Antifungal drug dosing adjustment in critical patients with invasive fungal infections

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Abstract: Critically ill patients suffer from invasive fungal infections, mainly due to Candida spp., but also to Aspergillus spp., Cryptococcus spp. and other more rare yeasts or filamentous fungi. These infections are prevented or treated with various antifungal agents belonging to one of the following classes: polyenes (mainly amphotericin B formulations with liposomal amphotericin B as the most frequently used compound), azoles (fluconazole, itraconazole, voriconazole, posaconazole and isavuconazole) or echinocandins (caspofungin, micafungin and anidulafungin). Administration of these agents may be challenging due to various factors in patients hospitalized in the intensive care unit (ICU). Such factors frequently found in these patients are renal and liver insufficiencies, extreme ages (prematurely born infants or elderly patients), obesity, thermal injury, other co-morbidities, and interactions with many simultaneously administered other drugs. In addition, sepsis itself may cause such hemodynamic changes resulting in increased clearance of antifungal agents. The use of continuous renal replacement therapy and extracorporeal membrane oxygenation needs special attention when antifungal agents are administered. It is very important that the physicians caring for these patients are aware of the impact of such factors on the pharmacokinetics and pharmacodynamics of the antifungal agents administered in the ICU. In addition, they should be aware of the adverse effects of these agents that they administer on the biology and physiology of host's various organs and the metabolism of other co-administered drugs occurring through these organs. This knowledge may lead to optimization of dosing of the antifungal agents and other interacting medications in order to maximize antifungal effect in the care of critically ill patients.

Keywords: Mycoses; antifungals; intensive care unit (ICU); critical care; pharmacokinetics; pharmacodynamics; renal insufficiency; liver dysfunction

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Invasive fungal infections in the critically ill pediatric and adult patient

Invasive fungal diseases (IFD) are increasing both in incidence and in spectrum globally due to the intense application of aggressive immunosuppressive treatments and the development and administration of new immune modifying drugs (1). In addition, IFDs can complicate the clinical course of immunocompetent groups of patients, such as critically ill patients hospitalized in intensive care units (ICUs) (2). Associated mortality is high, and depends on the underlying medical conditions, the type of pathogen involved, the length of time prior to diagnosis, and the appropriateness of management (3,4).
Candidemia has been found to represent a significant proportion of catheter- and non-catheter-related bloodstream infections and to be the most common IFD in the ICU (5,6). The patients in the ICU with candidemia may significantly differ in terms of heterogeneity and predisposing factors as well as in terms of pathogen and organ involvement. Emergency surgery, underlying malignancy, presence of vascular access devices, prior use of broad-spectrum antibiotics and previous bacterial sepsis appear to significantly predispose to the emergence of invasive candidiasis in the ICU (7). Candidemia and intra-abdominal Candida infections represent the largest proportion of IFD Candida infections (2). Species distribution varies compared to other risk groups, with predominance of non-albicans Candida species in many places (8). Of note, some of these non-albicans Candida species are fluconazole-resistant.

IFDs due to Aspergillus spp. are also encountered in the ICU, with reports of increasing incidence of pneumonia due to Aspergillus, with predilection for immunocompromised patients and those with chronic pulmonary disease or even influenza (9,10). Predominant species involved include Aspergillus fumigatus, Aspergillus flavus and Aspergillus niger with varying contribution worldwide (5). Other opportunistic fungal infections in the setting of an ICU are rare (i.e., invasive mucormycosis in patients with hematological malignancies and Pneumocystis jirovecii in patients with kidney transplantation or HIV infection), affect specific groups of patients (i.e., Cryptococcus and P. jirovecii in HIV-infected patients), and/or are endemic in specific areas of the world (i.e., Histoplasma infections in USA or India) (5).

When comparing IFDs in terms of incidence, risk factors, microbiology, and clinical outcome among different age classes, critically ill neonates and children cannot be considered little adults (11,12). Younger patients have different predisposing factors; prematurity and long stay of very low-birth weight neonates in the ICU, as well as hematologic malignancy and neutropenia in children account for the majority of cases.

Treatment of IFD in critically ill patients is challenging as these patients are usually characterized by different demographic characteristics (age, weight, organ function) and a variety of co-morbidities and other co-administered medications. Critically ill patients are hallmarked by altered intravascular hemodynamics, clearance, tissue perfusion and hypoalbuminemia, causing unpredictable drug distribution within the different compartments of the organism (13). Pharmacokinetics and drug elimination are further complicated by kidney or liver insufficiencies, co-administration of other interacting medications and interventions such as continuous renal replacement therapy and extracorporeal membrane oxygenation, warranting adjustments in such patients.

Antifungal agents: pharmacokinetic, pharmacodynamic and dosage considerations

Amphotericin B formulations

Amphotericin B preparations include amphotericin B deoxycholate (DAMB) and the lipid formulations: liposomal amphotericin B (LAMB) and amphotericin B lipid complex (ABLC). All preparations are administered intravenously, exhibit high protein binding (95–99%) in plasma and display non-linear pharmacokinetics. DAMB is eliminated by the kidney and bile (13). The elimination/metabolism of LAMB following intravenous administration has not yet been elucidated (13). The lipid formulations of amphotericin B are in vivo less potent than DAMB on a weight basis. However, due to their reduced nephrotoxicity they can be administered at significantly higher dosages than DAMB (14).

All amphotericin B preparations have concentration-dependent action, with $C_{\text{max}}/\text{MIC}$ being the pharmacodynamic (PD) index most predictive of efficacy. A $C_{\text{max}}/\text{MIC}$ ratio of 2–4 was associated with therapeutic efficacy of DAMB in animal models of invasive candidiasis and aspergillosis, with maximal efficacy at $C_{\text{max}}/\text{MIC}$ of 10 (15). Limited data in pediatric patients receiving LAMB suggest a mean $C_{\text{max}}/\text{MIC}$ of 68 associated with complete response (16). Amphotericin B preparations display a strong post-antifungal effect (PAFE) (17).

The usual dosage of DAMB for adults, children and neonates is 1 mg/kg/day (range: 0.6–1.5 mg/kg/day) administered in one dose. The usual dosage for the lipid formulations ranges between 3–5 mg/kg/day, also in one dose, except for treatment of invasive mucormycosis where a dose of ≥5 mg/kg/day is recommended. Currently available evidence does not support the routine use of therapeutic drug monitoring (TDM) for this class of antifungal agents (18).

Flucytosine

Flucytosine may be administered both intravenously...
and orally, as oral bioavailability is between 76–98%. It has low protein binding (3–4%) and is mostly (90%) eliminated by glomerular filtration (13). In animal models of invasive candidiasis treated with fluconosine, the PD index associated with net stasis was a \( T_\text{Time} > \text{MIC} \) of 40% (19). Fluconosine has a narrow therapeutic index with toxicity associated with peak levels. Given its very short PAFE and efficacy associated with \( T > \text{MIC} \), frequent (6 hourly) dosage is suggested for patients with normal renal function (15).

The usual dosage of fluconosine in adults and children ranges between 100–200 mg/kg/day divided into 4 doses. The recommended dosage for neonates is 100 mg/kg/day in 2 divided doses. TDM is strongly recommended, as peak concentrations >100 mg/L are associated with bone marrow suppression and hepatotoxicity, while trough levels <20–40 mg/L are associated with development of resistance (13).

**Azoles**

This class of antifungal agents comprises fluconosine, itraconosone and the triazoles voriconosone, posaconosone and isavuconosone. All of them are available as intravenous and oral formulations.

Fluconosine displays excellent oral bioavailability (>90%) and limited plasma protein binding (~12%). It is eliminated unchanged by the kidney, achieving very high concentrations in urine. Although it is not metabolized in the liver, it inhibits CYP3A4 and CYP2C9 activity; therefore, a number of interactions of fluconosine with other drugs, which are substrates of CYP3A4 or CYP2C9, may be observed (13). The usual dose of fluconosine is 200–400 mg once daily in adults depending on the indication (invasive or mucosal infection) and 12 mg/kg daily for children. For severe infections a loading dose of 800 mg for adults and 25 mg/kg for children may be considered. Neonates may be dosed at 12 mg/kg every 72 hours (if aged <14 days) or every 48 hours (if aged 14–28 days) (13).

Itraconosone oral formulations include capsules or suspension. Absorption however is highly variable and reduced when gastric acidity is decreased. Capsules are better absorbed with food; absorption of the suspension is better on empty stomach. Following oral or intravenous administration itraconosone exhibits very high plasma protein binding (>99%) (20). It is extensively metabolized in the liver, mostly by CYP3A4 enzyme. Numerous interactions with other drugs, which are CYP3A4 substrates, have been observed and complicate itraconosone treatment (18). In the intravenous formulation, the hydroxypropyl-β-cyclodextrin carrier is eliminated through glomerular filtration; this molecule may therefore be accumulated in patients with impaired renal function (13). The usual recommended dosage of intravenous itraconosone for adults is 200 mg once daily, with loading of 200 mg twice daily for the first 2 days. For children, corresponding dosage is 2.5 mg/kg daily with loading of 2.5 mg/kg twice daily for 2 days. Usual dosage for oral preparations ranges between 200–400 mg/day for adults and 2.5–5 mg/kg/day for children administered in 1 or 2 doses.

Voriconosone oral formulations (tablets, suspension) exhibit high bioavailability (~96%), which is not affected by gastric pH but may be reduced with high fat meals. Following oral or intravenous administration the plasma protein binding of voriconosone is approximately 58%. Voriconosone exhibits non-linear pharmacokinetics and is metabolized in the liver by P450 isoenzymes CYP2C19, CYP2C9 and CYP3A4 (21). Significant inter-patient variability in its clearance and exposure [area under the concentration-time curve (AUC)] may be observed, which is in part explained by genetic polymorphisms of CYP2C19 enzyme. In addition, a number of clinically significant interactions of voriconosone with other drugs (CYP450 substrates, inhibitors or inducers) have been observed (18,21). The intravenous formulation of voriconosone also contains a cyclo-dextrin carrier (hydroxypropyl-betadex), which is eliminated in the urine and may be accumulated in patients with creatinine clearance <50 mL/min. The usual recommended dosage of intravenous voriconosone for adults is 6 mg/kg/12 hours for the 1st day and subsequently 4 mg/kg/12 hours. For children corresponding dosage is 9 mg/kg/12 hours and 8 mg/kg/12 hours, respectively. Oral formulations are dosed at 400 mg/12 hours (1st day) followed by 200 mg/12 hours for adults, and 9 mg/kg/12 hours for children (no loading recommended).

Posaconosone oral formulations also include gastro-resistant tablets and suspension; the tablets display improved bioavailability compared to the suspension, resulting in more than 3 times higher exposure (AUC) (22). Absorption is improved with fatty meals. Posaconosone is highly bound to plasma proteins (>98%). It is mainly excreted unchanged in the feces and only partially metabolized to multiple glucuronide conjugates. It inhibits CYP3A4 but not other CYP450 enzymes; numerous interactions with CYP3A4 substrates may therefore be observed. The intravenous preparation of posaconosone contains betadex sulfobutyl ether sodium as a vehicle, which is excreted by the kidney.
and may be accumulated in case of moderate or severe renal impairment (creatinine clearance <50 mL/min) (22). The usual recommended adult dosage for posaconazole intravenous and tablet formulations is 300 mg/12 hours the 1st day and subsequently 300 mg once daily. For the suspension, the dosage for invasive infections is 200 mg/6 hours.

Isavuconazole oral formulation (capsule) exhibits very high bioavailability (98%), which is not significantly affected by food. Isavuconazole is highly bound (>99%) to plasma proteins, mainly albumin. It is metabolized in the liver by CYP3A4, CYP3A5 and subsequently by uridine diphosphate-glucuronosyltransferases (UGT) (23). It is a moderate CYP3A4 inhibitor and many drug-drug interactions are likely to be observed (23). The usual recommended adult dosage for both intravenous and oral formulation of isavuconazole is 200 mg/8 hours for the 1st 2 days and subsequently 200 mg once daily. A recent open-label, phase I study in patients aged 1–18 years suggest that a loading dose of 10 mg/kg/8 hours for days 1 and 2 followed by 10 mg/kg once daily provides exposure equivalent to adults (24).

Several in vivo studies have suggested that the PD index associated with efficacy (50% maximal effect) of azole agents in Candida infections is a free-drug AUC/MIC ratio of 25–50. This practically means that drug concentrations near the MIC for a 24-hour period would likely achieve this target (15). The correspondent index (free-drug AUC/MIC ratio) for azole efficacy in aspergillosis animal models is significantly lower, ranging from 1.7–11 in various studies (25,26). However, in a murine cryptococcal meningitis model, efficacy (stasis) was associated with a fluconazole AUC/MIC ratio of 389 (27). The azole agents exhibit variable PAFE in vitro, which appears to be related to their non-covalent binding to lipophilic cytoplasmic components of fungal cells (for example significant PAFE hydroxylation by CYP3A4, drug interactions are much less compared to the azoles (34). The usual adult dosage of caspofungin is 70 mg once daily (1st day) and subsequently 50 mg (or 70 mg if body weight >80 kg) once daily. Patients aged 1–17 years should be dosed at 70 mg/m$^2$ once daily (loading) followed by 50 mg/m$^2$ (potentially increased up to 70 mg/m$^2$). Neonates/infants <3 months of age and infants 3–11 months of age should be dosed at 25 mg/m$^2$ and 50 mg/m$^2$ once daily, respectively.

Micafungin is highly bound to plasma proteins (>99%), mainly albumin, and metabolized in the liver to several inactive metabolites. Although in vitro micafungin is a substrate for CYP3A, in vivo hydroxylation by CYP3A plays a minor role. Drug interactions are limited, as for caspofungin (34). The usual recommended therapeutic dosage for adults is 100 mg once daily (potentially increased to 200 mg), for children ≥4 months of age is 2 mg/kg once daily (potentially increased to 4 mg/kg) and for neonates/infants <4 months is 4–10 mg/kg once daily.

Anidulafungin is not an inducer or inhibitor of cytochrome P450 enzymes. No significant drug-drug interactions have been observed (35). The usual recommended dosage for adults is 200 mg once daily (1st day) and subsequently recommended for severe IFD’s or when there are increased MICs. Similar results were obtained for itraconazole and posaconazole, for which optimal outcome was observed with trough concentrations ≥1 μg/mL (33). Based on available clinical data and considerable inter-patient pharmacokinetic variability, TDM is strongly recommended for patients with invasive fungal infections treated with itraconazole, voriconazole and posaconazole. The need for TDM in the case of isavuconazole has not yet been established (18).

**Echinocandins**

The echinocandin class of antifungal agents includes caspofungin, micafungin and anidulafungin, all available only as intravenous formulations.

Caspofungin is extensively bound to plasma proteins (~95%) and metabolized in the liver by spontaneous degradation and, further, hydrolysis and N-acetylation. All echinocandins are metabolized in the liver via pathways other than the CYP450 enzyme system (13). Since caspofungin metabolism is independent from cytochrome P450, drug interactions are much less compared to the azoles (34). The usual adult dosage of caspofungin is 70 mg once daily (1st day) and subsequently 50 mg (or 70 mg if body weight >80 kg) once daily. Patients aged 1–17 years should be dosed at 70 mg/m$^2$ once daily (loading) followed by 50 mg/m$^2$ (potentially increased up to 70 mg/m$^2$). Neonates/infants <3 months of age and infants 3–11 months of age should be dosed at 25 mg/m$^2$ and 50 mg/m$^2$ once daily, respectively.

Clinical data for fluconazole and voriconazole in patients with invasive candidiasis suggest that the animal derived free-drug AUC/MIC ratio of 25–50 is indeed associated with optimal outcome (15,31). Studies on patients with invasive aspergillosis treated with azoles have mostly focused on the relationship of trough concentrations with outcome. For voriconazole, optimal outcome was associated with trough concentrations between 1–2 μg/mL (32). Higher trough levels of voriconazole (2–5 μg/mL) are
100 mg once daily. The equivalent pediatric dose is 3 mg/kg once daily (1st day) and subsequently 1.5 mg/kg once daily (36).

The echinocandins exhibit concentration-dependent activity, both in vitro and in vivo, and prolonged PAFE, especially caspofungin and anidulafungin (37). For determination of their in vitro activity against Aspergillus isolates the minimum effective concentration (MEC) is used instead of the MIC. The MEC is the lowest drug concentration producing short, stubby and highly branched hyphae (38). The PD parameters associated with therapeutic and fungicidal efficacy are AUC/MIC for Candida spp. (AUC/MEC for Aspergillus) or, even better, Cmax/MIC for Candida (Cmax/MEC for Aspergillus) (15,34). In animal models of invasive C. albicans infection, free-drug Cmax/MIC >1 or AUC/MIC of 10–20 were associated with stasis. Lower ratios were needed for stasis in Candida parapsilosis and Candida glabrata infections (15,39). In vivo models of invasive aspergillosis have suggested that a Cmax/MEC ratio of 10–20 is associated with maximal reduction in pulmonary fungal burden (40). Limited PD data from clinical studies of echinocandins in patients with invasive candidiasis are in agreement with those derived from animal models (15). Their activity against Candida biofilms, which rapidly form on the surface of foreign devices, such as central venous catheters has been established (41).

Echinocandins are excreted to a comparatively very low amount as unchanged drug in the urine; despite anecdotal reports of successful treatment of Candida urinary tract infections they are not considered treatment of choice. Their accumulation in renal parenchyma, however, is high (42). There are currently insufficient data to support the routine use of TDM in patients treated with echinocandins (18).

Renal insufficiency

When comparing patients with candidemia in the setting of ICU to patients with candidemia hospitalized in other hospital departments, ICU patients have more frequently chronic renal insufficiency as co-morbidity, as well as acute renal insufficiency treated by renal replacement therapy (43,44). In fact, among severely ill patients treated in the ICU, sepsis and renal replacement therapy are the only two parameters associated with a higher probability of invasive candidemia (9). ICU-acquired candidemia in chronic renal disease patients and especially developing in the context of acute renal function deterioration is associated with worse outcome and death (45). While data is not always consistent (46,47), dose adjustment may prove important (48).

Treatment of fungal infections in the context of renal impairment is challenging. Most of the antifungals (triazoles and echinocandins) are lipophilic and metabolized in the liver (49). As mentioned previously however, the use of the intravenous formulations of itraconazole, voriconazole and posaconazole is not without limitations due to accumulation of their solvent carriers. This side effect is of particular clinical importance in the case of voriconazole, a highly efficient drug against Aspergillus and other fungi. On the other hand, gastric absorption is severely compromised and unpredictable in critically ill patients worsening even more the situation of patients with renal insufficiency. Newer medications, such as isavuconazole have been designed to, among others, overcome these treatment infelicities. Broad-spectrum antifungals, e.g., conventional amphotericin B, with good penetration and availability in various body compartments, such as the renal parenchyma or the central nervous system have been associated with renal toxicity, driving research towards the development of less toxic formulations (50). Appropriate dosing of antifungals in the context of altered pharmacokinetics and pharmacodynamics in critically ill patients with renal impairment has yet to be fully addressed (51). In general, lipid formulations of amphotericin B do not need dose adjustment, nevertheless the probability of nephrotoxicity must be taken into account; fluconazole and fluconazole should be administered according to creatinine clearance and echinocandins do not require adjustment. During the methods of renal replacement such as continuous venovenous haemodiafiltration different antifungals require or not dose adjustment (47,48,52). Currently available renal function—adjusted dosing data are summarized in Table 1.

Hepatic insufficiency

Impaired liver function represents a major issue in the everyday practice of ICU both in terms of safety of use of antifungals in critically ill patients, as well as in terms of pharmacokinetics and necessary dose adjustment of the antifungal agents. The presence of liver pathology in ICU patients developing IFD severely impairs outcome and appears to be an independent predictor of 28-day mortality (63). Critically ill patients are already characterized by impaired liver blood flow, biliary excretion and plasma protein binding and cannot tolerate further drug-induced hepatotoxicity (64). On the other hand, cirrhotic patients admitted to the ICU have a higher probability of becoming colonized with fungi and
developing invasive fungal infections (65). Fungal infections usually follow bacterial infections and present preferentially in patients with advanced liver disease and organ failure (66).

All antifungal agents can induce liver damage ranging from mild asymptomatic abnormalities in liver function tests to acute liver failure. Drug-induced liver injury is categorized as hepatocellular, cholestatic and mixed injury, according to the ratio of alanine aminotransferase (ALT) to alkaline phosphatase (ALP) (67). The antifungal class associated with the most prominent toxic effect on liver function is the azoles, an effect that is not necessarily dose-dependent (68-70). Liver toxicity is observed frequently with their use; however, hepatic failure is uncommon (71). Main pattern of liver toxicity with this class of antifungals is liver enzymes elevation; itraconazole and posaconazole may induce cholestasis. Pre-existing liver disease is one of the most important predisposing factors. Among the triazoles used in ICU patients (fluconazole, voriconazole and posaconazole) dose reduction of 50% is recommended in the case of voriconazole; therapeutic drug monitoring is considered mandatory (64).

Polyenes are safer in patients with liver impairment; their use may be associated with mild hepatotoxicity regardless of the dose used, an effect that appears to be less frequent with the lipid formulations. They are excreted unchanged in the urine and feces (72). Elevation of liver function tests, however, was not associated with histopathologic changes in a series of 64 patients with hematological malignancies and invasive fungal infections (73).

As epidemiology of candidemia in critically ill patients is changing with the proportion of non-albicans Candida species especially fluconazole-resistant strains rising (74), echinocandins are administered as first line antifungal treatment in critically ill cirrhotic patients (75). Their pharmacodynamics includes good penetration in most tissues, except for the central nervous system/eye and the peritoneal cavity; their efficacy therefore in fungal peritonitis, the second most common fungal infection in critically ill cirrhotic patients, is questionable (76).

Among the three currently available members of echinocandin family, caspofungin is the one that warrants dose reduction in patients with severe liver impairment as the drug molecule becomes transformed in the liver and the recommended dose is 35 mg daily. Micafungin use in juvenile animals has been associated with the development of liver tumors; its use may therefore be restricted to cases where other therapeutic options are not available (74). However, no such toxicity has been observed.
after intense use in human neonates and children. For patients with severe hepatic insufficiency there are no data for the use of micafungin, and it should be avoided. Further studies need to be conducted to address the issue of altered pharmacokinetics and drug availability in critically ill patients and patient adjusted dosing. Initial data do not suggest however severely affected drug metabolism and levels. However, based on the aforementioned findings in experimental animals, EMA discourages use of micafungin in patients with severe, advanced and potentially preneoplastic liver conditions (77). There is no need for dose adjustment for anidulafungin even in patients with severe hepatic insufficiency. The currently recommended dose adjustments of antifungal agents used for patients with hepatic insufficiency are summarized in Table 2 (64).

Age-dependent factors

Invasive fungal infections show a predilection for elderly patients (78). More than half of the cases of candidemia occur in patients >65 years old with a significant associated mortality. Risk factors for invasive fungal infections in this age group, however, differ compared to other age and patient groups (79). Chronic pulmonary insufficiency, chronic kidney disease, diabetes mellitus and a higher Charlson comorbidity index are more frequently associated with the development of invasive fungal diseases in the elderly. Elderly people with invasive fungal diseases may present with more atypical features, and thus evade diagnosis (80). Moreover, physicians are usually more hesitant to apply invasive diagnostic procedures such as bronchoscopy or organ biopsies to patients in this age group. An additional contributing factor to the excess mortality associated with these infections in this age group is the increased resistance profile of the pathogens involved, due to different strain prevalence and previous exposure to antifungals. In general, the antifungal agents that are used in younger ages are also used in the elderly when they are hospitalized in the ICU, keeping in mind the higher probability of decreased renal and hepatic function that older patients in critical condition may have as well as a progressive reduction in total body water and lean body mass with advancing age, leading to a relative increase in body fat, thus affecting drug distribution (81).

However, one of the critical differences between these two extreme age groups when treated for IFIs appear to be the existing comorbidities, which are aggravated by critical illness, and the amount of other co-administered medications. Interactions of triazoles with co-administered medications may prove critical and need to be monitored. Co-medications in critically ill patients, whose levels may reach toxic levels (clinically relevant increase) through administration of triazoles include, among others, immunosuppressants, neuroleptic drugs, antiretroviral medications, acenocoumarol, and hypolipidemic drugs (82,83). With regard to the echinocandins, no particular interactions with other drugs are of clinical significance, with the exception of immunosuppressants, such as cyclosporine or tacrolimus, which may require increase of the administered dose.

Critically ill neonates especially premature neonates are prone to invasive fungal infections mainly candidiasis due to immaturity of immune system and multiple invasive procedures (11). Candidiasis in neonates with extremely low birth weight (ELBW) is frequent, is associated with high morbidity and may be followed by hematogenous Candida meningoencephalitis (HCME) found almost exclusively in this age group (84). Thus, in this age group and especially for ELBW neonates, antifungal fluconazole prophylaxis is justified as part of the antifungal prevention strategy.

The main antifungal agents commonly used in critically ill neonates include amphotericin B, fluconazole, caspofungin and micafungin because of differences in pathophysiology of invasive fungal infections as well as available data on antifungal drug PK/PD in this age group as compared to adults (85-87). In contrast to adults, DAMB is well tolerated by neonates and is recommended for neonatal candidiasis including HCME. Liposomal and lipid complex preparations of amphotericin B are recommended in neonatal invasive candidiasis based on limited PK data, whereas optimal dosing has not been established. Liposomal AmB is recommended at a dose of 3–5 mg/kg/d according to most recent IDSA guidelines (86). For the treatment of HCME in neonates, both DAMB and lipid formulations have shown similar efficacy based on few clinical studies as well as some preclinical models (86,88).

Fluconazole is used both for prophylaxis and treatment of invasive candidiasis in neonates (85,86). Fluconazole is in vitro active against most Candida species that are frequently isolated from neonates (C. albicans and C. parapsilosis) and resistance is low (<5%) at least in Europe and USA (89,90). It can be used as an alternative option for empiric treatment of invasive candidiasis in neonates who have not been exposed to antifungal prophylaxis with fluconazole and as a step-down option for the treatment of HCME (86).
For the treatment of invasive candidiasis in critically ill neonates and in contrast to critically ill adults, echinocandins are not first-line agents because of the lack of PK, safety and efficacy data (85,86,91). Micafungin is the only echinocandin that has been approved for use in neonates in Europe (92). It is used at higher doses (4–10 mg/kg/day) in neonates than older children especially for the treatment of HCME, for which micafungin is used at a dose of 10 mg/kg/day, according to preclinical data and very few clinical studies (93,94). The use of caspofungin in neonates is based on very limited data (95,96). Anidulafungin currently is not approved for use in neonates (36).

Beyond the neonatal period, general practices for the management of invasive fungal diseases in critically ill children are mainly derived from adults. However, significant differences exist in choosing optimal antifungal agents because of the limited clinical data and PK in critically ill children. For invasive candidiasis echinocandins are first-line agents and caspofungin is the most frequently used antifungal agent. In children caspofungin and micafungin have been approved for primary targeted therapy of invasive candidiasis in Europe (85). Pediatric data for the use of anidulafungin have just been published (36).

A recent meta-analysis comparing echinocandins (mainly caspofungin and micafungin) to other antifungal agents for the treatment of invasive candidiasis in children showed no significant difference in terms of efficacy and adverse events. However, the use of echinocandins was related with fewer discontinuations due to adverse events (97).

Liposomal amphotericin B is approved as first line therapy of invasive fungal infections in children. As in adults, lipid preparations of amphotericin B have better toxicity profile than DAMB (98).

Fluconazole can be used in invasive candidiasis in children when fluconazole-susceptible species are suspected

<table>
<thead>
<tr>
<th>Class</th>
<th>Child-Pugh score for cirrhosis mortality</th>
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<tr>
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</tr>
<tr>
<td></td>
<td>Dosage adjustment</td>
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<tr>
<td>Amphotericin B</td>
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<td>Itraconazole</td>
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<td>Voriconazole</td>
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<td></td>
<td>Maintenance: 1/2 of normal maintenance dose</td>
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<tr>
<td>Posaconazole</td>
<td>None</td>
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<tr>
<td>Isavuconazole</td>
<td>None or half dose (monitor transaminases)</td>
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<tr>
<td>Caspofungin</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Micafungin</td>
<td>None</td>
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<tr>
<td>Anidulafungin</td>
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Modified from (64). TDM, therapeutic drug monitoring; FDA, US Food and Drug Administration; EMA, European Medicines Agency.
and patients are in a stable condition. Voriconazole is first line therapy of invasive aspergillosis, scedosporiosis and fusariosis in children except neonates (99-101). A loading dose of 9 mg/kg/dose ×2 followed by a maintenance dose of 8 mg/kg/dose ×2 is currently recommended for intravenous use in children aged 2–11 years old with voriconazole levels desired 1–5.5 μg/mL (102). Higher doses, or even more frequently administered are suggested for children aged less than 2 years of age, but there are limited safety data (103). A full list of all antifungal dosage schemes for neonates and children for treatment or prophylaxis of invasive fungal diseases is out of the scope of this review and can be found in a recent updated review (87).

**Various underlying conditions**

**Sepsis**

In a multicenter European cohort study of critically ill patients the PK parameters of patients receiving fluconazole, anidulafungin and caspofungin were analyzed (Defining Antibiotic Levels in Intensive care, DALI study) (46). Fifteen patients received fluconazole, 9 anidulafungin and 6 caspofungin with a median SOFA score of 7, 6 and 3, respectively. Using a fix dose of 400 mg of fluconazole (4.9 mg/kg) the target PK/PD value (fAUCO-24/MIC ≥100) was achieved in 86%, 67% and 13% of patients when the assumed MIC was 1, 2 or 4 mg/L, respectively. Therefore, using a fix 400 mg dose of fluconazole in critically ill patients there is a 33% chance of achieving subtherapeutic levels. Adequate weight-based fluconazole dosing should be used in critically ill patients. In addition, high inter-individual variability was observed for the three antifungal agents included in this study (fluconazole, caspofungin and anidulafungin). Although the number of patients with caspofungin and anidulafungin was limited, in general antifungal exposure was found to be lower than healthy volunteers (46,104-107).

The jury is still out on whether the most adequate in terms of both cost and efficacy empirical antifungal treatment is fluconazole or an echinocandin in the management of a non-neutropenic critically ill patient. Apparently, there is more consensus on the need for a minimum maintenance dose of 6 mg/kg fluconazole, after the initial loading dose (12 mg/kg), a dose which is often not achieved with 400 mg/d (108). Where an echinocandin to be used, recently published data indicate variable PK/PD results among the different members of the class in the critically ill, with potentially better achieved targets in the case of caspofungin judging with better recorded clinical outcomes with its use; its use has limitations, especially in the context of co-existing liver impairment (104).

**Obesity**

The increasing proportion of critically ill patients with obesity has raised the question if variability of PK parameters commonly seen in critically ill patients may be heightened by the presence of obesity. Alobaid et al. studied population PK of fluconazole and analyzed the effect of body mass index (BMI) to PK parameters in 21 critically ill patients (109). Higher than recommended fixed fluconazole doses, adjusted to 12 mg/kg loading dose and 6 mg/kg/d maintenance dose and further adjusted for renal impairment if present, were needed to achieve better PK/PD targets for Candida strains with an MIC of 2 mg/L. A loading dose seems to improve PK/PD only when it is weight based rather than a fixed dose. Maintenance dose should also be based on mg/kg and be modified according to renal clearance. Similarly, population PK of micafungin in obese critically ill patients showed that a dose higher than recommended (100 mg/day) is needed to treat Candida infections (110). For C. albicans a fix dose of 150 mg/d was found adequate for patients weighing up to 115 kg and of 200 mg/d for those with weight more than 115 kg. Patients with C. glabrata a micafungin dose of 200 mg/d was adequate for obese patients weighing up to 115 kg (110).

**Thermal injury**

Patients with thermal injury have significant pathophysiological disturbances that may affect PK and PD parameters of antifungal agents (111,112). In most of the cases serum concentrations of antifungals may be subtherapeutic especially in the hypermetabolic phase of thermal injury. However, there are very limited data for each of antifungal agents (111). Most of the available data on antifungal PK parameters in patients with thermal injury are for fluconazole (113,114). In a small number of burn patients Boucher et al. found a 30% increase in fluconazole clearance during the first days of thermal insult (113). Using population pharmacokinetics, Han et al. found that fluconazole dose at 400 mg/day is sufficient in patients with major thermal injury for susceptible isolates (MIC equal or less than 2 μg/mL) (114). For Candida isolates with higher MICs, which may be frequent according to
local epidemiology, higher daily doses are recommended, as mentioned previously (114). Among echinocandins, both micafungin and caspofungin have been studied in burn patients (115,116). In a case series of adult patients with severe burns, plasma concentrations of micafungin, was similar or slightly lower than healthy volunteers, when given a high dose of 200–300 mg/day (115,116). Jullien et al. studied PK parameters of caspofungin in two patients with severe burns and found that the patient that had severe hypoalbuminemia had lower caspofungin exposure (50%) of that observed in healthy volunteers (117). More data are needed for patients with thermal injury to optimize antifungal dosing.

**Extracorporeal membrane oxygenation (ECMO)**

There are few data on antifungal PK during ECMO. Patients on ECMO may experience therapeutic drug failure due to low plasma concentration (high clearance or high volume of distribution) or drug toxicity due to organ dysfunction and decreased clearance (118).

Fluconazole population PK has been studied in children supported with ECMO (119). In this study, which included mainly infants and very few children older than 2 yrs of age, a higher than recommended loading dose is suggested (35 mg/kg instead of 25 mg/kd) for treatment of candidemia followed by standard daily maintenance dose (12 mg/kg) for children supported by ECMO without renal insufficiency or replacement therapy. In addition, according to local practices and especially when invasive candidiasis is more than 10% these patients with ECMO may benefit from fluconazole prophylaxis which should also be administered at higher than recommended dose (12 mg/kg loading dose followed by 6 mg/kg per day) because of the high volume of distribution (119).

Micafungin has been studied in neonates and children aged less than two years of age receiving ECMO (120). In this study infants supported by ECMO had higher volume of micafungin distribution and clearance, and for this reason higher doses (2.5 mg/kg for prophylaxis and 5 mg/kg for treatment) were suggested. This study could not be extrapolated to preterm infants that may have HCME, and higher micafungin doses are used (as previously discussed). In an ex vivo study using different ECMO circuits, micafungin was found to be extracted by the circuit whereas fluconazole was not (121).

Caspofungin administration during ECMO resulted in subtherapeutic plasma levels, even when higher than recommended doses were used in a child (122). Similarly, an adult patient who was on ECMO and received voriconazole, caspofungin and amphotericin B was found to have low or even undetectable concentrations of both caspofungin and voriconazole (123). In contrast, Spriet et al. presented two patients on ECMO, who were on caspofungin and voriconazole and found that caspofungin levels were not affected (59). In these cases voriconazole was affected during ECMO and low levels could be explained by sequestration in the circuit together with altered pharmacokinetics (59). Similarly, in a child supported with ECMO and invasive aspergillosis high voriconazole doses based on TDM were required (124). However, voriconazole as previously described, have significant interindividual PK level variation and the possible effect of ECMO cannot be assessed.

Published data for anidulafungin use in patients on ECMO, are limited to only few case reports and plasma levels were measured only in 1 adult patient with no significant differences (125,126).

It seems that there is a high complexity of interactions between ECMO circuit and antifungal agents (121). More studies are needed on patients receiving ECMO and are treated with antifungal agents including latest ECMO technology/ newer circuits to optimize correct dosage schemes.

**Conclusions**

As invasive fungal diseases, mostly invasive candidiasis, are a major disease burden in ICU regardless of age of patients, antifungal agents have to be administered optimally taking into account the many differences of the age, underlying conditions and co-existing factors that ICU patients have. Administration of these agents may be challenging due to various factors in patients hospitalized in the intensive care unit including extreme age, hemodynamic alterations and organ dysfunction of sepsis, underlying renal and hepatic insufficiency, thermal injury, excessive weight and modern organ function supporting measures. The physicians caring of these patients should be aware of the impact of such factors on pharmacokinetics and pharmacodynamics of antifungal agents as well as the drug interactions with other co-administered drugs. By having this knowledge they can adjust the regimens of the antifungal agents as well as those of other agents to achieve the best outcome of the critically ill patients.
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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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