ANTIFUNGAL CHEMOTHERAPY

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I. INTRODUCTION

Invasive fungal infections are associated with significant morbidity and mortality despite the availability of antifungal therapy. Globally it is estimated that life-threatening fungal infections occur in over 6.5 million people each year and account for approximately 2.5 million deaths.(1) These infections are more common in immunocompromised patients, thus increasing the reliance on active antifungal therapy to clear infections.

Treatment of invasive fungal infections often requires early initiation of antimicrobial therapy to decrease the patient's risk for significant morbidity and mortality.(1,2) As fungi are eukaryotes, identifying drug targets that do not effect mammalian cells has limited drug development. Treatment of systemic infections is limited to four primary groups of antifungals: amphotericin B, flucytosine, azoles and echinocandins. Terbinafine, griseofulvin and ibrexafungerp are three additional systemic antifungals used to treat superficial infections. Of the available options, these antifungals each have considerations for safety, drug interactions or are limited by route of administration. Additionally, antifungal exposure in healthcare or in the environment as fungicides can increase the risk of antifungal resistance (3,4), making it more difficult to start patients on appropriate therapy. The therapeutic options for treatment of fungal infections are detailed below and their use is further summarized in Table 1.

II. ANTIFUNGAL AGENTS

Amphotericin B

1. **Overview and Mechanism of Action:** First licensed in 1959 as amphotericin B deoxycholate, amphotericin B is a broad-spectrum antifungal agent often reserved for infections where other antifungals are inactive, inappropriate or unavailable. Amphotericin B is a polyene macrolide molecule produced by *Streptomyces nodosus.* It acts by insertion into the fungal cytoplasmic membrane and sequesters ergosterol from lipid bilayers which ultimately leads to cell death (5). There are four commercially available amphotericin B products for intravenous administration: amphotericin B deoxycholate (ABD), amphotericin B colloidal dispersion (ABCD; no longer marketed in the United States), amphotericin B lipid complex (ABLC), and liposomal amphotericin B

(L-AmB). While there is no difference in antifungal activity between products, the pharmacokinetic and adverse effect profiles between products do vary.

2. **Therapeutic Uses and Resistance:** Amphotericin B is active against most pathogenic fungi, including *Candida* spp., *Crypococcus neoformans*, *Aspergillus* spp., *Fusarium* spp., Mucorales, *Coccidioides* spp., *Histoplasma capsulatum,* and *Blastomyces dermatitidis*. While the development of resistance is rare in typically susceptible isolates, it is likely due mutations in genes responsible for ergosterol biosynthesis leading to decreased interaction of amphotericin B with the fungal cell membrane.(4) Additionally, alterations in ergosterol biosynthesis genes, ERG2, ERG 3, ERG5, ERG 6, and ERG 25, can also lead to reduced susceptibility or tolerance in *Candida albicans.* Intrinsic resistance to amphotericin B is common in *Candida lusitaniae, Aspergillus terreus, Scedosporium* spp., and *Trichosporon asahii*.

3. **Adverse Effects:** The adverse effect profile of amphotericin B administration limits first-line use for many fungal infections where other less toxic agents can be used. Infusion-related reactions, which can include fever, chills, rigors, hypoxia and arthrlagias, and nephrotoxicity are among the most common adverse effects of the conventional ABD preparation. Related to nephrotoxicity, azotemia and hypokalemia can also be seen. Lipid preparations like ABLC and L-AmB have demonstrated lower rates of both of these adverse effects compared to ABD (6). ABCD has demonstrated an overall decrease in the rate of nephrotoxicity, infusion-related reactions, however, were reported more frequently with ABCD compared to ABD (7). Other reported adverse effects include headache, nausea, vomiting and anemia.

Flucytosine

1. **Overview and Mechanism of Action:** Flucytosine is an oral antifungal with utility primarily limited to the treatment of cryptococcal infections in combination with amphotericin B. It is deaminated by fungal cytosine deaminase to 5-fluorouracil (5FU), a potent antimetabolite agent used for cancer chemotherapy. 5FU is further metabolized to 5-fluorouridine triphosphate which blocks fungal protein synthesis through incorporation into fungal RNA, and fluoro-deoxyuridine monophosphate which inhibits thymidylate synthetase thereby causing inhibition of fungal DNA synthesis.

2. **Therapeutic Uses and Resistance:** Flucytosine has demonstrated broad *in vitro* susceptibility for *Candida* spp. and *Cryptococcus neoformans*, and dematiaceous molds, but lacks activity for many molds including *Aspergillus* spp. and Mucorales (8).

   Resistance to flucytosine commonly develops when it is used as a single agent. Its role is typically limited to combination therapy for the treatment of cryptococcal meningitis along with amphotericin B. Some mechanisms of resistance have been described and include point mutations in FCY1, FCY2 and FUR1. Single point mutations in the FCY1 gene are common in *Candida* spp. and can result in alterations in cytosine deaminase, an enzyme responsible for converting flucytosine to 5FU (9). Mutations in FCY2 gene can lead to a deficiency in cytosine permease. This deficiency leads to an overall decrease in uptake of flucytosine by the fungal cell membrane. FUR1 encodes for uracil phosphoribosyltransferase. Mutations in this gene can lead to imitation conversions of flucytosine to 5-fluorouridine monophosphate, an active metabolite of flucytosine (8).

3. **Adverse Effects:** Mammalian cells are unable to deaminate flucytosine to its active 5FU which limits the adverse effect profile of the medication. The conversion of flucytosine to 5FU in the gastrointestinal tract by host microbiome is a likely mechanism for many of the adverse effects seen with administration of flucytosine. A more serious adverse effect seen is bone marrow suppression leading to leukopenia and thrombocytopenia. Other adverse effects include rash, nausea, vomiting, and diarrhea.

Azole Antifungals

1. **Overview and Mechanism of Action:** The azole antifungals are comprised of two main groups: triazoles and imidazoles. Triazoles, which include fluconazole, itraconazole, voriconazole, posaconazole and isuvaconazole, are the primary group of azoles used to treat invasive fungal infections. The imidazole group, which consists of ketoconazole, miconazole, clotrimazole, butoconazole, econazole, sertaconazole, tioconazole, efinaconazole and luliconazole, are primarily used as topical agents to treat superficial fungal infections and will not be discussed further in this chapter. Oteseconazole, a tetrazole is a newly approved long-acting azole antifungal developed for use in treatment and prevention of vulvovaginal candidiasis in patients with frequent recurrences. All azole antifungals bind and inhibit ERG11, the gene responsible for expression of 14-α-sterol demethylase, also known as cyp51, a cytochrome P450 enzyme responsible for metabolizing lanosterol to ergosterol. The result is a reduction in ergosterol and the accumulation of a toxic byproduct, 14-α-methyl-3,6-diol that stops fungal replication.

2. **Therapeutic Uses and Resistance:** The antifungal spectrum of activity varies by triazole agent. As a group, azoles have clinical activity against *C. albicans*, *C. tropicalis*, *C. parapsilosis*, *C. neoformans* and dimorphic fungi. *C. kruseii* and *C. auris* is resistant to fluconazole. Additionally, all triazoles have some activity for *C. glabrata*, however resistance is common. Fluconazole lacks activity against molds, whereas the other triazoles are against have activity against *Aspergillus* spp. and *Fusarium* spp. Posaconazole and isavuconazole also have activity against Mucorales.

   In *Candida* spp., azole resistance may occur through one of multiple mechanisms. Commonly, mutations in ERG11 prevent binding of the azole at the enzymatic site. Multiple genes coding for efflux pumps that decreases azole concentrations at the site of action can also be seen. CDR1 and CDR2 can code for these pumps and decrease susceptibility broadly to all azoles, whereas, MDR-encoded efflux pumps are generally specific for fluconazole (10). Up regulation of ERG11 has also been described but is not thought to contribute widely to resistance in *Candida* spp (11). A mutation in ERG3 can lead to bypass pathway for fungal replication. In these mutations, the formation of 14-α-methyl-3,6-diol is prevented and 14α-methylfecosterol is produced instead (12). This product replaces ergosterol in the now functional cell membrane. This mutation can lead to cross resistance with amphotericin B due to the depletion of ergosterol from the cell membrane.

   Similar mechanisms of resistance in *Aspergillus* species have also been described. In *Aspergillus fumigatus*, efflux pumps coded by the atrF gene leads to a reduction in azole exposure (13). Amino acid substitutions in the cyp51a and cyp51b genes, can lead to conformational changes that inhibit azole antifungals from binding and inhibiting 14-α-

sterol demethylase in *Aspergillus* (14). Additionally, overexpression on cyp51a leading to resistance in *A. fumigatus* to all azole antifungals has also been described. (15).

3. **Adverse Effects:** Overall azole antifungals have some differences with regards to safety. All azole antifungals interact with cytochrome P450 enzymes and can have significant drug interactions. Azole antifungals can also cause elevations in liver transaminases and have been shown to cause fetal malformations when given in pregnancy. With the exception of isavuconazole, most azole antifungals will also cause QT prolongation.

   Fluconazole is overall well tolerated but cases of nausea, vomiting, headache and rash have been reported. Additionally, alopecia has been known to occur with prolonged administration of 400 mg daily. Itraconazole has some serious adverse effects.

   Itraconazole has negative inotropic effects that can lead to symptoms or worsening of heart failure symptoms (16). Itraconazole can also cause hypokalemia, QT prolongation, and serious hepatoxicity. Oral formulations of itracolazole have variable absorption and the oral suspension is known to cause nausea, diarrhea, and abdominal cramping to a greater extent than the capsules.

   Voriconazole is metabolized by cytochrome P450 isoenzymes 2C19, 2C9, and 3A4. Significant variation in the expression of CYP2C19 occurs within the population such that wide variability in metabolism of voriconazole can occur. Poor metabolizers will be prone to significant toxicity where rapid metabolizers are at higher risk for therapeutic failure. For patients receiving prolonged treatment with voriconazole, therapeutic drug monitoring is recommended and pharmacogenomic testing to assess CYP2C19 expression may also be considered (17). Visual disturbances and toxicities of the central nervous system such as hallucinations, mental status changes and confusion, may occur and are more likely at high concentrations (18.). The intravenous formulation is co-formulated with sulfabutylether-β-cyclodextrin (SBECD). SBECD may be toxic to the kidney with accumulation and should be used with caution in patients with reduced renal function (creatinine clearance < 50 ml/min) although multiple studies in humans have failed to show an association (19, 20). Phototoxic rash may also occur while on therapy and has been associated with the development of squamous cell carcinoma (21).

   Gastrointestinal effects such as nausea, abdominal pain, diarrhea and vomiting, occur with posaconazole in approximately one-third of patients. While newer, isavuconazole appears to be fairly well tolerated. Constipation and other gastrointestinal effects, cough, hypokalemia and pyrexia are among the most common adverse effects reported. Also, while the clinical significance remains unclear, isavuconazole may also cause a shortening of the QT interval.

   Ketoconazole is no longer recommend for systemic treatment of fungal infections due to toxicities that can occur as a result of its inhibition of testosterone and cortisol at therapeutic doses. Ketoconazole is known to cause gynecomastia, sexual dysfunction, menstrual irregularity and adrenal insufficiency.

Echinocandins

1. **Overview and Mechanism of Action:** Echinocandins are generally well tolerated antifungals that work by inhibiting 1,3-β-D-glucan synthesis which leads to a reduction of cell wall integrity and cell death. Echinocandins bind to the Fks1p subunit of the glucan synthase complex which results in cell death seen with these agents. The echinocandin class includes caspofungin, micafungin, anidulafungin and the long-acting rezafungin.

2. **Therapeutic Uses and Resistance:** The spectrum of activity is similar throughout the class. They all have fungicidal activity against *Candida* species with some reduction in activity for *C. parapsilosis* and *C. guillermondii*. There is also activity against actively dividing *Aspergillus* spp. Echinocandins lack therapeutic activity for *Cryptococcus neoformans*, Mucorales, *Fusarium* spp., dimorphic fungi, or *Trichosporon asahii*.

   Resistance to echinocandins remains relatively low for *C. albicans* and most other *Candida* species. However, resistance in *C. glabrata* is increasingly reported (22,23). Of the *C. glabrata* that are resistant to echinocandins, approximately one-third are also resistant to fluconazole (24). Resistance in echinocandins is attributed to amino acid substitutions in the Fks subunits of the glucan synthase complex (25). FKS mutations will typically occur in two "hot spot" regions of FKS1 in *C. albicans* and *C. auris* and mutations can occur in either or both FKS1 and FKS2 in *C. glabrata* leading to resistance. *C. parapsilosis* and *C. guillermondii* have naturally occurring FKS polymorphisms that lead to the reduced susceptibility and increased MICs seen with these species.

3. **Adverse Effects:** These agents have been shown to be generally well tolerated. Gastrointestinal effects and histamine release during infusion may occur. Lengthening the infusion time may shorten the likelihood of histamine release. Elevations in aminotransferase and alkaline phosphatase may also occur.

Terbinafine

1. **Mechanism of Action:** Terbinafine inhibits squalene epoxidase that leads to accumulation of squalene in the fungus which can interfere with ergosterol and lead to cell death.

2. **Therapeutic Uses and Resistance:** Oral terbinafine accumulates in keratinized tissues and is primarily used for treatment of onychomycosis. Terbinafine has activity against dermatophytes.

3. **Adverse Effects:** Terbinafine is well tolerated. In some cases, terbinafine can cause photosensitivity, mild gastrointestinal effects, and headache. In rare cases, terbinafine can cause severe hepatotoxicity.

Griseofulvin

1. **Mechanism of Action:** Griseofulvin was first isolated from *Penicillium griseofulvum* in 1939. It has fungistatic activity that causes disruption of microtubule assembly of some fungi.

2. **Therapeutic Uses and Resistance:** Griseofulvin is an oral medication with clinical antifungal activity is primarily against dermatophytes including *Microsporum* spp., *Trichophyton* spp. and *Epidermophyton* spp; thus it is most clinically useful in superficial fungal infections.

3. **Adverse Effects:** Griseofulvin can cause gastrointestinal irritation leading to nausea, vomiting and diarrhea. Headaches, allergic reactions and photosensitivity may also be seen. Griseofulvin may worsen porphyria and lupus, and should be avoided in patients with either of these conditions. In rare cases, anemia and hepatotoxicity have occurred.

   Patients on griseofulvin should avoid alcohol as disulfiram-like reactions have been reported. Griseofulvin can also induce cytochrome P450 isoenzymes which can lead to drug interactions with multiple agents including warfarin.

Ibrexafungerp

1. **Mechanism of Action:** Ibrexafungerp is a newer oral triterpenoid antifungal (or "fungerp") that also works by inhibition of 1,3-β-D-glucan synthesis, similar to echinocandins.

2. **Therapeutic Uses and Resistance**: While currently only approved for the treatment and prevention of recurrent vulvovaginal candidiasis, ibrexafungerp is being studied for the treatment of invasive candidiasis. Similar to echinocandins, ibrexafungerp has broad coverage against *Candida* species including more resistant species like *C. glabrata*. Ibrexafungerp also has in vitro activity against *Aspergillus* spp., however additional clinical experience with this.

   Ibrexafungerp has been shown to retain activity against some strains of echinocandin-resistant *C. glabrata* although certain FKS mutations which result in echinocandin resistance can also lead to reduced susceptibility (26,27) . Additionally, novel mutations in FKS genes, primarily within FKS2, can also lead to reduced susceptibility or resistance in *C. glabrata*. (27)

3. **Adverse Effects:** Ibrexafungerp is overall well tolerated with gastrointestinal adverse effects being the most commonly reported.

Table 1: Summary of Chemotherapy of Fungal Infections

Class or Agent	Therapeutic Uses	Adverse Effects
Amphotericin B formulations: Amphotericin B deoxycholate (ABD) Amphotericin B Colloidal Dispersion (ABCD) Lipisomal amphotericin B (LAmB) Amphotericin B Lipid Complex (ABLC)	Invasive candidiasis Cryptococcosis Mold infections including invasive aspergillosis and mucormycosis Blastomycosis Coccidioidomycosis Histoplasmosis Sporotrichosis	Nephrotoxicity - highest with ABD Infusion-related reactions – highest with ABD and ABCD

Flucytosine	Cryptococcosis in combination with amphotericin B or fluconazole	Bone marrow suppression
Azoles Antifungals: Fluconazole Itrazonazole Voriconazole Posaconazole Isavuconazole	Fluconazole: invasive or superficial candidiasis, cryptococcosis, coccidioidomycosis; prophylaxis in immunocompromised patient Itraconazole: Blastomycosis, coccidioidomycosis, histoplasmosis, sporotrichosis, invasive aspergillosis Posaconazole: Mucomycosis; prophylaxis for *Candida* and aspergillus in immunocompromised patients Isavuconazole: Invasive aspergillosis and mucormycosis	All: GI upset, rash, potential for CYP450-related drug interactions and contraindicated during pregnancy; QTc prolongation with all except isavuconazole Itraconazole: avoid use in patients with heart failure Voriconazole: visual disturbances; may require therapeutics drug monitoring
Echinocandins: Caspofungin Micafungin Anidulafungin	Invasive candidiasis Aspergillosis salvage therapy Prophylaxis in immunocompromised patients	GI adverse effects, histamine-release with administration
Terbinafine	Onychomycosis Dermatophytosis of skin and hair	GI adverse effects, headache
Griseofulvin	Onychomycosis Dermatophytosis of skin and hair	GI effect, headache, allergic reactions Disulfiram-like reactions with alcohol Potential for CYP450-related drug interactions
Ibrexafungerp	Treatment and prevention of recurrent candidiasis	GI adverse effects GI, gastrointesinal

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