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 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: (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 jiroveci, Trichosporon loubieri, Trichosporon mucoides and Trichosporon mycotoxivorans and ascomycetous ones: Geotrichum candidum, Kodamaea ohmeri, Saccharomyces cerevisiae (incl. S. boulardii) and Saprochaete capitatae (Magnusiomyces (Blastochizomyces) 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 candidiasis 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 albidosimilis, Cryptococcus diffuens, Cryptococcus humicola and Cryptococcus uzbekistanensis, Trichosporon spp. others than those mentioned above, Blastobotrys proliferans, Millerozyma farinosa, Ogataea polymorpha and Geuromyces pullulans. Finally, the guideline was limited to true yeasts and hence the unicellular algae Protatheca wickerhamii and Protatheca 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 cause of invasive human disease included Cryptococcus albidosimilis, Cryptococcus diffuens, Cryptococcus humicola and Cryptococcus uzbekistanensis, Trichosporon spp. others than those mentioned above, Blastobotrys proliferans, Millerozyma farinosa, Ogataea polymorpha and Geuromyces pullulans. Finally, the guideline was limited to true yeasts and hence the unicellular algae Protatheca wickerhamii and Protatheca zopfii var. zopfii were excluded although we realize they have been misidentified as yeasts on occasion.

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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).

Sacharomyces 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 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.

<table>
<thead>
<tr>
<th>Anamorphic state</th>
<th>Teleomorphic state</th>
<th>Specific comment relevant in clinical context</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>C. africana</strong></td>
<td>Not described</td>
<td>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].</td>
</tr>
<tr>
<td><strong>C. auris</strong></td>
<td>Not described</td>
<td>Related to C. haemulonii. Fluconazole MICs higher than for C. albicans [8]</td>
</tr>
<tr>
<td><strong>C. brocariensis</strong></td>
<td>Not described</td>
<td>Closely related to C. glabrata. Susceptibility pattern as for C. glabrata (azole MICs elevated compared with C. albicans) [9].</td>
</tr>
<tr>
<td><strong>C. ciferrii</strong></td>
<td>Trichosporon deineri</td>
<td>Clinical significance uncertain. Inherent resistance to several antifungal compounds described [10].</td>
</tr>
<tr>
<td><strong>C. dubliensis</strong></td>
<td>Not described</td>
<td>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].</td>
</tr>
<tr>
<td><strong>C. fabianii</strong></td>
<td>Cyphellopsis fabianii</td>
<td>Clinical significance uncertain. Fluconazole MICs higher than for C. albicans [12].</td>
</tr>
<tr>
<td><strong>C. famata</strong></td>
<td>Debaryomyces hansenii</td>
<td>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]).</td>
</tr>
<tr>
<td><strong>C. guilliermondii</strong></td>
<td>Meyerozyma guilliermondii</td>
<td>Closely related to C. fermentati and C. palmiolophila. High echinocandin and azole MICs [13].</td>
</tr>
<tr>
<td><strong>C. haemulonii</strong></td>
<td>Not described</td>
<td>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 amphothericin B MICs are reported. Related to C. auris [14].</td>
</tr>
<tr>
<td><strong>C. helenica</strong></td>
<td>Zygosaccharomyces meyerae</td>
<td>Fungaemia and respiratory infection has been reported. Decreased susceptibility to fluconazole, itraconazole, caspofungin, susceptible to voriconazole [15].</td>
</tr>
<tr>
<td><strong>C. inopsicaea</strong></td>
<td>Not described</td>
<td>Closely related to C. norvegensis. Susceptibility pattern similar to C. krusei (intrinsically resistant to fluconazole) [16].</td>
</tr>
<tr>
<td><strong>C. intermediata</strong></td>
<td>Not described</td>
<td>Oropharyngeal colonizer, bloodstream infections, peritonitis. Susceptible to antifungal drugs except fluconazole [13].</td>
</tr>
<tr>
<td><strong>C. kefyr</strong></td>
<td>Kluyveromyces marxianus</td>
<td>No inherent resistance to antifungals described.</td>
</tr>
<tr>
<td><strong>C. lipolytica</strong></td>
<td>Yarrowia lipolytica</td>
<td>Clinical significance uncertain. Fluconazole MICs higher than for C. albicans.</td>
</tr>
<tr>
<td><strong>C. lusitaniae</strong></td>
<td>Claviceps lusitaniae</td>
<td>Not a good target for amphotericin B even if MICs are in the susceptible range (&lt;1 mg/L) [17].</td>
</tr>
<tr>
<td><strong>C. metapsilosis</strong></td>
<td>Not described</td>
<td>Closely related to C. parapsilosis. Susceptibility pattern similar to this species (high echinocandin MICs) [18].</td>
</tr>
<tr>
<td><strong>C. nivariensis</strong></td>
<td>Not described</td>
<td>Closely related to C. glabrata. Susceptibility pattern similar to this species (decreased susceptibility to azoles) [9].</td>
</tr>
<tr>
<td><strong>C. norvegensis</strong></td>
<td>Not described</td>
<td>Closely related to C. inopsicaea. Susceptibility pattern similar to this species (high echinocandin MICs) [18].</td>
</tr>
<tr>
<td><strong>C. palmiolophila</strong></td>
<td>Not described</td>
<td>Phenotypically related to C. guilliermondii. High azole MICs (but low echinocandin MICs in contrast to those for C. guilliermondii) [13].</td>
</tr>
<tr>
<td><strong>C. pelikulaea</strong></td>
<td>Wickerhamomyces anomalus (prev. Pichia anomala, Hansenula anomala)</td>
<td>Fluconazole MICs higher than for C. albicans [19].</td>
</tr>
<tr>
<td><strong>C. pulcherrima</strong></td>
<td>Pichia kudriavzevii (prev. Metschnikowia pulcherrima)</td>
<td>Clinical significance uncertain.</td>
</tr>
<tr>
<td><strong>C. rugosa</strong></td>
<td>Not described</td>
<td>Fluconazole MICs higher than for C. albicans [19].</td>
</tr>
<tr>
<td><strong>C. subbashi</strong></td>
<td>Not described</td>
<td>Clinical significance uncertain.</td>
</tr>
<tr>
<td><strong>C. vanuathii</strong></td>
<td>Not described</td>
<td>Clinical significance uncertain.</td>
</tr>
<tr>
<td><strong>C. zeylanoides</strong></td>
<td>Not described</td>
<td>Clinical significance uncertain.</td>
</tr>
</tbody>
</table>

### TABLE 2. Strength of the EFISG and ECMC recommendation and quality of evidence.

<table>
<thead>
<tr>
<th>Strength of a recommendation (SoR)</th>
<th>Grade A</th>
<th>Grade B</th>
<th>Grade C</th>
<th>Grade D</th>
</tr>
</thead>
<tbody>
<tr>
<td>ESCMID and ECMC strongly support a recommendation for use</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>ESCMID and ECMC moderately support a recommendation for use</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>ESCMID and ECMC marginally support a recommendation for use</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>ESCMID and ECMC support a recommendation against use</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Quality of evidence (QoE)</th>
<th>Level I</th>
<th>Level II</th>
<th>Level III</th>
</tr>
</thead>
<tbody>
<tr>
<td>Evidence from at least one properly designed randomized, controlled trial</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>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</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Evidence from opinions of respected authorities, based on clinical experience, descriptive case studies, or reports of expert committees</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
</tr>
</tbody>
</table>

*Added index: \( ^a \) Meta-analysis or systematic review of randomized controlled trials. \( ^b \) Transferred evidence, that is, results from different patients’ cohorts, or similar immune-status situation. \( ^c \) Comparator group is a historical control. \( ^d \) Uncontrolled trial. \( ^e \) Published abstract (presented at an international symposium or meeting).
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.

**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**

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>C. neoformans</td>
<td>3982</td>
<td>3668</td>
<td>3382</td>
<td>1,195</td>
<td>1,195</td>
</tr>
<tr>
<td>C. gattii</td>
<td>44 (1.1%)</td>
<td>188 (5.1%)</td>
<td>94 (2.8%)</td>
<td>11,240</td>
<td>11,240</td>
</tr>
<tr>
<td>C. laurentii</td>
<td>56 (1.4%)</td>
<td>357 (10.8%)</td>
<td>21 (5.1%)</td>
<td>462 (2.1%)</td>
<td>462 (2.1%)</td>
</tr>
<tr>
<td>C. albidus</td>
<td>4 (0.1%)</td>
<td>5 (0.1%)</td>
<td>2 (0.1%)</td>
<td>6 (0.0%)</td>
<td>6 (0.0%)</td>
</tr>
<tr>
<td>C. curvatus</td>
<td>0</td>
<td>1</td>
<td>1 (0.1%)</td>
<td>3 (0.0%)</td>
<td>3 (0.0%)</td>
</tr>
<tr>
<td>C. flavescens</td>
<td>0</td>
<td>2</td>
<td>2 (0.1%)</td>
<td>4 (0.1%)</td>
<td>4 (0.1%)</td>
</tr>
<tr>
<td>C. uniguttulatus</td>
<td>0</td>
<td>2</td>
<td>2 (0.1%)</td>
<td>4 (0.1%)</td>
<td>4 (0.1%)</td>
</tr>
<tr>
<td>C. uniguttulatus</td>
<td>0</td>
<td>2</td>
<td>2 (0.1%)</td>
<td>4 (0.1%)</td>
<td>4 (0.1%)</td>
</tr>
</tbody>
</table>

NA, Not available.


*Taxonomically also a Candida species (C. ribiusto).
<table>
<thead>
<tr>
<th>Organism</th>
<th>Pseudo-hyphae</th>
<th>Hyphae</th>
<th>Blastoconidia</th>
<th>Anneloconidia</th>
<th>Chlamydoconidia</th>
<th>Capsule</th>
<th>Monopolar budding</th>
<th>Arthroconidia</th>
<th>Urease</th>
<th>Appearance on CHROMagar</th>
<th>Specific comments regarding morphology</th>
<th>Identification to the species level requires*</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Cryptococcus</em> spp. other than <em>C. neoformans</em> &amp; <em>C. gattii</em></td>
<td>–</td>
<td>+</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>+</td>
<td>–</td>
<td>+</td>
<td>No data</td>
<td>India ink may visualize the capsule in clinical specimens</td>
<td>ITS 1 + 2 (2nd option D1/D2 domain) MALDI-TOF promising</td>
</tr>
<tr>
<td><em>Geotrichum</em></td>
<td>–</td>
<td>+</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>+</td>
<td>+</td>
<td>–</td>
<td>+</td>
<td>Variable, probably species dependent</td>
<td>White colonies, arthroconidia</td>
<td>ITS 1 + 2 (2nd option D1/D2 domain) MALDI-TOF promising</td>
</tr>
<tr>
<td><em>Kodamaea aloes</em></td>
<td>+</td>
<td>–</td>
<td>+</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>No data</td>
<td>Colour change on CHROMagar within 48 h</td>
<td>ITS 1 + 2 (2nd option D1/D2 domain) MALDI-TOF promising</td>
</tr>
<tr>
<td><em>Malassezia</em></td>
<td>–</td>
<td>–</td>
<td>+</td>
<td>–</td>
<td>–</td>
<td>+</td>
<td>+</td>
<td>–</td>
<td>+</td>
<td>No growth except <em>M. pachydermatis</em></td>
<td>Lipid dependent except <em>M. pachydermatis</em> white/cream colonies, monopolar budding Fusiform spindle-shaped elongated blastoconidia</td>
<td>Phenotypically or ITS 1 + 2 MALDI-TOF promising</td>
</tr>
<tr>
<td><em>Pseudozyma</em></td>
<td>–</td>
<td>+</td>
<td>+</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>+</td>
<td>No data</td>
<td><em>P. aphidis</em> forms rough green colonies. No data for the other species.</td>
<td>ITS 1 + 2 (2nd option D1/D2 domain)</td>
</tr>
<tr>
<td><em>Rhodotorula</em></td>
<td>–/(-)</td>
<td>–/(-)</td>
<td>+</td>
<td>–</td>
<td>–</td>
<td>(+)</td>
<td>–</td>
<td>–</td>
<td>+</td>
<td>No data</td>
<td>Red, orange-salmon coloured colonies</td>
<td>ITS 1 + 2 (2nd option D1/D2 domain) MALDI-TOF</td>
</tr>
<tr>
<td><em>Saccaromyces</em></td>
<td>–</td>
<td>+</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>No data</td>
<td>Larger cells compared with <em>C. glabrata</em>, poor growth on blood agar</td>
<td>Biochemical tests or MALDI-TOF</td>
<td></td>
</tr>
<tr>
<td><em>Saprocaroete capitata</em></td>
<td>–</td>
<td>+</td>
<td>–/(-)</td>
<td>+</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>+</td>
<td>No data</td>
<td>White, butyrous colonies, arthroconidia</td>
<td>ITS 1 + 2 (2nd option D1/D2 domain) MALDI-TOF promising</td>
</tr>
<tr>
<td><em>Sporobolomyces</em></td>
<td>–/(-)</td>
<td>–/(-)</td>
<td>+</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>+</td>
<td>No data</td>
<td>Red, orange-salmon coloured colonies; satellite colonies due to ballistoconidia</td>
<td>ITS 1 + 2 (2nd option D1/D2 domain) MALDI-TOF</td>
</tr>
<tr>
<td><em>Trichosporon</em></td>
<td>–</td>
<td>+</td>
<td>+</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>+</td>
<td>T. asahii: dirty green (others variable)</td>
<td>Colony becoming dry, arthroconidia</td>
<td>ITS 1 + 2 (2nd option D1/D2 domain) MALDI-TOF promising</td>
<td></td>
</tr>
</tbody>
</table>

*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 ID-32C. MALDI-TOF, matrix-assisted laser desorption/ionization time of flight mass spectrometry.
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. albicans (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°C for 2 weeks (with prolonged incubation in the case of rheumatoid factor [59], and the 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 level of the cryptococcal cell wall is much lower than in for example Candida albicans [50]). 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].

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

<table>
<thead>
<tr>
<th>Species</th>
<th>Surrogate markers</th>
<th>Strength of recommendation</th>
<th>Quality of evidence</th>
<th>Comment</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>All</td>
<td>Blood culture</td>
<td>A</td>
<td>II</td>
<td>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.</td>
<td>[32–34]</td>
</tr>
<tr>
<td>C. neoformans (and can therefore be differentiated from C. gattii)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cryptococcus other than C. neoformans and C. gattii</td>
<td>Cryptococcus antigen</td>
<td>C</td>
<td>III</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asp GM</td>
<td></td>
<td>D</td>
<td>III</td>
<td>Cross-reaction due to galactomannan in the fungal cell wall. However, sensitivity not examined.</td>
<td>[65]</td>
</tr>
<tr>
<td>Geotrichum candidum</td>
<td>β-1,3-D-glucan</td>
<td>D</td>
<td>II</td>
<td>β-1,3-D-glucan present in culture supernatant but no clinical data.</td>
<td>[63]</td>
</tr>
<tr>
<td>Malassezia</td>
<td>No data on surrogate markers</td>
<td>No data on surrogate markers</td>
<td>No recom-mendation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Malassezia</td>
<td>Isolator 10 Lysis centrifugation or BC bottle suppl. with palmitic acid</td>
<td>No recom-mendation</td>
<td>No data</td>
<td>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.</td>
<td>[107,108]</td>
</tr>
<tr>
<td>Pseudozyma rhodoferax</td>
<td>No data on surrogate markers</td>
<td>No data on surrogate markers</td>
<td>No recom-mendation</td>
<td>No data</td>
<td></td>
</tr>
<tr>
<td>Pseudozyma rhodoferax</td>
<td>β-1,3-D-glucan</td>
<td>No recom-mendation</td>
<td>No data</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Saccharomyces</td>
<td>β-1,3-D-glucan</td>
<td>C</td>
<td>III</td>
<td>β-1,3-D-glucan present in culture supernatant but in lower amount and but no clinical data.</td>
<td>[63,180]</td>
</tr>
<tr>
<td>Saprochaete capitata</td>
<td>Candida mannan antigen</td>
<td>C</td>
<td>III</td>
<td>Single clinical case and antigen similarity</td>
<td>[179]</td>
</tr>
<tr>
<td>Trichosporon</td>
<td>Cryptococcus antigen</td>
<td>B</td>
<td>II</td>
<td>Cross-reaction with cryptococcal polysaccharide and galactomannan Ags. Dual positivity may be suggestive for Trichosporon infection. However, sensitivity not examined.</td>
<td>[57,58,246–249]</td>
</tr>
<tr>
<td>Trichosporon</td>
<td>β-1,3-D-glucan</td>
<td>D</td>
<td>II</td>
<td>Low sensitivity</td>
<td>[238,250,251]</td>
</tr>
<tr>
<td>Population/manifestation</td>
<td>Antifungal</td>
<td>Strength of recommendation – quality of evidence</td>
<td>Comments</td>
<td>References</td>
<td></td>
</tr>
<tr>
<td>--------------------------</td>
<td>------------</td>
<td>-----------------------------------------------</td>
<td>----------</td>
<td>------------</td>
<td></td>
</tr>
<tr>
<td>Cryptococcus other than C neoformans and C gattii</td>
<td>Amphotericin ( ^\text{B-III} ) (( ^\text{f}' ) fluconazole)</td>
<td>B-III</td>
<td>MICs of S-FC, fluconazole and other azoles often elevated and particularly so for C albids, C laurenti and C unguillotum [97,106]</td>
<td>[44-46,49,69-74]</td>
<td></td>
</tr>
<tr>
<td>CNS and severe inf. Induction</td>
<td>Fluconazole ( \geq 400 \text{ mg/day} )</td>
<td>C-III</td>
<td>MICs of S-FC, fluconazole and other azoles often elevated and particularly so for C albids, C laurenti and C unguillotum [97,106]</td>
<td>[44-46,49,69-74]</td>
<td></td>
</tr>
<tr>
<td>Non-CNS, not severe inf.</td>
<td>Amphotericin ( ^\text{B-III} )</td>
<td>B-III</td>
<td>May be preferable to fluconazole for the less azole-susceptible species</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kodamaea ohmeri</td>
<td>Echinocandins ( ^\text{B-III} ) (( ^\text{f}' ) fluconazole)</td>
<td>B-III</td>
<td>Preferred agent is amphotericin B (w/wo S-FC).</td>
<td>[77-80]</td>
<td></td>
</tr>
<tr>
<td>Malassezia</td>
<td>Voriconazole ( ^\text{C-III} )</td>
<td>C-III</td>
<td>M. pachydermatis ( ^\text{NR} ) No data</td>
<td>[84,88,92]</td>
<td></td>
</tr>
<tr>
<td>Pseudazymo spp.</td>
<td>Amphotericin ( ^\text{B-III} )</td>
<td>B-III</td>
<td>Low MICs of amphotericin B, case stories reporting success.</td>
<td>[121-124]</td>
<td></td>
</tr>
<tr>
<td>Any, fungaemia</td>
<td>Fluconazole ( ^\text{C-III} )</td>
<td>C-III</td>
<td>In vitro resistant</td>
<td>[97,106]</td>
<td></td>
</tr>
<tr>
<td>Any, fungaemia</td>
<td>Voriconazole ( ^\text{C-III} )</td>
<td>C-III</td>
<td>In vitro resistant</td>
<td>[97,106]</td>
<td></td>
</tr>
<tr>
<td>Any, fungaemia</td>
<td>Fluconazole ( ^\text{D-IIu} )</td>
<td>D-IIu</td>
<td>Breakthrough cases on azoles and echinocandins.</td>
<td>[147,153,154]</td>
<td></td>
</tr>
<tr>
<td>Saccharomyces</td>
<td>Amphotericin ( ^\text{B-III} )</td>
<td>B-III</td>
<td>Most clinical experience; toxicity risk higher than for echinocandins</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any, fungaemia</td>
<td>Voriconazole ( ^\text{C-III} )</td>
<td>C-III</td>
<td>Two successful cases in the literature (( ^\text{f}' ) 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)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any, fungaemia</td>
<td>Fluconazole ( ^\text{D-III} )</td>
<td>D-III</td>
<td>Increased occurrence in patients exposed to fluconazole; high fluconazole MICs (similar to those for C glabrata)</td>
<td>[26,178]</td>
<td></td>
</tr>
<tr>
<td>Any, fungaemia</td>
<td>Discontinuation of probiotics ( ^\text{C-III} )</td>
<td>C-III</td>
<td>Probiotic containing S boulardii has been documented to be the origin of systemic infections.</td>
<td>[175,176]</td>
<td></td>
</tr>
<tr>
<td>Any, fungaemia</td>
<td>Amphotericin ( ^\text{B-III} ) (( ^\text{f}' ) fluconazole)</td>
<td>B-III</td>
<td>Most (but limited) experience. In vitro susceptibility of amphotericin B in the intermediate range, failures in hepatosplenic infections reported on amphotericin B monotherapy.</td>
<td>[186,194,196]</td>
<td></td>
</tr>
<tr>
<td>Any, fungaemia</td>
<td>Voriconazole ( ^\text{C-III} )</td>
<td>C-III</td>
<td>Possibly a treatment option but insufficient clinical data</td>
<td>[69,222,223,230]</td>
<td></td>
</tr>
<tr>
<td>Any, fungaemia</td>
<td>Voriconazole ( ^\text{C-III} )</td>
<td>C-III</td>
<td>Possibly a treatment option but insufficient clinical data</td>
<td>[69,225,230]</td>
<td></td>
</tr>
</tbody>
</table>
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. albipus (rather than C. laurentii), age above 45 years and central nervous system involvement [44]. In vitro susceptibility testing suggests that C. albipus, 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. albipus, 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 previousazole 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 haematology setting [75–77]. It is closely related to Saprochaete capitata (Magnusomyces 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 fungemia, 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. dermatis, 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 μm. 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 Gueho-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 amphoterocin 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 captured to 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-D-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-D-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 haematology-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 *Magnusiomycetes 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 to be 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, 2013 The Authors

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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 f-glucose has not been investigated. Due to the ubiquitous presence of Sporobolomyces contamination, transient colonization or pseudoinfection should be considered [223,224,229].

Sporobolomyces salmonicolor

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.; *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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OL is a consultant for Novartis, Fab Pharma and Gilead Sciences, and received grants or speaker’s fees from MSD, Roche, Astellas, Gilead Sciences and Pfizer.

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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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