



Choosing the Right Antifungal Agent in ICU Patients

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ABSTRACT

Fungi are responsible for around 20% of microbiologically documented infections in intensive care units (ICU). In the last decade, the incidence of invasive fungal infections (IFI), including candidemia, has increased steadily because of increased numbers of both immunocompromised and ICU patients. To improve the outcomes of patients with IFI, intensivists need to be aware of the inherent challenges. This narrative review summarizes the features of routinely used treatments directed against IFI in non-neutropenic ICU patients, which include three classes of antifungals:

polyenes, azoles, and echinocandins. ICU patients' pathophysiological changes are responsible for deep changes in the pharmacokinetics of antifungals. Moreover, drug interactions affect the response to antifungal treatments. Consequently, appropriate antifungal dosage is a challenge under these special conditions. Dosages should be based on renal and liver function, and serum concentrations should be monitored. This review summarizes recent guidelines, focusing on bedside management.

Keywords: Candidiasis; Intensive care patients; Invasive aspergillosis; Invasive fungi infection; Pharmacokinetics; Practical guidelines

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INTRODUCTION

Fungi are responsible for approximately 20% of microbiologically documented intensive care unit (ICU) infections [1]. In the last decade, the incidence of invasive fungal infections (IFI), including candidemia, has steadily increased as a result of the increasing numbers of both immunocompromised and critically ill patients [2–6].

Candida spp. are the third leading cause of infections in the ICU, accounting for 90% of fungal infections [1]. Invasive candidiasis (IC) includes bloodstream and deep infections

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caused by the *Candida* species. Studies have shown a cumulative incidence of 7.07 episodes of IC per 1000 ICU admissions [7]. Of note, over recent decades the incidence of *Candida albicans* infections has decreased with a relative increase in non-*albicans Candida* infections, including the fast emergence of *Candida auris* [8–10]. In ICU patients, IC became a challenge with a mortality rate approaching 40% [11]. Although attributable mortality is difficult to establish, candidemia has been identified as an independent predictor of mortality after controlling for confounders [12]. Delay in initiating adequate antifungal treatment is associated with increased mortality. Remarkably, antifungal treatment recommendations remain largely based on randomized clinical trials that were not restricted to ICU patients.

Invasive aspergillosis (IA) is an opportunistic infection that occurs mainly in patients with prolonged periods of neutropenia with or without hematological malignancies, patients who underwent allogeneic stem cell transplantation or solid organ transplantation, and patients with HIV/AIDS. In recent years, however, IA has increasingly been recognized as an emerging disease in non-neutropenic individuals, including patients with chronic obstructive pulmonary disease and other chronic lung or connective tissue diseases requiring corticosteroid therapy, decompensated liver cirrhosis or acute liver failure, solid cancer, chronic renal failure with replacement therapy, diabetes, severe influenza, and even ICU patients without any risk factors apart from a prolonged stay [13].

The incidence of *Aspergillus* spp. infections ranges from 0.3% to 6.9% in ICU patients [14]. Prompt administration of an effective treatment for IA is critical to reduce the mortality rate, which ranges from 60% to 90% [14]. Intensivists need to be aware of the specific risk factors for IFI as well as the diagnostic and therapeutic challenges to improve outcome.

The aim of this narrative review was to summarize clinically relevant knowledge on the currently used antifungals, focusing on non-neutropenic ICU patients. These patients are indeed at risk of IFI because of pathophysiological changes that influence drug pharmacokinetics (PK).

This article is based on previously conducted studies and does not contain any studies with human participants or animals performed by any of the authors.

ANTIFUNGAL DRUG CLASSES

Since the 1980s there has been an increasing but limited discovery of antifungal agents [15, 16]. The three principal classes of antifungal agents are polyenes, azoles, and echinocandins. Details on pharmacokinetics are provided in Table 1. Table 2 summarizes the features of antifungals in patients with renal or liver failure.

Polyenes

Polyenes (amphotericin B and nystatin) act in the fungal membrane by binding to ergosterol and causing disruption of the membrane structure promoting extravasation of intracellular constituents and, consequently, cell death (Fig. 1) [17]. They have a broad spectrum of action, fungicidal activity, and an activity against most *Candida*, most *Aspergillus*, and *Mucorales* species. However, many *Candida lusitanae* and *Aspergillus terreus* strains are resistant to amphotericin B (Tables 3, 4).

The standard amphotericin B formulation is associated with renal toxicity, caused by the vasoconstriction of the afferent arteriole, resulting in reduced renal blood flow and glomerular filtration rate combined with tubular injury, causing loss of potassium, magnesium bicarbonates, and amino acids. To reduce renal injury, liposomal amphotericin B allows lower absorption of amphotericin B by the reticuloendothelial system, resulting in a longer stay in the bloodstream.

Amphotericin B is contraindicated in patients with renal failure. Liposomal amphotericin B and amphotericin B lipid complex are less nephrotoxic than conventional amphotericin B, allowing a higher dosage because their PK are very different [20]. Since enteral absorption is negligible for all commercially available amphotericin B formulations, they must be administered by intravenous infusion.

Table 1 Overview on pharmacokinetics of antifungals

Drugs	Protein binding (%)	V_d (L/kg)	C_{max} ($\mu\text{g/ml}$)	$T_{1/2}$ (h)	Elimination	Dosage
Amphotericin	95–99	0.5–2	1.7–2.8	15–27	Bile, kidney (80%) No metabolite yet identified	0.3 mg/kg on day 1 + 5 mg per day until 1 mg/kg $T_{inf} > 4$ h mandatory
Liposomal amphotericin	95–99	0.05–2.2	14–29 (90)	13–24	Bile, RES long-term disposition, final elimination not yet clear, no metabolites identified	3–4 mg/kg per day $T_{inf} > 4$ h recommended
Fluconazole	12	0.7	9	30	Mainly unchanged via the kidney, tubular reabsorption	IV loading dose: 12 mg/kg once Maintenance dose: 6 mg/kg per 24 h
Voriconazole	58	4.5	4.4	6	Hepatic metabolism involving 2C9, 2C19, and CYP3A4 Strong inhibitor	IV loading dose: 6 mg/kg on day 1 Maintenance: 4 mg/kg per 12 h
Isavuconazole	98–99	6.5	2.6	80–120	Hepatic metabolism involving UGT, CYP3A4 Moderate inhibitor	IV loading dose: 200 mg day 1 and day 2 Maintenance dose: 200 mg per 24 h
Caspofungin	92–97	0.3–2	10	8	Independent from cytochrome P450	IV loading dose: 70 mg Maintenance dose 50 mg (70 mg if body weight > 80 kg)
Anidulafungin	99	0.6	7	40–50	Spontaneous degradation in plasma	Loading dose: 200 mg (T_{inf} 180 min) Maintenance dose: 100 mg (T_{inf} 90 min)
Micafungin	99.9	0.3	18	13–20	CYP involved	50 mg for prophylaxis, 100 mg for candidiasis, 150 mg for esophageal candidiasis

Details and references are displayed in the text

C_{max} peak level, $T_{1/2}$ half-life, Cl clearance, V_d apparent volume of distribution, T_{inf} infusion time, RES reticuloendothelial system, CYP cytochrome, UGT urindin diphosphate glucuronosyltransferase

Table 2 Overview on pharmacokinetics of antifungals in patients with renal or liver failure

Drug	Renal impairment	Liver impairment	Suggestions
Amphotericin	No indication	No dosage adjustment	
Liposomal amphotericin	Avoid (nephrotoxicity) No dose adjustment if continuous	No dosage adjustment	ICU patients: decreased plasma levels, increased dosage?
Fluconazole	Dose reduction by 50% for GFR 11–50 ml/min Enhanced dose if continuous RRT	No dosage adjustment	Obese critically ill: actual body weight ICU patient: enhanced doses Strong inhibitor of CYP3A4 and 2C9
Voriconazole	No dose adjustment Consider SBECD accumulation during intravenous infusion	Mild to moderate hepatic impairment: 50% dose reduction, TDM recommended	Strong inhibitor of CYP2C0 and 2C19 Moderate inhibitor of CYP3A4
Isavuconazole	No dose adjustment	Enhanced levels, no dosage reduction	Moderate inhibitor of CYP3A4, P-gp, and BCRP
Posaconazole	No dose adjustment for oral route	No dose adjustment	Strong inhibitor of CYP3A4 causing drug–drug interactions
Caspofungin	No dose adjustment	Enhanced exposure in moderate hepatic impairment: dosage reduction Dosage reduction in critically ill patients with liver dysfunction may cause underexposure	
Anidulafungin	No dose adjustment	Slightly lowered concentrations but no dosage adjustment recommended	
Micafungin	No dose adjustment RRT: no dose adjustment	Slightly lowered concentrations	Potential risk for liver tumors: use only if other antifungals are not appropriate

Details and reference are displayed in the text

RRT renal replacement therapy, SBECD sulfobutylether- β -cyclodextrin, TDM therapeutic drug monitoring, CYP cytochrome, P-gp P-glycoprotein, BCRP breast cancer resistance protein, UGT urindin diphosphate glucuronosyltransferase, GFR glomerular filtration rate

Infusion-related adverse events include chills, rigor, fever, hypotension or hypertension, hypoxia, nausea, vomiting, and hypokalemia, and affect about half of patients treated

with conventional amphotericin B. The adverse event mechanisms are driven by activation of proinflammatory pathways [21–23].

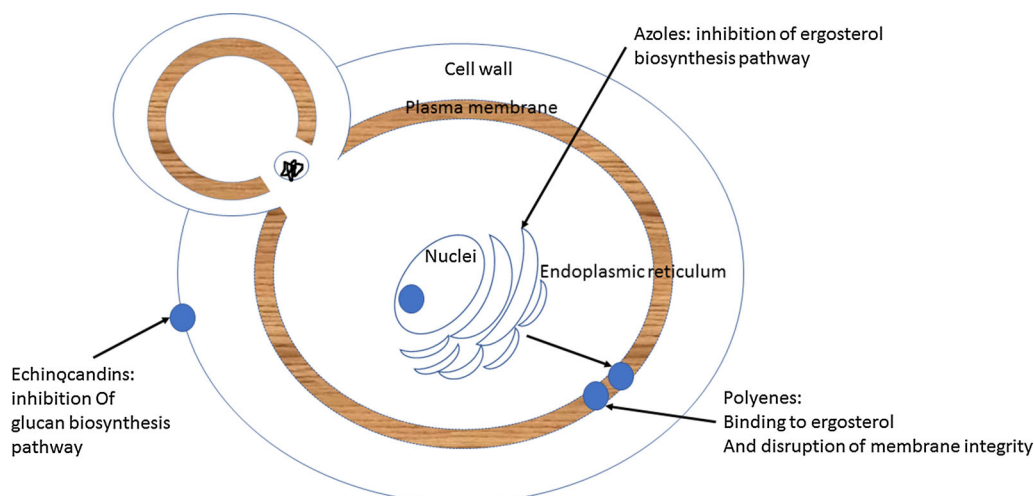


Fig. 1 Mechanism of action of traditional antifungal agents on cellular targets. Azoles inhibit the ergosterol synthesis in the endoplasmic reticulum of the fungal cell. They act by interfering with the enzyme lanosterol 14- α demethylase, involved in the transformation of lanosterol into ergosterol. Polyenes act in the fungal

membrane by binding to ergosterol and causing disruption of the membrane structure, promoting extravasation of intracellular constituents and consequent cell death. Echinocandins inhibit 1,3- β -D-glucan synthase, thereby preventing synthesis of glucan, which is present in the cell membrane of fungi [18]

Table 3 Profile of intrinsic susceptibility and resistance of *Candida* species [19]

Fungi	Fluconazole	Voriconazole	Amphotericin	Echinocandin
<i>Candida albicans</i>	S	S	S	S
<i>Candida dubliniensis</i>	S	S	S	S
<i>Candida glabrata</i>	S/R	S/R	S	S
<i>Candida parapsilosis</i>	S	S	S	R
<i>Candida tropicalis</i>	S	S	S	S
<i>Candida krusei</i>	R	S	S	S
<i>Candida kefyr</i>	S	S	S	S
Uncommon <i>Candida</i> species				
<i>Candida lusitanae</i>	S	S	R	S
<i>Candida auris</i>	S	S	S	S
<i>Candida guilliermondii</i>	S	S	S	S/R

Green, intrinsic susceptibility of the species and first line treatment recommended; red, intrinsic resistance; yellow, susceptibility to be tested

Table 4 Profile of susceptibility and resistance of *Aspergillus* species [19]

Fungi	Fluconazole	Isavuconazole	Voriconazole	Amphotericin	Echinocandin
<i>Aspergillus fumigatus</i>	R	S	S	S	S/R
<i>Aspergillus flavus</i>	R	S	S	R	S/R
<i>Aspergillus terreus</i>	R	S	S	S/R	S/R
<i>Aspergillus nidulans</i>	R	S	S	S	S/R
<i>Aspergillus niger</i>	R	R	R	S	S/R
<i>Aspergillus lentulus</i>	R	R	R	S	S/R

Green, intrinsic susceptibility of the species and first line treatment recommended; red, intrinsic resistance; yellow, susceptibility to be tested

Azoles

Azoles act by inhibiting ergosterol synthesis in the endoplasmic reticulum of the fungal cell (Fig. 1). They have fungistatic properties affecting cell growth and proliferation. *Candida krusei* and *Candida glabrata* strains may show resistance against azoles (Table 3) [24]; however, a large accumulation of toxic sterols can eventually lead to fungal cell death [25, 26].

Triazoles include fluconazole, itraconazole, voriconazole, posaconazole, and isavuconazole. The most frequent side effects induced by triazoles include liver toxicity, prolonged QTc, and emerging resistance among fungal isolates [27]. Moreover, triazoles inhibit most of the cytochrome P450 enzymes (including the CYP3A4), inducing variable drug–drug interactions. This plays a key role in metabolizing immunosuppressant drugs such as cyclosporine, tacrolimus, and sirolimus [28]. Thus, co-administration of a triazole with these immunosuppressant drugs increases the risk of toxicity, or upon discontinuation, increases the risk of rejection or graft-versus-host disease. Close therapeutic drug monitoring of both immunosuppressants and triazoles is therefore indispensable.

Fluconazole

Fluconazole is available for intravenous and oral administration with high bioavailability. It is active on most *Candida* species and is usually

well tolerated. ICU patients treated with fluconazole should receive a loading dose (12 mg/kg) followed by a maintenance dose (6 mg/kg) [29]. This dosage is supported because of impaired target site penetration in septic patients [30]. For obese ICU patients, fluconazole dosage should be based on actual body weight [31]. For patients with renal failure (creatinine clearance 11–50 mL/min) it is necessary to reduce the maintenance dose by 50% because of delayed elimination [32]. Large amounts of fluconazole are eliminated by renal replacement therapy.

Voriconazole

Voriconazole has high bioavailability and is available for intravenous and oral administration. It has a broad antifungal spectrum and is active against most *Candida* and *Aspergillus* species. Voriconazole is recommended as first-line treatment for IA because it had better clinical outcomes than amphotericin B deoxycholate in an open-label randomized clinical trial [33].

Renal failure has no relevant influence on voriconazole PK, but a considerable accumulation of the solvent sulfobutylether- β -cyclodextrin (SBECD) was found in patients with renal failure requiring intravenous administration of voriconazole. This solvent is a large cyclic oligosaccharide that is potentially nephrotoxic at high concentrations. The manufacturer

recommends oral administration in patients with a creatinine clearance below 50 mL/min. Of note, in solid organ transplant patients, the significant interaction of voriconazole with sirolimus contraindicates their concomitant use [32].

Posaconazole

Posaconazole has a wide antimycotic spectrum, including activity against *Mucorales*, and is licensed for antifungal prophylaxis in selected hematological high-risk patient. For a decade, posaconazole was available only as an oral suspension that displayed poor and highly variable absorption. An intravenous formulation and a tablet with improved bioavailability are now available. Posaconazole is a strong inhibitor of CYP3A4, which is responsible for drug–drug interactions. In a study that included ICU patients, the majority had subtherapeutic serum concentrations during treatment with standard doses of oral suspension [34]. Mild to moderate renal or liver impairment had no relevant influence on posaconazole's PK.

Isavuconazole

Isavuconazole is a new triazole agent that can be given once a day and offers a wider spectrum of antifungal activity than voriconazole, including activity against most *Mucorales*. It has an excellent bioavailability and predictable PK. It can be used in patients with renal failure given the absence of cyclodextrin in the intravenous formulation. A large double-blind randomized clinical trial showed non-inferiority for isavuconazole versus voriconazole in terms of all-cause mortality when used as a primary treatment for invasive fungal disease caused by *Aspergillus* species or other filamentous fungi [35]. In addition, a matched case–control analysis of isavuconazole versus amphotericin B provided evidence for the efficacy and superior safety profile of isavuconazole in the treatment of mucormycosis [36]. The most commonly reported side effects include gastrointestinal disorders such as nausea, vomiting, and diarrhea. A recent double-blind randomized clinical trial did not show non-inferiority of isavuconazole to caspofungin for primary treatment

of IC. Secondary endpoints were similar between both groups [37].

Gastrointestinal disorders and central nervous adverse effects are possible during isavuconazole treatment. Whereas prolongation of the QT interval is a common adverse effect of azole antifungals, shortening of the QT interval has been observed with isavuconazole [38]. Because isavuconazole is a moderate CYP3A4 inhibitor, interactions with immunosuppressants are reported to be less pronounced than those with voriconazole. However, increased serum concentrations of cyclosporine A, tacrolimus, sirolimus, and mycophenolate mofetil must be anticipated when isavuconazole is co-administered.

Echinocandins

The echinocandins belong to a class of semisynthetic lipopeptides that inhibit the synthesis of the 1,3-beta-D-glucan component of the fungi cell wall (Fig. 1). Echinocandins have a broad spectrum of fungicidal activity against the *Candida* species, and fungistatic activity against most *Aspergillus* species [39] (Tables 3, 4). Limitations for use of currently approved echinocandins include the absence of an oral formulation. Frequently reported side effects include headache, nausea, diarrhea, phlebitis, and pruritus. Severe side effects such as leukopenia, neutropenia, anemia, hypokalemia, and liver toxicity are rarely reported [40–42].

Caspofungin

The standard dose is 70 mg as a single loading dose followed by a maintenance dose of 50 mg once a day or 70 mg once a day when body weight exceeds 80 kg. It displays linear PK. Immediately after infusion caspofungin undergoes rapid distribution into tissue, mainly the liver. About 95% of caspofungin is typically bound to plasma proteins and it is metabolized in the liver. For non-ICU patients with moderate hepatic impairment (Child–Pugh score 7–9), reducing the maintenance dose to 35 mg per day is recommended [43]. ICU patients with moderate liver failure may achieve

subtherapeutic caspofungin exposure with the adjusted dose of 35 mg per day. The authors ascribed the low concentrations to typical physiological alterations occurring in ICU patients (hypoalbuminemia) [44] and recommended standard doses. Since caspofungin elimination is largely independent from renal function, standard doses are suggested in patients with renal failure, even those with terminal renal failure requiring hemodialysis [45–49].

Anidulafungin

Anidulafungin is licensed for the treatment of IC in adult patients. The recommended dose is 200 mg once a day on day 1 (loading dose) and then 100 mg daily (maintenance dose). Renal failure has no influence on anidulafungin elimination [40]. Unlike caspofungin, liver failure results in decreased exposure for anidulafungin; no dose adjustment is recommended. An increased degradation due to reduced protein binding and an enlarged volume of distribution has been suggested [50].

Micafungin

Micafungin was shown to be as effective as both λ -amphotericin B and caspofungin in randomized clinical trials [51, 52]. However, the potential risk for developing liver tumors indicates that use should be restricted to when other antifungals are not appropriate.

PHARMACOKINETICS FEATURES

ICU Patients

ICU patients, particularly those on broad-spectrum antimicrobial treatment, renal replacement therapy, total parenteral nutrition, or corticosteroid or other immunosuppressive agents, are at risk of IC. Timely and sufficient exposure to appropriate antifungals is required to eradicate fungus. Inadequate initial antifungal doses contribute to both poor outcomes [53–55] and emergence of resistance [26].

ICU patients have pathophysiological changes that are responsible for antifungal PK

alterations: organ failure, reduced protein binding, capillary leakage resulting in an altered drug volume of distribution, and use of organ support (i.e., renal replacement therapy and/or extracorporeal membrane oxygenation, ECMO). Moreover, interacting co-medications may result in variable PK of antifungals [56]. In ICU patients, PK may therefore be very different from PK of less compromised patients. Appropriate dosage of antifungals is challenging under these special conditions, because respective PK data are sparse.

The doses determined by data extracted from other patient groups are suboptimal. Investigators have attempted to assess the PK variability of antifungals. A multinational patient study defining antibiotic levels in the intensive care unit (DALI) found considerable intervariability with fluconazole, anidulafungin, and caspofungin, indicating that a large number of patients do not receive adequate treatment [57]. Those results confirmed previous findings, suggesting the need for routine monitoring of antifungal serum concentrations [50, 58].

RECOMMENDATIONS OF RECENT GUIDELINES

IC encompasses three entities: candidemia in the absence of deep-seated candidiasis, candidemia associated with deep-seated candidiasis, and deep-seated candidiasis in the absence of candidemia [59]. The most recent guidelines for IC management were provided by the Infectious Diseases Society of America (IDSA) in 2016 and by a task force of the European Society of Intensive Care Medicine–European Society of Clinical Microbiology and Infectious Diseases (ESCMID) in 2019 [29, 60]. The latter specifically focused on ICU patients (Fig. 2). Both documents came out against the universal use of antifungals in patients without clear signs or symptoms of infections (prophylaxis). However, guidelines from IDSA posed a weak recommendation (moderate quality evidence) for use of fluconazole prophylaxis in high-risk patients in ICUs with IC rates above 5% [29, 60, 61]. Both documents supported the use of empirical antifungal treatment (based on signs or

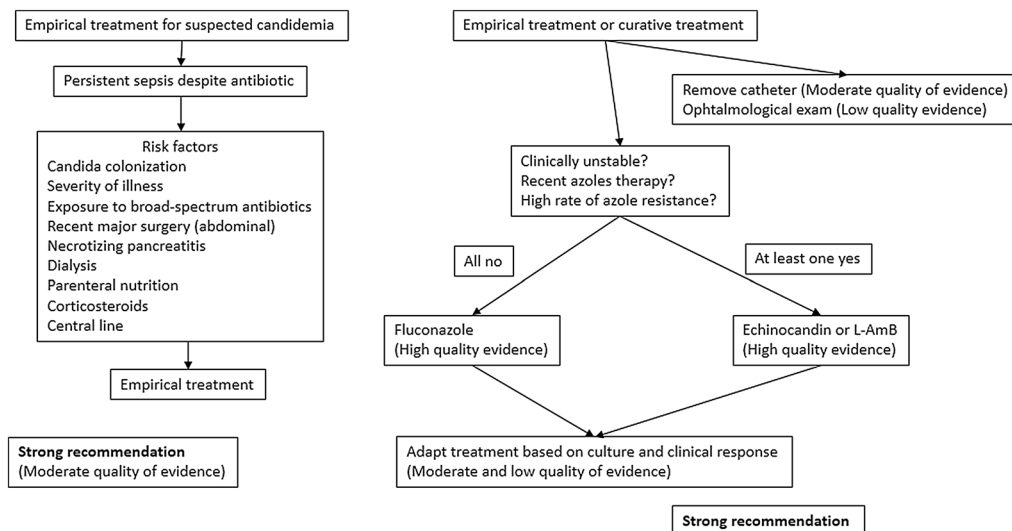


Fig. 2 Practical guidelines for empiric and curative treatment of candidiasis adapted from the IDSA guideline [60]

symptoms of infections without certain proof of candida infections) only in carefully selected patients with a high risk of IC, and in conjunction with other diagnostic tools and data (e.g., biomarkers such as beta-D-glucan; culture data from nonsterile sites) [29, 60]. Moreover, only patients with septic shock, multiple organ failure, no other causes of fever, and more than one extradigestive site of *Candida* spp. colonization (e.g., urine, mouth, throat, upper and lower respiratory tracts, skin folds, drains, operative site) should receive empirical antifungal treatment with an echinocandin as the first-line agent (strong recommendation; low-quality evidence) [29]. Fluconazole can be used in less severe patients (no septic shock and/or multiple organ failure) and in settings with a low rate of fluconazole resistance. Echinocandins should also be used in patients who are likely to be infected or colonized by fluconazole-resistant *Candida* spp. (i.e., *Candida krusei*, *Candida glabrata*). This regimen was also recommended for the targeted treatment of IC [29, 60].

Transition from echinocandin to fluconazole (de-escalation) is recommended in clinically stable patients who have an isolate susceptible to fluconazole [29] and have negative repeated blood cultures following the initiation of antifungal treatment [60]. The de-escalation should

not be considered in cases of difficult or impossible source control (e.g., removing central venous catheter, surgery for intra-abdominal candidiasis). The recommended treatment duration of candidemia without metastatic complications is 14 days after the first negative blood culture [29, 60], taken daily after the initiation of targeted treatment [60]. In case of inadequate source control (e.g., no removal of central venous catheter, no definitive surgical control or drainage for intra-abdominal candidiasis, endocarditis) the duration of therapy should be individualized [29]. The lipid formulation amphotericin B (3–5 mg per kg per day) is recommended for infections by azole- and echinocandin-resistant strains [60]. Of note, a recent meta-analysis found no evidence of a therapeutic or survival benefit from choosing between echinocandins, voriconazole, or amphotericin B formulations as first-line therapy for ICU adults with invasive infection of the *Candida* species [62].

Regarding IA infections in ICU patients, the 2018 ESCMID–European Confederation of Medical Microbiology–European Respiratory Society guidelines underlined the difficulty of diagnosis in ICU patients and suggested that early diagnosis and treatment of IA should be based on the integration of clinical findings, risk factors, radiological data, and

Table 5 Summary of practical guidelines for invasive aspergillosis

Primary therapy	Salvage therapy
IV administration of voriconazole (6 mg/kg per 12 h at day 1 then 4 mg/kg per 12 h until improvement) followed by oral administration of voriconazole (200 mg per 12 h) or itraconazole (400–600 mg per 24 h) until resolution or stabilization of all clinical and radiological manifestations	IV administration of caspofungin (70 mg at day 1 then 50 mg) or IV administration of micafungin (100–150 mg per 24 h) until improvement followed by oral administration of voriconazole (200 mg per 12 h) or oral administration of itraconazole (400–600 mg per 24 h) until resolution or stabilization of all clinical and radiological manifestations
OR	OR
IV administration of L-amphotericin B (3–5 mg/kg per 24 h) followed by oral administration of voriconazole (200 mg per 12 h) or itraconazole (400–600 mg per 24 h) until resolution or stabilization of all clinical and radiographic manifestations	Posaconazole (200 mg per 6 h initially then 400 mg per 12 h orally after stabilization of disease)

microbiological data [63]. A high cutoff (optical density index 0.5–1) of galactomannan, a pan-fungal antigen, in the bronchoalveolar lavage can be considered in decisions regarding when to start therapy [63]. Thin-section chest computerized tomography is the imaging of choice, but classic signs are rare in ICU patients, who usually present non-specific radiological findings [63]. It is still unclear if a prophylactic treatment may be cost-effective in high-risk non-neutropenic ICU patients. However, common risk factors to consider for *Aspergillosis* in the ICU are chronic obstructive pulmonary disease, steroid treatment, sepsis, and influenza-associated respiratory failure [63]. The first-line agent is voriconazole (2 × 6 mg per kg on day 1 and then 2 × 4 mg per kg intravenously) (Table 5). Combination with an echinocandin can be considered but the quality of the supporting evidence is low. Susceptibility testing is recommended for voriconazole and therapeutic drug monitoring in case of treatment failure [63].

CONCLUSION

Fungi infections are an increasing concern in ICU patients and have led to the development

of recent guidelines. Three treatment families are currently used for fungi infections, but because of the specific pathophysiological status of ICU patients, PK data on those treatments are still scarce and numerous questions remain. Therapeutic drug monitoring is an essential option for evaluating treatment efficacy and tolerance.

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and does not contain any studies with human participants or animals performed by any of the authors.

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