Fungal infections in the ICU: advances in treatment and diagnosis

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Purpose of review
The aim of this review is to give an update on the available diagnostic approaches and currently adopted therapeutic management of severe fungal diseases in the ICU setting.

Recent findings
In order to reduce the clinical impact of life-threatening *Candida* infections, prompt diagnosis and appropriate treatment are strictly required. Preemptive strategies, mainly based on serological markers [i.e., (1–3)-β-D-glucan assay] are progressively replacing prophylactic and empirical approaches, limiting inadequate antifungal use. For the diagnosis of aspergillosis new algorithm has been recently validated, supported by the better knowledge of galactomannan antigen kinetic as a clinical marker. Echinocandins and voriconazole are the first choice drugs for the treatment of invasive *Candida* and *Aspergillus* infections, respectively. Although rare, other fungal infections (i.e., *Pneumocystis jirovecii*, *Cryptococcus* spp., and *Mucorales* spp.) may be responsible for life-threatening diseases in ICU patients, and early diagnosis and appropriate treatment are also important.

Summary
Critically ill patients may frequently experience severe invasive fungal infections. Biomarkers-based diagnostic approaches give, at the same time, the possibility to early detect the ongoing infection and reduce inappropriate antifungal therapy in nonconfirmed cases. Potent and well tolerated drugs are now available for the treatment of proven cases but clinicians should carefully consider the risk of treatment failure and the availability of new monitoring and therapeutic tools.

Keywords
(1–3)-β-D-glucan assay, galactomannan, invasive fungal infection

INTRODUCTION

Invasive fungal infections (IFIs) are frequently diagnosed and managed by the ICU physicians in both immunocompromised or not immunocompromised patients. Despite different antifungal agents having been developed to combat these infections, fungi are a leading cause of mortality among critically ill patients admitted to ICUs [1,2]. The rise of IFIs in critically ill patients can be related to the presence of complex medical and surgical problems, disruption of natural barriers, multiple invasive procedures, and the wide use of devices. In addition, many ICU patients are treated with prolonged antibiotic therapies for real or presumed bacterial infections and this favors the onset of fungal infections. The majority of these life-threatening infections are caused by *Candida* species, mostly *Candida albicans* [3▪]. Invasive candidiasis includes candidemia, disseminated candidiasis with deep organ involvement and chronic disseminated candidiasis. Candidemia is frequently associated with a high attributable mortality, increased length of hospital stay and cost [4▪]. Stratifying ICU patients for mortality scores, the interaction between cause, resistance to antifungal therapy, biofilm production, and appropriate therapy plays an essential role in determining the outcome of patients with candidemia [5–9]. In particular, recent studies indicate that inadequate antifungal therapy and inadequate source control combined with the disease severity were the most important determinants of outcome among patients with septic shock attributable to *Candida* infection with positive blood cultures [10,11▪▪].

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KEY POINTS

- Early diagnosis and appropriate therapy of invasive fungal infections are of paramount importance in the ICU setting.
- Biomarkers-driven algorithms [i.e., (1–3)-β-D-glucan assay and galactomannan] have been widely implemented with the aim to reduce inadequate antifungal therapies and obtain invasive fungal infections diagnosis in the early phase of the disease.
- Fungicidal drugs are strictly needed in the acute phase of the disease. Drug–drug interactions and tissue distribution should be carefully considered too.

Although the leading fungal infection is candidemia, pulmonary aspergillosis has been recently reported as an additional important complication in ICU patients also without the classical risk factors, and other pathogens, including yeast-like and other filamentous fungi, have emerged as additional causes of severe infections [12▪▪].

Timely diagnosis is essential for a favorable outcome and apart from blood cultures, several laboratory tests have been developed in the last years to facilitate an earlier detection of fungal infections. In particular, biomarkers-based diagnostic approaches give, at the same time, the possibility to early detect the ongoing infection and reduce inappropriate antifungal therapy in nonconfirmed cases. The antifungal armamentarium has also been expanded and physicians can now choose among the old class of polyenes, the older and newer azoles and the echinocandins for the treatment of proven cases, but clinicians should carefully consider the risk of treatment failure and the availability of new monitoring and therapeutic tools [13].

In this review, we will focus on the advances in treatment and diagnosis of invasive fungal infections encountered in ICU patients.

ADVANCES IN DIAGNOSIS

Candida spp.

The diagnosis of invasive candidiasis in critically ill patients is a challenging task for ICU physicians. Blood culture positivity still represents the diagnostic gold standard for *Candida* spp. bloodstream infections, but the suboptimal sensitivity (≤50%) and the long incubation time significantly delay the prompt initiation of an adequate antifungal treatment [14,15]. Indeed, several clinical scores have been largely proposed with the aim to predict invasive candidiasis occurrence and promptly start antifungals [16]. Among these, in the last ten years, 'Candida Colonization Index' (CCI) and 'Candida Score' have been widely adopted in the clinical practice [17▪,18]. However, despite their undoubted usefulness as negative predictive tools, both lack diagnostic accuracy. Hence, more recently, a growing interest has been focused on new laboratory diagnostic methods.

(1–3)-β-D-Glucan is a cell wall content of *Candida* spp. and other fungi. Although several confounding factors are potentially able to influence patients' plasma level [19▪], its usefulness as early diagnostic tool has been largely proven in several studies on patients with hematological malignancies [20]. However, an increasing body of evidence in favor of its use in the ICU setting has been recently documented [21▪]. In one of the first ICU observational studies, including 16 invasive candidiasis, a single point (1–3)-β-D-glucan sampling showed higher positive and negative predictive values, compared with CCI and Candida Score (72.2% versus 57.1% and 27.3%; and 98.7% versus 97.2% and 91.7%, respectively) [22] (Fig. 1). These data have been recently confirmed by a multicenter cohort study of 434 critically ill surgical patients [23], in which (1–3)-β-D-glucan showed high accuracy for the early detection of blood culture negative abdominal candidiasis. Less consensus exists regarding the optimal cutoff level. For instance, increasing the threshold value from 80 to 350 and 800 pg/ml, Poissy *et al.* [24▪] observed an opposite relationship between specificity (from 0.31 to 0.86) and sensitivity (from 0.97 to 0.30). Nevertheless, (1–3)-β-D-glucan levels at invasive candidiasis diagnosis and their kinetic over time have been also described to be correlated with the clinical outcome [25–27].

During recent years, other rapid tests have been proposed and compared with (1–3)-β-D-glucan assay. Despite previous encouraging data [28], in a recent prospective investigation, single values of either Mannan-Anti-Mannan or Cand-Tec *Candida* antigen (a new latex agglutination test) assays were characterized by fairly low specificity and sensitivity values [29]. However, the combination of more than one serological biomarker may result in significantly higher overall positive and negative predictive values. This effect was clearly observed by Leon *et al.* [30] after combining, in a large population of ICU patients at risk of invasive candidiasis, (1–3)-β-D-glucan results with *Candida albicans* germ tube antibody positivity.

Nuclear acids *Candida* detection from the blood is one of the new targets for innovative diagnostic approaches. Despite some drawbacks regarding the possibility of false-positive results, the absence of

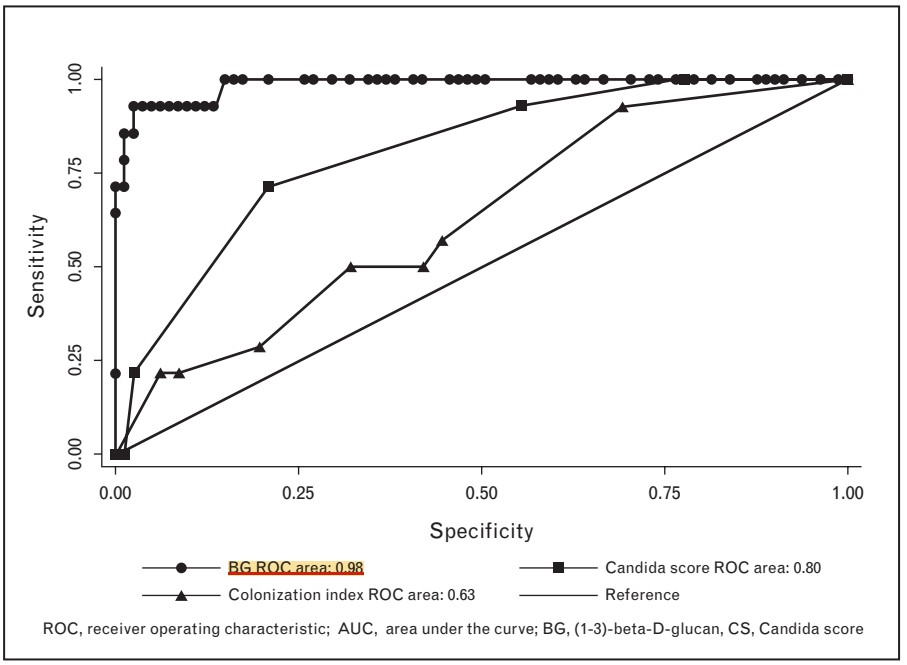

FIGURE 1. Comparison among receiver operating characteristic area under the curve of (1–3)-β-D-glucan, Candida score, and colonization index.

standardized techniques and the limited commercial availability, over the last few years numerous clinical studies have addressed this topic. A meta-analysis of 54 studies evaluating the diagnostic accuracy of PCR methods to detect *Candida* spp. in the whole blood showed a pool sensitivity and specificity of 0.95 (confidence interval 0.88–0.98) and 0.92 (0.88 0.92), respectively [31]. A multiplex nested PCR approach, which enables the detection up to seven *Candida* species, has been recently used in 54 critically ill pediatric patients at risk of invasive candidiasis, showing rapid and highly sensitive fungal detection, compared with blood culture results [32▪].

Finally, a new nanodiagnostic approach (T2 magnetic resonance) that directly analyzes blood specimens has showed encouraging results in a recent multicenter clinical trial [33▪▪], providing an overall specificity per assay of 99.4% and a mean time to negative results of 4.2–0.9 h.

Aspergillus spp.

The diagnostic gold standard for invasive aspergillosis is the direct histopathological identification in tissue biopsies. Frequently, in the critically ill setting, this criterion may not be satisfied and other elements should trigger the initiation of an antimold treatment [34]. In patients with hematological malignancies, current guidelines stratify invasive aspergillosis into proven, probable and possible, matching clinical, radiological, and microbiological findings [35]. However, in nonneutropenic ICU patients, the absence of classical risk factors and the low specificity of radiological findings impair the reliability of such approach [36▪]. Interestingly, a new clinical algorithm has been developed in order to discriminate *Aspergillus* spp. colonization from invasive pulmonary aspergillosis (IPA) in the intensive care setting (Table 1). Its application in a multicenter study involving 524 critically ill patients provided a 32% higher diagnosis rate, with a specificity of 61% and a sensitivity of 92% [37].

Among nonculture techniques, galactomannan assay is commonly tested in blood or other body fluids. This is a cell-wall component of *Aspergillus* spp., able to provide a rapid and accurate detection of actively growing molds [38,39]. However, its specificity and sensitivity may vary according to the cutoff level used [usually 0.5 and 1 of optical density index in the blood and bronchoalveolar lavage (BAL), respectively] [40]. Further, galactomannan positivity from BAL has shown high sensitivity, compared with serum galactomannan and respiratory cultures, for detecting IPA in ICU patients with chronic obstructive pulmonary disease [41]. On the contrary, the reliability of this assay in patients undergoing antimold prophylaxis/treatment is under debate. In an interesting 4-year study involving 262 hematological malignancies patients undergoing posaconazole prophylaxis, positive predictive value of the test was only 12%, especially during the preemptive surveillance phase [42▪▪]. Recent investigations have addressed the potential predictive role of galactomannan

Table 1. Clinical algorithm for the diagnosis of invasive aspergillosis in nonneutropenic patients

Proven invasive pulmonary aspergillosis
Follow EORTC/MSG criteria
Putative invasive pulmonary aspergillosis (all four criteria must be met)
1. Aspergillus-positive lower respiratory tract specimen culture
2. Compatible signs and symptoms (one of the following)
Fever refractory to at least 3 days of appropriate antibiotic therapy
Recrudescent fever after a period of defervescence of at least 48 h while still on antibiotics
and without other apparent cause
Pleuritic chest pain
Pleuritic rub
Dyspnea
Hemoptysis
Worsening respiratory insufficiency in spite of appropriate antibiotic therapy and ventilatory support
3. Abnormal medical imaging by portable chest radiograph or CT scan of the lungs
4. Either 4a or 4b
4a. Host-risk factors (one of the following conditions)
Neutropenia preceding or at the time of ICU admission
Underlying hematological or oncological malignancy treated with cytotoxic agents
Glucocorticoid treatment (prednisone equivalent, 20 mg/day)
Congenital or acquired immunodeficiency
COPD
Decompensated cirrhosis
4b. Semiquantitative *Aspergillus*-positive culture of BAL fluid without bacterial growth together with
a positive cytological smear showing branching hyphae
Aspergillus respiratory tract colonization
When more than one criterion necessary for a diagnosis of putative IPA is not met, the case is classified as *Aspergillus* colonization

BAL, bronchoalveolar lavage; COPD, chronic obstructive pulmonary disease; CT, computed tomography; EORTC/MSG, European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group and the National Institute of Allergy and Infectious Diseases Mycoses Study Group; IPA, invasive pulmonary aspergillosis. Adapted from [37].

trend over time during invasive aspergillosis treatment. The post-hoc analysis of a randomized trial showed how the decline of serum galactomannan index in patients undergoing voriconazole therapy was significantly associated with a good clinical response after 12 weeks [43▪].

As for invasive candidiasis, molecular diagnosis of invasive aspergillosis is challenged by the wide range of adoptable measurement approaches (i.e., targets, primers, amplification, and extraction). In hematological patients, there is growing evidence supporting the usefulness of PCR or other nuclear acid-based diagnostic methods, but robust data are still lacking in the ICU setting [44].

The relative simplicity of performing BAL in critically ill intubated patients is now fostering investigators to focus on molecular diagnosis of IPA by the direct detection of *Aspergillus* spp. nuclear acid in the epithelial lining fluid [45]. In a recent prospective study, involving 77 ICU and hematological patients, a new multiplex real-time PCR assay was compared with galactomannan [46]. The performance of the test in terms of sensitivity and specificity was high (ranging between 80 and 96%), also allowing fast differentiation of wild type from resistant strains, despite the negative results of traditional BAL cultures.

A novel test for IPA ('*Aspergillus* lateral-flow device') diagnosis has been recently tested in 221 patients with underlying respiratory diseases [47▪], providing better diagnostic performance than (1–3)-β-D-glucan and standard BAL cultures but lower accuracy compared with galactomannan.

However, as noted in invasive candidiasis, the combination of more than one biomarker, whenever possible, might represent the optimal diagnostic strategy. This concept has been recently shown in a multicenter trial in which 219 hematological malignancies high-risk patients were randomized to adopt a galactomannan versus galactomannan PCR surveillance approach for prompt detection and treatment of invasive aspergillosis [48▪]; not surprisingly patients allocated to the galactomannan PCR had

higher proven or probable invasive aspergillosis free survival ($P = 0.027$).

Other fungal infections

Although less common, also invasive fungal infections other than *Candida*/*Aspergillus* deserve rapid, accurate, and affordable new diagnostic tools [49].

Serum (1–3)-β-D-glucan detection may be considered a helpful tool for the diagnosis of *Pneumocystis jirovecii* pneumonia (PCP) in the ICU setting. In a recent clinical study, involving 260 PCP cases diagnosed by BAL microscopic or nuclear acid detection, (1–3)-β-D-glucan resulted the most accurate serologic marker followed by 'Krebs von den Lungen-6' antigen, lactate dehydrogenase, and S-adenosylmethionine. The use of (1–3)-β-D-glucan/Krebs von den Lungen-6 combination was associated with 94.3% sensitivity and 89.6% specificity [50]. Furthermore, (1–3)-β-D-glucan testing can be efficiently performed in BAL specimens [51].

Rapid diagnosis of cryptococcal invasive diseases relies on cryptococcal antigen detection from serum or cerebrospinal fluid, but a new reliable point of care assay is now available. This test (the dip-stick-formatted cryptoccal antigen lateral flow assay) has been compared with standard cultures and serological diagnostic approaches, showing very high sensitivity and specificity (both above 97%) [52].

Conventional histological mucormycosis diagnosis is improved by the adoption of advanced molecular amplification systems and antigen detection assays [53▪]. The use of quantitative PCR targeting different *Mucurales* species has been recently proposed as new tool for early diagnosis of mucormycosis. Although very attractive, the cost-effectiveness of such strategies in the ICU setting is the major issue limiting their clinical application.

ADVANCES IN TREATMENT

Candida spp.

Given the high morbidity and mortality rate of invasive *Candida* infection (ICI) in critically ill patients, a prompt and effective therapeutic approach, in the ICU setting, is strongly warranted. It is noteworthy how early initiation of an appropriate antifungal regimen is able to significantly improve the clinical outcome of such patients [5,7,8]. Indeed, many strategies have been recently implemented aiming to obtain this target. Apart from the prophylactic use of antifungals for a few peculiar scenarios, ICU physicians may adopt an empirical approach relying on clinical risk factors, signs, and symptoms of infection in absence of any identified pathogen [54–56]. Otherwise laboratory tests or radiographic findings may guide a preemptive therapy when a conclusive histopathological proof of invasive fungal infection is not available yet. Current guidelines suggest the use of empirical antifungal agents in critically ill patients at high risk of ICI, preferring a fungicidal agent in life-threatening conditions [57]. Currently, there is only one randomized controlled trial that addressed the efficacy of using empirical antifungals in ICU patients [58]. The study did not find any difference in terms of resolution of fever, presence of IFI, and major adverse events. Furthermore, recently, the empirical systemic antifungal approach failed to provide any clinical benefit in a large cohort of critically ill patients [59▪▪]. The low efficacy of this approach led clinicians to rely on more specific risk factors for ICI and new biomarkers. Hence, new preemptive approaches, especially (1–3)-β-D-glucan-driven strategies, are certainly attractive in the ICU setting and they appear a concrete alternative to the less cost-effective empirical therapy.

A preliminary randomized pilot study compared prophylactic antifungal approach versus (1–3)-β-D-glucan-guided preemptive therapy, using anidulafungin, in 64 ICU patients [60]. Preemptive anidulafungin was well tolerated and associated with a significant effect on (1–3)-β-D-glucan concentrations ($P < 0.001$) and excellent clinical response. In a recent larger trial, 222 ICU patients at risk for ICI were monitored with twice weekly (1–3)-β-D-glucan and treated with caspofungin according to a prophylactic/preemptive strategy [61▪]. This approach resulted well tolerated and associated with lower ICI rates for both prophylactic and preemptive approach (9.8% versus 16.7%, $P = 0.14$ and 18.8% versus 30.4%, $P = 0.04$, respectively). Also micafungin has been tested as preemptive therapeutic tool in 241 high-risk surgical patients. However, despite a reduction in the rate of *Candida* colonization, there were no differences between the two arms (micafungin versus placebo) in terms of ICI rate, mortality, and improvement of organ failures [4▪].

It is noteworthy that, given the high negative predictive value of (1–3)-β-D-glucan results, this biomarker may be also used as a tool for antifungal sparing strategies, avoiding unuseful empirical therapies only based on clinical risk factors.

Regarding the treatment of proven infections, the last European guidelines [57] recently updated the previous approach [15], recommending the use of fungicidal agents (echinocandins or lipid-based polyenes) for the initial treatment of ICI, and reserving azoles deescalations for stable patients with susceptible isolates. This approach is supported by the evidence of echinocandins' superiority over fluconazole for the early therapeutical management

of ICI, especially in critically ill patients [62]. However, while treating severe infections, antifungals' plasmatic concentrations are potentially influenced by interindividual variability and this drawback may be managed only by using therapeutic drug monitoring [63▪]. On the contrary, polyenes treatment is preferred for end-organ infections (meningitis, endocarditis, and osteomyelitis) or whenever other fungal pathogens (i.e., *Aspergillus* spp. or *Mucor* spp.) are suspected or documented.

There is no evidence supporting the use of combined antifungal regimens for ICI except for anecdotal cases wherein such approach has been successfully adopted as salvage therapy [15]. Once source control has been obtained, antifungal therapy should be prolonged for 14 days from the last negative blood culture [57]. In light of recent data on the use of (1–3)-β-D-glucan kinetic as a marker of treatment response [25,26], treatment duration could be shortened in those cases wherein a rapid and significant negative slope is observed. However, up to date, this approach is not supported by clinical evidence yet.

Aspergillus spp.

Early treatment at the stage of 'possible' *Aspergillus* spp. infection has been demonstrated to be associated with improved outcome [56,64]. In a recent observational investigation on ICU patients with invasive aspergillosis, each 1 day lag before initiating antifungal therapy was associated with 1.28 days' longer hospital stay and 3.5% increase in costs ($P < 0.0001$ for both) [65]. Recently, a multicenter cohort study showed that half of the ICU patients with a positive *Aspergillus* culture had either putative or proven invasive aspergillosis, sharing immunosuppression status and higher mortality rate [12▪▪]. Despite this, likewise for the prevention of ICI, anti-*Aspergillus* spp. prophylaxis is not recommended in the ICU setting, with the exception of deep immunosuppressed patients [66].

Indeed, it is quite unclear when to start an empirical treatment relying on the suspicion of a mold infection: nonneutropenic ICU patients are less likely to show symptoms but they share similar sensitivity regarding microbiological samples, antigen assays, and radiological findings [67]. In the ICU population a preemptive approach based on microbiological biomarkers (galactomannan or *Aspergillus* nuclear acid) should be adopted for early detection and prompt treatment of suspected invasive infections [67]. When using galactomannan with a preemptive therapeutic aim, BAL detection is more accurate than serum determinations. In a Spanish study including 51 patients, a cutoff value of 1 showed 100% sensitivity and 89.4% specificity for proven IPA; in addition, these values did not differ between neutropenic and nonneutropenic patients [68]. Azoles (voriconazole, itraconazole, and posaconazole), amphotericin B, and echinocandins are the three classes of drugs active in invasive aspergillosis. Voriconazole is the first-line treatment recommended by current guidelines, preferring intravenous administration in critically ill patients. The superiority of this drug compared with polyenes dates back to more than 10 years ago when, in a large randomized controlled trial, its use was associated with significantly higher successful rate and lower side-effects [66]. Recently, in a study on 67 ICU patients with acute respiratory failure and pulmonary isolation of *Aspergillus* spp., voriconazole use was associated with lower mortality rate, confirming its primary role in the management of invasive aspergillosis [69]. Similarly in a large prospective surveillance study conducted in North America between 2004 and 2008 voriconazole was the main antifungal used [70]. Even though this drug has an excellent oral bioavailability, the intravenous administration (loading bolus followed by maintenance multiple administrations) allows to achieve therapeutical levels as early as possible. In addition, it has an excellent tissue distribution: in a recent pharmacokinetic study very high epithelial-lining fluid concentrations were found in a cohort of lung transplant recipients, after oral administration [71]. Voriconazole is metabolized by CYP2C19 P450 enzyme and several drug–drug interactions have been reported. Anyway, mainly interacting molecules are well known, so they may be avoided or administered according to therapeutical drug monitoring (i.e., cyclosporine and tacrolimus) [34]. In patients with renal failure (creatinine clearance <50 ml/min), intravenous voriconazole should be carefully used, due to the potential toxic accumulation of sulfobutylether-β-cyclodestrin (SBECD). However, in critically ill patients, during continuous renal replacement therapy this drug may be safely used as the ultrafiltration process is able to efficiently remove this toxin [72▪]. On the contrary, the only way to optimize voriconazole therapy consists in monitoring drug plasma levels. Because of obvious cost implications such strategy might be advocated in peculiar conditions such as treatment failure, possible suboptimal dosing, suboptimal absorption, or suspected toxicity related to overdosing [34].

L-Amphotericin B still plays a role in the management of invasive aspergillosis when voriconazole may not be used for any reason [73]. All three ehinocandins are 'in-vitro' active against *Aspergillus* spp. but only caspofungin is approved for the treatment of invasive aspergillosis [74].

Limited experience is available on antifungal combinations [75▪]. Triazole–amphotericin combination should be avoided because of possible antagonistic interactions but voriconazole–echinocandins association may be used as salvage therapy in first-line nonresponsive cases [76].

Optimal duration of invasive aspergillosis therapy is not known. Biomarkers kinetic, radiological response, and baseline clinical conditions are the key elements to decide when stopping the treatment. Experts' opinion suggests to discontinue the antifungal therapy only when the patient is clinically stable and the complete resolution of radiographic abnormalities has been definitely obtained [34,36▪,39].

Other fungal infections

Trimethoprim–sulfamethoxazole (CTX) still represents the mainstay treatment of pneumonia caused by *P. jirovecii*. Pentamidine is considered a second-line choice in nonresponding patients or when CTX is contraindicated. Animal models support the possible use of CTX–echinocandins combination as first-line therapy in severe cases, but clinical evidence supporting a real benefit of this approach is still lacking [77]. Steroids are strongly recommended in patients with severe PCP and HIV infection but their usefulness has not been demonstrated in other categories of immunocompromised patients. However, in severe community-acquired pneumonia methylprednisolone use has been recently demonstrated to improve clinical outcome and radiological picture [78]. The recent mapping of the *P. jirovecii* genome represents a crucial starting point for advanced therapeutic opportunities such as new targets of folic acid biosynthesis pathway [79].

Treatment against cryptococcosis is essentially limited to three old drugs: 5-flurcytosine, liposomial amphotericin B, and fluconazole. Cryptococcal meningitis is frequently complicated by raised intracranial pressure and it sometimes deserves temporary ventricular drains [80]. Disseminated infections may be complicated by exaggerated systemic inflammatory response while the immune system progressively recovers (immune reconstitution inflammatory syndrome). In such conditions, steroids use, as well as other immunomodulatory therapies, may be taken into account: a large trial investigating this approach in HIV-infected patients with cryptococcal meningitis is ongoing (CRYPTODEX, www.controlled-trials.com/ISRCTN59144167).

Mucorales spp. treatment relies on three basic approaches: surgical management of primary focus, high-dose polyenes administration (up to 10 mg/kg of liposomial amphotericin B), and optimal control of underlying clinical conditions. Any new therapies have been recently approved for clinical use [81].

CONCLUSION

IFIs still represent a clinical challenge for ICU physicians. Critically ill patients may suffer from different patterns of immunosuppression (both host-related or ICU-acquired), being at high risk for fungal infections. *Candida* spp. infections represent the most frequent invasive fungal disease in the ICU: rapid diagnosis and prompt adequate therapy are of paramount importance to reduce disease-related morbidity and mortality. Biomarkers-based preemptive approaches (especially (1–3)-β-D-glucan-driven strategies) have been successfully used in critical settings, with the advantage to reduce inappropriate or delayed treatments. Echinocandins are the first-line drugs during ICI and a step down azole therapy may be considered only in stable patients. *Aspergillus* spp. invasive infections are increasing in the ICU setting, frequently affecting nonhematological patients. In absence of histopathological findings, IPA diagnosis may be difficult but the combination of host-specific risk factors, serum/BAL biomarkers (especially galactomannan) and peculiar radiological finding may support clinicians in the 'real life' practice. Voriconazole is the drug of choice for the treatment of invasive aspergillosis, but possible drug interactions should be carefully considered. Combination schemes may be adopted, without the support of strong clinical evidence though. Other IFIs are not so common in ICU patients but they may cause serious systemic and local diseases that deserve appropriate and aggressive treatments.

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Conflicts of interest

There are no conflicts of interest.

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