

Echinocandins for management of invasive candidiasis in patients with liver disease and liver transplantation

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Abstract: *Candida* species remains one of the most important causes of opportunistic infections worldwide. Invasive candidiasis (IC) is associated with considerable morbidity and mortality in liver disease (LD) patients if not treated promptly. Echinocandins are often recommended as a first-line empirical treatment for managing IC and can especially play a critical role in managing IC in LD patients. However, advanced LD patients are often immunocompromised and critically ill. Hence altered pharmacokinetics, drug interactions as well as tolerance issues of antifungal treatments are a concern in these patients. This comprehensive review examines the epidemiology, risk factors and diagnosis of IC in patients with LD and evaluates differences between three available echinocandins for treating this group of patients.

Keywords: anidulafungin, caspofungin, candidemia, micafungin

Introduction

Advanced liver disease (LD) is characterized by post-inflammatory fibrosis and retardation of liver structure and function. Advanced LD patients generally present with ascites and exaggerated fibrinolysis, while pain, fatigue, abdominal pain are also some common secondary symptoms.^{1,2} End-stage liver disease (ESLD) refers to advanced LD along with liver failure and decompensated cirrhosis.¹ Advanced LD patients generally have low host immunity and comorbidities such as renal impairment and diabetes, and are highly vulnerable to opportunistic infections, mainly invasive fungal infections (IFIs).^{3,4} Advanced LD leads to persistent systemic inflammation, which damages the cellular structure of the reticuloendothelial system, impairs the innate immune response and ultimately renders hepatic patients immunodeficient.^{5,6}

Increased numbers of dysfunctional monocytes and macrophages, the regulators of MER receptor tyrosine kinase, which are known to suppress the innate immune system, have been observed in patients with acute-on-chronic liver failure.⁷ Increase in the number of these regulators is linked with severity of inflammation and disease prognosis.⁷ In severe alcoholic hepatitis (sAH), there is higher immunosuppression compared to cirrhosis, which also correlates to increased incidence of infection. This is due to the enhanced immunosuppressive profile of T lymphocytes resulting from higher chronic lipopolysaccharide exposure observed in sAH (Figure 1).^{8,9} Another reason for increased risk of both opportunistic fungal infections and IFIs in sAH patients is due to prolonged steroid use, which is the first-line therapy to improve the patient outcomes in this group of patients.^{8,10,11} Similarly, other iatrogenic

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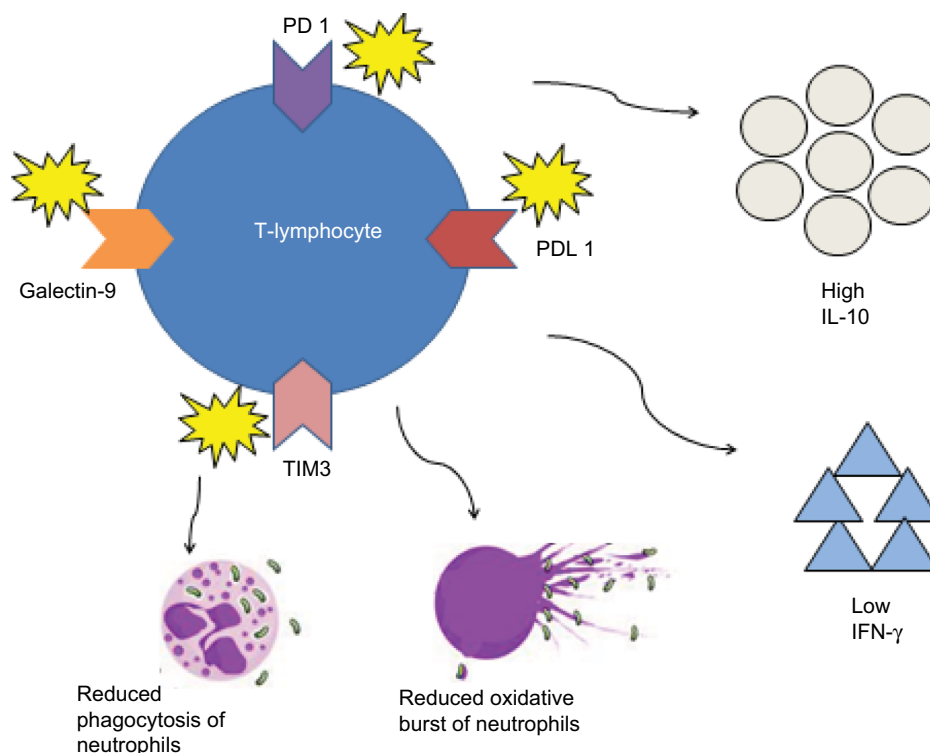


Figure 1 Pathophysiology for immunosuppression in severe alcoholic hepatitis.

Notes: Higher chronic lipopolysaccharide exposure leads to overexpression of inhibitory receptors (PD-1, PDL-1, TIM-3 and galectin-9) on T lymphocytes resulting in higher IL-10 and lower IFN- γ production as well as reduced neutrophil antimicrobial activities (e.g., phagocytosis and oxidative burst).

Abbreviations: IFN- γ , interferon- γ ; IL-10, interleukin-10; PD-1, programmed cell death protein 1; PDL-1, programmed death ligand 1; TIM-3, T-cell immunoglobulin mucin-3.

factors, such as immunosuppressive therapy, are additional risk factors for IFIs in liver transplantation patients, especially those with primary graft failure (repeated surgery/re-transplantation).¹²⁻¹⁴

Patients with LD in intensive care units (ICUs) are more susceptible to opportunistic fungal infections including invasive candidiasis (IC), mainly aggravated by nosocomial infection factors such as colonization of indwelling catheters by *Candida* spp.¹⁵ According to a 1-day, prospective, point prevalence multi-country study, *Candida* spp. were the third most common pathogen in ICUs, after *Staphylococcus aureus* and *Pseudomonas* spp., with an infection rate of 17%.¹⁶ Candidemia is the fourth most common blood infection in nosocomial settings, especially in ICU settings.¹⁷ It is important to highlight that IC includes not only candidemia, but also deep-seated tissue candidiasis. The latter can also potentially lead to secondary candidemia through hematogenous dissemination or inoculation in sterile sites.¹⁸

Fungal infections are an emerging problem in cirrhotic patients and are usually fatal.¹⁹ *Candida* spp. infection

accounts for 10% of total IFIs in cirrhotic patients.²⁰ Although IC may be a rare complication in hepatic patients, there is a high mortality risk if diagnosis and treatment are delayed.²⁰ Timely initiation of antifungal therapy is found to lower mortality rates in IC patients.²¹ Table 1 lists the major risk factors for development of IC in patients with LD.

Both Infectious Diseases Society of America (IDSA) and European Society of Clinical Microbiology and Infectious Diseases (ESCMID) guidelines recommend echinocandins as the first-line therapy for the initial management of IC (suspected or proven) using a stepdown approach.^{22,23} While IDSA guidelines recommend de-escalation for fluconazole-susceptible strains when the patient becomes stable and ESCMID guidelines recommend de-escalation after 10 days of intravenous treatment, de-escalation to fluconazole is probably started much earlier than recommended in clinical practice as shown in the AmarCAND 2 trial.²⁴

Though these international guidelines do not differentiate amongst the three available echinocandins, there are

Table 1 Major risk factors for invasive candidiasis in liver disease

Risk factors
<ul style="list-style-type: none"> • Prolonged ICU admission • Parenteral nutrition • Indwelling catheters • Anastomotic leakage after laparotomy • Recent antibiotic therapy and anti-fungal prophylaxis for liver transplant recipients • Internal prosthetic devices • immunosuppression therapy (e.g., corticosteroids)

Note: Data collated from Bassetti et al.²⁸ Thursz et al.¹⁰ and Vergis et al.¹³⁹

Abbreviation: ICU, intensive care unit.

major differences between them largely related to the route of metabolism, half-life and safety. These are important in selecting appropriate agents in patients with LD. In this review, we have examined the epidemiology, risk factors and diagnosis of IC in patients with LD as well as in patients with liver transplantation. We have also studied the differences between three available echinocandins for treating this group of patients.

Clinical presentation of invasive candidiasis

Clinical presentations of IC in LD patients can be similar to bacterial infections.²⁵ However, these patients may or may not present with associated bacterial infection and rather manifest as unimpeded fever after treatment with antibiotics, septic shock, leukocytosis as well as renal failure.²⁶ In addition, it is difficult to differentiate spontaneous fungal peritonitis (SFP) from spontaneous bacterial peritonitis (SBP) based on ascitic fluid analysis alone.¹⁹ Therefore, clinicians should have a high index of suspicion and risk factor analysis is highly relevant in this context.

Candidemia is 10 times more common among ESLD patients compared to other LD patients (both cirrhotic and non-cirrhotic).²⁷ Post-liver transplantation and cirrhotic patients generally present with candidemia (>50%). However, intraabdominal candidiasis (IAC) which includes peritonitis and abdominal abscesses is also commonly reported (40%).^{19,28} ICU admission and mortality are found to be higher in liver transplant recipients (LTRs) with candidemia compared to those with abdominal candidiasis.²⁹ More than one species of *Candida* spp. is frequently observed in patients presenting with abdominal candidiasis.^{28,30}

Recent evidence suggests that the occurrence of SFP due to *Candida* spp. among critically ill patients with

decompensated ESLD is comparable to SBP (10% and 14% respectively), which could mean that SFP may not be as rare a complication in LD patients as that described in previous studies.³¹ Also, SFP in patients with cirrhosis is associated with worse outcomes, specifically severe sepsis/septic shock (87.5% vs. 42.8%; $P=0.0023$), admission in the gastroenterology ICU (87.5% vs. 24.4%; $P=0.001$) and higher overall (62.5 vs. 31.9%; $P=0.039$) or 30-day mortality (50.0 vs. 24.4%; $P=0.034$), compared to SBP.³² Ascitic fluid lactate dehydrogenase, blood leukocyte count and urea nitrogen, invasive procedures and longer admission time are all independent risk factors for SFP as compared with patients without any infection.³²

Epidemiological characteristics of *Candida* spp. in liver disease patients

Until recently, the most common isolated species during nosocomial IC was *C. albicans*; however, with changing epidemiology depending on geographical location, non-*C. albicans* has emerged as the predominant species in many countries.³³ *C. glabrata* is recognized as the most common cause of candidemia in the USA and Europe.^{34,35} However, in Asian countries such as India and Singapore, the proportion of *C. tropicalis* was found to be one of the highest non-*C. albicans* in ICU settings, even outweighing the proportion of *C. albicans*.^{36,37}

Candida spp. trends in LD patients relate to the epidemiological data of Asian countries. Although *C. albicans* infections are still a majority of *Candida* infection among LD patients, there has been increasing prevalence of non-*albicans* isolates.³⁸ However, the proportion of *C. parapsilosis* appears to be higher in LTRs (Table 2). This pattern seems similar to patients with neutropenia where the second most isolated species is *C. parapsilosis*.³⁹ Central venous lines and the use of parenteral nutrition are also more likely to be associated with *C. parapsilosis* compared to other fungal species.⁴⁰ Increasing prevalence of infection by non-*albicans* spp., especially fluconazole-resistant *C. parapsilosis* among post-liver transplant patients is probably also due to long-standing adoption of antifungal prophylaxis among these patients and coincides with the history of temporal trend of prevalent use of fluconazole in mid- and late-1990s.^{41–43} Table 2 summarizes the common *Candida* spp. responsible for IC in LD and liver transplantation patients.

Table 2 Common *Candida* spp. responsible for IC in liver disease and liver transplantation patients

Study	Patient characteristics	Common <i>Candida</i> spp. types
Zicker et al ⁴⁰	Post-liver transplant patients with candidemia (n=40) from Brazil	<i>C. albicans</i> : 20% <i>C. glabrata</i> : 15% <i>C. parapsilosis</i> : 18%
Sganga et al ⁴¹	Post-liver transplantation patients with proven candidemia (n=26) from Italy	<i>C. albicans</i> : 58% <i>C. parapsilosis</i> : 19.2% <i>C. glabrata</i> : 15.4%
Bassetti et al ³⁰	Cirrhotic patients with candidemia and IAC (n=241) from Europe	<i>C. albicans</i> : 54.4% <i>C. glabrata</i> : 14.5% <i>C. parapsilosis</i> : 14.1%
Bassetti et al ²⁸	Liver transplant recipients with candidemia (n=42) from Europe and Brazil	<i>C. albicans</i> : 59.5% <i>C. parapsilosis</i> : 7.1% <i>C. glabrata</i> : 4.8%
Alexopoulou et al ¹⁹	Spontaneous fungal peritonitis patients with positive cultures obtained from ascetic fluid (n=126) in Greece	<i>C. albicans</i> : 58% <i>C. parapsilosis</i> : 11% <i>C. spp.</i> : 11%
Lahmer et al ³¹	Spontaneous fungal peritonitis among critically ill patients with liver cirrhosis (n=205) from Germany	<i>C. albicans</i> : 60% <i>C. glabrata</i> : 13% <i>C. krusei</i> : 13%

Abbreviations: IAC, intra-abdominal candidiasis; IC, invasive candidiasis.

Candida susceptibility to antifungals in invasive candidiasis affecting liver disease patients

In spite of antifungal therapy, mortality can exceed 30%–40% in IC patients.¹⁸ Due to the increased dispensing of fluconazole for treating candidemia in LTRs with IC, resistance to fluconazole has reached 57% mostly among non-*albicans* *Candida* spp., and class effects of drug resistance among azoles have also been reported.^{41,44,45}

More recently, emerging resistance to echinocandins among *C. glabrata* has also been observed.⁴⁶ Elevation of chitin levels in *C. albicans* cell wall was shown to decrease echinocandin's susceptibility in vitro, and in vivo resistance to caspofungin was observed in both isolates of *C. albicans* and non-*albicans* (e.g., *C. parapsilosis* and *C. krusei*).^{47,48} Above all, echinocandin resistance is significant among LTRs with IAC (4.8%), especially in those under long exposure.^{28,49,50} This may be attributed to the development of point mutations of *FKS* genes among resistant species.⁵¹

Although echinocandin-resistant isolates are rare in the Asian setting, evidence suggests that non-*albicans* species such as *C. tropicalis* and *C. glabrata* are becoming more resistant to echinocandins due to *FKS* mutations.⁵² Moreover, *C. parapsilosis* has higher minimal inhibitory concentration

(MIC) to echinocandins than others, and the effects of echinocandins on *C. parapsilosis* are inconstant.⁵³ In clinical trials, however, there has been a response to most *C. parapsilosis* complex infections with echinocandin therapy, regardless of reduced in vitro susceptibility.⁵⁴ This may be probably explained by the species' relatively lower virulence.⁵⁴ The recent emergence of novel species aggravates resistance, for example, *C. auris*, which is resistant to multiple classes of drugs including echinocandins.⁵⁵

In a recent retrospective study of candidemia and IAC in patients with liver cirrhosis, higher mortality rates were associated with *C. tropicalis* candidemia compared to *C. parapsilosis*.³⁰ *C. tropicalis* is considered highly virulent due to its ability to form true hyphae, complex biofilm in vitro and produce proteinases, phospholipases and hemolysins.⁵⁶

Formation of biofilms by Candida

Candida infections can form biofilms on both biotic and abiotic surfaces.⁵⁷ Biofilm formation by *Candida* spp. is clinically associated with higher mortality and currently there is no reference method available for antifungal susceptibility testing of biofilms.^{58,59} Central venous catheters (CVCs) and peripherally inserted central catheters are the common sites of biofilm formation by *Candida* spp. in nosocomial environments that persist as a reservoir of infective cells and may even inhibit the entry of antifungal drugs into the matrix.^{58,60,61} The problem is further exacerbated due to different complex mechanisms for each species, which are still not fully known.^{62,63} Biofilm formation is more frequently reported in non-*albicans*, especially *C. tropicalis* (70%) and *C. glabrata* (63.6%) compared to *C. albicans* (26.2%).⁶⁴ *C. auris* also has strong biofilm forming capability, which even renders echinocandins inactive.^{65–67}

Medical devices such as urinary catheters and CVCs are particularly prone to forming biofilms as they can act as potential substrates for fungal growth.⁶⁸ Since hepatic patients in the ICU setting often need medical devices such as CVCs, biofilm formation by *Candida* spp. is highly relevant as it can potentially complicate the implications of candidiasis in LD patients.

Studies have demonstrated that adherent host immune cells may actively produce factors that promote biofilm formation of *C. albicans*.⁶⁹ Biofilms can also act as an interactive physiological shear, where leucocytes can adhere and generate pro-inflammatory cytokines while downregulating other anti-inflammatory cytokines to render a favorable environment for biofilm growth.^{69,70} In advanced LD patients,

systemic inflammation is manifested as a form of activated circulating immune cells and increased serum levels of pro-inflammatory cytokines, which in turn increases the likelihood of biofilm formation.⁵

Diagnosis

Delayed diagnosis of *Candida* infection among LD patients is associated with a poor prognosis and high mortality.⁷¹ Timely initiation of antifungal treatment for IC can improve patient outcomes and health care costs.^{72,73} It follows that established early diagnosis through risk factor analysis, epidemiology and novel predictive markers are all important to determine the timely use of antifungal agents in these patients.^{74,75}

Diagnosis of IC is largely based on blood culture, although it can be nonspecific, insensitive and takes at least 48–72 hours due to slow multiplication rate of *Candida*.^{39,76} Blood cultures may take much longer than nonculture tests to diagnose IC, and sensitivity for blood culture was lowest (17%) compared to other non-culture methods such as (1,3)- β -D-glucan (BDG) (62%) and PCR (88%) for deep-seated candidiasis.^{77,78} Some clinical guidelines and studies suggest that BDG could be used to establish IC in LTRs and

correlates with higher mortality.⁷⁹ Combination of mannan antigen and anti-mannan antibody had sensitivity of 83% and specificity of 86%.⁵⁶ A meta-analysis of PCR-based methods on blood samples for the diagnosis of IC reported an overall sensitivity and specificity of 0.95 (95% CI: 0.88–0.98) and 0.92 (95% CI 0.88–0.95), respectively.⁸⁰ However, various different assays were included. The performance of individual assays varied with sensitivity as low as 0.77. Additional standardization is required to optimize the utility of PCR-based tests in the diagnosis of IC.

Although non-invasive tests can facilitate diagnosis, they are not superior compared to blood culture, which is the current gold standard.⁸¹ They may still lack sensitivity, specificity or both, and are unable to differentiate between active infection and inactive/dormant stage of microbes.⁷⁷ The aforementioned disadvantages of currently available invasive and non-invasive diagnostic tools principally contribute to a delay in diagnosis. Table 3 lists various advantages and disadvantages of the diagnostic tests for IC in LD and liver transplantation patients.

As delayed culture report results can postpone treatment initiation and increase morbidity and mortality, many

Table 3 Advantages and disadvantages of invasive and non-invasive diagnostic tests for invasive candidiasis in liver disease and liver transplantation patients

Diagnostic tests	Advantages	Disadvantages
Non-invasive tests		
(1,3)- β -D-glucan	<ul style="list-style-type: none"> Useful for ruling out a diagnosis of IFI (high negative predictive value)¹⁴² 	<ul style="list-style-type: none"> False positive common in ICU patients¹⁴³ False negative found for some <i>Candida</i> spp. such as <i>C. parapsilosis</i>⁸¹ Limited sensitivity and poor positive predictive value in LTRs¹⁴⁴
Galactomannan	<ul style="list-style-type: none"> High negative prediction values for LD patients even for children¹⁴⁵ 	<ul style="list-style-type: none"> Limited clinical utility and false negative common in LTRs¹⁴⁶ Interference with piperacillin-tazobactam (false positive)^{146,147}
Real-time PCR	<ul style="list-style-type: none"> Highly specific and sensitive for suspected IC patients⁸⁰ Fastest among all diagnostic tests, allowing prompt definitive therapy for critically ill patients¹⁴⁵ 	<ul style="list-style-type: none"> No reference standard and approved validation¹⁴⁸
Invasive tests		
Blood culture	<ul style="list-style-type: none"> Gold standard for IC⁷⁵ 	<ul style="list-style-type: none"> Long incubation time⁷⁷ Limited sensitivity for deep-seated candidiasis^{77,149} <i>C. glabrata</i> takes longer time to positivity than <i>C. albicans</i> in IC patients¹⁵⁰
Peritoneal fluid culture	<ul style="list-style-type: none"> Gold standard for diagnosis of SFP¹⁵¹ Good sensitivity, positive and negative predictive values for peritonitis observed in ICU patients with high risk factors¹⁵² Associated with mortality in ICU patients¹⁵³ Easy to differentiate between SFP and peritonitis resulting from preexisting liver disease¹⁵⁴ 	<ul style="list-style-type: none"> Long turnover time for growth of <i>Candida</i> spp.³ Difficult to distinguish true <i>Candida</i> spp. from contaminants¹⁵⁵ False negative due to culture techniques or prophylactic antifungal treatments¹⁵⁶

Abbreviations: IC, invasive candidiasis; ICU, intensive care unit; IFI, invasive fungal infection; LD, liver disease; LTRs, liver transplant recipients; SFP, spontaneous fungal peritonitis.

risk prediction models for IC have been designed based on risk factors, clinical and microbiological parameters. These models are used for identifying high-risk groups and help in the early initiation of antifungal therapy. These include the *Candida* score and *Candida* colonization index. The *Candida* score targets ICU patients with length-of-stay >7 days. Four parameters are included in the *Candida* score (multifocal colonization, 1 point; surgery, 1 point; parenteral nutrition, 1 point; and severe sepsis, 2 points). A score >3 implies a high probability of developing IC (sensitivity: 77.6% and specificity: 66.2%).³⁹ The *Candida* colonization index, which is a ratio of a division of a number of different body sites colonized by same strains by the total number of body sites investigated, is another score to predict the risk of developing IC (specificity: 79%, sensitivity: 67% and predictive validity: 66%).^{82,83} These scores have good negative predictive value (range: 84%–96%) but have poor positive predictive value (range: 25%–47%).⁸⁴ These risk models are more useful in identifying patients who are unlikely to benefit from antifungal therapy and help minimize unnecessary use of antifungal agents.⁸⁴ Traditionally, these risk models are used for evaluating patients admitted to ICU. Although these scoring systems provide a framework for assessing risk factors for IC, the applicability of these scoring systems in patients with chronic LD has not been validated. Further evaluation of risk factors for IC in this unique patient group is required to establish appropriate risk scoring tools.

Antifungal susceptibility testing of fungal species determines the MIC, which may predict the likelihood of efficacy of the antifungal therapy.⁸⁵ However, caspofungin susceptibility testing has been reported to have limited reproducibility between different testing laboratories.⁸⁶ In addition, characteristic mutations in *FKS* genes among non-*albicans* isolates is the only independent risk factor of failure of echinocandins, and testing for *FKS* mutations can be a better predictor of therapeutic responses as well as indicator of likelihood of treatment success for echinocandins.⁸⁷

Role of echinocandins in invasive candidiasis

With increasing prevalence of azole-resistant non-*albicans* spp., most guidelines recommend echinocandins as a first-line treatment for IC, especially in critically ill patients.^{88,89} Generally low MICs of echinocandins for all *Candida* spp. and low resistance compared to azoles make them favorable for eradication of different *Candida* spp.⁹⁰

Echinocandins are also active within biofilms.⁹¹ However, definitive treatment should be always modified according to

the culture data, and stepdown definitive therapy to azole should be considered if possible.^{92,93}

Empirical treatment presupposes the likelihood of microbial infection and is largely driven by the minimal indications such as fever.²³ However, inappropriate choice of antifungals for empirical therapy for IC can increase selective pressure of *Candida* and hence result in microbial resistance.

The American Association for the Study of Liver Diseases and the American Society of Transplantation particularly recommend caspofungin for prophylactic usage in LD patients with high risks such as those who would undergo choledochojejunostomy or re-transplantation.⁹⁴ The guidelines, however, do not differentiate among caspofungin, anidulafungin and micafungin for treatment of IC, as none of them is found to be superior to the other.^{95,96} It is also important to note that there are differences in approved indications, for instance, anidulafungin is not approved for prophylaxis of IC or for pediatric use.

Echinocandins: similar yet different

There are currently no data demonstrating head-to-head superiority among echinocandins. Some limited retrospective studies, including a switching study in cancer patients with hepatotoxicity, have, however, observed an improvement in liver function after switching patients from caspofungin to anidulafungin.^{97,98}

Yet, there are still differences in structure, pharmacokinetics and pharmacodynamics, which may have potential implications on drug selections. Table 4 compares these features among the three available echinocandins for management of IC.

Echinocandins comprise of a cyclic lipopeptide core (nucleus) with an N-linked acyl fatty acid chain, which is the most important structural feature of this class.⁹⁹ Structurally, anidulafungin's side chain is markedly lipophilic in comparison with the side chains of the other two echinocandins.⁹⁹ Unlike caspofungin and micafungin, anidulafungin's metabolic pathway does not involve liver and it is rather spontaneously degraded by itself in plasma.¹⁰⁰ Also unlike caspofungin and micafungin, which are readily soluble in plasma, anidulafungin does not freely dissolve in plasma.¹⁰¹ These differences probably account for anidulafungin's longer distribution (due to the lipophilic side chain) and mean elimination half-lives (due to slow degradation in plasma) as well as greater volume of distribution. Table 4 summarizes a detailed comparison among the three echinocandins for treatment of IC.

Table 4 Comparison of echinocandins for treatment of invasive candidiasis

Parameter	Caspofungin	Micafungin	Anidulafungin
Structure ⁹⁹	C56 H96N10O19 Side chain: fatty acid	C56H70N9NaO23S Side chain: aromatic (3,5-diphenyl-substituted isoxazole)	C58H73N7O1 Side chain: lipophilic alkoxytriphenyl (terphenyl)
Metabolism ¹⁰⁶	Liver metabolism via peptide hydrolysis and N-acetylation	Liver metabolism via arylsulfatase and COMT	No liver metabolism—slow degradation in plasma Degraded products eliminated into feces by biliary route
Protein binding ¹⁰¹	>95%	>99%	>99%
Pharmacokinetics ^{100,106,121,157}	Cmax (ug/mL): 12 AUC (ug h/mL): 118 CL (mL/min): 10–12.5 Total half-life (hours) : 8–10 Mean elimination half-life (hours): 8–10 VD (L): 9.67	Cmax (ug/mL): 18 AUC (ug h/mL): 101.6 CL (mL/min): 10.5 Total half-life (hours): 13–20 Mean elimination half-life (hours): 12–17 VD (L): 18–19	Cmax (ug/mL): 7.7 AUC (ug h/mL): 106 CL (mL/min): 16.67 Total half-life (hours): 40–50 Mean elimination half-life (hours): 24–26 VD (L): 30–50
Pharmacodynamics ^{103–105,158}	AUC/MIC: For <i>C. glabrata</i> : • Wild type: 2.04 • FKS mutation: 2.67 PAFE: For <i>C. albicans</i> : >12 hours at >MIC For <i>C. parapsilosis</i> : 33→120 hours at MIC For <i>C. glabrata</i> : >120 hours at 2x MIC	AUC/MIC: For <i>C. glabrata</i> : • Wild type: 6.78 • FKS mutation: 0.90 PAFE: For <i>C. albicans</i> : Shorter than the other two agents (~9.8 hours on average) For <i>C. parapsilosis</i> : 0–8 hours at MIC For <i>C. krusei</i> : >20.1 hours* was observed at 4x MIC concentration	AUC/MIC: For <i>C. glabrata</i> : • Wild type: 13.2 • FKS mutation: 3.43 PAFE: For <i>C. albicans</i> : >12 hours, at >MIC, PAFE even observed at sub-MIC concentration For <i>C. parapsilosis</i> : 33→120 hours at MIC, but longer than caspofungin when 2x MIC For <i>C. glabrata</i> : >120 hours at 2x MIC
Dose ^{114,137}	70 mg as a single loading dose on first day, followed by a maintenance dose of 50 mg once daily or 70 mg once daily, when the body weight exceeds 80 kg No dosing adjustment needed	100 mg once daily No loading dose required	200 mg as a single loading dose on first day, followed by 100 mg dose once daily
Dosing in renal patients without replacement therapy ¹⁰⁶	No dosing adjustment needed	No dosing adjustment needed	No dose adjustment needed
Dosing in renal patients with replacement therapy ^{115,159–164}	Generally no dosing adjustment is needed. However, in critically ill patients on continuous venovenous hemodiafiltration, dose escalation to 100 mg (loading dose) or 200 mg once daily may be required	No dose adjustment is required for patients undergoing continuous renal replacement therapy However, increase in dose is recommended after 8-hour plasma exchange therapy	Filter absorption is observed yet clinical significance is unknown No dosing adjustment is needed
Drug interactions ^{110,111,121–123,127,129,130,138,165}	• Powerful CYP inducers or inhibitors* (clinically insignificant) • Rifampicin (clinically significant) • Tacrolimus (clinically significant) • Cyclosporine (clinically significant)	• Cyclosporine (clinically significant) • Sirolimus, nifedipine (clinically insignificant)	• Cyclosporine (clinically insignificant)

(Continued)

Table 4 (Continued)

Parameter	Caspofungin	Micafungin	Anidulafungin
Precautions and contraindications ^{106,166–168}	<ul style="list-style-type: none"> • Relatively safe • Common ADR (>10%): diarrhea, pyrexia, increase in liver enzymes (AST/ALT) and serum alkaline phosphatase 	<ul style="list-style-type: none"> • Common ADR (>10%): fever, infusion-related reaction, phlebitis, skin rash • Hepatotoxicity (unknown incidence) • Hepatocellular tumors found in vitro in rats when micafungin is given for more than 3 months • Restricted indication, to be used only if other agents are not appropriate 	<ul style="list-style-type: none"> • Safe • Less frequent ADR (1%–4%): hypokalemia, nausea and vomiting

Note: *For example, phenytoin, carbamazepine, nevirapine, nelfinavir, dexamethasone.

Abbreviations: ADR, adverse drug reaction; ALT, alanine aminotransferase; AST, aspartate transaminase; AUC, area under the curve; CL, clearance; COMT, catechol-O-methyltransferase; MIC, minimum inhibitory concentration; PAFE, post-antifungal effects; VD, volume of distribution.

In a study comparing the in vitro activity of echinocandins, the MIC of caspofungin for *C. albicans* was found to be greater than the MIC of micafungin and anidulafungin.¹⁰² Caspofungin also showed the weakest sterilizing activity compared to the other two echinocandins.¹⁰² Another study reported that the AUC/MIC for anidulafungin is greater than the other two echinocandins for both wild-type and *FKS*-mutated *C. glabrata*.¹⁰³ Although post-anti-fungal effects (PAFE) are variable depending upon MIC concentration as well as *Candida* spp., PAFE of anidulafungin and caspofungin is reported to be longer than that of micafungin for *C. albicans* and *C. parapsilosis*.^{104,105}

Differences among echinocandins in liver disease patients

Pharmacokinetics (PK) of echinocandins, especially with regards to metabolism and elimination, can be affected by hepatic impairment in LD patients.¹⁰⁶ Multiple organ failure is also common in LD patients, mostly triggered by viral hepatitis and alcoholic hepatitis.¹⁰⁷ One retrospective study reported that 94% of the patients with cirrhosis required admission to the ICU within a 10-year period.¹⁰⁸ LD patients admitted to ICU have a reported mortality rate of 34%–69%.^{109,110}

Half to one-third of *Candida* infections also occur in critically ill (ICU) patients where pathophysiological alterations in terms of hemodynamics and plasma protein levels also modify the distribution of the drugs.^{106,111} Therefore, PK of drugs in LD patients, especially those who are critically ill, can appear to be variable and difficult to predict.¹⁰⁶ Table 5 summarizes the PK of echinocandins in LD and critically ill patients.

Caspofungin

Caspofungin is transformed in the liver. It is hydrolyzed to M0 (main metabolite) and M1. M2 is formed by N-acetylation of M1. These metabolites are then eliminated via urine. A slight elevation in caspofungin concentrations has been observed in mild hepatic insufficiency, but was judged as clinically irrelevant. For patients with moderate hepatic impairment, reduction of the maintenance dose to 35 mg/d is required. However, dose reduction in critically ill patients with moderate hepatic dysfunction may achieve sub-therapeutic caspofungin exposure and efficacy if the dose is adjusted. This is probably because of hypoalbuminemia and effects of low albumin levels on caspofungin metabolism.^{112,113} Advanced LD is also associated with hypoalbuminemia and a similar trend may also be observed.

Among surgical ICU patients, higher exposure of caspofungin was observed in one study.¹¹⁴ However, in the non-surgical ICU setting, caspofungin PK was comparable to that in non-critically ill patients.^{115,116}

Although there are few drug interactions with echinocandins in general, caspofungin interacts the most with other medications among the three echinocandin drugs. Caspofungin is a poor substrate for cytochrome P450 enzymes, hence co-administration with powerful CYP inducers or inhibitors such as phenytoin and carbamazepine may result in altered clearance and plasma concentration, which are found to be clinically insignificant. However, there have been speculations that caspofungin may interact with halogenated penicillins such as flucloxacillin, nafcillin and dicloxacillin as they have potential to induce CYP3A4 enzyme.^{117–120} Drugs interactions with rifampicin

Table 5 Pharmacokinetics of echinocandins in LD patients

Study	Study characteristics	PK in LD patients
Caspofungin		
Mistry et al ¹¹²	Single-dose, open-label study of 70 mg per day for 14 days	<ul style="list-style-type: none"> • Increased AUC, C_{min} and β-phase half-life compared with the healthy control subjects • Dose reduction to 35 mg daily following 70 mg is recommended for moderate and severe LD patients
Spriet et al ¹⁶⁹	Case study of ICU patient with Child-Pugh score B9 (70 mg on day 1 followed by maintenance dose of 50 mg/day)	<ul style="list-style-type: none"> • AUC is comparable to that of healthy subjects (no higher systemic exposure is observed) • Dose reduction is not recommended
Spriet et al ¹⁶⁹	Case study of ICU patient with Child A liver cirrhosis and transjugular intrahepatic portosystemic shunt	<ul style="list-style-type: none"> • Similar exposure and PK parameters compared to the healthy volunteers • Dose reduction not recommended
Micafungin		
Undre et al ¹²⁴	Single dose, open-label with severe hepatic dysfunction (Child-Pugh score 10–12)	<ul style="list-style-type: none"> • Low C_{max}, low AUC in severe LD patients compared to healthy subjects (not clinically relevant)
Hebert et al ¹²⁵	Phase I, parallel-group, open-label PK study of single dose IV micafungin in eight moderate LD patients (Child-Pugh score 7–9)	<ul style="list-style-type: none"> • Lower AUC, C_{max} in moderate LD patients compared to healthy volunteers, but no difference in clearance and volume of distribution or half-life • No change in unbound plasma concentration compared to that of healthy controls. • Given that low AUC is attributed to weight difference, dose reduction is not recommended
Anidulafungin		
Dowell et al ¹³³	Phase I, open-label, single-dose prospective study in adult patients at two clinical sites	PK parameters of mild and moderate LD patients were comparable to healthy controls. Decreases in AUC and C _{max} in severe LD patients were observed compared to healthy subjects (not clinically relevant, probably due to increase in VD due to ascites and edema). However, half-life in LD patients was comparable to healthy subjects

Abbreviations: AUC, area under the curve; ICU, intensive care unit; LD, liver disease; PK, pharmacokinetics; VD, volume of distribution; β -phase half-life, elimination half-life.

have also been documented. A momentary increase in AUC (61% increase) of caspofungin was found on day 1, while its trough concentration dropped to 14%–31% after 14 days.¹²¹ Dose adjustment of tacrolimus may also be necessary as reduction of C_{max} of tacrolimus (up to 20%) was observed when co-administered with caspofungin.¹²² The most relevant drug interaction is with cyclosporine; co-administration with cyclosporine increases the plasma concentration of caspofungin up to 35%.¹²³

Micafungin

Micafungin is metabolized in the liver by non-CYP enzymes largely into the inactive metabolites M-1, M-2 and M-5. These metabolites are excreted mainly via feces.¹⁰⁶ It is also a weak inhibitor of CYP3A, but its clinical significance is unknown.¹⁰⁶

Micafungin is known to have low hepatic extraction ratio with high plasma protein binding, and hence theoretically although its total plasma concentration may decrease in some clinical scenarios, its unbound concentration is likely to remain the same at steady state level.¹²⁴ However, as these enzymes are also present in other organs besides the liver, the

extent of the overall impact of impairment in these enzymes in LD patients that will contribute to the metabolism of these drugs is unknown.¹²⁵ While lower AUC in moderate and severe LD patients has been reported, the changes are however clinically irrelevant and dose adjustments are not recommended for any severity of LD patients.¹²⁵

In some studies, increase in micafungin clearance was observed due to decreased protein binding resulting from low albumin levels in LD patients; the clinical relevance in LD patients is, however, not conclusive.¹²⁶

The PK of micafungin is very well defined in non-critically ill patients and seems to be similar in critically ill patients.¹²⁷ However, increase in dose is recommended for critically ill patients infected with higher MIC *Candida* spp or *C. parapsilosis*.¹²⁶ With regards to PK of micafungin in ICU patients, AUC is reported to be lower than the reference population, and strong positive correlation of AUC and sequential organ failure assessment (SOFA) score as well as negative correlation of AUC level and body weight has been observed.¹²⁸

The most clinically significant drug interaction is with cyclosporine. A 15% reduction in clearance of cyclosporine

when co-administered with micafungin was observed to be clinically significant.¹²⁹ Although interactions with nifedipine and sirolimus have not been widely mentioned in the literature, there are speculations that they may affect the PK of micafungin, and hence caution should be applied when micafungin is given with these medications concomitantly.¹³⁰

Hepatotoxicity and potential for hepatic tumors, however, is a concern with micafungin.¹⁰⁶ Abnormal liver function tests have been noted after administration of micafungin to healthy volunteers. In rats, foci of altered hepatocytes and hepatocellular tumors were found to emerge with micafungin exposure after 3 months.¹⁰⁰ Therefore, the European Medicines Agency and other regulatory authorities have restricted the indication of micafungin as follows: “The decision to use Mycamine should take into account a potential risk for the development of liver tumors. Mycamine should therefore only be used if other antifungals are not appropriate”.^{131,132}

Anidulafungin

Anidulafungin undergoes non-hepatic slow degradation and the metabolites are eliminated via biliary excretion in feces. No difference in anidulafungin PK was observed in LD patients compared to that in the healthy volunteers, implying that no dose adjustment is needed.¹²¹ Statistically significant yet not clinically relevant decreases of AUC and C_{max} were, however, found in patients with severe LD compared to healthy controls.¹³³ This was attributed to ascites and edema, leading to increase in volume of distribution.

In critically ill patients, anidulafungin exposure was slightly lower yet comparable to healthy volunteers.^{134,135} Also, the Model for End-Stage Liver Disease score and albumin levels were not found to affect the PK of anidulafungin in critically ill patients.¹³⁶ This slightly low exposure of anidulafungin in critically ill patients was attributed to many different factors such as body weight, body water volume and altered renal clearance.¹³⁷

Not many drug interactions with concomitant medications have been known except a slight increase in AUC when co-administered with cyclosporine, which was found clinically insignificant.¹³⁸

Conclusion

The precise differences between the three echinocandins in the antifungal armamentarium are still unfolding. There is no prospective comparative efficacy and safety data for echinocandins and hence the guidelines do not differentiate the echinocandins for management of IC. Conversely, there are major pharmacokinetic and pharmacodynamic

differences within three echinocandins that are likely to play an important role in selection of appropriate agents especially in patients with LD. Hence, the “one-size-fits-all-approach” may be successful for some patients but may not be successful for management of IC in LD patients. Careful selection of appropriate echinocandin is required in this subset of patients to achieve the goal of precision medicine to target the right medicine to the right patient. Among the three echinocandins, anidulafungin has possible advantages mainly due to its unique non-hepatic metabolism, more predictable PK and good tolerability. However, this needs to be further supported by future large-scale prospective comparative studies.

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Author contributions

All the authors were involved in conception, design, analysis and interpretation of data. All the authors were also involved in preparation of the manuscript, revising it for important intellectual content and final approval before submitting for publication.

Disclosure

Dr. Stephen Lin, Mr. Dennis Yeo and Dr. Sajita Setia are employees of Pfizer, manufacturer of anidulafungin. Mr. Tae Jin Lee underwent indirect patient care pharmacy training for 3 months at Pfizer, Singapore. The other authors report no conflicts of interest in this work.

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