Emerging opportunistic yeast infections

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A growing population of immunosuppressed patients has resulted in increasingly frequent diagnoses of invasive fungal infections, including those caused by unusual yeasts. The incidence of non-albicans species of *Candida* is increasing compared with that of *Candida albicans*, and several species, such as *Candida glabrata* and *Candida krusei*, may be resistant to azole antifungal therapy. *Trichosporon* species are the second most common cause of fungaemia in patients with haematological malignant disease and are characterised by resistance to amphotericin and echinocandins and poor prognosis. *Rhodotorula* species belong to the family Cryptococcaceae, and are a cause of catheter-related fungaemia, sepsis, and invasive disease in severely immunosuppressed patients. An increasing number of sporadic cases of invasive fungal infections by non-neoformans cryptococci have been reported in immunocompromised hosts, especially for patients with advanced HIV infection or cancer who are undergoing transplant. Other uncommon yeasts that can cause invasive disease in severely immunosuppressed patients include *Geotrichum*, *Hansenula*, *Malassezia*, and *Saccharomyces*. Host immune status is a crucial determinant of the type of invasive fungal infection a patient is at risk for. Diagnosis can be challenging and relies heavily on traditional cultures of blood and other sterile sites, although serum (1,3)-β-D-glucan testing might have an adjunctive role. Although rare yeasts are emerging as opportunistic human pathogens, diagnosis remains challenging and treatment suboptimal.

Introduction

Candida albicans is the predominant cause of invasive fungal infections from yeasts.[1,2] Nevertheless, the epidemiology of yeast infections is rapidly evolving and non-albicans *Candida* species and other rare yeasts have emerged as major opportunistic pathogens (panel). Horn and colleagues[1] showed that prevalence of candidaemia caused by non-albicans *Candida* species was 54·4%. Other yeasts that are less common than candida have been associated with life-threatening infections in immunocompromised hosts.[3–6] Although the importance of these emerging opportunistic yeasts is recognised, little is known about present epidemiological traits of these pathogens. Indeed, these pathogens are frequently difficult to identify by phenotypic methods and show variable susceptibility profiles to antifungal drugs.[7,8] We address the epidemiological, diagnostic, and therapeutic aspects of emerging yeast infections.

Emerging yeasts

Non-albicans *Candida* species

Although *C albicans* is the most common cause of invasive fungal infections in hospital settings, the growing number of new infections from non-albicans *Candida* species is increasingly recognised as a major source of infection. In most surveys and treatment studies in the USA, *Candida glabrata* is the second most common *Candida* species leading to invasive fungal infections. The ARTEMIS Global Antifungal Surveillance Program[9] showed that *C albicans* was the most common (63–70%) candidal cause of invasive fungal infections, followed by *C glabrata* (44%), *Candida tropicalis* (6%), and *Candida parapsilosis* (5%).[9] However, geographical and institutional differences are widely reported, and, outside of the USA, *C glabrata* is less frequently isolated.[10] For example, in Brazil,[11] *C tropicalis* and *C parapsilosis* are the second and third most common *Candida* species, respectively, whereas in Australia,[12] *C parapsilosis* and *C glabrata* are the next most common species. Worldwide, *C tropicalis* and *C parapsilosis* have increased in prevelance, as have rarer species such as *Candida guilliermondii*, *Candida pelliculosa*, *Candida kefyr*, *Candida rugosa*, and *Candida famata*.[7,13–17]

C parapsilosis is one of the principal causes of invasive candidosis. Individuals at the highest risk for severe infection are neonates and patients in intensive care units. *C tropicalis* and *Candida krusei* are key causes of invasive fungal infections in patients undergoing bone marrow or stem-cell transplantation, and in patients with malignant haematological disease.[18,19] Pfaller and colleagues[20] reported in a surveillance study that *C guilliermondii* and *C rugosa* were most prevalent in Latin America, whereas *Candida inconspicua* and *Candida norvegensis* were most abundant in eastern Europe. *C kefyr* is notable for outbreaks in haematology wards, and has been identified in dairy products.[15,21] An increasing number of less-common *Candida* species that lead to infections in people have been identified, including *Candida orthopsilosis*, *Candida metapsilosis*, and *Candida nivariensis*.[7,22] European studies[23,24] have

***Panel:* Synonyms of yeast species mentioned in this Review**

- *Hansenula* (*Pichia*)
- *Candida krusei* (*Pichia kudriavzevii*)
- *Candida guilliermondii* (*Meyerozyma guilliermondii*)
- *Candida pelliculosa* (*Wickerhamomyces anomalus*)
- *Candida kefyr* (*Kluyveromyces marxianus*)
- *Candida norvegensis* (*Pichia norvegensis*)
- *Cryptococcus humicolus* (*Asterotremella humicola*)
- *Cryptococcus uniguttulatus* (*Filobasidium uniguttulatum*)
- *Geotrichum capitatum* (*Dipodascus capitatus*)
- *Hansenula anomala* and *Pichia anomala* (both *Wickerhamomyces anomalus*)

also reported the role of *C nivariensis* as a human pathogen that can be acquired from hospital gardens or potted plants.

Candida species usually exist as commensals in the gastrointestinal tract and genital tract of healthy hosts, but they are also opportunistic pathogens that have the ability to cause various superficial and systemic infections. Yeast forms of candida are unicellular, reproduce by budding, and grow well in routine automated blood culture bottles and on agar plates. *C glabrata* grows smaller, elliptical, unicellular budding yeasts than do *C albicans*, *C krusei*, *C parapsilosis*, and *C tropicalis*.

One of the main reasons for candida's virulence is its versatility in adaptation to various different habitats, and the formation of biofilms that enhance its ability to adhere to surfaces and cause infection.[25] Biofilm cells are organised into structured communities embedded within a matrix of extracellular material.[25] *C albicans* forms fungal biofilms most often, but non-albicans *Candida* species are also indicated in biofilm-associated infections. Silva and colleagues[26] showed that non-albicans *Candida* species can form biofilms, although they were less widespread for *C glabrata* than they were for *C parapsilosis* or *C tropicalis*. In the same study,[26] production of *C parapsilosis* biofilms was very dependent on strain, a feature that was not observed with *C glabrata* and *C tropicalis*.

Candida species become pathogens when the host's resistance to infection is impaired locally or systemically. For example, neutropenia, neutrophil dysfunction, and disruption of mucosal barriers are the main risk factors for disseminated infections. In an immunocompromised host, translocation from the gastrointestinal tract and intravascular catheters are the two main portals of entry for disseminated candida infection.

Although *Candida* species are regular flora in the gastrointestinal and genitourinary tracts of human beings, they have the propensity to invade and cause disease when an imbalance is created in their ecological niche. Immune response of the host is a key determinant of the type of infection caused by *Candida* species. Clinical manifestations of infection with *Candida* species range from localised superficial involvement to deep organ involvement and disseminated infection. Invasive focal infections, such as pyelonephritis, endocarditis, and meningitis, most often occur after haematogenous candidosis.

Resistance of non-albicans candida isolates to available antifungal drugs is a major challenge for future empirical therapeutic and prophylactic strategies (table). Azole resistance is a potential issue with *C glabrata*, *C krusei*, and other uncommon species. *C guilliermondii* shows reduced susceptibility to fluconazole (75% susceptibility), but is largely susceptible to voriconazole (91%).[27] *C rugosa* isolates are 40·5% susceptible to fluconazole and 61·4% to voriconazole.[28] *Candida lusitaniae* can develop secondary resistance to amphotericin,[29] and *Candida dubliniensis* can develop stable fluconazole resistance, especially in patients with HIV/AIDS.[30] Clinical isolates of *C nivariensis* have shown cross-resistance to azoles.[7]

Nevertheless, nearly all global clinical isolates of *Candida* species are susceptible to echinocandins,[31] although there have been some reports[32] of reduced susceptibility or resistance to these antifungals in the setting of severe immunosuppression, recurrent candidaemia, and prolonged exposure to echinocandins. *C glabrata*, *C parapsilosis*, *Candida lipolytica*, *C lusitaniae*, and *C tropicalis* can cause breakthrough mycoses despite prophylactic or therapeutic use of echinocandins.[33]

C parapsilosis is usually susceptible to echinocandins in a clinical setting, but often has a higher minimum inhibitory concentration for caspofungin, and failure of caspofungin treatment can occur.[31,34]

Biofilm formation is a major challenge to treatment of candida infections related to biomaterial. However, in many critically ill patients with biomaterial-related or catheter-related candida infections, removal or replacement of the infected device is difficult or very risky. In addition to standard antifungal therapy, alternative strategies have been proposed for the conservative management of complications associated with a central venous catheter, including use of antibiotic lock therapy,[35] although more data are needed before this strategy can be recommended.

Trichosporon species

Trichosporon was the third most commonly isolated non-candidal yeast from clinical specimens in the ARTEMIS Global Antifungal Surveillance Program (10·7% of 8821 isolates).[9] Invasive fungal infection caused by *Trichosporon* species is the second most common cause of yeast fungaemia in patients with malignant haematological disease (after *Candida* species). The main *Trichosporon* species leading to invasive fungal infections are *Trichosporon asahii*, *Trichosporon asteroides*, *Trichosporon cutaneum*, *Trichosporon inkin*, *Trichosporon mucoides*, and *Trichosporon ovoides* (formerly all classified as *Trichosporon beigelii*).[36]

Trichosporon is a basidiomycetous yeast genus that produces septate hyphae, arthroconidia, yeasts, and pseudohyphae. Presence of blastoconidia with hyphae differentiates *Trichosporon* from *Geotrichum*. Because of shared antigens that are cross-reactive with the capsular antigen of *Cryptococcus neoformans*, a positive cryptococcal latex test can occur in patients with disseminated trichosporon infection.[37]

Trichosporon species can be found in soil and fresh water, and are part of the normal flora of the human skin and gastrointestinal tract. Infection can be superficial, subcutaneous, or systemic. *T ovoides* causes white piedra, which is a superficial infection occurring most commonly in tropical and subtropical regions. *Trichosporon dermatis* and *T asahii* are associated with summer-type hypersensitivity pneumonitis, which is a disease reported mostly in Japan.[38]

	Azoles		Polyenes	Echinocandins
	Fluconazole	Voriconazole	Amphotericin formulations	Caspofungin
Candida species				
Candida glabrata	Susceptible (dose dependent) to resistant	Susceptible (dose dependent) to resistant	Susceptible to intermediate susceptibility	Susceptible*
Candida tropicalis	Susceptible	Susceptible	Susceptible	Susceptible*
Candida parapsilosis	Susceptible	Susceptible	Susceptible	Susceptible to resistant*
Candida krusei	Resistant	Susceptible (dose dependent) to resistant	Susceptible to intermediate susceptibility	Susceptible
Candida kefyr	Susceptible	Susceptible	Susceptible	Susceptible
Candida lusitaniae	Susceptible	Susceptible	Susceptible to resistant	Susceptible*
Candida dubliniensis	Susceptible to resistant	Susceptible	Susceptible	Susceptible
Candida rugosa	Very low activity	Low activity	Susceptible	Susceptible
Candida guilliermondii	Low activity	Susceptible	Susceptible	Susceptible
Trichosporon species				
Trichosporon asahii	Low activity	Susceptible	Resistant	Resistant
Trichosporon beigelii (cutaneum)	Low activity	Low activity	Resistant	Resistant
Rhodotorula species	Very low activity	Variable susceptibility/ very low activity	Susceptible	Resistant
Non-*neoformans* cryptococcus species				
Overall	Low activity	Susceptible	Susceptible	NA
Cryptococcus laurentii	Very low activity	NA	Susceptible*	Resistant
Other uncommon yeasts				
Geotrichum species	Variable susceptibility	Susceptible	Susceptible	NA
Hansenula anomala	Fluconazole: low activity; itraconazole: very low activity	Susceptible	Susceptible	Susceptible
Malassezia species	Fluconazole: low activity; itraconazole: susceptible	Susceptible	Variable susceptibility	NA
Saccharomyces species	Low activity/variable susceptibility	Susceptible	Susceptible	NA

Resistant was defined as less than 40% of isolates tested reported as active. Susceptible was defined as more than 90% of isolates tested reported as active. Low activity was defined as 60–89% of isolates tested reported as active. Very low activity was defined as 40–59% of isolates tested reported as active. NA=data not available. *Susceptible but resistance reported after exposure (ie, breakthrough infections).

Table: **Activity of different antifungal drugs against emerging yeasts**

Invasive trichosporon infection has been increasingly identified during the past 30 years. Most cases occur in patients with haematological diseases, particularly those patients with acute leukaemia.[6] Invasive trichosporon infection has been shown to occur in patients with extensive burns, AIDS, chronic corticosteroid use, and heart valve surgery.[6,39] Fungaemia, including catheter-related fungaemia, is the most frequent presentation of invasive trichosporon infection, and can occur as a breakthrough invasive fungal infection on antifungal therapy with high mortality.[4] Clinical features of disseminated infection include positive blood cultures, renal failure, pulmonary infiltrates, skin lesions, and chronic hepatic disease.[40]

Amphotericin lacks fungicidal activity against trichosporon, and in-vitro susceptibility to this drug is variable; flucytosine and echinocandins are ineffective against trichosporon infections (table).[41,42] Clinical and in-vitro studies[9,41,43] suggest that azoles, especially voriconazole and posaconazole, have greatest effectiveness against trichosporon. *T mucoides*, *T inkin*, and *T ovoides* seem to be much more susceptible to fluconazole than are *T asahii (T beigelii)* or *T cutaneum*. Voriconazole has very good activity against *Trichosporon* species, apart from *T beigelii* or *T cutaneum*.[9] However, prognosis is poor without recovery of immune function.[44]

Rhodotorula species

Rhodotorula species are emerging opportunistic pathogens, particularly in immunocompromised patients. In the ARTEMIS surveillance project,[9] *Rhodotorula* species were the fourth most common non-candidal yeasts isolated from clinical specimens (4·2% of 8821 isolates). Rhodotorula infections occur worldwide but are most frequently isolated in the Asia–Pacific region (48·8%). *Rhodotorula mucilaginosa* (also known as *Rhodotorula rubra*) is the most common cause of *Rhodotorula* species fungaemia, followed by *Rhodotorula glutinis* and *Rhodotorula minuta*.[9,45] Overall mortality from rhodotorula fungaemia is 15%.[45] Patients with cancer (including those undergoing bone marrow transplantations) and patients with AIDS are at highest

risk for systemic rhodotorula infection. Patients who have had abdominal surgery, cirrhosis, autoimmune diseases, or burns are also at risk.[45]

Rhodotorula is a basidiomycetous yeast genus that produces carotenoid pigments (yellowish to red), multilateral budding cells, rudimentary pseudohyphae, and occasionally a faint capsule. Individual colonies are usually pink or coral in colour, yeast-like, smooth, and sometimes mucoid in appearance. *Rhodotorula* species are environmental fungi that can be found in soil, fresh water, fruit juice, and milk, or on shower curtains and toothbrushes.[46,47]

Previously regarded as non-pathogenic, *Rhodotorula* species have emerged as opportunistic pathogens with the ability to colonise and infect susceptible patients. Most cases of rhodotorula infection are fungaemia associated with catheters, endocarditis, and meningitis.[45] Non-systemic rhodotorula infections such as endophthalmitis and peritonitis (usually associated with continuous ambulatory peritoneal dialysis) have been reported in immunocompetent patients.[48–50]

Rhodotorula species are susceptible to amphotericin and flucytosine in vitro, but not to fluconazole or caspofungin; susceptibility to triazoles such as voriconazole is variable (table).[51,52] *Rhodotorula* species, including *R mucilaginosa (R rubra)* and *R glutinis*, are often resistant to fluconazole and voriconazole. Amphotericin is the antifungal agent of choice for treatment of rhodotorula infections.[9]

Non-neoformans cryptococcus species

Non-neoformans cryptococci are saprophytes and are rarely reported as human pathogens. However, sporadic cases of non-neoformans cryptococcal infections have been reported in immunosuppressed patients, especially those with advanced HIV infection and patients with cancer who are undergoing transplant surgery.[53] *Cryptococcus laurentii* and *Cryptococcus albidus* cause 80% of cases. However, *Cryptococcus curvatus*, *Cryptococcus humicolus*, and *Cryptococcus uniguttulatus* have also been associated with opportunistic infections in human beings.[53]

Non-neoformans cryptococci are basidiomycete (encapsulated) yeasts that are prevalent worldwide and have been identified from various environmental sources including air, soil, water, pigeon droppings, and foods such as cheese, milk, beans, and wine.

Cryptococcus species can colonise human beings through the respiratory and gastrointestinal tracts. In patients with impaired cellular immunity, such as HIV infection, *Cryptococcus* species can become opportunistic pathogens. Clinical manifestations are usually indistinguishable from those of *C neoformans* infections. The most common sites of infection are the bloodstream and CNS, followed by pulmonary sites and the skin, eyes, gastrointestinal tract, and peritoneum in patients receiving ambulatory peritoneal dialysis.[53–57]

Data for drug resistance in non-neoformans cryptococci are scarce, and are chiefly based on information provided in case reports. Most clinical isolates are susceptible to amphotericin,[53] but antifungal-resistant *C laurentii* strains have been reported in at least two patients who were previously exposed to this drug (table).[55]

Fluconazole and flucytocine have poor activity against non-neoformans cryptococci.[9,53] Fluconazole resistance is more frequent in patients with previous exposure to azoles compared with azole-naive patients.[53] *Cryptococcus* species are innately resistant to echinocandins.[42]

Other uncommon yeasts

Geotrichum species are a rare cause of invasive fungal infections in immunocompromised hosts. By contrast to the worldwide distribution of *Trichosporon* species, *Geotrichum capitatum* is predominantly found in Europe (particularly in Italy).[6] Geotrichum occurs sporadically, chiefly in patients with haematological disease and then most often in those with acute leukaemia.[6] Geotrichum is a very similar yeast to trichosporon, and is reported widely in the environment, including in soil, water, plants, and as a human coloniser. Invasive fungal infections caused by *Geotrichum* species present as a bloodstream or disseminated infection,[6] although pulmonary, CNS, hepatosplenic, and urinary tract involvement have been reported; central line involvement is rare. Few data for antifungal susceptibilities exist, but strains resistant to fluconazole have been reported.[58] In vitro, amphotericin and voriconazole are the most active antifungal agents, compared with the variable activity of fluconazole, flucytosine, and itraconazole.[59]

Outbreaks of the *Hansenula anomala* (*Pichia anomala*) yeast have been reported in neonatal and paediatric intensive care units,[60,61] surgical intensive care units,[62] and in immunocompromised patients,[63] including as breakthrough invasive fungal infections.[64] Incidence is low and distribution sporadic. This yeast is found associated with plants, soil, and fruit juices, but has been reported[65,66] to produce transient human colonisation. It can cause a wide range of invasive infections, but fungaemia, especially in association with a central venous catheter, is most common.[63,67] In vitro, amphotericin, fluconazole, voriconazole, and caspofungin have activity against *P anomala*, although high drug concentrations were required for inhibition; conversely, itraconazole is poorly active against this yeast.[68]

Malassezia species are lipophilic yeasts that colonise the skin and can cause tinea versicolor (especially *Malassezia globosa*) and other dermatological disorders in immunocompetent patients, and folliculitis and catheter-related invasive fungal infections in neonatal, paediatric, and immunocompromised patients (especially *Malassezia furfur*). Distribution of new cases is sporadic or associated with nosocomial outbreaks in patients in intensive care units, especially in paediatric settings. Typically, *M furfur* causes fungaemia that is related to

lipid infusion in immunocompromised patients, but the organism is often less virulent than are other fungal pathogens.[69] In vitro, *Malassezia* species are susceptible to itraconazole, ketoconazole, and voriconazole;[70] susceptibility to amphotericin is variable.[71]

Fungaemia from *Saccharomyces cerevisiae* has been linked to use of live yeast capsules (called *Saccharomyces boulardii*), which are taken for prevention of diarrhoea associated with use of antibiotics and adjunctive therapy for diarrhoea associated with *Clostridium difficile*.[5] Patients at high risk of such fungaemia include those in intensive care units and those with central venous catheters. Nosocomial transmission can occur through airborne contamination or transmission from health-care workers to patients with indwelling central catheters.[72] Clinical presentations include unexplained fever, fungaemia, sepsis, peritonitis, and endocarditis. Very few data are available for drug efficacy, but amphotericin and voriconazole seem to be active in vitro against *S cerevisiae*,[73] whereas fluconazole might be variable in activity (table).[74]

Multiple yeast infections

Patients at a high risk for fungal infection (eg, candida, aspergillus, and mucor) can have more than one occurrence concomitantly or successively. Use of antifungal agents selects for resistant pathogens, much the same as occurs in antibacterial resistance. Prolonged use of voriconazole for prophylaxis or treatment can result in breakthrough fungal infections such as mucormycosis.

Jensen and colleagues[75] showed that mixed fungaemia occurred in 15 (3%) of 530 cases of fungaemia and *C albicans* was the most commonly isolated species (13 cases), followed by *C parapsilosis* (4), *C tropicalis* (2), *C dubliniensis* (2), *C krusei* (2), and *S cerevisiae* (1). Clinical presentation, risk factors, and outcomes for patients with mixed fungaemia were not different from those of monomicrobial fungaemia.[75] In a retrospective study[76] of mixed candidaemia, *C albicans* and *C glabrata* was the most frequently reported combination. Although further discussion about this topic is beyond the scope of our review, clinicians should be aware of the possibility of multiple and breakthrough yeast and mould fungal infections.

Role of host status

Host and pathogen interactions are crucial in pathogenesis of invasive fungal infections. Traditionally, severity and outcomes from fungal infections are attributed to the pathogen's capability to overcome host immune defence and inflict tissue damage. However, whether host immunity is impaired, uncontrolled, or hyper-reactive affects the severity and outcome of invasive mycosis.[77–79]

Phagocytic cells (neutrophils and mononuclear phagocytes) are the effector cells of the innate immunity.[80] Neutrophils are crucial for the initial host response against candida. Neutrophils damage candida hyphae through oxidative and non-oxidative mechanisms. Thus, neutropenia is the main risk factor for disseminated candidosis. Equally, patients with abnormal neutrophil function (eg, chronic granulomatous disease) are at risk for invasive candidosis.[81]

Phagocytic cells of the lung (chiefly denditric cells and alveolar macrophages) are the first immune cells exposed to *C neoformans* on inhalation of the organism into the respiratory tract. Phagocytosis and exposure to soluble glycoantigens or fungal DNA ultimately lead to cytokine and chemokine release and yeast destruction. However, whether this initial innate immune response to *C neoformans* contributes to early clearance or the late development of adaptive immunity is unclear.[82]

Although local phagocytes (innate immune response) are first to attempt to control fungal infection, cell-mediated immunity (acquired immunity) is the major host defence mechanism (figure).[81] Activation of naive T helper (Th0) cells will cause differentiation into very distinctive effector cells dependent on the cytokine environment. Historically, only Th1 and Th2 were described as the main two types of effector T cells, but new lineages of T cells (regulatory T cells [Tregs] and Th17) have been recognised as functionally different subsets. Typically, the presence of interleukin 12 will polarise towards a Th1 response and interleukin 4 will induce a Th2 response. Several reports[83–85] suggest that, in the presence of transforming growth factor β (TGFβ) and interleukins 6 and 23, Th0 will develop into Th17, and that in the presence of TGFβ alone (without interleukin 6) Th0 will promote polarisation toward a Treg response (figure).

For many years, host immune response to fungal infections was explained in terms of Th1 and Th2 response, in which either pathway would elicit specific Th responses depending on the pathogen. Balance between Th1 and Th2 immune responses is crucial for determination of the severity and outcome in immunocompromised hosts with invasive fungal infections (eg, extended neutropenia and acute and chronic graft versus host disease).[81]

Analysis of recent data suggests that Th17 is associated with extended inflammation and defective clearance of fungi. In mice,[79] interleukin 23 and Th17 were important negative regulators of the Th1 immune response against fungi. The Th17 pathway in particular was associated with an extended inflammatory response and impaired pathogen clearance in candida and aspergillus infection. Zhang and colleagues[86] showed that, in mice, a robust Th1 and Th17 immune response has an initial protective role in pulmonary clearance but was insufficient to provide protection against lethal dissemination of *C neoformans* to the brain. These newly described immune regulatory pathways seem to have implications for pathogenesis of chronic mucocutaneous candidosis and intractable mould infections occurring after engraftment

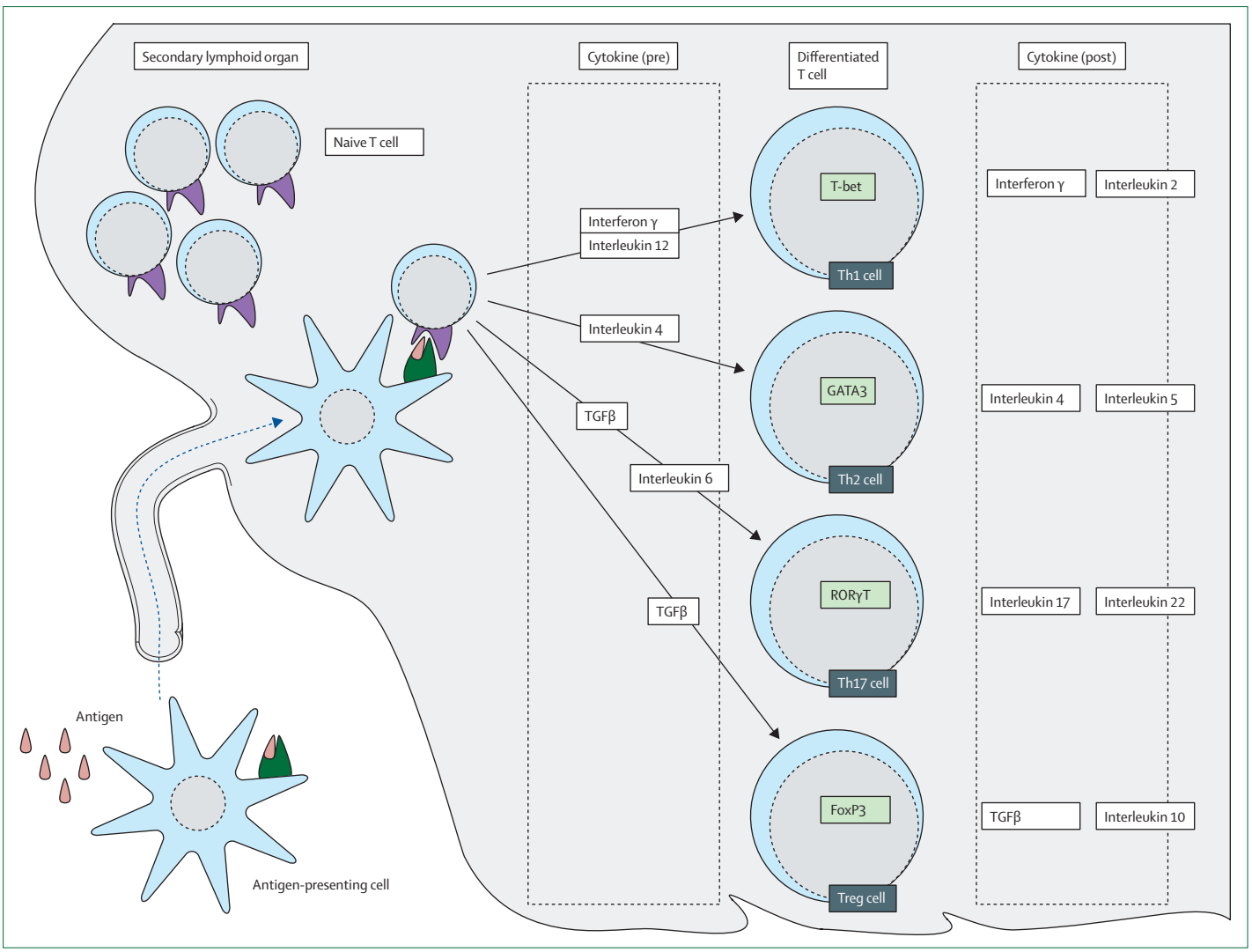

Figure: **Helper-T-cell differentiation**
Antigen recognition triggers naive T-cell activation and differentiation into distinctive effector cells depending on the cytokine environment, inducing the expression of specific transcript factors involved in Th-cell differentiation. Th=Helper T cell. TGF=transforming growth factor. ROR=RAR-related orphan receptor. Fox=Forkhead box. Treg=regulatory T cell.

in recipients of allogenic transplantations. A role has been suggested for Treg and Th17 pathways in the pathogenesis of immune reconstitution syndrome occurring in patients undergoing solid organ transplant[87] and haemopoietic stem cell transplant[77] with invasive fungal infections.[78] Research aimed at elucidation of future implications of these new pathways is in progress.

Diagnostic considerations

Diagnosis of emerging yeast infections depends largely on traditional microbiological culture and identification methods and histopathology. Yeast fungaemia, especially that caused by *Candida* species, can be detected with blood cultures, although supplementation of lipids is usually required for growth of *Malassezia* species.[88] Growth of *Candida* species from blood or normally sterile sites nearly always represents true infection and should be treated as such. However, growth of *Candida* species from non-sterile sites (ie, sputum, skin, and stool) often indicates colonisation or contamination. For instance, growth of *Candida* species in the urine must be interpreted in clinical context, including assessment of signs and symptoms consistent with a urinary tract infection and the presence of pyuria and other biochemical markers of urinary tract infection.[89] Isolation of *Candida* species from many non-sterile sites may be an indicator of occult infection in high-risk patients;[90,91] thus, diagnosis of invasive candidosis can be difficult.

Several studies[92–94] reviewed diagnosis of *Candida* species with techniques that are not reliant on culture. Because of the low sensitivity and specificity of conventional assays for

the detection of invasive fungal infections, new assays have been developed. These methods include antigen-detection systems, such as ELISA and molecular methods (ie, PCR assays). However, these techniques need to be assessed in large patient cohorts and are not standardised at present.

(1,3)-β-D-glucan (BG), which is a unique cell-wall component of many fungi, can be detected and quantified by use of a bioassay based on the horseshoe crab clotting cascade.[95] In addition to detection of *Candida* species in serum samples, the BG test can detect aspergillus, fusarium, trichosporon, saccharomyces, and acremonium, but not cryptococcus or zygomycetes.[96–98]

Investigators assessed the clinical usefulness of the BG test in a multicentre study of 188 febrile patients with haematological malignant disease (167 patients) or other chronic illness (21 patients). 41 (20%) of 202 febrile episodes were caused by candida, cryptococcus, trichosporon, or aspergillus, and 59 (29%) were non-fungal in origin. 37 (90%) of 41 patients with fungal infections and none of the 59 patients with non-fungal infections had positive BG tests.[99] In a multicentre study[100] of various patients (20·2% with haematological malignant disease), BG had a sensitivity and specificity of 69·9% and 87·1% (BG cutoff >60 pg/mL), respectively, for diagnosis of proven or probable invasive fungal infections (according to European Organisation for Research and Treatment of Cancer and Mycoses Study Group criteria). These diagnoses were mostly of candida infections, and some aspergillus, and the test had a sensitivity of 81·3% for candidosis (BG cutoff >60 pg/mL). As expected, the BG test was unable to detect mucor, rhizopus, and cryptococcus infections.

In a prospective study of 95 adult patients with acute lymphoblastic leukaemia, 30 cases of proven or probable invasive fungal infections (15 candidosis, 13 aspergillosis, and two mixed) were diagnosed among 190 episodes of neutropenia.[101] Overall sensitivity and specificity of the BG test was 63% and 96%, respectively. In a range of other studies of patients with candidaemia with or without invasive candidosis, the BG test achieved a sensitivity of 58·0–93·3%, and a specificity of 52·7–83·0%.[102–105]

The effectiveness of the BG test for patients in intensive care units is unproven. Although BG concentrations are raised in critically ill patients with established fungal infections, they are also raised in patients who have been in intensive care units for a long time.[106]

Thus, detection of fungal BG is potentially useful for diagnosis of invasive fungal infections in specific populations of patients, especially by use of serial serum BG testing for those with malignant haematological disease.[104] However, substantial limitations of the BG test include its specificity, since false-positive reactions can occur in various settings, and an inability to distinguish between fungal species.[107] Therefore, BG testing is worthy of consideration as an adjunctive test for invasive fungal infections in patients with malignant haematological disease, but it needs refinement.[108]

Search strategy and selection criteria

We searched PubMed for articles published in English or Spanish between January, 1990, and March, 2010, with the terms "unusual yeasts", "emerging fungal infections", "non-albicans *Candida*", "*C. guilliermondii*", "*C. krusei*", "*C. parapsilosis*", "*C. tropicalis*", "*C. pseudotropicalis*", "*C. lusitaniae*", "*C. dubliniensis*", "*C. glabrata*", "*C. pelliculosa*", "*C. kefyr*", "*C. rugosa*", "*C. famata*", "*C. inconspicua*", "*C. norvegensis*", "*C. kefyr*", "*C. orthopsilosis*", "*C. metapsilosis*", "*C. nivariensis*", "*Trichosporon* sp", "*Rhodotorula* sp", "non-neoformans cryptococcus species", "*Geotrichum* sp", "*Hansenula anomala Malassezia* sp", "host immune response and fungal infections", "(1,3)-beta-D-Glucan", "IFN-γ and invasive candidiasis", "antifungal agents", "antifungal resistance", "antifungal treatment", "antifungal prophylaxis", "adjunctive therapy" and "yeast infection" for studies on the epidemiologic, diagnostic and therapeutic aspects of emerging yeast infections. Review articles were excluded.

Controversies for treatment and prevention

Additional strategies to improve outcomes for patients with invasive fungal infections include use of immunomodulators and combination therapies. Adjunctive interferon γ might be indicated for refractory cryptococcosis.[109] The role of interferon γ in invasive candidosis and other emerging yeast infections is undefined. Although combination therapy is well established for treatment of cryptococcal meningitis, its use in invasive candidosis is less clear. Combination therapy is recommended for candida endocarditis and other difficult-to-treat presentations. Few data are available for other emerging opportunistic yeast infections, although combination regimens might be useful as salvage therapy.

Guidelines for management of central venous catheter infections with *Candida* species include recommendation of line removal when feasible.[109] This approach is strongly recommended in non-neutropenic patients, or in infections caused by *C parapsilosis*, which is often associated with central venous catheterisation. In neutropenic patients, this recommendation is more controversial, as the candidaemia might originate from the gastrointestinal tract.[110]

Antifungal prophylaxis is recommended for high-risk patients undergoing liver, pancreas, and small-bowel solid organ transplantations, for patients with chemotherapy-induced neutropenia, recipients of stem cell transplantation with neutropenia, and it can be considered for adults in intensive care units who are at high risk for invasive candidosis.[109] Standard use of antifungal prophylaxis and therapy has probably shifted the epidemiological traits of invasive fungal infections to these emerging yeast infections.

Conclusions

Non-albicans *Candida* species and other rare yeasts are emerging as key opportunistic pathogens. Early and specific diagnosis is crucial, and the decision to treat a patient with these unusual infections is often based on little clinical and microbiological information. Treatment decisions need careful consideration of the institutional epidemiological factors and the immune status of the population at risk.

Contributors

MHM and SAL designed this Review, JAD drew the figure, and all authors contributed to writing and editing.

Conflicts of interest

SAL is on the speakers' bureau of Pfizer and Astellas. JAD and MHM declare that they have no conflicts of interest.

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