Antifungal Therapy for Invasive Fungal Infection

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ABSTRACT

Globally Invasive fungal infections are on the rise. Invasive mucormycosis and invasive aspergillosis are always considered rare diseases and hence data generated through randomized controlled studies are sporadic. The pharmacotherapeutic options are limited and antifungal development pipeline is dry. Current crisis of Covid Associated Mucormycosis (CAM) has exposed the ground reality of limited options in fungal pharmacotherapy. The pharmacokinetic and pharmacodynamic properties of antifungals are very variable and have important implications in clinical management of patients. Amphotericin B is the most trusted antifungal agent but its different formulations add to complexities. Long duration therapies are difficult to manage due to associated toxicity and non-availability of oral switch. Echinocandins are now a days are the drug of choice against candidemia. They are the safest antifungal class available however they cannot be used for urinary candidiasis which is one of the common forms of invasive candidal infection in India. Voriconazole is being increasingly used now a days as the incidence of invasive aspergillosis has increased in medical ICUs in the patients, who have nontraditional risk factors like COPD. The newer antifungals (Posaconazole and Isavuconazole) have limited toxicities with extended antifungal spectrum. They can be safely used in invasive mould infections for a longer duration. However therapeutic drug monitoring is essential part which is often forgotten due to non-availability of lab assays and cost associated with it.

Introduction :

The incidence of invasive fungal infection has grown over the past few years with significantly increased morbidity and mortality. Despite recent advances in both the diagnosis and prevention of invasive fungal infections (IFIs), the incidence of disease, treatment failure and attributable mortality remains unacceptably high in these group of patients. While amphotericin B deoxycholate has been the main-stay of treatment for IFIs since the early 1950s, treatment options have expanded considerably in the last couple of years. The addition of lipid-based formulations of amphotericin B, expanded-spectrum triazoles (i.e., voriconazole and posaconazole and isavuconazole) as well as the echinocandins has increased options for both prevention and treatment. This article has tried to summarize the place of each antifungal in invasive fungal infection along with other important information for clinical use.

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A. ROLE OF AMPHOTERICIN B IN INVASIVE FUNGAL INFECTIONS :

Amphotericin B exerts its antifungal effect by disruption of fungal cell wall synthesis because of its ability to bind to sterols, primarily ergosterol, which leads to the formation of pores that allow leakage of cellular components. This affinity may also account for its toxic effects against select mammalian cells. Amphotericin B is generally considered cidal against susceptible fungi at clinically relevant concentrations. With the exception of neonatal candidiasis and treatment of Candida urinary tract infections, lipid-based formulations (liposomal amphotericin B) have largely replaced amphotericin B deoxycholate due to their improved tolerability.

Antifungal Spectrum :

Activity of amphotericin B has been demonstrated in vitro against a wide variety of clinical fungal isolates, including most Candida spp, Aspergillus spp, the Mucorales, all of the endemic mycoses, and most hyaline and brown-black molds. Fungal pathogens that are usually resistant to amphotericin B include the organisms that cause Chromoblastomycosis,

Classification of Antifungals

Class	Subclass	Example
Antibiotics	Polyenes	**Ampho B,** Nystatin,
	Heterocyclic Benzofurans	Grisofulvin
	Echinocandins	**Caspofungin, Micafungin, Anidulafungin**
Antimetobolites	NA	Flucytosine
Azoles	Imidazole	Clotrimazole, Ketoconazole
	Triazoles	**Fluconazole, Voriconazole, Posaconazole, Isavuconazole**
Allylamine	NA	Terbinafine
Topical agents	NA	Ciclopirax olamine

Aspergillus terreus, Candida lusitaniae, Scedosporium spp, and some Fusarium spp[1]

Pharmacokinetics[2] :

The drug is highly protein bound and extensively distributed throughout the body, with a volume of distribution of approximately 4 L/kg. Amphotericin B concentrations can be measured in various body tissues and fluids, including liver, spleen, pleural fluid, peritoneal fluid, joint, vitreous body, and aqueous humor. Drug elimination is biphasic, with a terminal half-life of up to 15 days. The primary route of elimination of amphotericin B is not known; urinary and biliary excretion account for less than 5 percent of the administered dose. Serum concentrations are not influenced by hepatic or renal function or by hemodialysis or peritoneal dialysis.

The usual dose for most invasive mycoses is 0.5 to 1 mg/kg per day. Doses exceeding 1 mg/kg per day are generally reserved for treatment of mucormycosis and azole-refractory invasive coccidioidomycosis (such as meningitis). Infusion times are traditionally 4 to 6 hours. Bladder irrigation and intraperitoneal instillation of amphotericin B is no more recommended[1]. Intrathecal administration of amphotericin B deoxycholate in the lumbar subarachnoid space has been used primarily for the treatment of coccidioidal meningitis. However these patients can develop severe arachnoiditis. Intravitreal and intracameral (into the aqueous humor) injection of amphotericin B has become very popular after current epidemic of covid associated mucormycosis.

Adverse effects Amphotericin B

1. ***Infusion-related reactions*** **-** Infusion-related reactions, particularly nausea, vomiting, chills, and rigours, are common with IV amphotericin B deoxycholate administration, usually occurring either during infusion (within 15 minutes to 3 hours following initiation) or immediately following administration of the dose.
2. ***Nephrotoxicity*** **-** IV administration of any formulation of amphotericin B may result in nephrotoxicity. With amphotericin B deoxycholate, a reversible and often transient decline in glomerular filtration rate (GFR) has been described in 5 to 80 percent of patients. Severe renal failure due to amphotericin B deoxycholate alone is less common, but not rare due to other concomitant nephrotoxic therapy.[3]
3. ***Electrolyte abnormalities*** **-** Hypokalemia, hypomagnesemia, and hyperchloremic acidosis are common.
4. ***Other reactions*** **-** A reversible, normochromic, normocytic anemia occurs in most patients receiving IV amphotericin B, but the onset may be delayed for as long as 10

weeks after the initiation of therapy[4]. Other hematologic side effects have also been described, including severe leukopenia.

Is Lipid-based formulations of amphotericin B are better than amphotericin b Deoxycholate ??

These have been introduced in an attempt to reduce the toxicities associated with amphotericin B deoxycholate. In a meta-analysis of randomised trials, the incidence of nephrotoxicity was significantly lower with liposomal amphotericin B compared with amphotericin B deoxycholate (15 versus 33 percent)[5]. A trial comparing liposomal amphotericin B to amphotericin B deoxycholate for empiric therapy in patients with persistent fever and neutropenia found no difference in composite rates of successful treatment and patient outcomes[6]. However, significantly fewer patients given liposomal amphotericin B had breakthrough fungal infections, infusion-related fever, chills or rigours, or nephrotoxicity. This was the first trial to note a reduction in infusion-related reactions associated with the liposomal formulation of amphotericin B.

Liposomal amphotericin B has a lower incidence of infusion-related reactions than amphotericin B deoxycholate. However, a type 1 hypersensitivity reaction (labeled as complement activation-related pseudoallergy [CARPA]) is thought to be a consequence of complement activation with resulting mast cell and basophil secretory response Symptoms develop within five minutes and include chest pain, dyspnea, hypoxia, abdominal pain, flushing, and urticaria.[7]

Due to primarily its long half-life, the dosing interval for liposomal amphotericin B can be extended to three times weekly (ie, 5 mg/kg three times weekly).This is important when patient still requires continuation of treatment but adverse effects need to be mitigated.

B. ROLE OF FLUCYTOSINE IN FUNGAL INFECTIONS

Flucytosine (5-FC) exerts its antifungal effects by interfering with both DNA and protein synthesis.

Antifungal spectrum :

5-FC has activity in vitro against Cryptococcus neoformans, many Candida spp, Rhodotorula spp, Saccharomyces cerevisiae, most of the organisms responsible for chromoblasto-mycosis, and some dematiaceous fungi. Approximately 25% of Candida albicans isolates are resistant to flucytosine, but most C. glabrata isolates are susceptible.[1]

Clinical use of flucytosine[8] :

5-FC (in combination with amphotericin B deoxycholate or a lipid formulation of amphotericin B) is the induction therapy of choice for cryptococcal meningoencephalitis and severe cryptococcal pneumonia. The favourable pharmacokinetics of flucytosine in the urinary tract and proven efficacy in a variety of forms of urinary tract candidiasis make it a consideration for patients who are able to take oral medications and for whom fluconazole cannot be used.

Due to a high incidence of primary and/or acquired resistance, use of flucytosine as monotherapy is significantly restricted.

Summary of Pharmacokinetic features of different formulation of Amphotericin B

	Amphotericin B - Deoxycholate	Liposomal Amphotericin B	Amphotericin B Lipid Complex	Amphotericin B Colloidal Dispersion
Dose	0.1 - 1 mg / kg	3 - 5 mg / kg	5 mg / kg	3 - 4 mg / kg
Nephrotoxicity	High	Low	Low	Low
Infusion Reaction	High	Mild	Moderate	Moderate
AUC		High	Low	Low
Tissue concentration	High	Low	high	High

Pharmacokinetics and adverse effects :

Approximately 80 to 90 percent of 5-FC is absorbed following oral administration. The usual dosing of 5-FC in patients with normal renal function is 25 mg/kg orally every six hours. Dose modification is necessary in patients with renal dysfunction. The most significant toxicities of 5-FC are hematologic, hepatic, and gastrointestinal

C. ROLE OF AZOLES IN INVASIVE FUNGAL INFECTION

The drugs in this class offer activity against many fungal pathogens without the serious nephrotoxic effects observed with amphotericin B. The azole antifungals work primarily by inhibiting the cytochrome P450-dependent enzyme lanosterol 14-alpha-demethylase. The triazoles are generally considered fungistatic against Candida species. For Voriconazole, fungicidal activity against Aspergillus species has been demonstrated.

Antifungal spectrum :

The introduction of posaconazole and isavuconazole has expanded the spectrum of the azole agents to include the Mucorales while maintaining activity against yeasts and moulds

Clinical use[2] :

Agents within the azole class vary importantly with regards to spectrum of activity, pharmacokinetic profiles, and toxicities. Fluconazole has excellent activity against yeasts but offers no activity against molds. An extended spectrum is provided by itraconazole, but inconsistent bioavailability limits use of this agent in severely ill patients. Voriconazole is the first-line agent for the treatment of invasive aspergillosis, but its bioavailability is unpredictable and genetically determined, it is associated with unique side effects, and it lacks activity against the Mucorales. Among the azoles, posaconazole and isavuconazole have the broadest spectrum of activity. Both are available as intravenous and oral formulations. The azoles have significant drug-drug interactions.

Pharmacokinetics[9] :

No two triazole agents offer the same pharmacokinetic profile. It is important to know the differences in bioavailability, metabolism, and toxicities among these agents.

Fluconazole :

A single dose of fluconazole is widely distributed into body fluids and tissues, with only 10 to 12 percent being protein bound. High concentrations can be measured in urine as well as prostatic tissues. Fluconazole distributes well into the cerebrospinal fluid (CSF), with levels reaching 60 to 80 percent of serum levels. The long serum half-life (approximately 24 hours) allows once-daily dosing. Fluconazole dose

Antifungal Spectrum of Azoles

	FLU	ITRA	VORI	POSA	ISAVU
Candida	+++	++	++	++	++
C glabrata	++	+	++	++	++
C. krusei	-	+	++	++	++
Cryptococcus	++	++	++	++	++
Sporothrix	-	++	++	++	++
Aspergillus	-	+	++		
Dematiaceous Fungi	-	++	++	++	++
Scedosporium	–	+	+	+	+
Fusarium	-	+	++	++	++
Mucorales	-	-	-	++	++

adjustments are necessary in patients with compromised renal function.

Itraconazole :

The bioavailability of itraconazole is highly variable. The capsule formulation has a bioavailability of approximately 55%. Itraconazole capsules require food and an acidic gastric pH for absorption. Impaired absorption is greatest with proton pump inhibitors. Unbound itraconazole is highly lipophilic and extensively distributed in human tissues, reaching high concentrations in the lungs, kidneys, and epidermis . High levels are observed in the skin, nails, liver, adipose tissue, and bone.

Voriconazole :

The oral tablet formulation of voriconazole has a bioavailability of greater than 90%. Administration on an empty stomach, one to two hours before or after a meal, is preferable. The use of the intravenous preparation is limited to patients who have CrCl > 50 mL/min due to beta cyclodextrin vehicle which can be nephrotoxic.

CYP2C19 gene polymorphisms appear to play an important role in the inter individual variability that has been observed with voriconazole[10]. Voriconazole is also an inhibitor of cytochrome P450 3A4. Drug interactions should be anticipated and managed. Urine concentrations of voriconazole do not reach therapeutic levels and should not be relied upon to treat urinary tract infections. Voriconazole trough concentrations should be checked four to seven days into therapy for all patients who are receiving treatment for invasive fungal infections. A goal of achieving serum trough concentrations > 1 mcg/mL and < 5.5 mcg/mL has been suggested[11]

Posaconazole - Posaconazole is available as an oral suspension**,** delayed-release tablets and IV formulation for the prophylaxis of invasive Aspergillus and Candida infections in patients at high risk for these infections, such as those with haematological malignancies with prolonged chemotherapy-induced neutropenia and hematopoietic cell transplant recipients with graft-versus-host disease.

Effective absorption of the oral suspension requires oral intake, optimally with a high-fat meal. For the delayed-release tablets, administration with food is recommended; however, this formulation demonstrates less variability in pharmacokinetic parameters related to food when compared with the oral suspension. Other studies have shown that patients taking the delayed-release tablets achieve higher serum concentrations than patients taking the oral suspension.[12]

The elimination half-life of the active (parent) compound of the oral suspension is approximately 27 hours in patients with normal hepatic function. unchanged parent drug is primarily eliminated via the fecal route (77 percent). Therefore, only minimal amounts are recovered in the urine; the drug cannot be relied upon to treat urinary tract infections, and dose reductions are not required for patients with renal insufficiency.

Posaconazole concentration monitoring is desired, trough concentrations should be obtained after four to seven days of therapy. A trough concentration = 0.7 mcg/mL for prophylaxis and at least 1.0 mcg/mL for the treatment of severe infections[13]

Isavuconazole[14] :

It is formulated as the prodrug, isavuconazonium sulfate, and it is available as an IV formulation and an oral formulation (capsules). Isavuconazole has a prolonged half-life (T½) of 130 hours, which enables once-daily dosing following two days of every eight hour dosing (six loading doses), and has as a large volume of distribution of about 450 L, suggesting a high degree of tissue penetration . The oral capsules are well absorbed with an absolute bioavailability of 98 percent that is essentially unaltered by food intake. Isavuconazole clearance is highly dependent upon hepatic CYP3A4 metabolism and thereby subject to significant drug interactions.

Adverse effects :

Gastrointestinal (GI) symptoms are most frequently reported, including nausea, abdominal pain, vomiting, and diarrhea. Hepatotoxicity is the main concern with azole therapy. These range from mild elevations in transaminases to severe hepatic reactions including hepatitis, cholestasis, and fulminant hepatic failure. The approximate incidence of mild transient transaminase abnormalities associated with azole drugs is reported to be from 2 to 12 percent. Careful monitoring of liver enzymes is recommended for all patients receiving azole therapy, since this adverse effect does not appear to be associated with duration of antifungal therapy or other identifiable risk factors. High-dose therapy, drug interactions, and genetic polymorphisms that increase systemic exposure to azoles may increase the risk of hepatotoxicity.

Voriconazole Associated Toxicities[2] :

Voriconazole is associated with several unique adverse reactions; these include

- Transient vision changes,
- Photosensitivity rash,
- Alopecia,
- Periostitis,
- Visual hallucinations (serum concentrations of voriconazole > 5.5 mcg/mL).
- Neurologic toxicity may also have confusion, agitation, myoclonic movements, and auditory hallucinations.
- Peripheral demyelinating neuropathy of the lower extremities, reported mostly in transplant recipients who are also taking tacrolimus.[15] (Rare side effect)
- Cardiac toxicity - Cases of QT prolongation, torsades de pointes, cardiac arrest, and sudden death

Posaconazole Associated Toxicities - Gastrointestinal symptoms are commonly noted with the oral suspension. Incidence of QTc prolongation was described as occurring in 1 percent of 428 patients treated for neutropenic fever or refractory invasive fungal infection in phase II and III clinical trials.[16] Posaconazole can interfere with the steroid synthesis pathway and this can present as adrenal insufficiency.[17]

Isavuconazole Associated Toxicities - The most common adverse reactions associated with isavuconazole are nausea, vomiting, diarrhea, headache, elevated transaminases, hypokalemia, and peripheral edema. Isavuconazole may also cause serious side effects including hepatotoxicity and infusion reactions (chills, dyspnea, and hypotension). In a phase II trial that compared isavuconazole with voriconazole for the treatment of mold infections, drug-related side effects were lower with isavuconazole than voriconazole (42 versus 60 percent)[18]. Isavuconazole is associated with shortening of the QT interval (in contrast with most other azoles, which cause prolongation of the QT interval.

D. ROLE OF ECHINOCANDINS IN INVASIVE FUNGAL INFECTIONS :

The development of echinocandins, the first class of antifungals to target the fungal cell wall, was a milestone achievement in antifungal chemotherapy. Three semi-synthetic echinocandin derivatives have been developed for clinical use: caspofungin, micafungin, and anidulafungin.

Beta-glucans and the intracellular beta-glucan synthase complex blocked by echinocandins are not present in human cells. For this reason, the echinocandins cause less collateral toxicity than amphotericin B formulations or the triazoles and are implicated in fewer drug-drug interactions.

Antifungal spectrum[1] :

However, the echinocandins are primarily effective against Candida and Aspergillus species, with relatively weak activity against other molds and yeasts, including Cryptococcus neoformans. All three of the echinocandins exhibit excellent potency against Candida spp C. albicans, C. glabrata, and C. tropicalis are

highly susceptible to all three agents, whereas elevated minimum inhibitory concentrations (MICs) have been seen for C. parapsilosis and C. guilliermondii. Worldwide surveillance data from the SENTRY program (2016 to 2018) have reported echinocandin resistance rates ranging from 2.1 to 3.2 percent[19]. Most Candida auris isolates are susceptible to the echinocandins. Echinocandins are unique among the systemic antifungal agents in their activity against biofilm-embedded Candida species e.g (prosthetic device or catheter-associated infections). Echinocandins lack clinically useful activity against Cryptococcus neoformans, and Cryptococcus gattii, dimorphic fungi. It has weak activity against aspergillus and other molds.

Clinical use[2] :

Echinocandins are widely used for the treatment of invasive candidiasis, especially in critically ill and neutropenic patients. They are also used for empiric antifungal therapy in patients with neutropenic fever. They are also used in combination with a triazole for the initial treatment of invasive aspergillosis or as part of a combination antifungal regimen as salvage therapy of invasive aspergillosis. The major advantage of echinocandins relative to other antifungal agents is their fungicidal activity against Candida spp, including fluconazole-resistant C. glabrata and C. krusei, combined with their relatively low potential for renal or hepatic toxicity or serious drug-drug interactions Caspofungin has been approved in children over 3 months of age. Caspofungin has also been FDA approved as an empiric antifungal agent for febrile neutropenia and for salvage therapy of invasive aspergillosis in patients who have failed or are intolerant of other antifungal agents in adults and children over 3 months of age.

Pharmacokinetics[20] :

All 3 echinocandins exhibit a high degree of binding to plasma proteins and distribute minimally to cerebrospinal fluid, urine, and the eye. Echinocandins are not primarily metabolized by cytochrome P450. Dose adjustment is unnecessary for patients with renal insufficiency. However, dose reduction for severe hepatic insufficiency is recommended. Several drugs induce metabolism of caspofungin : rifampin, nevirapine, efavirenz, carbamazepine, dexamethasone & phenytoin

Use in Hepatic insufficiency Anidulafungin is inactivated by gradual spontaneous degradation and not metabolized hepatically; therefore, dose adjustment for hepatic insufficiency is not needed. Micafungin does not require dose reduction for mild or moderate hepatic insufficiency, and no recommendation is available for use in severe hepatic insufficiency. For moderate hepatic insufficiency (Child-Pugh class B; score 7 to 9), the prescribing information recommends no reduction in the loading dose but a reduction in the maintenance dose to 35 mg once daily. No recommendation is available for use in severe hepatic insufficiency (Child-Pugh score > 9).

Important drug interactions[21] :

Echinocandins generally have a lower risk for pharmacokinetic drug-drug interactions compared with other systemic antifungals. Caspofungin decreases tacrolimus serum concentrations by approximately 20 percent; however, no additional interventions are recommended beyond routine monitoring of tacrolimus blood levels, and dosage adjustment is necessary to avoid effects of subtherapeutic levels, including acute graft rejection. Micafungin modestly reduces the clearance of cyclosporine, sirolimus (rapamycin), and nifedipine. Among the echinocandins Anidulafungin does not alter the metabolism or clearance of cyclosporine. This information is important to remember while using echinocandins in post liver transplant patients.

Summary :

Amphotericin B is still a gold standard broad spectrum antifungal agent which has proved its worth in current pandemic of covid associated mucormycosis. The liposomal form is the most

suitable form for therapy due to its remarkable pharmacokinetic superiority over all other formulations and ability to continue long term treatment with less adverse effects.

Flucytosine is the suitable oral drug to treat urinary candidiasis. The newer azoles like posaconazole and isavuconazole are the most promising drugs in the armamentarium of antifungal therapies. Lot of data is still coming for isavuconazole and non inferiority trials with amphotericin B are underway. It has few drug drug interaction and no major adverse effect on organ system with an advantage of availability of effective oral formulation. Echinocandins are the first line cidal therapy for all forms of invasive candidiasis.

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