32–34]. Emerging evidence has highlighted the additional yield obtained for candidaemia when a fungal blood culture bottle is included to specifically support the growth of fungi and at the same time avoid suppression by concomitant faster growing microorganisms [35–38]. It remains to be demonstrated if this applies to the detection of fungaemia due to the yeasts described herein. In the following sections the general characteristics for the different pathogens will be reviewed (in alphabetical order). Specific characteristics concerning the epidemiology and species identification are summarized in Tables 2 and 3. In most cases, identification to the species level requires the adoption of new tools including matrix-assisted laser desorption/ionization time of flight mass spectrometry (MALDI-TOF-MS) or DNA sequencing. In this context it is important to underline that the performance of these techniques depends on the quality of the databases employed. However, these approaches appear promising for most of these species and are expected to play an important role in the future (Table 4). Recommendations regarding use of blood culture and surrogate markers are summarized in Table 5. Finally, recommendations regarding appropriate first-line antifungal treatment options are summarized in Table 6.

Cryptococcus

Introduction

Cryptococcus is an anamorphic basidiomycetous yeast genus that comprises 70 species [39] but only two species *C. gattii* and *C. neoformans* are regularly causing infections. The diagnosis and management of these have been described in detail elsewhere and are not included in the present guideline because they are not uncommon or rare infections [40–43].

Other *Cryptococcus* species (e.g. *C. albidus*, *C. curvatus*, *C. laurentii*) are prevalent worldwide and have been identified from various environmental sources including air, soil, water, pigeon droppings and food items such as cheese, milk, beans and wine [39]. The species are able to grow at 37°C and have been described as a cause of invasive human infections, with *C. albidus* and *C. laurentii* accounting for 80% of the non-*neoformans*/non-*gattii* cryptococcal infections [44]. *Cryptococcus uniguttulatus*, *C. adeliensis* and *C. flavescens* have also been implicated in cases of meningitis, albeit less frequently [45–48]. The clinical presentation is similar to that for *C. neoformans* but the cryptococcal antigen test is often negative and intrinsic susceptibility patterns are characterized by higher MICs for several agents [49]. Therefore, diagnosis and optimal management depend on a high index of suspicion and a skilled mycology laboratory service. In the literature, cultures were not always performed and species identifications were in many cases based solely on phenotypic methods. Therefore, reports on infections caused by the individual species should be interpreted with caution unless coming from reference laboratories.

Risk factors and clinical presentation

Cryptococcus adeliensis, *C. albidus*, *C. curvatus*, *C. flavescens*, *C. laurentii* and *C. uniguttulatus* have been recovered from various clinical specimens [44–48,50]. The most common underlying risk factor is impaired cellular immunity, of which 16% was related to human immunodeficiency virus infection in a recent review of 44 previously published cases [44]. In addition, *C. laurentii* has been linked to the presence of invasive devices [44]. Clinical presentation involves bloodstream infection in 33–55% of the cases, neurological manifestations in 20–33%

TABLE 4. Identification of the rare yeasts; laboratory characteristics and tools for identification to the species level

Organism	Pseudo-hyphae	Hyphae	Blastoconidia	Anneloconidia	Chlamydo-conidia	Cap-sule	Monopolar budding	Arthro-conidia	Urease	Appearance on CHROMagar	Specific comments regarding morphology	Identification to the species level requires[a]
Cryptococcus spp. other than *C. neoformans* & *C. gattii*	–	–	+	–	–	+	–	–	+	No data	India ink may visualize the capsule in clinical specimens	ITS 1 + 2 (2nd option D1/D2 domain) MALDI-TOF promising
Geotrichum	–	+	–	–	+/(–)	–	–	+	–	Variable, probably species dependent	White colonies, arthroconidia	ITS 1 + 2 (2nd option D1/D2 domain) MALDI-TOF promising
Kodamaea ohmeri	+	–	+	–	–	–	–	–	–	Gradually pink to blue	Colour change on CHROMagar within 48 h	Biochemical tests or ITS 1 + 2
Malassezia	–	–	+	–	–	–	+	–	+	No growth except *M. pachydermatis*	Lipid dependent except *M. pachydermatis* white/cream colonies, monopolar budding	Phenotypically or ITS 1 + 2 MALDI-TOF promising
Pseudozyma	–	+	+	–	–	–	–	–	+	*P. aphidis* forms rough green colonies. No data for the other species.	Fusiform spindle-shaped elongated blastoconidia	ITS 1 + 2 (2nd option D1/D2 domain)
Rhodotorula	–/(+)	–/(+)	+	–	–	(+)	–	–	+	No data	Red, orange-salmon coloured colonies	ITS 1 + 2 (2nd option D1/D2 domain)
Saccharomyces	–	–	+	–	–	–	–	–	–	Dark pink	Larger cells compared with *C. glabrata*, poor growth on blood agar	Biochemical tests or MALDI-TOF
Saprocaete capitata	–	+	+/–	+	–	–	–	+	–	No data	Whitish, butyrous colonies, arthroconidia	ITS 1 + 2 (2nd option D1/D2 domain) MALDI-TOF promising
Sporobolomyces	–/(+)	–/(+)	+	–	–	–	–	–	+	No data	Red, orange-salmon coloured colonies; satellite colonies due to ballistoconidia	ITS 1 + 2 (2nd option D1/D2 domain)
Trichosporon	–	+	+	–	–	–	–	+	+	*T. asahii*: dirty green (others variable)	Colony becoming dry, arthroconidia	ITS 1 + 2 (2nd option D1/D2 domain) IGS1 necessary for some species MALDI-TOF promising

[a]ITS 1 + 2: Sequencing of the Internal transcribed spacer 1 and 2 of the rDNA, 2nd option D1/D2 domain: Sequencing of the D1/D2 domain of the large subunit (LSU) ribosomal DNA 09rDNA recommended if species identification is not obtained by ITS 1 + 2 sequencing, IGS1: Sequencing of the Intergenic spacer 1 region of the rDNA is necessary for correct species identification of some *Trichosporon* species. Biochemical tests: correct species identification can be obtained by biochemical tests such as the Vitek 2 and API ID32C. MALDI-TOF, matrix-assisted laser desorption/ionization time of flight mass spectrometry.

TABLE 5. Summary of and recommendations regarding use of blood culture and surrogate markers

Species	Surrogate markers	Strength of recommen-dation	Quality of evidence	Comment	References
All	Blood culture	A	II	Volume of blood is essential. Adults: 40–60 mL either one venepuncture or separate immediately after each other. Repeated if signs and symptoms of fungaemia persist.	[32–34]
	Blood culture fungal medium	B	II[t]	Several studies have documented better yield for *Candida* and BACTEC and BacT/ALERT BC systems if a mycosis medium is included. Not shown specifically for rare yeasts.	[26,35–38]
Cryptococcus other than *C. neoformans* and *C. gattii*	Cryptococcus antigen	C	III	Cerebrospinal fluid and serum. Sensitivity lower than for *C. neoformans*. (4/17 in one study). Negative result does not exclude cryptococcosis.	[44,45]
	Asp GM	D	III	Cross-reaction due to galactomannan in the fungal cell wall. However, sensitivity not examined.	[65]
	β-D-glucan	D	II	β-D-glucan is not part of the cryptococcal cell wall.	[63]
Geotrichum	No data on surrogate markers	No recom-mendation	No data		
Kodamaea ohmeri	No data on surrogate markers	No recom-mendation	No data		
Malassezia	Isolator 10 Lysis centrifugation or BC bottle suppl. with palmitic acid with prolonged incubation (2 weeks)	B	III	Positive microscopy and negative culture may be suggestive, due to the lipid dependence of most species. Subculture: Sabouraud overlaid with sterile olive oil, Dixon agar or other lipid-containing agar.	[107,108]
Pseudozyma	No data on surrogate markers	No recom-mendation	No data		
Rhodotorula	β-D-glucan	C	III	β-D-glucan present in culture supernatant but in lower amount and but no clinical data.	[63]
Saccharomyces	β-D-glucan	C	III	β-D-glucan present in culture supernatant but no clinical data.	[63,180]
	Candida mannan antigen	C	III	Single clinical case and antigen similarity	[179]
Saprochaete capitata	Asp GM	C	III	Cross-reaction due to galactomannan in the fungal cell wall. However, sensitivity not examined.	[208,209]
	β-D-glucan	C	III	β-D-glucan present in culture supernatant but no clinical data.	[63]
Trichosporon	Cryptococcus antigen	B	II[u]	Cross-reaction with cryptococcal polysaccharide and galactomannan Ags. Dual positivity may be suggestive for *Trichosporon* infection. However, sensitivity not examined.	[57,58,246–249]
	Asp GM	C	III		
	β-D-glucan	D	II	Low sensitivity	[238,250,251]

and pulmonary infection in 5–11% of the cases, but other body sites may also be involved including skin, eyes, peritoneum (secondary to peritoneal dialysis) and lymph nodes (5–10% each). *Cryptococcus laurentii* was associated with no mortality in contrast to *C. albidus* (28% mortality) [44].

Diagnosis

Cryptococci are budding, encapsulated, round to oval yeast cells with a size from 3 to 8 μm in fluids or tissues. The cells can be visualized by mixing the pellet (cerebrospinal fluid, pleural fluid or bronchoalveolar lavage) with India ink. The capsule surrounding the cell will appear transparent as a halo resembling an egg-white around the yolk. Tissue sections can be stained with mucicarmine or Alcian blue to highlight the capsule and so exclude other yeasts with similar morphology. Clinical specimens should be incubated on Sabouraud or other selective fungal agar at 30–35°C (for up to 4 weeks in case of prior antifungal treatment). Lysis centrifugation or culture of the buffy coat improves the yield of fungaemia detection [40]. Creamy mucoid colonies are obtained and the colour may darken with age. The genus is non-fermentative and identified by the presence of a capsule, urease production and assimilation pattern using commercial kits [39]. When cultured on bird seed agar most species do not form brown to black colonies (and can therefore be differentiated from *C. neoformans* and *C. gattii*). There are few exceptions such as *Cryptotrichosporon anacardii* [51] and *Cryptococcus podzolicus* [52]. Species identification requires sequencing of internal transcribed spacer (ITS) 1 + 2 regions of rDNA and/or D1/D2 domains [39,47,48,53]; MALDI-TOF-MS is a promising tool for future identification of uncommon yeasts including *Cryptococcus* species; however, its performance will depend on the quality of the database (T. Boekhout, unpublished observations) [54–56].

Despite sharing several capsular antigens with *C. neoformans*, cryptococcal antigen detection is not a reliable diagnostic test for non-*neoformans*/non-*gattii* cryptococcal species with only 4/17 bloodstream cases being positive and at low titres [44,45]. Whether the poor sensitivity is attributable to differences in capsule structure (versus *C. neoformans*) or lower fungal burden remains to be clarified. False-positive results have been reported during invasive *Trichosporon* infections [57,58] and in the case of rheumatoid factor [59], *Capnocytophaga canimorsus* septicaemia [60], *Stomatococcus mucilaginosus* bacteraemia [61], soaps and disinfectants [62]. The amount of β-1-3-D-glucan in the cryptococcal cell wall is much lower than in for example *Candida albicans* and the β-1-3-D-glucan test has not been found useful in the diagnosis of cryptococcal disease, as exemplified by only two of 12 patients with cryptococcosis positive at a cut-off value of 80 pg/mL [63,64]. Therefore the test is not recommended in this context. Finally, cross-reaction with the

TABLE 6. Targeted antifungal treatment of emerging invasive yeast infections. Note: intention is to cure manifest infection

	Population/ manifestation	Antifungal	Strength of recommendation – quality of evidence	Comments	References
Cryptococcus other than *C. neoformans* and *C. gattii*	CNS and severe inf. Induction	Amphotericin[a] (±flucytosine[b])	B-III	MICs of 5-FC, fluconazole and other azoles often elevated and particularly so for *C. albidus*, *C. laurentii* and *C. uniguttulatum* [29,30,33,54–59]	[44–46,49,69–74]
	CNS and severe inf. Consolidation	Fluconazole ≥400 mg/day	C-III	If *in vitro* susceptible	
	Non-CNS, not severe inf.	Fluconazole ≥400 mg/day	C-III	MICs of 5-FC, fluconazole and other azoles often elevated and particularly so for *C. albidus*, *C. laurentii* and *C. uniguttulatum* [29,30,33,54–59]	
	Non-CNS, not severe inf.	Amphotericin[a]	B-III	May be preferable to fluconazole for the less azole-susceptible species	
	Any	Echinocandins	D-II	Intrinsically resistant	
Geotrichum candidum	Any	Amphotericin[a] (±flucytosine[b])	B-III	Preferred agent is amphotericin B (w/wo 5-FC).	[77–80]
	Any	Fluconazole	D-III	No human data and high MIC values	[77,82]
	Any	Voriconazole	NR	Low MIC values. One breakthrough failure case (while on micafungin), but voriconazole TDM levels not reported.	[77,78,81]
	Any	Echinocandins	D-II	*In vitro* resistant	[77]
Kodamaea ohmeri	Any	Amphotericin[a]	B-III	Most (but limited) clinical experience w amphotericin B;	[83,85,86,92,95,96]
	Any	Fluconazole	C-III	Elevated MICs for some isolates. Fluconazole successful in 5/6 paediatric cases, in 1/1 adult immunocompromised patient case (fluconazole followed by itraconazole) unsuccessful in one adult case of cellulitis [70,74,78].	[84,88,92]
	Any	Echinocandins	C-III	Two case reports showed successful outcome for one patient each on micafungin and caspofungin respectively (MICs higher than for *C. albicans*)	[91,93]
	Any	Voriconazole	NR	No data	
Malassezia	Severe cases	Amphotericin[a]	B-III		[97,106]
	Non-severe cases	Fluconazole	B-III	*M. pachydermatis* may be less susceptible *in vitro*	[97,106]
	Any	Voriconazole	C-III	*In vitro* activity, no clinical data, exposure issues particularly in the paediatric population	[97,106]
	Any	Echinocandins	D-III	No reference susceptibility test for *Malassezia*; modified susceptibility tests suggest intrinsic resistance	[97,106]
	Any	Flucytosine[b]	D-III	No reference susceptibility test for *Malassezia*; modified susceptibility tests suggest intrinsic resistance	
Pseudozyma spp.	Any, fungaemia	Amphotericin[a]	A-II[u]	Low MICs of amphotericin B, case stories reporting success.	[121–124]
	Any, fungaemia	Fluconazole	D-II	5/6 clinical isolates had high MICs of fluconazole	[121–124]
	Any, fungaemia	Echinocandins	D-II	*In vitro* resistant	[123,124]
	Any, fungaemia	Flucytosine[b]	D-II	*In vitro* resistant (MIC >64 mg/L)	[121,123]
	Any, fungaemia	Voriconazole	C-III	*In vitro* activity, no clinical data, exposure issues	[123,124]
Rhodotorula	Any	Amphotericin[a] (±flucytosine[b])	A-II	*In vitro* susceptible only to these two agents. Good response in the case reports available.	[131,153,154]
	Any	Azoles	D-II[u]	Breakthrough cases on fluconazole and echinocandins. *In vitro* resistant to all azoles and echinocandins	[131,147,148,153,154]
	Any	Echinocandins	D-II	Breakthrough cases on azoles and echinocandins. *In vitro* resistant	[147,153,154]
Saccharomyces	Any	Amphotericin[a]	B-III	Most clinical experience; toxicity risk higher than for echinocandins	[178,182,183]
	Any	Echinocandins	C-III	Two successful cases in the literature (± neutropenic), no emergence of *S. cerevisiae* after intro of echinocandins as first line agents for candidaemia, two recent failure cases neutropenic (Arendrup MC unpublished data)	[27,182,183]
	Any	Amphotericin B[a] + Flucytosine[b]	B-III	Excellent *in vitro* susceptibility. May be used in severe cases or when penetration into an infected focus is challenging.	[70,170,181,184,185]
	Any	Fluconazole	D-III	Increased occurrence in patients exposed to fluconazole; high fluconazole MICs (similar to those for *C. glabrata*	[26,178]
	Any	Discontinuation of probiotics	A-III	Probiotic containing *S. boulardii* has been documented to be the origin of systemic infections.	[175,176]
Saprochaete capitata	Any	Amphotericin[a] (±flucytosine[b])	B-III	Most (but limited) experience. *In vitro* susceptibility of amphotericin B in the intermediate range, failures in hepatosplenic infections reported on amphotericin B monotherapy.	[186,194,196]
	Any	Voriconazole	B-III	Less data available, but promising *in vitro* susceptibility	[186]
	Any	Echinocandins	D-II	*In vitro* resistant and a case report document breakthrough infections on an echinocandin.	[211,212]
	Any	Fluconazole	NR	*In vitro* resistant – but animal model data suggest activity	[211–213]
	Any	CSF or interferon-γ in combination w antifungal treatment	C-III	Improved *in vitro* phagocytic activity has been observed	[194,195,206]
Sporobolomyces	Any	Amphotericin[a]	C-III	Possibly a treatment option but insufficient clinical data	[69,222,223,230]
	Any	Voriconazole	C-III	Possibly a treatment option but insufficient clinical data	[69,225,230]

Table 6 (*Continued*)

	Population/ manifestation	Antifungal	Strength of recommendation – quality of evidence	Comments	References
	Any	Echinocandins	D-II	*In vitro* resistant	[69,230]
	Any	Fluconazole	D-II	*In vitro* resistant	[69,230]
Trichosporon	Any	Voriconazole	B-III	Preferred therapy, but as data are scarce	[233,237,238,259,260]
	Any	Fluconazole	C-III	Some clinical evidence for usefulness, but also some isolates with higher MICs	[192,232,238]
	Any	Echinocandins	D-II	*In vitro* resistant	[237–239,256,262]
	Any	Amphotericin[a]	D-III	Low success rates on amphotericin B and *in vitro* resistance reported	[192,232,261,265–267,270]
	Any	Flucytosine[b]	D-III	*In vitro* resistant	

5-FC, flucytosine; CNS, central nervous system; inf., infection; TDM, therapeutic drug monitoring; w/wo, with/without.
[a]Amphotericin, wherever mentioned, includes amphotericin B deoxycholate and its lipid formulations. Lipid formulations are preferred due to lower toxicity and liposomal amphotericin B specifically whenever central nervous system penetration is warranted.
[b]Flucytosine, wherever mentioned, is a possible option particularly in cases where penetration issues (e.g. central nervous system infection) or severity, suggest combination therapy may improve outcome. Flucytosine should only be used in combination due to the risk of selection of resistance and therapeutic drug monitoring is highly recommended due to the narrow therapeutic index.

Aspergillus galactomannan antigen test (Platelia Aspergillus; BioRad, Marnes la Coquette, France) has been observed due to the presence of galactoxylomannan in the cryptococcal capsule [65]. A commercially available cryptococcal lateral flow antigen detection device (IMMY; Immuno-Mycologics, Inc., Norman, OK, USA), has recently been introduced as a point-of-care test for the early diagnosis of cryptococcosis. The test has proven effective both for serum, cerebrospinal fluid and urine samples in comparison with conventional techniques of antigen detection but the performance for the detection of infections due to cryptococci other than *C. neoformans* has not been evaluated [66–68].

Susceptibility testing and treatment

Cryptococci are intrinsically resistant to echinocandins. The optimal treatment for invasive infections due to other *Cryptococcus* species has not been established. Amphotericin B alone or in combination with flucytosine and fluconazole either alone or after induction therapy with amphotericin B has been used. Predictors for mortality were infection with *C. albidus* (rather than *C. laurentii*), age above 45 years and central nervous system involvement [44]. *In vitro* susceptibility testing suggests that *C. albidus*, *C. curvatus* and *C. laurentii* are susceptible to amphotericin B with MICs comparable to those for *C. neoformans* [49]. On the contrary, MICs of flucytosine, fluconazole and other azoles are in most studies elevated and particularly so for *C. albidus*, *C. laurentii* and *C. uniguttulatus*, suggesting that these organisms may be less susceptible [45,46,49,69–74]. Moreover, fluconazole resistance has been reported more frequently in patients with previous azole exposure (83% versus 50%) [44]. The clinical implication of these observations remains to be understood. However, initial induction therapy with amphotericin B until clear clinical improvement and careful evaluation of fluconazole susceptibility if step-down to this agent is considered appears to be a sound and safe strategy.

Geotrichum candidum

Geotrichum candidum (*Galactomyces candidus*) is a filamentous ascomycetous yeast that forms arthroconidia and that has rarely been reported to be responsible for disseminated infections in the haemato-oncology setting [75–77]. It is closely related to *Saprochaete capitata* (*Magnusiomyces capitatus*) and *Saprochaete clavata* (see below). A recent literature review of 12 invasive cases reported since 1971 revealed that 8/12 patients had underlying malignancy [77]. It has been anecdotally reported as a cause of invasive skin infection [78]. The preferred agent for invasive infections is amphotericin B with or without concomitant flucytosine as most experience exists with this agent [77,79,80]. Voriconazole may be a promising agent, as suggested by good *in vitro* susceptibility, but only a single case is reported in the literature with an unsuccessful outcome of a breakthrough infection (while on micafungin) [77,78,81]. Neither echinocandins nor fluconazole can be recommended because of high MICs and no clinical support for efficacy [77,82].

Kodamaea ohmeri

Introduction

Kodamaea (*Pichia*) *ohmeri* is a rarely occurring yeast that has recently been identified as a cause of fungaemia, endocarditis, cellulitis, funguria and peritonitis in neonates and children [83–87], and in both immunocompromised [88–91] and immunocompetent [92,93] adult patients. The anamorphic state is *Candida guilliermondii* var. *membranaefaciens*, and has been confused with *Candida guilliermondii* (for which the teleomorphic state is *Meyerozyma guilliermondii*). Recent literature invariably does not acknowledge the anamorphic state (and readers may therefore not recognize this species as a *Candida* sp.), so we have included *K. ohmeri* in this guideline. *Kodamaea ohmeri* may be

misidentified as *Candida tropicalis* [84], *Candida haemulonii* or *Candida parapsilosis* [94] by traditional methods and molecular identification is mandatory.

Risk factors/clinical presentation

There are <30 cases described in the world literature, which are mainly sporadic reports but also include two Asian series with several cases [84,94]. In one of these, the hands of a healthcare worker at a surgical ward were colonized with *K. ohmeri*, suggesting a nosocomial outbreak [84].

Diagnosis

Blood culture remains the cornerstone in the diagnosis of invasive infection. On solid media, *K. ohmeri* forms *Candida*-like colonies, which on CHROMagar (BioMérieux, Marcy l'Etoile, France) change colour from pink to blue within 48 h [88]. Although mis-classification as *Candida tropicalis* has been reported, correct species identification can be obtained by biochemical tests such as the Vitek 2 and API ID32C or sequencing of the rDNA loci [84,88].

Susceptibility testing and treatment

Susceptibility testing suggests that the susceptibility pattern mirrors that for *Candida glabrata* with azole MICs higher than those for *Candida albicans* (fluconazole: 2–64 mg/L; voriconazole: 0.03–8 mg/L, posaconazole 0.06–4 mg/L, respectively), but amphotericin B and echinocandin MICs in the range that would be interpreted as susceptible for *Candida albicans* (amphotericin B: 0.25–1 mg/L, caspofungin: 0.125–1 mg/L, micafungin: 0.03–0.06 mg/L, respectively) [84,94]. Most cases have been treated with liposomal amphotericin B (or amphotericin B deoxycholate) and with good response [83,85,86,92,95,96]. Fluconazole was successful in 5/6 paediatric cases, in 1/1 adult immunocompromised patient (fluconazole followed by itraconazole) and was associated with failure in one adult case of cellulitis [84,88,92]. Finally, caspofungin or micafungin treatment has been successful in one case each [91,93]. Hence, although there are insufficient data to support a firm treatment recommendation, amphotericin B appears to be an attractive first-line agent and echinocandins are possibly promising alternative candidates. Susceptibility testing is recommended not only to guide treatment but also to provide MIC–outcome relationships and hence data for future optimized treatment recommendations.

Malassezia

Introduction

Malassezia species are basidiomycetous yeasts and part of our normal skin microbiota. The genus includes 14 species of which 13 are lipid dependent. These include *M. furfur*, *M. sympodialis*, *M. globosa*, *M. obtusa*, *M. restricta*, *M. slooffiae*, *M. dermatitis*, *M. japonica*, *M. nana*, *M. yamatoensis*, *M. equina*, *M. caprae* and *M. cuniculi*. *Malassezia pachydermatis*, however, is able to grow on routine media without the addition of oil or other sources of lipid. *Malassezia sympodialis*, *M. globosa*, *M. slooffiae* and *M. restricta* are the most frequently found species responsible for colonization of humans.

Risk factors/clinical presentation

Malassezia species may cause various skin manifestations including pityriasis versicolor, seborrhoeic dermatitis, dandruff, atopic eczema and folliculitis and less commonly onychomycosis [97]. These skin manifestations are common and are typically diagnosed and managed in the primary healthcare sector or by dermatologists [97]. For their management, we would refer the reader to local and international guidelines. However, skin colonization and infection may be a source for transmission to vulnerable patient groups susceptible to invasive infections [97]. Both the non-lipid-dependent species *M. pachydermatis* and the lipid-dependent *Malassezia* spp. (almost all reported as caused by *M. furfur*) have been reported to cause systemic infections [97–99]. As an example, *M. pachydermatis*, which is known to cause external otitis in dogs, has been isolated from the hands of dog owners, including healthcare providers such as nurses, and associated with clusters of infections in neonates [98,100–102]. Apart from contact with a potential carrier, other risk factors for *M. pachydermatis* include increased median neonatal acute physiology score and more than 9 days of arterial catheterization [98]. Notably, *M. pachydermatis* can persist for a long time on surfaces of incubators, which may serve as a source of infection for neonates [103].

Systemic infections due to lipid-dependent *Malassezia* species mainly occur in the following host groups: (i) infants on lipid-containing parenteral nutrition and (ii) children and adults with various forms of immunosuppression and underlying diseases [97,104]. Risk factors for fungaemia related to non-lipid total parenteral nutrition are the following: chronic ambulatory peritoneal dialysis (due to lipids leaking from the gastrointestinal tract), haematological malignancy, cancer and Crohn's disease and most cases arise in patients with a CVC [97,105,106].

Diagnosis

The diagnosis of invasive *Malassezia* infections is challenging because of the lipid-dependent nature of most species. Hence, special media, such as modified Dixon or modified Leeming and Notham agar, or the use of Sabouraud agar with the addition of a few drops of sterile olive oil is required. The

performance of the various modern automated blood culture systems for the detection of *Malassezia* species has not been systematically studied, however, the use of the Isolator 10 system (with subculture of lipid-containing agar) or supplementation of the blood culture flask with palmitic acid has been shown to be required for the detection of lipid-dependent species in earlier blood culture systems [107,108]. Inoculated blood culture media should be incubated for up to 2 weeks. Colonies on solid agar are cream to beige. Yeast cells are round or oval with thick walls with a size varying from 2 to 8 m. Cell division is via monopolar budding with buds that may be nearly as broad as the mother cell in many cases, leading to a flask-like appearance of the cells.

Malassezia species may be distinguished phenotypically using morphology and a series of biochemical tests as well as using molecular tools [109–111] and by MALDI-TOF-MS (T. Boekhout, unpublished observation). Full protocols for phenotypic identification are provided by Guého-Kellermann *et al.* [112]. For clinical management at the level of the individual patient, species identification is less important, although it is obviously needed for epidemiological surveillance and outbreak investigation.

Susceptibility testing and treatment

Susceptibility testing of *Malassezia* has not been standardized because growth is not supported on the standard RPMI growth medium recommended for yeast and mould testing by CLSI and EUCAST. Significant variation and broad range MICs have been reported in various publications depending on the medium used, which may result in random/erroneous susceptibility classification [113]. Some reports suggest that *in vitro* fluconazole resistance may be encountered more often in *M. pachydermatis* [114,115]. The clinical implication of this finding remains unclear. So far susceptibility testing for guiding treatment cannot be recommended. As for the other rare invasive yeast infections, larger patient series are lacking, and hence evidence-based treatment recommendations cannot be made. The key factors in the management of invasive *Malassezia* infection are removal of the CVC, discontinuation of the parenteral lipid and institution of systemic antifungal treatment. Most experience is with fluconazole and amphotericin B, which are the preferred agents [106,116,117]. In general MICs are lower for voriconazole than for fluconazole for most species, however, so is the voriconazole exposure, particularly in the paediatric population, which is a reason to strongly consider therapeutic drug monitoring if voriconazole is prescribed [118–120]. Additionally, voriconazole is associated with more side-effects and drug–drug interactions and is not licensed for neonates or children <2 years old. Future studies are warranted to elucidate which antifungal treatment is optimal. *In vitro* resistance to flucytosine and echinocandins appears to be a consistent finding and therefore these drug classes are not recommended [101,116].

Pseudozyma

Introduction

Pseudozyma species are basidiomycetous plant pathogens, which belong to the Ustilaginales. The genus today contains at least 20 species and was not recognized as a human pathogen until 2003 when three *Pseudozyma* species—*Pseudozyma antarctica*, *Pseudozyma parantarctica* and *Pseudozyma thailandica*—were isolated from the blood of three Thai patients [121]. Fungaemia due to *Pseudozyma aphidis* was subsequently reported from the USA in 2008 [122] and recently in a neonate from India [123].

Risk factors/clinical presentation

So far infections due to *Pseudozyma* have been reported from Asia (Korea, China, India, Thailand), Brazil and the USA [123]. Risk factors associated with invasive *Pseudozyma* infections are similar to those of non-*albicans Candida* spp., i.e. extremes of age, cancer chemotherapy, neutropenia (<3000 cells/μL), presence of a CVC and severe thrombocytopenia [121–124]. Invasive *Pseudozyma* spp. infection most often presents with fungaemia. Moreover, deep-seated focal infections including brain abscess [125] and pleural cavity have been reported [124]. Finally, a single case of a mycetoma due to co-infection with *Nocardia* after traumatic inoculation in an Asian farmer has been described [126].

Diagnosis

The main stay in the diagnosis of invasive *Pseudozyma* spp. infection is blood culturing and when, focal infection is suspected, culture of relevant tissue samples. On Sabouraud agar *Pseudozyma* species form rapidly expanding moist, tan-yellow and wrinkled yeast colonies [122,124] and on CHROMagar Candida medium *P. aphidis* forms rough green colonies after 48–72 h of incubation at 37°C (no data for the other species). Microscopic examination shows fusiform spindle-shaped elongated blastoconidia and the presence of hyphae. Germ tube test and chlamydoconidia formation are negative. Isolates show positive test for diazonium blue B and hydrolyse urea. Growth is inhibited on 0.1% cycloheximide-containing medium. API ID 32C and VITEK2 compact generally give non-conclusive profile(s). Amplification and sequencing of the ITS and/or D1/D2 domain is necessary for a proper identification [121–123,125,126].

Susceptibility testing and treatment

Low MIC values of amphotericin B, posaconazole (0.03 mg/L), voriconazole (0.06 mg/L) and isavuconazole (0.25 mg/L) have been reported. Susceptibility of itraconazole was variable and 5/6 isolates had MICs of fluconazole in the range of 4 to greater than 64 mg/L. The echinocandins (>4 mg/L) and flucytosine (>64 mg/L) are not active against *Pseudozyma* [123]. Although the available data are too limited to provide firm treatment recommendations, first-line options may be amphotericin B or voriconazole whereas echinocandins, fluconazole and flucytosine should be avoided.

Rhodotorula

Introduction

Clinically relevant red yeasts belong to two genera: *Rhodotorula* and *Sporobolomyces* (see below). *Rhodotorula* species are common environmental basidiomycetous yeasts, which can be found in soil, ocean and lake water, fruit juice and milk, and on shower curtains and toothbrushes [30,127]. Today, the genus contains 46 species [128] of which three have been described as rare human pathogens: *R. mucilaginosa* (also known as *R. rubra*), *R. glutinis* and *R. minuta* [30,129,130]. The association of *R. mucilaginosa* with humans is well documented and this yeast has been isolated from skin, sputum and digestive tract samples including faeces, forming part of the normal human microbiota. This species accounts for the majority of the infections (74–79%) followed by *R. glutinis* (7.7%) [130,131]. In a significant proportion of the reported cases the species identification is not available (17%); furthermore, species identification is not reliable by methods normally available in the routine microbiology laboratory, and identification using sequence analysis of the D1D2 domains of the large subunit ribosomal DNA (rDNA) and the ITS 1 + 2 regions of the rDNA is needed [30,130].

Risk factors/clinical presentation

Opportunistic fungal infections due to *Rhodotorula* have emerged after the first case was reported in 1985, and the most common predisposing factor appears to be the presence of a CVC and underlying haematological disease [28,127,130–135]. However, *Rhodotorula* fungaemia, peritonitis, endocarditis or meningitis have also been reported in other vulnerable patient groups, including patients with AIDS, extensive burns, continuous ambulatory peritoneal dialysis, cirrhosis, those who have undergone intra-abdominal surgery, intravenous drug abusers and critically ill ICU patients [130,136–146]. Notably, a significant number of cases are breakthrough infections during fluconazole or echinocandin treatment [131,134,135,147,148]. Infections appear to be less common in Nordic countries compared with the warmer regions [26,28,149]. Moreover, *Rhodotorula* has also been found on the hands of healthcare workers in Egypt [150], and it has a high affinity to adhere to plastic surfaces and can form biofilms [28,151]. Hence, medical equipment including flexible endoscopes, various utensils and furniture in the patient's room can easily become colonized. These observations suggest geographical differences in the epidemiology and possibly a potential role of differences in hygiene procedures [30,148,150].

Diagnosis

The mainstay in the diagnosis of invasive *Rhodotorula* spp. infection is blood culture as 79% of the systemic infections presents as fungaemia [130]. Of note, isolates of *Rhodotorula* have been found to cross react with the *Candida glabrata*/*Candida krusei* probe in the commercially available fluorescence *in situ* hybridization test for presumptive species identification of positive blood cultures, which might lead to inappropriate echinocandin treatment [152]. A CVC is often involved and therefore the catheter tip should be cultured when the CVC is removed to capture cases where blood cultures are falsely negative [127]. *Rhodotorula* isolates are easily recognizable in the laboratory by their distinctive orange to salmon-coloured mucoid colonies. Cells of *Rhodotorula* spp. are subglobose, oval to elongate, with or without small capsules, may sometimes form rudimentary hyphae but not ballistoconidia, produce urease but fail to ferment carbohydrates.

Antigen detection has not been reported in clinical cases of systemic *Rhodotorula* infections. β-1-3-D-glucan has been detected in the supernatant from three isolates of *R. mucilaginosa* (syn. *R. rubra*) at an average concentration of two-thirds of that of *Candida* spp. [63]. Whether the β-1-3-D-glucan test would be useful as a surrogate marker for invasive *Rhodotorula* infection remains to be investigated.

Susceptibility testing and treatment

Susceptibility testing has yielded amphotericin B MICs of <1 mg/L and flucytosine MICs of <0.5 mg/L, but fluconazole MICs of >32 mg/L and voriconazole, itraconazole and posaconazole median MICs of 2 mg/L, which is above the breakpoints for not only *Candida albicans* but also *Aspergillus fumigatus* [153–157]. Hence, *Rhodotorula* species are regarded as intrinsically resistant to azoles and echinocandins, but susceptible to amphotericin B and flucytosine [153,158,159]. This is further supported by the finding that many cases have been breakthrough infections during fluconazole or echinocandin treatment [131,147,148]. Consequently, the preferred treatment of choice is with any kind of amphotericin B preparation. With such treatment, an overall mortality was reported as 13.8% in the haematological setting and ranges

from 0% in patients with non-Hodgkin's lymphoma to 21% in patients with acute leukaemia [30,127,131,160]. If present, withdrawal of CVC is strongly recommended [130–133,135,147] and sometimes reported to be efficacious without any accompanying antifungal treatment [28,161]. Furthermore, cases of chronic ambulatory peritoneal dialysis-associated *Rhodotorula* peritonitis have been diagnosed and successfully treated (5/6 patients cured) with catheter removal (5/6 patients) and systemic or intraperitoneal antifungal therapy (amphotericin B in 5/6 patients or ketoconazole 1/6 patients, which is today regarded as an obsolete compound for oral administration, in one case) [130,138,162,163]. There are anecdotal reports indicating improvement of fungal infection under fluconazole and miconazole treatment despite *in vitro* resistance and in patients without antifungal treatment [130,164]. However, since there are no confirmatory trials for treatment of *Rhodotorula* infections, such practice should be avoided, especially in seriously ill patients.

Saccharomyces

Introduction

Saccharomyces cerevisiae, also known as baker's or brewer's yeast, is a low pathogenic ascomycetous yeast. *Saccharomyces boulardii*, a genetically similar subtype [165,166], is used as a probiotic for prevention and treatment of various sorts of diarrhoea and recurrent *Clostridium difficile*-associated diarrhoea [167–169] and should be avoided in immunocompromised hosts. The anamorphic state of *S. cerevisiae* is sometimes referred to as *Candida robusta*. As the species is closely related to *Candida glabrata* phylogenetically it is not surprising that the clinical and microbiological characteristics are similar to this species.

Risk factors/clinical presentation

Saccharomyces cerevisiae may be found as a harmless and transient digestive commensal and colonizer of mucosal surfaces of normal individuals. It can, however, also be involved in mucosal infections like vaginitis, particularly in fluconazole-exposed women with recurrent vulvo-vaginal candidiasis, and in bloodstream infections, again particularly in fluconazole-exposed patients [35,170]. Cases of fungaemia and disseminated infection have been described in vulnerable patients after treatment with the *S. boulardii* probiotic compound [171–176], and also as nosocomial infection in a patient that shared a room with a patient receiving probiotic, suggesting transfer via contaminated hands of the nursing staff [177]. In a recent review of 92 cases of invasive *Saccharomyces* infections, *S. boulardii* accounted for half of these, was less often associated with an underlying immunocompromised condition and more often associated with a favourable outcome [178]. Use of probiotics in debilitated patients, in ICU, in neutropenic patients, in preterm newborns or in patients with central lines should be carefully considered.

Diagnosis

Invasive infection is most often diagnosed by microscopy and culture. Yeast cells are round to oval and larger than *Candida glabrata* cells. Ascospores are occasionally seen and short pseudohyphae may be formed but are not typical; urease activity is absent. *Candida* mannan antigen positivity has been anecdotally reported in patients with fungaemia but it remains unclear if this test can be used for diagnosis [179]. Similarly, β-1-3-D-glucan has been found in culture supernatant from *S. cerevisiae* at quantities of approximately 85% compared with that from *Candida* cultures and this test has been reported positive in case reports of *Saccharomyces* bloodstream infection and on culture supernatants from *S. cerevisiae* cultures, but the diagnostic performance has not been systematically studied [63,180].

Susceptibility testing and treatment

The *in vitro* susceptibility pattern is similar to that of *Candida glabrata*, with elevated azole MICs, but echinocandin MICs only a few dilutions higher than for *Candida albicans* and low amphotericin B and flucytosine MICs [70,170,181]. Most clinical experience exists with fluconazole and amphotericin B, for which favourable outcome was observed for 60% and 77.7%, respectively [178]. The clinical experience with the echinocandin class of drugs is limited. Two cases have been reported in the literature and were successfully treated [182,183]. However, two recent failures, one of which with autopsy documented multi-organ dissemination, have also been observed (M. C. Arendrup, unpublished observations). Finally, amphotericin B with or without flucytosine has been used in severe or recurrent cases [184,185] but the role of this combination remains to be established. In addition to the systemic antifungal therapy, it is strongly recommended that probiotics containing *S. boulardii* are discontinued and indwelling foreign bodies are removed, when possible, because this organism, like many other yeasts, is capable of forming biofilms [176].

Saprochaete

Introduction

Saprochaete capitata (Teleomorph: *Magnusiomyces capitatus*, previously named *Geotrichum capitatum*, *Trichosporon capitatum* or *Blastoschizomyces capitatus*) is a non-fermentative, non-encapsulated, urease-negative ascomycetous yeast. It is found in environmental sources such as wood and soil, in

animals (including bovine mastitis and poultry faeces) and has been found in dishwashers [133,186–188]. In addition, *S. capitata* is part of the normal microbiota of human skin and is frequently isolated from sputum and the digestive tract of healthy people [186].

Risk factors/clinical presentation

Saprochaete capitata is a rare, but emerging yeast mostly responsible for often lethal fungaemia in patients with profound neutropenia in the haematology setting [186,189–191]. This patient category represents up to 92% of reported cases and 75% of them have been reported from Italy, Spain and France [192]. Mortality associated with disseminated infections has been estimated to be 57% in the haematology population [192,193]. Of note, *Geotrichum* spp. represented 5% (2/41) of non-*Candida*, non-*Cryptococcus* fungaemia cases among haematological patients in a tertiary cancer centre in Houston, suggesting that this species is still a rare invasive pathogen [28]. In the haemato-oncology setting, 60–80% of patients present with deep organ involvement [193]. Indeed, it has been recognized as a cause of skin lesions similar to those observed during disseminated candidiasis, hepatosplenic abscesses [194,195], pancreatic infections [196], brain abscesses [195], funguria [197], acute renal failure due to fungal occlusion of glomeruli [198] and osteomyelitis, mostly with vertebral involvement [199–201]. Central venous catheters have been recognized as a potential portal of entry [193].

A common hospital source has been advocated for several clusters [186,202] and more recently, it has been confirmed by sequencing that *S. capitata* in milk vacuum flasks was the origin of an outbreak in four patients in Barcelona [203]. No subsequent cases occurred when the identified contaminated source was withdrawn [203].

Outside the oncology context, *S. capitata* has been responsible for prosthetic valve endocarditis [204], pneumonia [205], fungaemia due to contaminated intravenous fluid [206] and meningitis [207].

Diagnosis

Most cases of *S. capitata* fungaemia have been diagnosed by means of blood culture. On solid media, *S. capitata* colonies are white to cream and isolates produce true hyphae, pseudohyphae, blastoconidia, arthroconidia and annelloconidia. *In vitro* and *in vivo* studies have revealed that *Magnusiomyces capitatus* antigens may cross-react with the *Aspergillus* galactomannan assay [208,209]. β-1-3-D-glucan can be detected *in vitro* in culture supernatant at amounts of 88% compared with that for *Candida* spp. [63], but there is no experience of glucan detection during invasive human cases. The species can also be identified by MALDI-TOF-MS (T. Boekhout, unpublished observation).

Susceptibility testing and treatment

In vitro susceptibility data suggest that *S. capitata* is susceptible to flucytosine (MIC values 0.25–0.5 mg/L), itraconazole, voriconazole and posaconazole (MIC ranges: 0.12–0.50, 0.25–0.5 and 0.03–0.25 mg/L, respectively), but not to fluconazole (MIC between 16 and 32 mg/L) [193,202,210]. The MICs for amphotericin B ranged between 0.5 and 2.0 [186]. *Saprochaete capitata* can be considered intrinsically resistant to echinocandins and *S. capitata* was the cause of at least five reported episodes of breakthrough infection in neutropenic patients receiving echinocandins [211,212]. Finally, various combination regimens were not superior to high-dose fluconazole in an experimental animal model of *Blastoschizomyces capitatus* infection (MICs of 8 and 16 mg/L) [213]. The clinical implication of the conflicting observations regarding *in vitro* and *in vivo* activity of fluconazole remains to be understood.

There are not enough clinical data to assess the optimal treatment for *S. capitata* in haematology patients. However, based on *in vitro* data and the limited clinical data available, any amphotericin B formulation with or without flucytosine can be recommended [186,196]. Failure despite high-dose liposomal amphotericin B (7 mg/kg) has been reported in the context of hepatosplenic infection and neutropenic sepsis [191,194]. Voriconazole exhibits a promising activity *in vitro* [186] and some authors have suggested the use of voriconazole and amphotericin B combination therapy [193,214]. Of note, in the above-mentioned animal model, high-dose fluconazole was more efficacious than amphotericin B, flucytosine or voriconazole monotherapy [213]. Although echinocandin MIC values are elevated, isolated case reports have suggested the potential interest of the combination of caspofungin and voriconazole [215,216]. The role of echinocandins as part of combination therapy for *S. capitata* infections remains to be clarified.

Early removal of the catheter is an important complementary treatment as it has been the likely source of the infection in some cases [186,189] and as removal was shown as a prognostic indicator for success in one study [193]. Other adjuvant therapies to improve the phagocytic activity such as colony-stimulating factors, granulocyte transfusions and interferon-γ have been combined with antifungal drugs with some success [194,195,217].

Saprochaete clavata (*Geotrichum clavatum*), which is closely related to *S. capitata*, has only very infrequently been described as involved in invasive human infection. However, 33 cases of *S. clavata* invasive infections were recently reported in France from January 2009 to August 2012, of which 17 cases were diagnosed within 2 months as part of an outbreak in haematology wards in 2012 (Vaux, ECCMID 2013,

O 505). It remains to be determined if the low number of reported cases is the result of difficult species identification and confusion with related species or if it is indeed a very uncommon infection outside isolated outbreaks.

Sporobolomyces

Introduction

Sporobolomyces species are usually red-to-orange pigmented basidiomycetous yeasts, that, next to regular budding cells, form ballistoconidia. Phylogenetically, they are closely related to *Rhodotorula* species. The 53 species occur widely in nature, especially on leaf surfaces, but also in soil, fruits etc. and *Sporobolomyces* is detected in indoor air, particularly in the summer season [218–221].

Risk factors/clinical presentation

Sporobolomyces have been reported as the cause of sporadic invasive bloodstream infections particularly in AIDS patients [222,223]. A single case of meningitis due to *Sporobolomyces roseus* has been described in an immunocompetent cocaine abuser presenting with a 1-week history of severe headache and neck stiffness but no cerebrospinal fluid pleocytosis [224]. The cerebrospinal fluid was culture negative but the yeast was detected by molecular assays in two separate cerebrospinal fluid specimens. Amphotericin B has been efficacious in fungaemic and meningitis cases [222,224]. A single case of endogenous endophthalmitis due to *Sporobolomyces salmonicolor* in a patient with a history of pelvic inflammatory disease 2 years earlier has been reported [225]. The patient recovered following intravitreal amphotericin B (5 μg) and systemic voriconazole 200 mg twice daily. Finally, dermatitis due to *Sporobolomyces holsaticus* and allergic respiratory disease linked to *Sporobolomyces* exposure have been reported [226–228].

Diagnosis

Colonies of *Sporobolomyces* species are usually red or orange in colour and are similar to those of *Rhodotorula* species. They differ from the latter by the formation of ballistoconidia that are actively discharged, which usually lead to the formation of many small satellite colonies. The optimal growth temperature is 25–30°C. Some isolates may fail to grow well at 35–37°C [218]. Species identification requires sequence analysis of the D1/D2 domains and the ITS1 + 2 regions of the rDNA. The performance of indirect tests such as β-1-3-D-glucan has not been investigated. Due to the ubiquitous presence of *Sporobolomyces* contamination, transient colonization or pseudoinfection should be considered [223,224,229].

Susceptibility testing and treatment

In vitro susceptibility testing has been investigated for a limited number of *Sporobolomyces salmonicolor* isolates and suggests that this species is intrinsically resistant to fluconazole and echinocandins (MIC ranges 8–256 and ≥128 mg/L of fluconazole and micafungin, respectively), but susceptible to voriconazole and terbinafine (0.03–2 and 0.06–0.12 mg/L, respectively) [69]. The MIC range of amphotericin B and itraconazole was 0.5–8 and 0.03–4 mg/L, respectively, suggesting variable susceptibility [69,230]. Although the available data are too limited to provide firm treatment recommendations, first-line options may be amphotericin B or voriconazole whereas echinocandins and fluconazole should be avoided [69,222,223,225,230]. Susceptibility testing is recommended.

Trichosporon

Introduction

Trichosporon species are urease-positive, non-encapsulated basidiomycetous yeasts with no known sexual state. They are widely distributed in the environment and regularly found on normal skin, particularly in the peri-genital areas, and occasionally as part of the normal gastrointestinal or upper respiratory microflora [133,231]. The most characteristic morphological feature is the formation of cylinder-shaped arthroconidia in addition to pseudohyphae, septate hyphae and blastoconidia. The genus has undergone a major taxonomic reclassification and today 37 species are described that belong to at least five phylogenetic clades [231]. However, only 16 species have been associated with human infection [231]. The vast majority of cases is caused by *Trichosporon asahii* (74%), followed by *T. dermatis* (12%) [232]. An obvious challenge in this respect is that a significant part of the existing literature does not provide a correct or unique species identification and hence species-specific data are limited.

Risk factors/clinical presentation

In humans, *Trichosporon* has been associated with white piedra and hypersensitivity pneumonia particularly in hot and humid climates (16–30%). In the immunocompromised host, invasive infections such as fungaemia, endocarditis, peritonitis and meningitis have also been reported. Most common risk factors for invasive infections are underlying malignant haematological disease with long-term neutropenia [192,232,233] or with neutrophil dysfunction such as chronic granulomatous disease [234]. Finally, a recent report suggests that *T. mycotoxinivorans* may be an emerging pulmonary pathogen in patients with cystic fibrosis [235]. Males more often contract the infection and predisposing factors are the presence of a CVC, ICU stay,

peritoneal dialysis, steroid use and cytotoxic chemotherapy [192,231,232,236]. Previous other fungal systemic infection is not uncommon and breakthrough cases in patients receiving fluconazole or echinocandin have been described [237–239]. The infection most commonly presents as fungaemia (75%), in approximately 50% of the cases associated with metastatic skin lesions [232,233]. Renal involvement may occur and be associated with haematuria and funguria [232]. In immunocompromised patients, *Trichosporon* is increasingly seen at some centres among invasive yeast infections other than *Candida* and *Cryptococcus* and associated with a mortality rate of up to 80% [236,240,241], though 55% has been reported in a more recent report from Taiwan [232]. Of note, rare clinical cases have been reported in neonates and in intravenous drug abusers [242–244].

Diagnosis

The cornerstone in the diagnosis of invasive infection is microscopy (for the detection of fungal disease) and culture. On solid media, colonies are white, but on CHROMagar *T. asahii* forms characteristic dirty green colonies. *Trichosporon* species share antigens with *Cryptococcus* and *Aspergillus* and a number of reports have demonstrated cross-reaction for the cryptococcal antigen and/or galactomannan antigen kits [57,58,245–249]. Therefore, dual positivity in these tests may be an indicator of invasive trichosporonosis; however, the sensitivity and specificity of this approach has not been defined [57,231,245]. On the other hand the β-1-3-D-glucan tests have been associated with a low diagnostic sensitivity for trichosporonosis [245,250,251]. Molecular tests, including direct detection on blood or formalin-fixed paraffin-embedded tissue samples, are being developed but are not yet standardized [252–255]. Reliable species identification requires molecular identification with sequencing of the ITS 1 + 2 (±D1/D2 domain) or even the intergenic spacer region (IGS1) of the rDNA [256–258]. MALDI-TOF-MS appears to be a promising identification tool (with an extensive database) [259].

Susceptibility testing and treatment

Emerging experience suggests that azoles are the primary drug class for the treatment of invasive trichosporonosis [192,232,233,237,238,260,261]. Several of the species are resistant *in vitro* to amphotericin B with MICs ≥2 mg/L, including *T. asahii* [256,257,262,263]. *Trichosporon* species are resistant to flucytosine (MICs 4–128 mg/L) and to the echinocandins (MICs >16 mg/L) [239,263,264]. In patients with systemic trichosporonosis and underlying haematological disease poor response rates (i.e. between 16% and 24%) on amphotericin B have been reported and therefore this agent is not recommended for invasive infections [192,231,265–267]. Triazoles on the other hand have been found to be superior to other antifungal drug classes in prophylaxis and treatment [232,238,268]. Most published experience concerns the use of fluconazole. However, variations in susceptibility *in vitro* may suggest that not all species and isolates are equally susceptible to this agent [257]. Voriconazole is the preferred agent because it displays good *in vitro* activity against most *Trichosporon* species and isolates and has been associated with good *in vivo* outcome in most cases of clinical and animal studies [232,233,256,261,263,269–271]. In addition to triazole treatment, resolution of myelosuppression and removal of vascular catheters are other confounders related with increased survival [28,192,231,237,238].

Conclusion

Rare yeasts other than *Candida* and *Cryptococcus neoformans/gattii* are commonly found in the environment and as skin or mucosal colonizers in humans. Some of them may be considered as true emergent opportunistic pathogens in Europe, although the number of reported episodes remains low because of their low pathogenicity even in patients with severely compromised immunity, particularly those with haematological malignancies and a CVC.

Several of these rare yeasts possess intrinsic or variable resistance to antifungals including echinocandins (to which only *Saccharomyces* spp. and *K. ohmeri* are presumably susceptible) and even polyenes (*Trichosporon* spp.) or azoles (*Rhodotorula* spp.; some *M. capitatus* isolates). This may explain the occurrence of breakthrough infections during empiric antifungal therapy in neutropenic patients. Amphotericin B is among the recommended first-line treatment options for these infections except for *Trichosporon*. Combination with flucytosine may be considered particularly in severe cases or cases where drug penetration may be suboptimal provided the infecting organism is susceptible. In agreement with the recommendations provided in the *Candida* guideline amphotericin B lipid formulations may be considered preferable to conventional deoxycholate amphotericin B for toxicity reasons and liposomal amphotericin B particularly for infections involving the CNS [3,5,6,272,273].

Genus identification is mandatory for clinical management and should be performed and provided in a timely manner. Species identification of these rare yeasts, however, remains difficult and often requires reference expertise and adoption of modern techniques including molecular analysis or MALDI-TOF-MS (with an extensive database). Whether or not the precise species identification (outside cryptococcosis) may

have an impact on the individual clinical management remains to be documented; however, its use and value for epidemiological surveillance and outbreak investigation has been documented beyond doubt.

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Transparency Declarations

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LP has received honoraria from Gilead Sciences, Schering-Plough, Astellas Pharma, Merck and Pfizer Pharmaceuticals, he has been speaker for Gilead Sciences, Schering-Plough, Merck, Pfizer Pharmaceuticals and Astellas Pharma.

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