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Candida and invasive mould diseases in non-neutropenic critically ill patients and patients with haematological cancer

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Critically ill patients and patients with haematological cancer are HIV-negative populations at high risk of invasive fungal infections. In intensive-care units, candidaemia and intra-abdominal candidiasis predominate, but aspergillosis has emerged as a lethal, under-recognised cause of pneumonia. In patients with haematological malignancies or who have undergone stem-cell transplantations, pulmonary disease due to aspergillus and other mould diseases predominate. In this Series paper, we provide an update on risk assessment, new diagnostic strategies, and therapeutic approaches. New concepts have emerged for use of risk prediction rules and an evidence base now exists for inclusion of biomarkers (eg, galactomannan, 1,3-β-D-glucan, and PCR assays for *Aspergillus* spp) into early diagnostic and therapeutic strategies. Imaging techniques remain helpful for early diagnosis of pulmonary mould diseases, with PET techniques offering potential improvements in diagnostic specificity and evaluation of clinical response. Echinocandins and triazoles have been validated extensively for prophylaxis, empirical therapy, and targeted therapy, but an increase in intrinsically resistant fungi and emergence of secondary resistance as a result of drug-induced selection pressure are of major concern. Echinocandins remain a major component of treatment of invasive candidiasis and new triazoles are the best alternative for prophylaxis and therapy of invasive aspergillosis.

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This is the second in a Series of eight papers about fungal infections

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Introduction

Despite their differences in terms of medical scenarios, critically ill patients and patients with haematological cancer are two major groups at risk for developing invasive candida and aspergillus infections.[1,2] In patients who are critically ill, candidaemia and intra-abdominal candidiasis are two major concerns in terms of morbidity and mortality due to fungal infections, but aspergillosis has emerged in several medical centres as one of the most lethal and under-recognised causes of fungal pneumonia.[2,3] In haematological malignancies and stem cell transplant recipients, because of the widespread use of prophylaxis against candida infections, aspergillus and other moulds have emerged as the most common group of fungal infections causing morbidity and mortality.[4–6]

Over the past 2 decades, a large number of newer diagnostic and therapeutic tools have been developed for the clinical management of fungal infections.[7,8] At present, there are three echinocandins and three new triazoles that have been extensively validated in different regimens of prophylaxis, empirical, and targeted therapy. Unfortunately, most clinicians are still not familiar with the pros and cons of new diagnostic tests and there is strong evidence suggesting that up to 40–70% of antifungal drugs are used inappropriately in tertiary care hospitals.[9,10]

Considering the relevance of medical education for any activity of antifungal stewardship, the main focus of this paper is to present to clinicians a critical review on recognition, diagnosis, and best practice management of invasive candidiasis and mould infections documented in critically ill patients and patients with haematological cancer.

Fungal infections in non-neutropenic patients in intensive care

Epidemiology

Among patients with invasive candidiasis in the intensive-care unit (ICU), two-thirds will have candidaemia, and 80% of non-candidaemic patients will have intra-abdominal candidiasis. Although candiduria has been documented in around 20% of patients in the ICU, associated tissue infection or secondary candidaemia occur in fewer than 5% of patients.[2,11–13]

Incidence of ICU-acquired candidaemia varies by region and institution: 2·1 per 1000 admissions (range 0·5–6·5) develop such disease in Australia;[14] 6·7 per 1000 admissions in France;[15] and 6·1 per 1000 admissions (range 3·6–9·0) in India.[16] Crude mortalities of 17–85% and attributable mortalities of 0–49%, have been reported for ICU-acquired candidaemia.[4,17,18] Attributable mortalities of 26–60% in intra-abdominal candidiasis are highest in patients with secondary or tertiary peritonitis.[4,19]

In recognition of the limitations of the International Classification of Diseases, 9th Revision coding, a multicentre US study of 2·57 million ICU patients with invasive aspergillosis yielded a prevalence of invasive aspergillosis of 0·017%, and 46% in-hospital mortality.[20] In Europe, 3·7% of ICU patients had proven or probable invasive aspergillosis on the basis of European Organisation for Research and Treatment of Cancer/Mycoses Study Group (EORTC/MSG) definitions for immunocompromised patients,[21] with an in-ICU mortality of 87–97%;[3] these figures probably underestimate invasive aspergillosis incidence and overestimate mortality.[22]

Key messages

- *Candida* spp are the leading cause of invasive fungal diseases in the ICU setting. Both candidaemia and other forms of invasive candidiasis have high attributable morbidity and mortality.
- Chronic obstructive pulmonary disease, influenza, and decompensated cirrhosis are increasing and understudied populations at risk for invasive pulmonary aspergillosis in the ICU.
- Studies combining prediction rules with fungal biomarkers are necessary to validate new strategies for early therapy of invasive candidiasis and invasive pulmonary aspergillosis in the ICU.
- Despite its lower sensitivity, blood and other sterile fluid culture remain the gold standard diagnostic method for invasive candidiasis. Species identification and antifungal susceptibility are highly recommended.
- Galactomannan in bronchoalveolar lavage fluid is more sensitive than serum galactomannan and culture in diagnosing invasive pulmonary aspergillosis in critically ill patients. The best optical density index cutoff value for a positive result is not well established.
- Invasive mould diseases caused by *Aspergillus* spp, Mucorales, *Fusarium* spp, and *Scedosporium* spp are a major cause of morbidity and mortality in patients with haematological cancer. Mortality rates of invasive aspergillosis, but not other mould infections, have decreased substantially in the last decade with the use of new diagnostic and therapeutic tools.
- Close monitoring of clinical and radiological findings, complemented by detection of fungal biomarkers in serum and bronchoalveolar lavage, might substantially reduce the inappropriate use of antifungal prophylaxis and empirical therapy in patients with haematological cancer.
- Optimisation of the benefits of anti-mould prophylaxis in neutropenic patients should take into consideration individual patient heterogeneity with respect to environmental exposure, age, host genetics, microbiome, comorbidities, performance status, and treatment of malignant disease.
- Considering that persistent neutropenia and T cell immunosuppression remain the two most relevant prognostic factors of invasive mould diseases among patients with haematological cancer, the use of adjunctive immunotherapy should be explored in future clinical trials.
- Echinocandins are major players for the treatment of invasive candidiasis, and new triazoles are the main contenders for preventing and treating invasive mould diseases.

ICU=intensive care unit.

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See Online for appendix

Species distribution and antifungal resistance

Candida albicans, *Candida glabrata*, *Candida parapsilosis*, *Candida tropicalis*, and *Candida krusei* are the most common pathogens in fungal infections.[14,16,23] Species prevalence varies with geography, institution, case-mix, host risk, and clinical practice. *C albicans* predominates globally (44–70% of cases), with *C tropicalis* the most common species in India, Singapore, and Thailand (46% of patients hospitalised with candidaemia).[16,24] *C glabrata* is ranked second in the USA, UK, northern Europe (including Finland, Norway, and Denmark), and Australia. *C parapsilosis* is ranked second in southern Europe (including Portugal and Spain). In Brazil, *C tropicalis* and *C parapsilosis* share equal second position.[18,25] *Candida auris* has emerged more recently, causing 5·2% of ICU candidaemias in India.[16] Although species can predict drug susceptibility, local epidemiological patterns vary and affect the value of species prediction.

Overall, more than 95% of *C albicans* and *C parapsilosis* isolates remain azole-susceptible,[26] although in one Chinese study, 10% of *C albicans* isolates and 19% of *C parapsilosis* isolates were azole-resistant.[27] *C tropicalis* is usually azole-susceptible (roughly 97% of isolates), but 15% of blood isolates are resistant in Australia (SC-A Chen, unpublished). *C glabrata*, *C krusei*, and *C auris* are intrinsically less susceptible than other species to fluconazole, with 4–15% of isolates azole cross-resistant.[16,26] Clinical echinocandin resistance is more accurately predicted by mutations in *FKS* genes than by minimum inhibitory concentrations.[28] In many countries, echinocandin resistance is uncommon, but in some US centres, resistance rates of 18–20% have been reported.[28,29] Furthermore, up to 10% of azole-resistant *C glabrata* isolates are echinocandin resistant.[30] Higher echinocandin minimum inhibitory concentrations in *C parapsilosis* are due to naturally occurring polymorphisms in *FKS* genes.[28]

Approximately 95% of invasive aspergillosis is due to the *Aspergillus fumigatus* complex.[3,31] A higher proportion of *Aspergillus terreus* disease has been reported in Austria.[32] In Europe, azole resistance is 3·3% on average (0–26% in different countries).[33]

Risks

Urinary catheters are the main risk factor for candiduria, which might lead to ascending upper urinary tract infection. Additional risk factors for candiduria include female sex, presence of diabetes, and proximate use of broad-spectrum antimicrobials.[11]

Risk factors for invasive candidiasis in the ICU are summarised in the appendix. To better target early antifungal therapy and improve outcomes, prediction rules that identify populations at increased risk of invasive candidiasis have been derived. These incorporate clinical or *Candida* spp colonisation parameters (table 1).

Although effective in excluding risk of invasive candidiasis, the positive predictive value (PPV) of these prediction rules is often low,[2,34] and they might not do well outside their derivation cohorts.[2] A ten-point summation score identified three patient categories: those at high risk, in whom prophylaxis should be considered (score ≥6, 4·8% of cohort, PPV 11·7%); those at low risk, in whom prophylactic or empirical antifungal therapy is not required (score ≤2, 43·1% of cohort, PPV 0·24%); and those at intermediate risk (score 3–5, 52·1% of cohort, PPV 1·46%), for whom further investigation, including use of biomarkers, should be considered.[2]

Invasive pulmonary aspergillosis is most common in severe chronic obstructive pulmonary disease requiring high dose steroid therapy,[35] but it can complicate H1N1 influenza[36] and Child-Pugh C hepatic cirrhosis (appendix).[3]

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	Derivation setting	Model parameters
Colonisation index[S1]	Single Swiss ICU (n=29)	Colonisation index=number of positive sites/number of cultured sites (threshold 0·5); corrected colonisation index=number of sites with heavy growth (graded as 0, 1+, 2+, 3+)/number of positive sites (threshold 0·4)
Clinical prediction rule[S2]	12 US/Brazilian ICUs (n=2890); underlying IC 3·0%	Either systemic antibiotics (days 1 to 3) or central venous catheter (days 1 to 3), plus two other risk factors: total parenteral nutrition (days 1 to 3), dialysis (days 1 to 3), major surgery (days –7 to 0), pancreatitis (days –7 to 0), steroids (days –7 to 3), other immunosuppressive agents (days –7 to 0)*
Clinical prediction rule[S3]	Six US ICUs (n=597); underlying IC 3·7%	All of ventilation (days 1 to 3), broad spectrum antibiotics (days 1 to 3), and central venous catheter (days 1 to 3), plus one other risk factor: total parenteral nutrition (days 1 to 3), dialysis (days 1 to 3), major surgery (days –7 to 0), pancreatitis (days –7 to 0), steroids (days –7 to 3), other immunosuppressive agents (days –7 to 0)*
Candida score[S4]	73 Spanish ICUs (n=1669); underlying IC 5·7%	Sepsis (2 points), surgery (1 point), total parenteral nutrition (1 point), multifocal candida colonisation (1 point); threshold 2·5 points
UK FIRE study risk predictive model (end day 3 in ICU)[S5]	96 UK ICUs (n=60 778); underlying IC 0·6%	Pancreatitis, central venous catheter(s), surgical drains in situ, highest heart rate ≥100 min (first 24 h), one or more sites colonised with *Candida* spp
Three-tiered risk predictive model, Australia[S6]	Seven Australian mixed medical-surgical ICUs (n=6685); underlying IC 1·4%	Summation score of ten independent variables: emergency gastrointestinal or hepatobiliary surgery, non-coated central venous catheter, total parenteral nutrition, admitted from operating theatre, emergency department, or other hospital, steroids ≥50 mg/day, blood transfusion, use of carbapenem or tigecycline, use of third or fourth generation cephalosporin, positive urine culture, positive throat culture

For references, see supplementary material. ICU=intensive care unit. IC=invasive candidiasis. *From ICU admission.

Table 1: **Prediction rules for invasive candidiasis in the ICU setting**

Clinical presentation and diagnosis

In candiduria, colonisation of indwelling urinary catheters is common. Routine diagnostic methods detect bacteria and yeasts, although growth of *C glabrata* can take 72 h.[11] Neither pyuria nor quantitative cultures distinguish colonisation from infection, hence findings such as unexplained fever, leucocytosis, and coexisting risk factors for invasive candidiasis should be investigated.[11] Imaging of the urinary tract (ultrasound or CT scan) might reveal renal abscesses, hydronephrosis, urinary tract obstruction, or fungus balls.[11]

Invasive candidiasis typically presents with fungaemia (84–90%) 8–15 days after ICU admission,[16,37,38] or intra-abdominal candidiasis.[39]

In candidaemia, chorioretinitis, although not clinically specific, occurs within 10–14 days in 5–16% of cases; endophthalmitis (with vitreal involvement) is uncommon (1·6%), and haematogenous renal candidiasis and endocarditis each occur in fewer than 5% of cases.[11,40]

Candidaemia usually originates from biofilms on indwelling intravascular devices or the gastrointestinal tract, and localised infection should be sought. However, loss of mucosal integrity due to ischaemia-reperfusion syndrome, together with a microbiome altered by broad spectrum antimicrobial use, or mucosal atrophy associated with bowel rest and prolonged total parenteral nutrition, promote clinically silent translocation.[13]

Clinical features of intra-abdominal candidiasis are non-specific; patients with recurrent gastrointestinal tract perforations, necrotising pancreatitis, or repeated gastrointestinal tract surgery are at highest risk.[12,19] Secondary peritonitis or abdominal abscesses account for more than 70% of cases.[12] Cultures should be obtained from blood, central lines, abdomen, and probable sites of metastatic infection. To optimise blood culture sensitivity, collection of 40–60 mL of blood from adults is recommended.[13]

Culture-based diagnosis is problematic because it is slow (1–7 days) and has poor sensitivity. Only about 50% of cases of invasive candidiasis are candidaemic;[7] bacteraemia coexists in approximately 20% of cases.[38] In intra-abdominal candidiasis, the sensitivity of intra-abdominal fluid or cultures from infected sites is less than 50%, and only 4–20% of cases will be candidaemic.[4] Concurrent bacterial infection is common (roughly 70% of cases).[4] In secondary peritonitis, *Candida* spp can be visualised by direct microscopy in peritoneal fluid and cultured. Because of a high incidence of candida colonisation, growth from drain fluid is only diagnostic if the drain has been in place for less than 24 h.[41]

Rapid diagnostic methods (eg, PCR) are not more sensitive than culture (both have a limit of detection of one to five colony forming units per mL, depending on the quantity of blood sampled), but accelerate diagnosis. Sensitive multiplex PCRs that distinguish common fungal species have been developed in-house and commercially.[42,43] Matrix-assisted laser desorption ionisation time-of-flight mass spectrometry enables rapid speciation once fungal growth is evident, and has also been used for direct identification of yeasts in blood cultures applying commercial (SepsiTyper, Bruker Daltonics; Bremen, Germany) or in-house protein extraction protocols.[44] An automated system that combines PCR and T2 magnetic resonance relaxivity (T2Candida, T2Biosystems; Lexington, MA, USA) is applicable to anticoagulated blood and appears promising; using spiked samples, the detection limit was

one to three colony forming units per mL, sensitivity 91% and specificity more than 99%, with a turnaround time of 4–5 h.[45]

Serology-based diagnostics for invasive candidiasis include mannan and antimannan and 1,3-β-D-glucan assays (table 2). In patients with blood-culture negative invasive (mostly intra-abdominal) candidiasis, 1,3-β-D-glucan assay out-performed blood cultures and PCR, with sensitivities of 88% versus 67% and 21%, respectively.[42] In patients undergoing emergency surgery for intra-abdominal infection, serum 1,3-β-D-glucan correlated with a diagnosis of invasive candidiasis, whereas mannan and antimannan levels did not.[46]

Further clinical investigation is needed to establish the role of non-culture-based diagnostics in the workup of patients at high risk of invasive candidiasis. It has been suggested that diagnostic triggers include patients at high risk of intra-abdominal candidiasis,[47] with pretest probabilities of 15–35% for invasive candidiasis, or ICU patients identified as being at intermediate risk of invasive candidiasis.[2]

Diagnosis of invasive pulmonary aspergillosis in ICU populations requires a high index of suspicion. Patients with risk factors (appendix) who develop pulmonary infiltrates despite receiving broad-spectrum antibiotics, require investigation for invasive pulmonary aspergillosis.

	Specimen (cutoff)	Test performance	Comments
Invasive candidiasis			
1,3-β-D-glucan	Serum (>80 pg/mL)*	Pooled:[S1-5] sensitivity 65–81%; specificity 57–83%; PPV 22–63%; NPV 77–96%	Time-consuming, not user-friendly, and costly. All materials used during the procedure must be free of glucan. Whole plate must be used when doing the test, even if only a few samples are being analysed. Two consecutive positive samples increase specificity and PPVs. False positives: blood transfusions, blood-derived products including immunoglobulins, haemodialysis or haemofiltration, some Gram-positive bacteria, β-lactam antibiotics, cellulose dressings, contamination of specimens by organic material, and enteral nutrition. False negatives: antifungal therapy, sanctuary sites or poorly vascularised sites of infection, and *Candida parapsilosis* infection.[S6]
Mannan-Ag and mannan-Ab	Serum (mannan-Ag ≥0·5 ng/mL, mannan-Ab ≥10 AU/mL	Pooled:[S5,7-11] sensitivity 54–94%; specificity 59–95%; PPV 17–94%; NPV 89–94%	*C parapsilosis* and *Candida krusei* release lower amounts of mannan and patients infected by these species might have negative results.[S9,12]
Multiplex real-time PCR (probes targeting ribosomal DNA)	Whole blood, serum, plasma	Pooled:[S3-5] sensitivity 84–96%; specificity 33–97%; PPV 27–93%; NPV 87–99%	More than one PCR test per patient might be associated with higher specificity. DNA extraction with commercial kits might be associated with higher specificity than of methods based on mechanical lysis.[S13]
T2 Candida panel (multiplex PCR-based method with detection of amplified product with magnetic resonance)	Whole blood	Sensitivity 91%; specificity 98·1%; PPV 84·2%; NPV 99.0%[S14]†	Probes designed to detect *Candida albicans* or *Candida tropicalis*, *C parapsilosis*, and *C krusei* or *Candida glabrata*. More extensive validation is required, including a larger number of patients with candidaemia documented by blood cultures.
Invasive aspergillosis			
1,3-β-D-glucan	Serum (>80 pg/mL)*	Pooled:[S15,16] sensitivity 48–80%; specificity 76–79%; PPV 44–48%; NPV 79–94%	Utility for diagnosis of invasive pulmonary aspergillosis in critically ill patients is lower than that of galactomannan determination in BALF. Time-consuming, not user-friendly, and costly. Several sources for false positive results in the intensive care unit setting, including infections by other fungi containing 1,3-β-D-glucan in the cell wall, such as *Candida* spp and *Pneumocystis jirovecii*.
Galactomannan	Serum (ODI ≥0·5)	Pooled:[S15-17] sensitivity 41–78%; specificity 89–100%; PPV 55–100%; NPV 79–89%	Utility for diagnosis of invasive pulmonary aspergillosis in critically ill patients is lower than that of galactomannan determination in BALF. In patients with COPD, initial negative tests might become positive on repeat testing.[S18] False positive results: treatment with β-lactams (eg, piperacillin and tazobactam, and amoxicillin and clavulanate; eventually found in generic formulations of the antibiotics), presence of other invasive mycoses (eg, *Penicillium* spp, histoplasmosis, or blastomycosis), or patients with intestinal mucositis.
Galactomannan	BALF (ODI ≥0·5)	Pooled:[S15,17,19] sensitivity 80–89%; specificity 47–93%; PPV 47–73%; NPV 89–95%	Higher cutoff (ODI ≥0·8) improved specificity in critically ill patients with COPD.[S17]
Galactomannan	BALF (ODI ≥1·0)	Sensitivity 80%; specificity 97%; PPV 89%; NPV 95%[S15]	Despite good performance, insufficient multicentre validation.
Lateral-flow device	BALF (qualitative: positive or negative)	Sensitivity 80%; specificity 81%; PPV 49%; NPV 96%[S20]	Insufficient comparison with other non-culture-based methods and multicentre validation.
Multiplex real-time PCR-AsperGenius (probes targeting ribosomal DNA)	BALF (C_T <36)	Sensitivity 80%; specificity 93%; PPV 80%; NPV 93%[S21]	Despite good performance, insufficient multicentre validation. Approved by the European Union for in-vitro diagnosis. Also detects *CYP51A* mutations in *Aspergillus fumigatus*.

For references, see supplementary material. PPV=positive predictive value. NPV=negative predictive value. Ag=antigen. Ab=antibody. BALF=bronchoalveolar fluid. ODI=optical density index. COPD=chronic obstructive pulmonary disease. C_T=optimal threshold cycle value. *Cutoff for the Fungitell assay (Associates of Cape Cod, East Falmouth, MA, USA). Other assays have been commercialised in Japan with different cutoff values: Fungitec G (Seikagaku Corporation, Tokyo, Japan), β-glucan test (Wako Pure Chemical Industries, Tokyo, Japan), and BGSTAR β-glucan test (Maruha, Tokyo, Japan). †Based on a candidaemia prevalence of 10%.

Table 2: **Non-culture based methods for diagnosis of invasive candidiasis and invasive bronchopulmonary aspergillosis in non-neutropenic critically ill patients**

Thoracic CT scans usually reveal patchy or nodular lesions, necrotic cavities, or both. Halo and air-crescent signs, or wedge consolidation, occur in less than 20% of cases. In one study, the specificity of multiple nodules distributed along bronchovascular bundles on chest CT was 92·5%.[48] Serum galactomannan assays do poorly in non-neutropenic patients with invasive aspergillosis, but might be of value when measured in bronchoalveolar lavage (BAL) fluid (table 2).[49]

In patients with endotracheal aspirates positive for *Aspergillus* spp, colonisation should be distinguished from invasive pulmonary aspergillosis. A validated algorithm,[22] which defined probable invasive pulmonary aspergillosis (positive endotracheal aspirates, compatible clinical signs, abnormal thoracic imaging, and either host factors or positive BAL fluid for *Aspergillus* spp on direct microscopy and culture) and proven invasive pulmonary aspergillosis (as per EORTC/Invasive Fungal Infections Cooperative Group and the National Institute of Allergy and Infectious Diseases Mycoses Study Group definitions), yielded PPVs of 61% and negative predictive values (NPVs) of 92%.[22]

Clinical management in the ICU

In candiduria, high urinary and tissue concentrations make fluconazole the first-line drug for prophylaxis in high-risk groups (eg, patients with neutropenia or post-urinary tract instrumentation), and for treatment of urinary tract infections caused by susceptible strains. Colonised indwelling catheters should be removed when feasible.[7] Amphotericin B deoxycholate bladder irrigation (50 mg/L sterile water daily for 5 days) might cure cystitis due to fluconazole-resistant species or in renal failure, when urine fluconazole levels are low.[50] Removal of fungus balls and replacement of stents or nephrostomy tubes is recommended.[7]

In candidaemia and intra-abdominal candidiasis, although fluconazole prophylaxis reduces invasive candidiasis, its effect on mortality is unclear. Prophylaxis with caspofungin[51] or micafungin[46] did not reduce invasive candidiasis in two studies, one of which was in patients with a more than 30% risk of intra-abdominal candidiasis.[51] Universal prophylaxis is not recommended.[7]

Despite an absence of proven benefit, empirical antifungal therapy could be considered in high-risk patients (table 3 and appendix) with sepsis without a clear source;[7,52] such therapy might be ceased in patients with negative serum biomarkers and absence of multifocal colonisation,[53,54] or those at low risk on the basis of a published risk prediction rule.[2]

Two consecutively positive serum 1,3-β-D-glucan results can predict invasive candidiasis.[55] Antifungal pre-emptive therapy driven by positive serum 1,3-β-D-glucan results could be especially useful in patients at highest risk of intra-abdominal candidiasis, such as patients with recurrent gastrointestinal tract perforation or necrotising pancreatitis.[19] Prospective, randomised trials are needed to substantiate this approach.

Echinocandins are the preferred first-line therapy for proven invasive candidiasis.[7,52] In patients with susceptible *Candida* spp, triazoles might be initiated after clinical improvement and negative blood cultures. Lipid amphotericin B formulations should be considered in patients with CNS involvement, endocarditis, or intolerance or resistance to echinocandins.[7,52]

In invasive pulmonary aspergillosis, empirical antifungal therapy is warranted, since treatment of possible invasive pulmonary aspergillosis has resulted in a shorter ICU stay, lower costs, and better outcomes.[20,56] A pre-emptive approach, based on early measurement of galactomannan in BAL fluid, appears promising.[49]

Voriconazole is the first-line therapy for invasive pulmonary aspergillosis.[8] Because of metabolism of voriconazole by hepatic CYP2C19 P450, drug interactions are potentially problematic and therapeutic drug monitoring is recommended (table 3). Amphotericin B lipid formulation (except for *A terreus*) and isavuconazonium sulfate are alternatives if voriconazole is contraindicated or not tolerated.[8,57]

Intravenous therapy should be de-escalated to one oral agent, typically continued for 6–12 weeks, after clinical improvement, but should be tailored to clinical and radiological responses.[8] There are no published data correlating clinical responses with serum galactomannan levels in the setting of non-neutropenic critically ill patients.[8]

Fungal infections in patients with haematological cancer

Epidemiology and risks

Evolving treatments for haematological malignancy and allogeneic haemopoietic stem-cell transplantation (HSCT) affect risk and timing of invasive fungal infections (IFIs).[58] Reduced-intensity conditioning regimens have shortened the duration of neutropenia and shifted IFI occurrence later post-transplantation.[59] Alternative donor sources (umbilical cord blood, matched unrelated, or mismatched unrelated donors) have expanded HSCT availability but increased the risk of IFIs.[6] In critically ill patients, the spectrum of IFI is influenced by patterns of antifungal use,[60] geographical factors,[61] patient mix, and type and number of HSCTs.[6]

Risk factors for IFI include underlying malignancy, status and treatment of underlying malignancy, other comorbidities, performance status, and environmental exposure.[62,63] Risk factors evolve and should constantly be reviewed to optimise antifungal prophylaxis and empirical therapy.

Invasive candidiasis

Candidaemia in haematological malignancy has a mortality of 40%.[64] Disseminated invasive candidiasis is rare, probably because of widespread use of antifungal prophylaxis.[65] HSCT recipients in the USA had an

	First-line therapy	Alternatives	Comment
Candidaemia			
Targeted therapy	Echinocandin (caspofungin: 70 mg loading dose, then 50 mg daily; micafungin: 100 mg daily; anidulafungin: 200 mg loading dose, then 100 mg daily)[S1–4]	Fluconazole: 800 mg (12 mg/kg) loading dose, then 400 mg (6 mg/kg) daily; liposomal amphotericin B (3–5 mg/kg daily; amphotericin B lipid complex 5 mg/kg as alternative); intravenous voriconazole: 400 mg (6 mg/kg) loading dose twice daily for two doses, then 200 mg (3 mg/kg) twice daily[S6–8]	Despite a higher minimum inhibitory concentration of echinocandins against *Candida parapsilosis* isolates, outcomes of echinocandin-treated and fluconazole-treated patients are similar;[S5] antifungal susceptibility should be established; fluconazole can be used initially if the patient is not critically ill and resistance is unlikely, and can be used as a stepdown from echinocandin after 5–7 days if the patient is clinically stable, the isolate is susceptible, and blood cultures are negative on therapy;[S6–8] voriconazole can be considered for isolates not susceptible to fluconazole, but drug–drug interactions, limitations of intravenous formulation in renal impairment, and need for therapeutic drug monitoring should be considered; therapy should be kept to a minimum of 2 weeks after the first negative blood culture in cases without metastatic complications; eye examination is required for all patients; central venous catheters should be removed as early as possible in the course of candidaemia when the source is presumed to be the catheter[S6–8]
Empirical therapy	Echinocandin (caspofungin: 70 mg loading dose, then 50 mg daily; micafungin: 100 mg daily; anidulafungin: 200 mg loading dose, then 100 mg daily)[S6–8]	Fluconazole: 800 mg (12 mg/kg) loading dose, then 400 mg (6 mg/kg) daily[S6–8]	Value of empirical therapy is unproven but is reasonable for patients at high risk according to one of the predictive rules for invasive candidiasis, with no explanation for fever; treatment should be ceased if there is no evidence of colonisation in multiple sites or if biomarkers are measured and tests are consecutively negative; otherwise, therapy should be kept to a minimum of 2 weeks[S9,10]
Prophylaxis	Fluconazole: 400 mg (6 mg/kg) daily[S6–8]	Echinocandins (caspofungin: 70 mg loading dose, then 50 mg daily; micafungin: 100 mg daily; anidulafungin: 200 mg loading dose, then 100 mg daily)[S6–8]	Indicated only in high-risk patients (threshold recommended by experts varies, >10% incidence); echinocandin is not better than fluconazole, and evidence for use is weak[S6–8]
Intra-abdominal candidiasis			
Targeted therapy	Echinocandin (caspofungin: 70 mg loading dose, then 50 mg daily; micafungin: 100 mg daily; anidulafungin: 200 mg loading dose, then 100 mg daily)[S6–8]	Fluconazole: 800 mg (12 mg/kg) loading dose, then 400 mg (6 mg/kg) daily; liposomal amphotericin B (3–5 mg/kg daily; amphotericin B lipid complex 5 mg/kg daily as alternative); intravenous voriconazole: 400 mg (6 mg/kg) loading dose twice daily for two doses, then 200 mg (3 mg/kg) twice daily[S11]	Choice of antifungal therapy should be the same as for candidaemia; duration of therapy should be individualised according to clinical response and source control; source control includes drainage of abscesses and necrotic tissue debridement[S6–8]
Empirical therapy	Echinocandin (caspofungin: 70 mg loading dose, then 50 mg daily; micafungin: 100 mg daily; anidulafungin: 200 mg loading dose, then 100 mg daily)[S6–8]	Fluconazole: 800 mg (12 mg/kg) loading dose, then 400 mg (6 mg/kg) daily[S6–8]	Although unproven, treatment should be considered if clinical evidence of refractory sepsis, intra-abdominal infection, recent abdominal surgery, anastomotic leaks, or necrotising pancreatitis is present; choice of antifungal therapy should be the same as for candidaemia[S6–8]
Prophylaxis or pre-emptive therapy	No recommendation	No recommendation	Insufficient evidence to support the use of prophylaxis or pre-emptive treatment, even in subgroups of high-risk patients[S12]
Endocarditis			
Targeted therapy	Liposomal amphotericin B (3–5 mg/kg daily; amphotericin B lipid complex 3–5 mg/kg daily as alternative) plus or minus flucytosine (25 mg/kg four times daily)[S6–8]	High dose echinocandin (caspofungin 150 mg daily, micafungin 150 mg daily, anidulafungin 200 mg daily)[S6–8]	Azoles can be used for stepdown therapy provided that patients are clinically stable, isolates are susceptible and blood cultures are negative; valve replacement is recommended; duration of therapy should be at least 6 weeks after surgery; for patients who cannot undergo valve replacement or those with prosthetic valve endocarditis, chronic suppression with fluconazole (400–800 mg per day) is recommended; for infections related to implantable cardiac devices (implantable cardioverter defibrillator, ventricular assist device, pacemaker), antifungal therapy is the same as that recommended for endocarditis and disposals have to be removed[S6–8]
Endophthalmitis			
Targeted therapy	Fluconazole: 800 mg (12 mg/kg) loading dose, then 400–800 mg (6–12 mg/kg) daily; voriconazole: 400 mg (6 mg/kg) loading dose twice daily for two doses, then 300 mg (4 mg/kg) twice daily[S6–8]	Liposomal amphotericin B (5 mg/kg daily; amphotericin B lipid complex 5 mg/kg daily as alternative) plus or minus flucytosine (25 mg/kg four times daily)[S6–8]	Duration of treatment should be at least 4–6 weeks, with the final duration depending on resolution of the lesions as determined by repeated ophthalmological examinations; with vitreal involvement, additional intravitreal injection of either amphotericin B deoxycholate (5–10 μg per 0·1 mL sterile water, or voriconazole (100 μg per 0·1 mL sterile water or normal saline), is recommended; echinocandins penetrate poorly into the eyes[S6–8]
Meningitis			
Targeted therapy	Liposomal amphotericin B (5 mg/kg daily) plus or minus flucytosine (25 mg/kg four times daily) or fluconazole 400 mg (6 mg/kg) daily[S6–8]	Fluconazole: 400–800 mg (6–12 mg/kg daily); intravenous voriconazole: 400–800 mg (6–12 mg/kg daily)[S6–8]	The optimal length of therapy has not been evaluated; several weeks of therapy are suggested before transitioning to oral azole therapy; fluconazole can be an option for stepdown therapy; infected CNS devices should be removed; if infected devices cannot be removed, amphotericin B deoxycholate could be administered through the device (0·01–0·50 mg in 2 mL 5% dextrose in water); echinocandins and posaconazole penetrate poorly into the CNS; voriconazole should be considered for stepdown therapy for fluconazole-resistant *Candida* spp isolates[S6–8]

For references, see supplementary material.

Table 3: **Main strategies for the management of invasive candidiasis conditions**

invasive candidiasis incidence of 1% at 6 months and 1·1% at 12 months,[6] whereas in Europe, fungaemia occurred in 1·55% of HSCT recipients, and 90% of cases were due to *Candida* spp.[6,64]

Breakthrough candidaemia (a positive blood culture after ≥3 days of antifungal therapy) accounts for up to 50% of candidaemias.[64,65] Previous antifungal exposure increases the likelihood of fluconazole, echinocandin, or multidrug resistance.[64,66]

Established candidaemia risk factors (appendix), especially neutropenia and disruption of the gastrointestinal tract mucosa after chemotherapy, radiotherapy, or surgery, also apply to patients with haematological malignancy.[64,66] At the time of fungaemia, most patients with haematological malignancy have acute leukaemia in relapse and bone marrow hypoplasia.[64]

Yeasts other than *Candida* spp, such as *Malassezia* spp, *Rhodotorula* spp, *Saccharomyces* spp, and *Trichosporon* spp, are uncommon pathogens but crude mortalities could be up to 70%.[64,67] Infections often originate from intravascular catheters. The intrinsically highly drug resistant *Trichosporon* spp should be considered in breakthrough infections.[68] As with other IFIs, there are geographical variations in incidence; *Trichosporon* spp are more prevalent in warm, moist climates.[68]

Invasive mould infections

Rates of invasive mould infections, most commonly invasive pulmonary aspergillosis, are similar in haematological malignancy and HSCT patients globally, and are higher than invasive candidiasis.[6,69] Invasive mould infections occur in an estimated 11–18% of patients with acute myeloid leukaemia,[70,71] 5–10% of allogeneic HSCT recipients,[6,69,70] up to 10% of patients with acute lymphoid leukaemia,[72] and in heavily treated patients with chronic lymphoid leukaemia.[73] Intensive chemotherapy regimens for adult acute lymphoid leukaemia probably explain the apparent increase in infection in these patients, in whom frequent vincristine administration excludes mould-active azole prophylaxis.[72] Mould infections occur in less than 2% of autologous HSCT recipients.[6,70] Much higher incidences of haematological malignancy and HSCT-associated IFIs (27%) were noted in a centre undertaking aggressive diagnostic approaches.[74]

A fumigatus complex causes most mould infections; however, *Aspergillus flavus* is more frequent in tropical climates[68] and *A terreus* in Austria.[32] Mucormycosis ranks second in some centres,[75] particularly in patients with sinusitis, diabetes, or corticosteroid use,[76] although in the USA mucormycosis accounted for only 8% of fungal infections and aspergillus accounted for 43%.[6] In Brazil, fusariosis frequency is second to aspergillosis.[70] Mould infections other than aspergillosis present later after HSCT[6] or after extensive antifungal exposure,[75] and mortality is 70–80%.[6,75] By contrast, mortality from aspergillosis has fallen (≤40%), probably because of improved diagnostics and better tolerated treatments.[73]

Although the use of molecular methods has resulted in identification of multiple genera and genotypes of moulds in some clinical samples and histopathology specimens,[77,78] the prevalence and clinical relevance of such findings need further investigation.

Risk factors for IFIs include environmental exposure and host factors, such as status and treatment of underlying malignancy, comorbidities, history of previous fungal infections, and exposure to antifungal prophylaxis (panel).[5,63,69–71]

***Panel*: Host, disease, treatment, and environmental factors associated with invasive fungal disease in haematological malignancy and stem-cell transplant recipients**

Patient factors
- Age
- Hypoalbuminaemia*
- Genetics*
- Poor performance status (Eastern Cooperative Oncology Group performance status ≥2)
- Chronic obstructive pulmonary disease*
- Diabetes and hyperglycaemia

Disease-related factors
- Acute myeloid leukaemia remission-induction chemotherapy
- Adverse cytogenetic or gene mutation profile
- Allogeneic stem cell transplants
  - Transplant factors (cord blood, haploidentical, mismatched donor)
  - Pre-transplantation factors (invasive fungal disease before transplantation, active leukaemia at transplantation)
  - Post-transplantation factors (graft *vs* host disease—high grade acute and chronic extensive, cytomegalovirus disease, cytomegalovirus viraemia,* viral respiratory tract infections, iron overload)
- Acute lymphoblastic leukaemia therapy*
- Multiple lines of treatment in lymphoproliferative disorders*

Treatment-related factors
- Prolonged neutropenia (longer than 2–3 weeks)
- Corticosteroids
- Lymphopenia or lymphocyte dysfunction
- Monocytopenia
- Cytarabine
- Ganciclovir*
- Alemtuzumab*
- High-grade oesophagitis (>2 as per WHO scale)

Environmental factors
- Hospital building works
- High-efficiency particulate air filtration (protective)
- Laminar airflow (protective)
- Dry weather with high temperatures
- Ambient mould spore counts*
- Living in rural areas*
- High risk occupation or activity (farming, construction, gardening)
- Smoking

For references, see supplementary material. *Risk not well characterised or quantified, or identified in only one study.

Clinical presentation and diagnosis of yeast fungaemia

Patients with yeast fungaemia present non-specifically, with fever unresponsive to antibiotics, but deep-seated infection in the liver, spleen, heart, and eye might also occur. Skin lesions (<10% of cases) appear as erythematous small papules and macules. Eye involvement (<10%) and hepatosplenic candidiasis typically occur upon recovery from neutropenia (<5% of cases).[64,74] Rapid pathogen identification and antifungal susceptibility tests are essential to direct antifungal therapy.[79]

Clinical presentation

Invasive mould diseases can involve almost any body site, but fungal pneumonitis is the most common presentation, together with sinusitis and fungaemia. Other clinical entities, clinical and radiological images, and laboratory findings are presented in the appendix. The lung is the most common site of mould diseases.[80] For fungal pneumonia, asymptomatic colonisation should be distinguished from tracheobronchitis, invasive lung disease, empyema, and disseminated disease.[80] Infection might begin insidiously, with a persistent cough, fever, or malaise. Tracheobronchitis causes hoarseness, stridor, and airway obstruction. Haemoptysis, chest pain, and dyspnoea might be present.[80,81] As clinical features are not pathogen-specific, aggressive diagnostic investigation is required and bronchoscopy or lung biopsy or aspirate might be needed.[80]

Radiographic characteristics of invasive fungal pneumonia include nodules, masses, or infiltrates. On CT, surrounding ground glass opacities, halo sign (appendix), central air cavity, or air bronchograms are characteristic, especially of invasive aspergillosis.[82] Multiple nodules (ten or more), pleural effusions, and reverse halo sign are more likely in pulmonary mucormycosis than in invasive pulmonary aspergillosis (appendix).[79]

High-resolution CT angiography can detect angio-invasion, and vessel occlusion was reported to be highly sensitive for diagnosis of invasive pulmonary aspergillosis.[83] Additionally, use of aspergillus-specific labelled monoclonal antibody with PET scanning is expected to revolutionise the diagnosis of invasive pulmonary aspergillosis, by differentiating it from other fungal (and bacterial) pneumonias.[84]

For invasive fungal sinusitis, aspergillus remains the commonest pathogen in immunocompromised people, but fusarium, *Scedosporium prolificans* (originally named *Lomentospora prolificans*), and mucorales also cause sinus, sino-pulmonary, and orbital-cerebral disease.[76] Symptoms result from local invasion of sinus tissue and cranial nerves, and the brain and intracranial vascular structures are commonly involved. Typical physical findings include sinus tenderness, ophthalmoplegia, and proptosis. Nasofibroscopy might reveal pale lesions in the nasal mucosa, suggestive of local ischaemia, which usually precede black eschar-like lesions.[85,86] Necrotic black eschar-like lesions in the oral cavity and palate are a late sign. CT scans or MRI show evidence of soft tissue masses and bony destruction. The aetiological fungus should be sought in biopsy or aspirated material.

All pathogenic moulds are angioinvasive. *Fusarium* spp and *Scedosporium* spp, but not *Aspergillus* spp, undergo intravascular adventitious sporulation, which releases spores into the bloodstream and results in fungaemia (appendix). Blood cultures are positive in 60–75% of cases of disseminated fusariosis and 30–35% of cases of disseminated scedosporiosis.[87,88] Conversely, fungaemia is rare in invasive aspergillosis and mucormycosis.

Diagnostic strategies

In fungal respiratory tract infections, since new technologies are not yet applicable to all fungi, histopathological examination, culture, and other conventional diagnostic methods remain the cornerstone of diagnosis, despite being slow and poorly specific.[89] Molecular and antigen-based diagnostics should also be done when possible.[8]

Dried or preserved fungal hyphae can be visualised histopathologically using stains such as Gomori's methenamine silver or periodic acid Schiff, whereas in fresh specimens, fluorescent dyes such as calcofluor-white reveal hyphae typical of IFIs and might help distinguish between hyalohyphomycetes and mucorales. Immunohistochemical techniques using fungus-specific fluorescent antibodies are promising, but not yet validated.[90]

Panfungal PCR, DNA sequencing assays, or fungal species-specific assays can identify pathogens directly in tissue, blood, serum, or sputum.[89] These methods were sensitive and specific in small case series,[91,92] but are mostly unstandardised.

Mucorales DNA has been detected with good sensitivity in fresh and paraffin-embedded tissue specimens using conventional and real-time PCR targeting 18 and 28S rRNA.[76] A sensitive, multiplex PCR also appears promising for early detection of mucorales in blood.[93]

Fungal biomarkers may be useful for screening and diagnostic strategies. The combination of galactomannan and aspergillus PCR done in BAL fluid obtained from haematology patients during the high-risk period for invasive aspergillosis or early in the course of invasive aspergillosis has proven sensitive and specific.[94] Serum galactomannan testing might be less sensitive than BAL galactomannan in patients with invasive pulmonary aspergillosis[95] (although colonisation is not easily distinguished from invasive infection). These tests should always be interpreted along with clinical and radiological information, and consideration should be taken for causes of false positive results.[96]

There are no biomarkers specific for non-aspergillus mould diseases; the galactomannan test shows cross reactivity between *Aspergillus* spp and *Fusarium* spp.[97] Similarly, 1,3-β-D-glucan, a cell wall constituent of many fungi, can be positive in invasive aspergillosis and

non-aspergillus mould diseases, with the exception of mucormycosis.[98] The clinical use of 1,3-β-D-glucan might be its high NPV, when it can be used to exclude IFIs.[98]

Antifungal therapeutic strategies for patients with haematological cancer

Echinocandins are the preferred first-line therapy for patients with invasive candidiasis. Lipid formulations of amphotericin B are alternatives in patients with CNS involvement, patients intolerant to echinocandins, or infections due to azole-resistant candida strains.

Guidelines recommend mould-active prophylaxis, mainly with new triazoles or inhaled amphotericin B, in high-risk haematology patients.[99,100] However, these strategies are best directed to patients with a more than 10% risk for developing invasive aspergillosis, to offset the cost and toxicity of antifungals, and risk of future antifungal resistance.[62,101]

For patients at intermediate risk for developing invasive aspergillosis (3–10%), monitoring of serum galactomannan and aspergillus PCR is useful for early diagnosis of invasive aspergillosis when combined with aggressive CT

	Strategy	First-line therapy	Alternatives	Comment
Invasive aspergillosis*	Targeted therapy	Intravenous voriconazole: 400 mg (6 mg/kg) loading dose twice daily for 2 doses, then 300 mg (4 mg/kg) twice daily[S1]	Liposomal amphotericin B: 3–5 mg/kg daily (as alternative, amphotericin B lipid complex 5 mg/kg daily); isavuconazole: 200 mg 8 hourly for 2 days, then 200 mg daily if voriconazole is contraindicated or not tolerated[S1-3]	Intravenous posaconazole, 300 mg every 12 h on day 1, then 300 mg daily, is undergoing evaluation as a first-line therapy; *Aspergillus terreus* should be treated with an azole rather than polyene antifungal; antifungal susceptibility profile should be determined, particularly where environmental azole resistance is prevalent, where there has been previous antifungal exposure, or when the patient is failing therapy. In regions with environmental resistance rates of ≥10%, a liposomal amphotericin B or voriconazole-echinocandin combination were favoured as initial therapy unless the patient had CNS aspergillosis, in which case liposomal amphotericin B and flucytosine is recommended;[S4] drug–drug interactions, limitations of intravenous formulation in renal impairment, and need for therapeutic drug monitoring should be considered;*†‡ therapy should be for a minimum of 6–12 weeks depending on response and host immune recovery;[S4] after clinical improvement, maintenance therapy can be done with oral formulation of voriconazole, posaconazole, or isavuconazole
Mucormycosis	Targeted therapy	Liposomal amphotericin B: 5 mg/kg per day (as alternative, amphotericin B lipid complex 5 mg/kg daily if there is no CNS invasion)[S5]	Intravenous posaconazole: 300 mg every 12 h on day 1, then 300 mg daily; or intravenous isavuconazole: 200 mg every 8 h for 2 days, then 200 mg daily for intolerance or salvage therapy[S5,6]	Prompt and aggressive surgical debridement of necrotic tissue is required; doses of liposomal amphotericin B of up to 10 mg/kg per day have been suggested for refractory disease;[S5,7] after clinical improvement, maintenance therapy can be with oral formulation of posaconazole or isavuconazole
Fusariosis	Targeted therapy	Liposomal amphotericin B: 3–5 mg/kg daily (as alternative, amphotericin B lipid complex 5 mg/kg daily); or intravenous voriconazole: 400 mg (6 mg/kg) loading dose twice daily for 2 doses, then 300 mg (4 mg/kg)[S8-10]	Intravenous posaconazole: 300 mg every 12 h on day 1, then 300 mg daily; or intravenous isavuconazole: 200 mg every 8 h for 2 days, then 200 mg daily[S8-10]	Combination therapy might be considered for persistently neutropenic patients failing therapy; surgical debridement of localised infection should be considered; therapeutic drug monitoring for voriconazole and posaconazole should be considered;[S9-11] after clinical improvement, maintenance therapy can be with oral formulation of voriconazole, posaconazole, or isavuconazole
Scedosporiosis	Targeted therapy	Intravenous voriconazole: 400 mg (6 mg/kg) loading dose twice daily for 2 doses, then 300 mg (4 mg/kg)[S10]	Intravenous posaconazole: 300 mg every 12 h on day 1, then 300 mg daily; or intravenous isavuconazole for intolerance or salvage therapy[S10]	Combination therapy with addition of terbinafine or an echinocandin to voriconazole should be considered for *Scedosporium prolificans* infection;[S10] surgical debridement of localised infection should be considered; therapeutic drug monitoring for voriconazole and posaconazole should be considered‡; after clinical improvement, maintenance therapy can be with oral formulation of voriconazole or posaconazole
Mould infection	Empirical therapy	Liposomal amphotericin B: 3–5 mg/kg daily (as alternative, amphotericin B lipid complex 5 mg/kg daily); echinocandin (caspofungin: loading dose of 70 mg, then 50 mg daily)[S12,13]	Intravenous voriconazole: 400 mg (6 mg/kg) loading dose twice daily for 2 doses, then 300 mg (4 mg/kg)[S14]	Rationale of empirical therapy is unproven, but is reasonable for patients at high risk of mould infection with no explanation for ongoing fever and clinical deterioration, or clinical symptoms suggestive of mould infection, while investigations such as CT scanning of chest or sinuses, BAL including non-culture-based diagnostics, or lung biopsy, are undertaken; empirical therapy should be ceased if there is no evidence of invasive mould infection on investigation; amphotericin B lipid formulation or voriconazole are preferred to an echinocandin;[S15] after clinical improvement, maintenance therapy can be with oral formulation of voriconazole
Mould infection	Prophylaxis	Posaconazole: tablet or intravenous formulation, 300 mg 12 hourly day 1, then 300 mg daily[S16]	Posaconazole: oral solution 200 mg every 8 h; voriconazole oral formulation: 200 mg (3 mg/kg) twice daily	Indicated only in high-risk patients (threshold recommended by experts varies, 8–10% prevalence);[S9,17] to overcome pharmacokinetic limitations associated with the suspension of posaconazole, a new gastro-resistant tablet is advisible[S18]

For references, see supplementary material. BAL=bronchoalveolar lavage. *A randomised, double-blind, comparison of intravenous posaconazole versus voriconazole for invasive pulmonary aspergillosis is underway (NCT01782131).†Voriconazole trough concentrations ≥1 mg/L are more efficacious, but if >4–6 mg/L there is an increased risk of toxicity. In patients with a creatinine clearance <50 mL/min, voriconazole can be administered safely using continuous veno-venous haemofiltration, which selectively removes its potentially toxic vehicle, sulfobutylether-β-cyclodextrin sodium.[S19,20] ‡Posaconazole trough concentrations >1 μg/L are recommended for treatment of mould infection. Isavuconazole levels should be monitored pending further information about pharmacokinetics in real-world patients, although target levels for treatment of mould infection have not been defined. Measurement of trough serum concentrations within the first 5–7 days after initiation of therapy are recommended.[S5,7]

Table 4: **Principles for the management of invasive mould diseases**

Search strategy and selection criteria

We searched PubMed for articles on invasive fungal infections in the intensive care setting and in patients with haematological cancer that were published between January, 1996 and December, 2016. We made all efforts to identify papers addressing strategies for risk assessment, fungal diagnosis and antifungal therapy in two different scenarios: intensive care units and patients with haematological cancer. Search terms were not restricted, but included various combinations as follows: "intensive care unit", "intensive care", "critically ill patient", "cancer", "neutropenia", "stem cell transplantation", "candida infection", "invasive candidiasis", "candidemia", "candida bloodstream infection", "intra-abdominal candidiasis", "peritoneal candidiasis", "candida peritonitis", "aspergillus infection", "invasive aspergillosis", "fusarium infection", "invasive fusariosis", "zygomycosis", "mucormycosis", "scedosporium infection", "invasive scedosporiosis", "epidemiology", "risk factors", "risk assessment", "diagnosis", "prophylaxis", "treatment", "diagnostic-driven", and "empirical therapy". We reviewed all articles retrieved from these search terms and relevant references cited in those articles. There were no language restrictions.

scanning of the lungs and sinuses, and could safely replace the conventional approach of empirical antifungal therapy for persistent febrile neutropenia.[62,102,103]

Persistently negative serum galactomannan, 1,3-β-D-glucan, aspergillus PCR, and organ imaging have a high NPV and effectively exclude invasive aspergillosis. Conversely, sequentially positive biomarkers, especially when used in combination, should trigger aggressive diagnostic tests for invasive aspergillosis and initiation of pre-emptive antifungal therapy; this has proven effective for earlier diagnosis of invasive aspergillosis in patients who are at high risk.[74,102,104] Such an approach is more sensitive than are culture and galactomannan alone, and reduces the use of undirected or empirical antifungal therapy. It should be noted, however, that in patients receiving mould-active prophylaxis and undergoing regular surveillance testing, false positives outnumber true positives because of the associated low pre-test probability.[95] Patients receiving mould-active prophylaxis should undergo intensive diagnostic investigations, including imaging, and serum and BAL galactomannan testing, if they develop a new episode of fever or other features suggesting the possibility of fungal infection.[102,103,105]

Voriconazole, with monitoring of serum levels, remains the treatment of choice for aspergillosis (table 4). Amphotericin B lipid formulation is an alternative. There is no evidence supporting combination antifungal therapy. Isavuconazole was equally effective and less toxic than was voriconazole in a randomised clinical trial, but more real-world experience in populations unbiased by exclusion criteria used in clinical trials is needed.[57]

Amphotericin B lipid formulation and voriconazole have been recommended for fusariosis treatment (table 4).[62] Treatment of mucormycosis is based on: control of underlying disease and predisposing factors (diabetes control, neutropenia, discontinuation or tapering of immunosuppressants, or discontinuation of desferrioxamine mesilate), prompt and aggressive surgical debridement of necrotic tissue, and a lipid formulation of amphotericin B (table 4).[86] Most experience has been with liposomal amphotericin B.[86] An analysis of 106 cases of mucormycosis in patients with haematological malignancies showed no benefit from combination versus monotherapy.[75] Antifungal therapy should be continued until clinical and radiological resolution of disease.[86] PET scanning might be useful to monitor response.[106] Additional alternatives for antifungal therapy of mucormycosis and treatment recommendations for *Scedosporium* sp infections are also used (table 4).

Conclusions

Pathogenic *Candida* spp and moulds cause substantial morbidity and mortality in ICUs and in patients with haematological cancer. Knowledge of incidence and epidemiology, globally and locally, is essential for the selection of appropriate, early antifungal therapy and local adaptation of antifungal guidelines. Understanding new risks and risk prediction algorithms assists with identifying patient categories that benefit most from early intervention strategies. Appreciation of clinical manifestations is also essential. There are increasing data to support use of one or more serological or molecular fungal biomarkers as diagnostic modalities, both for screening and in established IFIs. Standardisation of these tests and improved, validated, diagnostic algorithms are required as a priority. Newer imaging techniques, such as PET, are expected to have an increasing role in diagnostics. Management of IFIs in vulnerable patients includes antifungals, ancillary therapies such as immunomodulation, and surgery where appropriate. Finally, effective liaison between clinicians and diagnostic laboratories is essential to improve antifungal drug use and outcomes.

Contributors

All authors drafted and reviewed the full manuscript. TCS and JNdAJ made major contributions on fungal infections in ICU patients. MAS, SC-AC, and ALC made major contributions on fungal infections in patients with haematological cancer.

Declaration of interests

ALC has received educational grants from Pfizer, Gilead Sciences-United Medical (Brazil), Merck Sharp and Dohme, and a research grant from Astellas, Pfizer. SC-AC has received grants from Merck Sharp and Dohme, sat on advisory boards for Merck Sharp and Dohme and Gilead Sciences, and received travel support and honoraria unrelated to the current work from Merck Sharp and Dohme and Gilead Sciences. MAS has received grants from Merck Sharp and Dohme and Gilead Sciences, sat on advisory boards for Merck Sharp and Dohme and Gilead Sciences, and received travel support and honoraria unrelated to the current work from Merck Sharp and Dohme and Gilead Sciences. The other authors declare no competing interests.

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