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Caspofungin

In Pediatric Patients with Fungal Infections

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Contents

Abstract

▲ Caspofungin is the first echinocandin to be approved for the treatment of fungal infections in pediatric patients. The antifungal properties of caspofungin result from interference with fungal cell-wall integrity.

▲ *In vitro*, caspofungin is fungicidal against *Candida* spp. and fungistatic against *Aspergillus* spp., but has little or no fungicidal or fungistatic activity against *Cryptococcus neoformans*, the Zygomycetes, *Fusarium* spp., or *Trichosporon beigelii*.

▲ Caspofungin was effective as empirical antifungal therapy in pediatric patients with persistent fever and neutropenia. Almost half (46%) of caspofungin recipients and one-third (32%) of liposomal amphotericin B recipients achieved an overall favorable response in a randomized, double-blind trial.

▲ Caspofungin was also effective in pediatric patients with fungal infections (invasive candidiasis, invasive aspergillosis refractory to or intolerant of standard antifungal agents, or esophageal candidiasis). Positive responses to treatment were seen in 30 of 37 patients with invasive candidiasis, 5 of 10 patients with invasive aspergillosis, and in the one patient with esophageal candidiasis, in a noncomparative, open-label trial.

▲ Caspofungin was generally well tolerated in the clinical trials in pediatric patients with febrile neutropenia requiring empirical antifungal treatment, or with fungal infections. Few caspofungin recipients reported serious drug-related adverse events or discontinued treatment as a result of drug-related adverse events.

Features and properties of caspofungin (Cancidas®)			
Indications			
In pediatric patients with febrile neutropenia or severe candida infections, or those with invasive aspergillosis who have antifungal therapy-refractory disease or are intolerant of other antifungal therapy			
Mechanism of action			
Inhibits synthesis of β-(1,3)-D-glucan (essential to fungal cell-wall integrity)			
Dosage and administration			
Loading dose	70 mg/m^2		
Maintenance dosage	50 mg/m^2 once daily		
Maximum loading or maintenance dose	70 mg		
Route of administration	1-h intravenous infusion		
Pharmacokinetic profile in neutropenic pediatric patients (mean values after repeated doses of 50 mg/m^2 once daily)			
Age	3–23 mo	2–11 y	12–17 y
Concentration at 1 h (μg/mL)	17.2	15.6	12.9
Concentration at 24 h (μg/mL)	1.6	1.5	2.2
Area under the concentration-time curve from time 0 to 24 h (μg • h/mL)	130.3	115.0	117.0
Terminal elimination half-life (h)	8.8	8.2	11.2
Most frequent adverse events (reported in ≥10% of patients in a comparator-controlled study of empirical antifungal therapy in febrile neutropenic patients)			
Pyrexia, rash, chills, vomiting, tachycardia			

The incidence of invasive fungal infections in immunocompromised pediatric patients is continuing to increase.[1,2] The most common fungal species responsible for such infections are *Candida* spp. and *Aspergillus* spp., both of which are associated with high mortality rates (19–31% for *Candida* infections and 68–77% for aspergillosis).[2]

Treatment guidelines for candidiasis[3] and aspergillosis[4] are available from the Infectious Diseases Society of America. Current treatment options include the following four drug classes: polyenes (such as amphotericin B), azoles (such as voriconazole), nucleoside analogs (such as flucytosine), and echinocandins (such as caspofungin [Cancidas®]).[2] While each class is effective, there is an increasing incidence of fungal infections with species that are resistant to treatment,[2] resulting in a need for as many options for treatment as possible. There are also tolerability issues with amphotericin B use,[1,2] some of which have been diminished by the development of lipid-associated formulations, such as liposomal amphotericin B.[1,2,5] Moreover, some azoles are fungicidal against some species but only fungistatic against others.[1,6] Additionally, potential drug-drug interactions can limit azole use.[1,6]

Caspofungin is the first echinocandin to be approved for use in adult and pediatric patients. It is indicated for pediatric use for empirical antifungal therapy in febrile neutropenia, the treatment of serious *Candida* infections, and, in selected patients, the treatment of invasive aspergillosis (see section 7 for specific indications).[7,8] Caspofungin use in adult patients has been reviewed elsewhere.[9-11]

This article provides a brief overview of the pharmacologic properties of caspofungin and reviews the clinical trial data available on the efficacy and tolerability of the drug in pediatric patients with febrile neutropenia requiring empirical antifungal treatment, or with fungal infections. Medical literature on the use of caspofungin in these patients was identified using MEDLINE and EMBASE, supplemented by AdisBase (a proprietary database of Wolters Kluwer Health | Adis). Additional references were identified from the reference lists of published articles.

1. Pharmacodynamic Profile

The pharmacodynamic properties of caspofungin have been extensively reviewed elsewhere.[9-11] An overview of these and more recent data and discussion of the *in vitro* activity of caspofungin in isolates from pediatric patients are presented in this section.

Mechanism of Action

- Caspofungin is a member of the echinocandin class.[7] Its antifungal properties result from inhibition of the synthesis of the glucose homopolymer β-(1,3)-D-glucan, which is not present in mammalian cells, but is a component essential to *Candida* spp. and *Aspergillus* spp. cell-wall integrity.[7]

In Vitro Antifungal Activity

This section focuses on caspofungin activity against *Candida* spp. and *Aspergillus* spp., as these are of greatest clinical interest. The Clinical and Laboratory Standards Institute (CLSI) interpretive guidelines for *in vitro* susceptibility testing of *Candida* spp. indicate that the minimum inhibitory concentration (MIC) susceptibility breakpoint for caspofungin is ≤2 μg/mL in tests performed using CLSI standardized methods for yeasts.[12] Interpretive standards for caspofungin activity against *Candida* spp. apply only to CLSI microbroth dilution techniques for MIC read at 24 hours.[7]

No interpretive guidelines for *in vitro* susceptibility testing of *Aspergillus* spp. have yet been established.[13] The minimum effective concentration (MEC; i.e. the drug concentration at which morphological changes of microscopic aberrant hyphal tips are evident), rather than the MIC at which an 80% reduction in macroscopic turbidity is evident, has been suggested to be the more consistent and reproducible of the two endpoints for determining caspofungin activity.[13] Recently, researchers have developed a method other than MEC for assessing antifungal activity against some *Aspergillus* spp.[14] This is known as a 2,3-bis-(2-methoxy-4-nitro-5-sulfophenyl)-2*H*-tetrazolium-5-carboxanilide (XXT) reduction assay and measures drug-induced changes in fungus metabolic activity.[14]

- *In vitro*, caspofungin is fungicidal against *Candida* spp. and fungistatic against *Aspergillus* spp., in that it inhibits growth and replication of fungal hyphae.[11] Caspofungin has demonstrated little or no fungicidal or fungistatic activity against *Cryptococcus neoformans*, the Zygomycetes, *Fusarium* spp., or *Trichosporon beigelii*,[11] and has mixed activity against other filamentous fungi.[15] The presence or absence of *in vitro* activity, however, may not necessarily correlate with a lack of *in vivo* activity.[12]
- Caspofungin activity against *Candida* spp. is dose dependent.[11] The drug is active *in vitro* against a range of *Candida* isolates, including those with multiple resistance transport mutations, or with acquired or intrinsic resistance to fluconazole, amphotericin B, and 5-flucytosine.[8]
- Surveillance studies conducted since 2001 in >7500 clinical isolates indicate that caspofungin is active against a wide range of *Candida* spp. *in vitro* (table I).[16-20] MIC_{90} (minimum concentration required to inhibit 90% of organisms) values were ≤1 μg/mL against *C. albicans*, *C. glabrata*, *C. tropicalis*, *C. lusitaniae*, and *C. kefyr*, and ≤2 μg/mL against *C. parapsilosis*, *C. krusei*, and

C. guilliermondii. At breakpoint (≤2 μg/mL), caspofungin inhibited 95–100% of isolates (table I).

- The predominant species collected during a large, global surveillance study were *C. albicans* (54% of isolates), *C. parapsilosis* (14%), *C. glabrata* (14%), and *C. tropicalis* (12%).[16] There was no evidence of geographic variation in activity or change in susceptibility to caspofungin or the other echinocandins assessed (anidulafungin and micafungin) during the 6-year assessment period.
- In an *in vitro* study of 197 clinical isolates of *Candida* spp. collected from pediatric hospital patients in 2003, caspofungin showed good activity against *C. albicans*, *C. parapsilosis*, *C. glabrata*, *C. tropicalis*, and *C. lusitaniae*, with MIC_{90} values of 0.25–0.5 μg/mL (read at 24 hours).[21] At an MIC of ≤1.0 μg/mL, caspofungin inhibited 98–100% of isolates.
- The *in vitro* antifungal activity of caspofungin against the *Candida* spp. shown in table I was generally similar to or greater than that of other antifungal agents, such as amphotericin B, fluconazole, voriconazole, and posaconazole, in surveillance studies[18-20] and in isolates from pediatric patients.[21]
- A clinical study investigating caspofungin safety in pediatric patients with proven esophageal candidiasis, proven invasive candidiasis, or proven/probable invasive aspergillosis, discussed in section 4, also reported low caspofungin MICs.[22] Most *Candida* spp. isolates (*C. albicans*, *C. parapsilosis*, *C. tropicalis*, *C. glabrata*, *C. lusitaniae*, *C. lambica*, *C. guilliermondii*, and *C. krusei*) had MICs of ≤0.015–0.5 μg/mL; *C. lusitaniae* had an MIC of 1 μg/mL.
- Caspofungin has high antifungal potency *in vitro* against clinical isolates of azole-resistant *C. glabrata*[23] and *C. albicans*.[24] Of the 50 clinical isolates of *C. glabrata* that were resistant to multiple azoles, all demonstrated high susceptibility to caspofungin (MIC at 48 hours was ≤1 mg/L in 100% of isolates).[23] Of the 54 clinical isolates of *C. albicans* that were resistant to one or more azoles, all were associated with a caspofungin MIC_{50} at 24 hours of ≤0.5 μg/mL.[24]
- Caspofungin had a varying postantifungal effect against clinical isolates of *C. albicans* (0–3 hours at 1×MIC,[25] >12 hours at 1–4×MIC,[26] 5.6 hours at 2–8×MIC,[27] and 3.0–8.3 hours at 32×MIC).[25]
- *Aspergillus* spp. appear to be susceptible to caspofungin *in vitro*, with MECs of 0.06–0.12 μg/mL (table I).[15] The *in vitro* antifungal activity of caspofungin against the *Aspergillus* spp. shown in table I was generally similar to or greater than that of other antifungal agents, such as amphotericin B, voriconazole, and posaconazole.[15]
- In the study investigating caspofungin safety in pediatric patients, the four *Aspergillus* spp. isolates (*A. fumigatus*, *A. terreus*, *A. flavus*, and *A. niger*) had MICs of 0.03–0.06 μg/mL.
- Studies using the XXT reduction assay method revealed that echinocandins, including caspofungin, show dose-dependent activity against filamentous fungi, and that to elicit the same effect on fungus metabolism, higher drug concentrations were required against germinated than against non-germinated *Aspergillus* conidia.[14] When a broth microdilution-based method was used, MEC values for caspofungin were 0.5–1 μg/mL against nongerminated and 1 μg/mL against germinated *A. fumigatus*, *A. terreus*, and *A. flavus* conidia.[14]
- Caspofungin had a short postantifungal effect (≤0.5 hours) against *A. fumigatus*.[27]
- Caspofungin has mixed activity against other filamentous fungi. *Penicillium* spp. (table I) and *Paecilomyces* spp. (MEC 0.03–8 μg/mL and 83% susceptible at MEC of ≤1 μg/mL) appear to be susceptible; however, caspofungin showed no activity against *Fusarium* spp., *Rhizopus* spp., and *Mucor* spp. (table I).[15]
- The addition of amphotericin B to a caspofungin antifungal treatment regimen for *C. albicans* or *A. fumigatus* does not appear to have antagonistic effects *in vitro*.[7]
- *In vitro* data have demonstrated a potential synergistic effect of combination therapy with posaconazole and caspofungin against *Aspergillus* spp. and against *C. glabrata*.[6]

In Vivo Antifungal Activity

- Studies involving immunocompetent and immunocompromised animal models of invasive candidiasis have demonstrated fungicidal activity, reduced fungal burden, and extended survival on administration of caspofungin;[7,11] these results were also observed in models of infections caused by azole-resistant *Candida* spp.[7,11] A juvenile mouse model of disseminated candidiasis with CNS involvement demonstrated caspofungin efficacy equivalent to or better than that of amphotericin B.[28]
- Immunocompetent and immunocompromised animal models of disseminated or pulmonary aspergillosis caused by *A. fumigatus* also demonstrated extended survival on caspofungin administration, despite showing inconsistent effects on fungal burden.[7,11,29,30]
- There was no evidence of antagonism with the combination of caspofungin plus amphotericin B for *C. albicans* or *A. fumigatus* infections in animal models.[7] However, there was no additive effect with the combination in invasive pulmonary aspergillosis caused by *A. fumigatus*.[30] No antagonism between the drugs has been observed for *C. albicans*- or *A. fumigatus*-infected animals.[7]

Table I. *In vitro* activity of caspofungin against clinical strains of molds and yeasts. Results of global[16] or national[17-20] surveillance studies of antifungal susceptibility of *Candida* spp. collected during 2001–6, and *Aspergillus* spp. and other filamentous fungi collected from 20 different centres in the US and Canada during 2000–1.[15] Antifungal activity[a] was assessed using Clinical and Laboratory Standards Institute (CLSI) broth microdilution methods[12,16]

Species	No. of isolates	MIC_{90} 24-h incubation (μg/mL)	MEC_{90} 48-h incubation (μg/mL)	Percent susceptible[b]	References
Candida spp.					
C. albicans	4256	0.06–0.5		100	16-20
C. glabrata	1199	0.06–1.0		99.9	16-20
C. parapsilosis	1152	1–2.0		99.9	16-20
C. tropicalis	834	0.06–1.0		99.8	16-20
C. krusei	218	0.25–2.0		100	16-19
C. guilliermondii	88	1.0–2.0		95.1	16,17
C. lusitaniae	70	0.5–1.0		100	16,17
C. kefyr	58	0.015–0.5		100	16,17
***Aspergillus* spp.**					
A. fumigatus	256		0.06	99.2	15
A. flavus	30		0.06	100	15
A. niger	29		0.06	100	15
A. versicolor	20		0.12	90.5	15
A. terreus	16		0.06	100	15
Other filamentous fungi					
Penicillium spp.	35		0.12	97.4	15
Fusarium spp.	11		>8	0	15
Rhizopus spp.	5		>8[c]	0	15
Mucor spp.	3		>8[c]	0	15

a The tentative CLSI susceptibility breakpoint for caspofungin against *Candida* spp. is ≤2 μg/mL.[12] Interpretive guidelines for *in vitro* susceptibility testing for *Aspergillus* spp. has not been established.[13]

b At breakpoint (*Candida* spp.)[16-20] or at MEC of ≤1 μg/mL (*Aspergillus* spp. and other filamentous fungi).[15]

c Only MEC_{50} values were reported for these species.

MEC = minimum effective concentration; **MEC_{50} or MEC_{90}** = MEC required to show morphological changes in 50% or 90% of organisms; **MIC_{90}** = minimum inhibitory concentration required to inhibit the growth of 90% of organisms.

• Combination therapy with caspofungin and posaconazole had a synergistic effect *in vivo* against *Aspergillus* spp.[6] Mice infected with *A. fumigatus* or *A. flavus* were treated with combination posaconazole and caspofungin; the combination therapy was associated with greater survival than monotherapy with either drug, and no antagonism was observed between the drugs.[6]

Resistance

• Resistance criteria for caspofungin against *Candida* spp. have not yet been established, as there are currently insufficient data to define activity categories other than susceptible or nonsusceptible.[7,12] Development of resistance to caspofungin in *Aspergillus* spp. *in vitro* has not been reported.[8]

• An *in vitro* study demonstrated that the repeated exposure of *C. albicans* to caspofungin (at sub-inhibitory concentrations) for 40 passages did not significantly change the MIC, nor was there any microscopic morphological change.[31] However, there have been reports of *Candida* strains emerging that have elevated MICs correlating with clinical treatment failure following caspofungin exposure.[32,33]

• Mechanisms of *Candida* spp. resistance to caspofungin generally result from gene mutations.[34] Mapping studies in echinocandin-resistant fungal species have shown mutations in the genes coding for the units of the glucan synthase enzyme complex,

such as *FKS1*, implying that these mutations are responsible for drug resistance.[34] Another possible mechanism of caspofungin resistance is the overexpression of *SBE2* (involved in fungal cell-wall formation).[34] However, *FKS1* mutations are the only mechanisms implicated in clinical resistance.[34]

- While it is well established that cross-resistance between caspofungin and fluconazole does not exist, *FKS1*-mutant *Candida* strains resistant to caspofungin are cross resistant to other echinocandins, including micafungin and anidulafungin.[34]
- The cause of the reduced susceptibility (higher MIC values) to caspofungin and other echinocandins observed in *C. parapsilosis*, *C. orthopsilosis*, and *C. metapsilosis* is likely a naturally occurring proline-to-alanine substitution in Fks1p.[35] Clinical isolates of *C. albicans* and *C. glabrata* with this mutation also demonstrated increased caspofungin MIC values.
- Other possible mechanisms of resistance are yet to be defined. A small proportion of isolates (22% of *C. albicans* and 11% of other *Candida* spp.) in a group of studies showed paradoxical turbid growth in *in vitro* studies, when exposed to high concentrations of caspofungin (up to 12.5 μg/mL).[36]
- Similar results have been observed in *Aspergillus* spp.; at higher caspofungin concentrations, a paradoxical increase in metabolic activity of some *Aspergillus* spp. was evident (50% of the maximal increase was detected at a caspofungin concentration of 4.2 μg/mL).[14] However, it appears this paradoxical effect is not related to resistance mechanisms or upregulation, but may be a laboratory-related phenomenon with no relevance in the clinical setting.[34]

2. Pharmacokinetic Profile

Caspofungin pharmacokinetics in pediatric patients have been investigated in two studies: one in older infants and toddlers (aged 3–24 months) with fever and neutropenia[37] and one in neutropenic children (aged 2–11 years) and adolescents (aged 12–17 years).[38] Multiple-dose data from patients receiving caspofungin 50 mg/m^2 once daily as a 1-hour infusion in these studies are reported in this section (n = 9,[37] 10,[38] and 8,[38] respectively). A body surface area-based dosage regimen was selected for pediatric patients because it achieved systemic exposure to caspofungin consistent with values seen in adult patients, whereas a weight-based regimen resulted in suboptimal drug concentrations.[38] Additional data in this section are taken from the manufacturer's prescribing information.[7,8]

- The pharmacokinetics of caspofungin are moderately nonlinear, with increasing accumulation occurring as doses increase; time to reach steady state during multiple-dose administration (14–21 days in healthy men[39]) is dose dependent.[8]
- Following multiple doses of caspofungin 50 mg/m^2/day, in infants/toddlers,[37] children,[38] and adolescents,[38] the pharmacokinetics of caspofungin were generally consistent with values seen in adult patients receiving caspofungin 50 mg/day (figure 1).
- For instance, the least-squares mean area under the concentration-time curve (AUC) from time 0 to 24 hours (AUC_{24}) values were 130, 115, and 117 μg • h/mL, respectively; the concentrations at 1 h (C_1; end of infusion) were 17.2, 15.6, and 12.9 μg/mL, and the concentrations at 24 h (C_{24}; trough concentration) were 1.6, 1.5, and 2.2 μg/mL.[37,38] C_1 values in all three pediatric age groups and AUC_{24} values in infants/toddlers were significantly higher than those in adults ($p < 0.05$), while C_{24} values in children were significantly lower ($p = 0.036$).[37,38] However, these differences were not considered to be clinically significant.[37,38]
- Conversely, patients aged <3 months with documented or highly suspected candidiasis appeared to require a lower dosage of caspofungin than older patients to achieve comparable plasma concentrations.[40] Following multiple doses of 25 mg/m^2/day in these patients, the geometric mean C_1 and C_{24} values were 11.1 and 2.4 μg/mL; the respective geometric mean ratios relative to adult patients with esophageal/oropharyngeal candidiasis receiving 50 mg/day were 1.18 (95% CI 0.95, 1.46) and 1.21 (95% CI 0.90, 1.63). The pediatric patients all received concomitant amphotericin B (either deoxycholate or a lipid preparation) throughout.

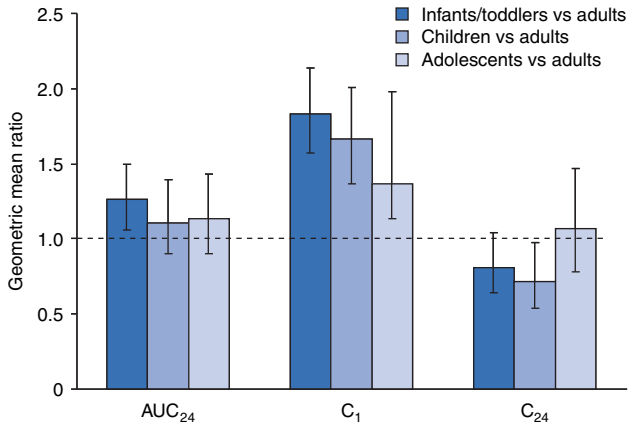

Fig. 1. Comparison of caspofungin pediatric and adult pharmacokinetics. Data from neutropenic infants/toddlers,[37] children,[38] and adolescents[38] (n = 9, 10 and 8, respectively) were compared with historic data from adults (n = 38–60) with oropharyngeal and/or esophageal candidiasis.[37,38] The geometric mean ratio (pediatric : adult) of selected caspofungin pharmacokinetic data for infants/toddlers (aged 3–24 mo),[37] children (aged 2–11 y),[38] and adolescents (aged 12–17 y)[38] versus adults following multiple doses (geometric mean ratios of all values obtained during days 3–14[38] or at day 4[37] are shown). Bars indicate the 95% confidence interval. **AUC_{24}** = area under the concentration-time curve from time 0 to 24 h (μg • h/mL); **C_1** = concentration at 1 h (end of infusion; μg/mL); **C_{24}** = concentration at 24 h (trough concentration; μg/mL).

Caspofungin use is not currently recommended in the US for use in neonates or infants <3 months of age[7] (see section 7), and efficacy data are not available in this patient population.

- Approximately 97% of caspofungin is bound to albumin, and there is only low distribution into red blood cells.[7,8] In plasma, the unbound fraction of caspofungin is 7.6% in patients with invasive candidiasis.[8]
- Distribution is the dominant mechanism influencing plasma clearance of caspofungin.[7,8] After a single 70 mg dose of radioactively labeled caspofungin, ≈92% of the drug was distributed in tissues within 36–48 hours.[7,8] A true volume of distribution cannot be estimated as a distribution equilibrium is not required for elimination; only a small fraction of the caspofungin that was distributed in tissues is believed to return to the plasma as parent compound.[8]
- Caspofungin undergoes slow metabolism by hydrolysis and N-acetylation, as well as spontaneously degrading to L-747969, an open-ring peptide compound.[7] Hydrolysis results in the production of the constitutive amino acids of caspofungin and their degradates, including dihydroxyhomotyrosine and N-acetyl-dihydroxyhomotyrosine, both of which are found only in the urine.[7]
- The elimination of caspofungin is slow, and is characterized by three distinct phases.[7] Immediately following a 1-hour infusion there is a short α-phase, followed by a β-phase with a half-life of ≈8–11 hours (in pediatric patients),[37,38] and, finally, a γ-phase, with a half-life of 40–50 hours (in an unspecified age group).[7,8]
- The multiple-dose β-phase half-life of caspofungin 50 mg/m^2/day among infants/toddlers and children was approximately one-third lower than that of caspofungin 50 mg/day in adults (harmonic means 8.8[37] and 8.2[38] vs 13.0 hours; p-value not reported and $p = 0.002$, respectively). The value of this measure in adolescents (11.2 hours) was not significantly different from that in adults.[38]
- Mean caspofungin clearance among infants/toddlers, children and adolescents did not differ from that among adults at day 1 (6.05–7.78 vs 6.07 mL/min/m^2).[37,38] Plasma clearance appears to be dominated by distribution rather than excretion or biotransformation. While plasma concentrations of radioactively labeled caspofungin were unquantifiable after 6–8 days postdose, overall radiolabeling remained quantifiable for 22.3 weeks postdose.[7]
- A total of 35% and 41% of caspofungin and its metabolites are excreted in feces and urine, respectively.[7,8] Only ≈1.4% of caspofungin is excreted unchanged in the urine.
- There are no pharmacokinetic data available for caspofungin in pediatric patients with renal insufficiency or hepatic impairment. However, in adult patients with invasive aspergillosis, candidemia, or other *Candida* infections receiving caspofungin 50 mg/day, the pharmacokinetics of the drug were unaffected by mild to severe renal impairment; consequently, dosage adjustment is not required.[7] Dosage adjustment is also not required in adult patients with mild or moderate hepatic impairment; the pharmacokinetics of caspofungin in patients with severe hepatic impairment have not been studied.[7]

Drug Interactions

- Caspofungin does not inhibit any cytochrome P450 (CYP) enzyme, is not an inducer of CYP3A4 metabolism of other drugs, and is a poor substrate for CYP enzymes. It is not a substrate for P-glycoprotein.[7,8]
- Caspofungin pharmacokinetics are not altered by concomitant treatment with itraconazole, amphotericin B, mycophenolate, nelfinavir, or tacrolimus, and it does not alter the pharmacokinetics of itraconazole, amphotericin B, or the active metabolite of mycophenolate.[7,8] However, trough concentrations of tacrolimus are reduced by ≈26% when the drug is coadministered with caspofungin. Tacrolimus blood concentrations should be monitored in patients receiving concomitant caspofungin and tacrolimus treatment, and dosage adjustments may be required.[7,8]
- Regression analyses from pediatric pharmacokinetic data show that concomitant treatment with caspofungin and dexamethasone may decrease caspofungin trough concentrations to a clinically meaningful extent.[7,8] This possibility has been extended to other inducers of drug clearance, and has led to the recommendation that clinicians consider administering caspofungin at a dosage of 70 mg/m^2/day (maximum 70 mg/day) in pediatric patients already receiving rifampin (rifampicin), efavirenz, nevirapine, phenytoin, dexamethasone, carbamazepine, or other inducers of drug clearance.[7,8]
- While concomitant administration of caspofungin with cyclosporine (ciclosporin) did not alter cyclosporine plasma concentrations, systemic exposure to caspofungin (assessed using AUC values) increased by ≈35%.[7] This may potentially result in transient increases in ALT and AST levels.[7,8] The manufacturer's prescribing information recommends that concomitant treatment with these drugs should be limited to patients for whom the potential benefit outweighs the potential risk, and close monitoring of liver enzymes is required during concomitant therapy.[7,8]

3. Therapeutic Efficacy

The therapeutic efficacy of intravenous caspofungin at an initial dose of 70 mg/m^2 followed by a daily dose of 50 mg/m^2, not exceeding 70 mg/day, has been evaluated in two multicenter trials, in pediatric patients (aged 3 months to 17 years) with febrile

neutropenia requiring empirical antifungal treatment[41] or fungal infections.[22] The first study was a randomized, double-blind trial comparing the safety and efficacy of caspofungin with those of intravenous liposomal amphotericin B 3 mg/kg/day as empirical antifungal therapy in patients aged 2–17 years with persistent fever and neutropenia, and was published as an abstract,[41] with additional data from the manufacturer's prescribing information.[7,8] The second study was a fully published, noncomparative trial investigating the safety and efficacy of caspofungin in patients aged 3 months to 17 years with esophageal candidiasis, invasive candidiasis, or invasive aspergillosis.[22]

The efficacy of caspofungin as combination therapy with other antifungal medication has not yet been investigated in prospective trials in solely pediatric patients. Combination treatment data available from one prospective, noncomparative study including 'young' patients aged 6–24 years reported potentially positive efficacy for caspofungin in combination with liposomal amphotericin B.[42] This trial is not discussed further.

Empirical Antifungal Therapy

In the trial of the use of caspofungin as empirical antifungal therapy, pediatric patients with persistent fever and neutropenia were randomized to intravenous treatment with either caspofungin (n = 56) or liposomal amphotericin B (n = 26 [one patient was later excluded from analysis as result of not meeting inclusion criteria[7]]).[7,41]

Randomization was stratified based on whether patients were considered to have a high (i.e. had relapsed acute leukemia or had undergone allogenic stem cell transplantation[7]) or low risk of fungal infection.[7,41] At baseline, 27% of patients were classified as high risk,[7,41] and 51% had prior antifungal prophylaxis.[41]

While the primary objective of the trial was to assess safety,[41] efficacy was also investigated; however, no statistical comparisons were conducted. Patients who achieved a validated 5-point composite endpoint were considered to have an overall favorable response.[41] The five components were no documented breakthrough fungal infections for 7 days after treatment completion, survival for 7 days after treatment completion, no discontinuation of treatment as a result of drug-related adverse events or lack of efficacy, fever resolution during the neutropenia period, and successful treatment of baseline invasive fungal infections.[7,41] Results are reported in the modified intent-to-treat population.

- Caspofungin was effective as empirical antifungal therapy in pediatric patients aged 2–17 years with persistent fever and neutropenia. Almost half of caspofungin recipients and one-third of liposomal amphotericin B recipients achieved an overall favorable response (figure 2).[7,41] Subgroup analyses indicated that ≈40% of low-risk patients in either treatment group achieved an overall response. However, in the high-risk group, 60% of caspofungin recipients, but none of the liposomal amphotericin B recipients, achieved this outcome (figure 2).[7]

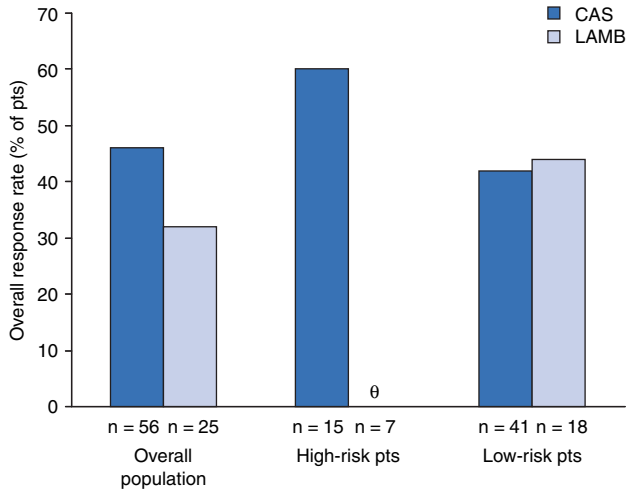

Fig. 2. Efficacy of intravenous caspofungin (CAS) and liposomal amphotericin B (LAMB) as empirical antifungal therapy in pediatric patients (pts). Overall response rates in a randomized, double-blind, multicenter trial in pts (aged 2–17 y) with persistent fever and neutropenia who received CAS at an initial dose of 70 mg/m^2 followed by a daily dose of 50 mg/m^2, not exceeding 70 mg/day (n = 56), or LAMB 3 mg/kg/day (n = 25) in the total population, and in the high- (n = 15 and 7) and low-risk (n = 41 and 18) subgroups. An overall response was defined as meeting a validated 5-point composite endpoint (no documented breakthrough fungal infections for 7 days after treatment completion, survival for 7 days after treatment completion, no discontinuation of treatment as a result of drug-related adverse events or lack of efficacy, fever resolution during the neutropenia period, and successful treatment of baseline invasive fungal infections). Analyses are in the modified intent-to-treat population.[7,41] θ indicates zero.

Treatment of Proven/Probable Fungal Infection

Efficacy data for caspofungin in patients with invasive candidiasis or aspergillosis, or esophageal candidiasis are limited to a single, small study in 48 patients.[22] In this open-label study, patients (aged 3 months to 17 years) who met the European Organization for Research and Treatment of Cancer/Mycoses Study Group criteria for invasive candidiasis, invasive aspergillosis, or esophageal candidiasis received caspofungin as a 1-hour intravenous infusion as either primary or salvage monotherapy.[22] Treatment duration varied, based on immune status, response to treatment, and the underlying medical condition of the patient.[22] The caspofungin dosage could be increased from 50 to 70 mg/m^2/day if there was no response after 4 days of treatment, provided the maximum dosage of 70 mg/day was not exceeded.

Patients with *Aspergillus* infections were required to be refractory to or intolerant of standard antifungal therapy.[22] Previous treatment for invasive aspergillosis included amphotericin B, itraconazole, voriconazole, or amphotericin B plus voriconazole; all patients were refractory to these treatments.[22]

The primary endpoint was the percentage of patients who achieved a favorable response at the end of treatment.[22] The definition of response varied between infection types: in patients with invasive candidiasis, a favorable response was a complete or partial clinical response plus proven (or presumed in non-blood infections) microbiological eradication; in invasive aspergillosis, a favorable response was a complete or partial clinical response; and in esophageal candidiasis, a complete or partial clinical response, based on symptomatic and endoscopic criteria, was required.

The mean age of patients was 8 years (range 6 months to 17 years), and more than two-thirds were aged <12 years. A total of 37 eligible patients had invasive candidiasis (35 with blood infection), 10 had invasive aspergillosis (8 with definite/probable lung infection; 2 of these patients had multiple infection sites), and 1 had esophageal candidiasis.[22]

At baseline, the species of *Candida* causing invasive candidiasis included *C. albicans* (n = 13), *C. parapsilosis* (n = 8), *C. tropicalis* (n = 5), *C. glabrata* (n = 4), *C. lusitaniae* (n = 3), *C. lambica* (n = 2), *C. guilliermondii* (n = 1), and *C. krusei* (n = 1).[22] A microbiologic diagnosis of *Aspergillus* infection is difficult, and other methods are often used to confirm the diagnosis. Only 4 of the 10 patients with invasive aspergillosis had microbiologically proven disease.

The mean duration of caspofungin treatment was 42.7 (range 6–87) days in patients with invasive aspergillosis, 11.8 (2–42) days in those with invasive candidiasis, and 32 days in the patient with esophageal candidiasis.[22] Dose escalation because of non-response at 4 days was required in five patients. Three patients responded to the higher dosage, while treatment was withdrawn from the remaining two patients because of unfavorable response and poor prognosis.

- Caspofungin was effective in pediatric patients with invasive candidiasis or aspergillosis, or esophageal candidiasis.[22] A favorable response was observed in 81% (30 of 37) of patients with invasive candidiasis, 50% (5 of 10) of those with invasive aspergillosis, and in the one patient with esophageal candidiasis.[22] The five patients with invasive aspergillosis who did not respond to caspofungin therapy were either neutropenic at study entry or had received chemotherapy for the underlying condition during the study.
- None of the 34 patients who responded to treatment and were assessed during the follow-up period had a relapse at 14 days after ceasing treatment.[22] At 28 days after ceasing treatment, only one patient (in the invasive candidiasis group) had relapsed.
- In patients with invasive candidiasis, all 10 of those with *C. glabrata*, *C. guilliermondii*, *C. lambica*, and *C. lusitaniae* infections achieved a favorable response. High response rates were also seen in patients with *C. parapsilosis* (88%; 7 of 8 patients) and *C. albicans* (85%; 11 of 13 patients) infections. However, patients with *C. tropicalis* infections had a poor response rate (40%; 2 of 5 patients), and the one patient with a *C. krusei* infection did not respond to treatment.[22] Baseline MICs for these isolates indicated susceptibility to caspofungin (section 2); however, response rates were not related to MIC at baseline.[22]

4. Tolerability

Descriptive tolerability data for intravenous caspofungin in pediatric patients with febrile neutropenia requiring empirical antifungal treatment[41] or fungal infections[22] are available from the two trials discussed in section 4. This section focuses on the results of the comparative study of caspofungin 50 mg/m^2/day versus liposomal amphotericin B 3 mg/kg/day as empirical antifungal therapy in patients aged 2–17 years,[41] including data reported in the manufacturer's prescribing information[7] and the US FDA review and evaluation of caspofungin.[43]

- Caspofungin was generally well tolerated among pediatric patients receiving empirical antifungal therapy.[7,41,43] In the comparative trial, serious drug-related adverse events occurred in 1 of 56 caspofungin and 3 of 26 liposomal amphotericin B recipients. Two caspofungin and three liposomal amphotericin B recipients discontinued treatment as a result of drug-related adverse events.[43]
- Most patients receiving caspofungin or liposomal amphotericin B empirical antifungal therapy reported at least one clinical adverse event (96% vs 89%).[7] The most common (incidence ≥10% in either treatment group) adverse events, including histamine-mediated symptoms such as pyrexia and rash, are shown in figure 3.
- The incidences of clinical drug-related adverse events (48% vs 46%) or laboratory drug-related adverse events (11% vs 19%) did not differ between caspofungin and liposomal amphotericin B recipients.[41]
- Systemic infusion-related adverse events occurring during or up to 1 hour after the infusion were reported in 22% of caspofungin and 35% of liposomal amphotericin B empirical antifungal therapy recipients.[7] Histamine-mediated symptoms, such as rash, facial swelling, pruritus, sensation of warmth, or bronchospasm, have been reported with caspofungin administration,[7,8] including in pediatric patients (figure 3).[7,43]

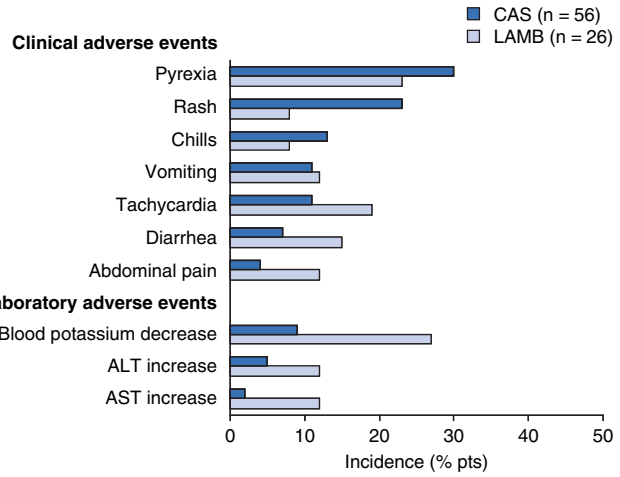

Fig. 3. Tolerability profile of intravenous caspofungin (CAS) as empirical antifungal therapy in febrile neutropenic pediatric patients (pts). Treatment-emergent clinical and laboratory adverse events with an incidence of ≥10% in either treatment group among pediatric pts (aged 2–17 y) receiving empirical antifungal treatment with intravenous CAS (initial dose of 70 mg/m^2 followed by a daily dose of 50 mg/m^2, not exceeding 70 mg/day) or liposomal amphotericin B (LAMB) [3 mg/kg/day].[7]

- Caspofungin was also generally well tolerated among pediatric patients with proven or probable fungal infections. In the study in patients aged 6 months to 17 years with proven esophageal candidiasis, proven invasive candidiasis, or proven/probable invasive aspergillosis, caspofungin was not associated with any serious drug-related adverse events, and no patients discontinued treatment as a result of adverse events.[22] The tolerability profile of caspofungin in this study was consistent with that seen in the trial of caspofungin as empirical antifungal therapy.
- Although tolerability data are limited for treatment durations of longer than 4 weeks, the tolerability of caspofungin appears to continue at a similar level for longer courses (up to 87 days) in pediatric patients.[7]
- There is the potential for abnormalities in liver function tests with caspofungin treatment;[7] however, a causal relationship has not been demonstrated.[7] Elevations in AST and ALT levels were observed in the two trials in pediatric patients.[7,22,41] The US prescribing information recommends monitoring for evidence of worsening hepatic function among patients who develop abnormal liver function test results, and a risk/benefit evaluation should be considered.[7]

5. Dosage and Administration

Caspofungin should be administered as an intravenous infusion over 1 hour.[7,8] The recommended initial dose of caspofungin for pediatric patients is a single 70 mg/m^2 loading dose on day 1, followed by a single daily dose of 50 mg/m^2 from day 2 onwards. The maximum daily dose should not exceed 70 mg, and dosage should be based on the patient's body surface area, calculated by the Mosteller Formula.[7,8]

The duration of caspofungin therapy is dependent on the indication, and is similar to that for specific indications in the treatment of adults.[7,8] Empirical antifungal therapy should continue until neutropenia is resolved; in patients found to have a fungal infection, treatment should last ≥14 days and continue for ≥7 days after neutropenia and clinical symptoms are both resolved. Treatment of candidemia (and other *Candida* infections) should last ≥14 days after the last positive culture; persistently neutropenic patients may require an even longer duration of treatment. Treatment of invasive aspergillosis should continue for a period dependent on the underlying disease severity, immunosuppression recovery, and clinical response of the patient.

Caspofungin use is not currently approved for use in patients aged <3 months in the US.[7]

Local prescribing information should be consulted for detailed information, including contraindications, warnings, precautions, drug interactions, and use in special patient populations.

6. Caspofungin: Current Status in Pediatric Patients with Fungal Infections

In the US, caspofungin is approved for pediatric use (in patients aged 3 months to 17 years) for empirical antifungal therapy in febrile, neutropenic patients; treatment of candidemia and *Candida* intra-abdominal abscesses, peritonitis, and pleural space infections; treatment of esophageal candidiasis; and treatment of invasive aspergillosis in patients who are intolerant of other antifungal treatments or who have treatment-refractory disease.[7]

In the EU, caspofungin is approved for pediatric use for empirical antifungal therapy for presumed fungal infections in febrile, neutropenic patients; treatment of invasive candidiasis; and treatment of invasive aspergillosis in patients who are intolerant of or with disease that is refractory (infection progression or failure to improve after ≥7 days' treatment) to amphotericin B, lipid formulations of amphotericin B, and/or itraconazole.[8]

Clinical trial data demonstrate that caspofungin is effective and generally well tolerated in pediatric patients when used in its approved indications.

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The manuscript was reviewed by: **S.I. Blot**, Department of General Internal Medicine, Ghent University Hospital, Gent, Belgium; **P.H. Chandrasekar**, Department of Infectious Diseases, Wayne State University School of Medicine, Detroit, Michigan, USA.

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