Pocket Guide for Antifungal Pharmacotherapy

Antifungal Mechanisms of Action

Drugs of Choice

Candida species
Consider echinocandins if extensive azole exposure or critically ill
Alternative: amphotericin B
Fluconazole or echinocandin

Aspergillus species
Echinocandins not recommended for primary therapy
Alternatives: amphotericin B, posaconazole, echinocandins
Voriconazole

Cryptococcus species
Severe disease includes CNS and disseminated infection
Severe: amphotericin B ± 5-FC
Non-severe or consolidation phase: fluconazole

Blastomyces species & *Histoplasma* species
Severe disease includes CNS and disseminated infection
Severe: amphotericin B
Itraconazole

Coccidioides species
May consider higher doses of fluconazole up to 2 g/day
Alternative: amphotericin B
Fluconazole

Fusarium species
High rates of resistance to all available antifungal agents
Alternatives: amphotericin B or posaconazole
Voriconazole

Mucormycetes
Antifungal therapy is adjunct to surgical debridement
Alternative: posaconazole
Amphotericin B ± echinocandin

More information: www.idsociety.org/idsa_practice_guidelines

Therapeutic Drug Monitoring (TDM)

Drug	Reason	Target Range (mcg/mL)	Timing
Itraconazole	Efficacy	>0.5 (prophylaxis), >1.0 (treatment)	Trough after 5-7 days
Voriconazole	Efficacy & toxicity	>2 (efficacy), <6 (toxicity)	Trough after 5-7 days
Posaconazole	Efficacy	>0.7 (prophylaxis), >1.0 (treatment)	Trough after 5-7 days
Flucytosine (5-FC)	Toxicity	<100	Peak after 3-5 days

trough = 30 minutes before dose, peak = 1-2 hours post-dose

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Antifungal Spectrum of Activity Against Common Fungi

Organism	AmB	Flu	Itra	Vori	Posa	Isa	Anid	Caspo	Mica	5-FC
Aspergillus species	+	--	+	+	+	+	+	+	+	--
A. flavus	+/-	--	+	+	+	+	+	+	+	--
A. fumigatus	+	--	+	+	+	+	+	+	+	--
A. niger	+	--	+/-	+	+	+	+	+	+	--
A. terreus	--	--	+	+	+	+	+	+	+	--
Candida species	+	+	+	+	+	+	+	+	+	+
C. albicans	+	+	+	+	+	+	+	+	+	+
C. glabrata	+	+/-	+/-	+/-	+/-	+/-	+	+	+	+
C. krusei	+	--	+/-	+	+	+	+	+	+	+/-
C. lusitaniae	--	+	+	+	+	+	+	+	+	+
C. parapasilosis	+	+	+	+	+	+	+/-	+/-	+/-	+
C. tropicalis	+	+	+	+	+	+	+	+	+	+
Cryptococcus neoformans	+	+	+	+	+	+	--	--	--	+
Coccidioides species	+	+	+	+	+	+	+/-	+/-	+/-	--
Blastomyces species	+	+	+	+	+	+	+/-	+/-	+/-	--
Histoplasma species	+	+	+	+	+	+	+/-	+/-	+/-	--
Fusarium species	+/-	--	--	+	+	+	--	--	--	--
Scedosporium apiospermum	+/-	--	+/-	+	+	+	--	--	--	--
Scedosporium prolificans	--	--	--	+/-	+/-	+/-	--	--	--	--
Mucormycetes (Zygomycetes)	+/-	--	--	--	+	+	--	--	--	--

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Antifungal Pharmacotherapy by Class

Refer to Guidelines for Dosing in Renal Failure for renal dose adjustments

Drug	Dose	Forms	Interactions	Significant ADRs	Clinical Pearls
Polyenes - binds to ergosterol in fungal cell membrane, disrupting permability and resulting in rapid cell death					
Amphotericin B deoxycholate Fungizone ®	0.7-1.0 mg/kg daily	Intravenous	None	Nephrotoxicity, K+ and Mg++ wasting, infusion-related reactions, anemia (long-term use)	Saline loading may reduce nephrotoxicity Premedications (acetaminophen, prednisone) may lessen infusion reactions Meperidine can be given for rigors
Liposomal amphotericin B Ambisome ®	3-6 mg/kg daily	Intravenous	None	Nephrotoxicity, K+ and Mg++ wasting, infusion-related reactions, hepatotoxicity, anemia (long-term use)	Less nephrotoxicity but similar efficacy Infusion reactions include flushing, hypoxia, and chest or flank pain (can be reduced or prevented with diphenhydramine)
Lipid complex amphotericin B Abelcet ®	3-6 mg/kg daily	Intravenous	None	Nephrotoxicity, K+ and Mg++ wasting, infusion-related reactions, hypoxia, hepatotoxicity, anemia, (long-term use)	Less nephrotoxicity but similar efficacy Infusion reactions include flushing, hypoxia, and chest or flank pain (can be reduced or prevented with diphenhydramine)
Echinocandins - inhibits production of (1,3)-beta-D-glucan, an essential component in the fungal cell wall					
Anidulafungin Eraxis ®	200 mg x 1 , then 100 mg daily	Intravenous	None	Histamine-mediated infusion-related reaction (uncommon) Elevated LFTs but hepatitis rare	Cidal against yeasts, static against molds Poor CSF, urine, & eye penetration Reduced activity against *C. parapsilosis* & *C. guilliermondii*?
Caspofungin Cancidas ®	70 mg x 1 , then 50 mg daily	Intravenous	Increase to 70 mg daily with drug inducers (e.g. rifampin, efavirenz)	Histamine-mediated infusion-related reaction (uncommon) Elevated LFTs but hepatitis rare	Cidal against yeasts, static against molds Poor CSF, urine, & eye penetration Reduced activity against *C. parapsilosis* & *C. guilliermondii*?
Micafungin Mycamine ®	100 mg daily	Intravenous	None	Histamine-mediated infusion-related reaction (uncommon) Elevated LFTs but hepatitis rare	Cidal against yeasts, static against molds Poor CSF, urine, & eye penetration Reduced activity against *C. parapsilosis* & *C. guilliermondii*?
Azoles - inhibits conversion of lanosterol to ergosterol, an essential component of the fungal cell membrane					
Fluconazole Diflucan ®	400 mg daily (6 mg/kg)	Tablets Oral suspension Intravenous	**Inhibits 2C19**, 2C9, 3A4	Generally very well-tolerated GI effects, hair loss and alopecia Elevated LFTs (rare)	Higher doses (12 mg/kg) for *C. glabrata* Highly bioavailable, PO = IV Alopecia more common with chronic use >400 mg/day
Itraconazole Sporanox ®	200 mg TID x 3 days, then 200 mg BID	Capsules Oral solution ~~Intravenous~~	**Inhibits 3A4**, p-glycoprotein 3A4 substrate	GI effects (cyclodextrin in PO solution) Hepatotoxicity, negative inotrope Unique triad of hypertension, hypokalemia, and edema	TDM - add concentrations of itraconazole and active metabolite (hydroxyitraconazole) Capsules - take with food & acidic conditions Oral solution - take on empty stomach
Voriconazole Vfend ®	6 mg/kg BID x 2, then 4 mg/kg BID	Tablets Oral suspension Intravenous	**Inhibits 3A4, 2C19, 2C9** 2C19, 2C9, 3A4 substrate	Visual disturbances (mild, transient) Visual/auditory hallucinations Hepatotoxicity, QT prolongation, phototoxicity, fluoride toxicity (periostitis)	"Rule of 30" - visual disturbances in 30% of patients, 30 mins post-dose, lasts 30 mins IV - contains cyclodextrin which builds up with renal failure but unclear toxicity risk Highly bioavailable, PO = IV
Posaconazole Noxafil ®	200 mg QID 400 mg BID	Oral suspension	**Inhitibits 3A4**	Generally well-tolerated GI effects Hepatotoxicity (rare)	NOT equivalent to tablets or IV forms Increased absorption with high-fat meal, acidic conditions, higher frequency (q6h) No absorption benefit with >800 mg/day
Posaconazole Noxafil ®	300 mg BID x 2, then 300 mg daily	Tablets Intravenous	**Inhitibits 3A4**	Generally well-tolerated GI effects Hepatotoxicity (potentially more than oral suspension)	Tablets - no absorption issues with fat/acid but cannot be crushed IV - contains cyclodextrin which builds up with renal failure but unclear toxicity risk
Isavuconazole Cresemba ®	372 mg TID x 6, then 372 mg daily	Capsules Intravenous	Inhibits, 3A4, p-glycoprotein 3A4 substrate	Generally well-tolerated GI effects Hepatotoxicity	Available as prodrug, isavuconazonium sulfate (186 mg contains 100 mg isavuconazole) NOT formulated with cyclodextrin May <u>shorten</u> QT interval (dose-related)
Fluoropyrimidines - blocks both DNA and protein synthesis in fungal cell					
Flucytosine Ancobon ®	25 mg/kg q6h	Oral capsules Oral suspension (compounded)	None	Mild GI effects Bone marrow suppression (leukopenia, thrombocytopenia, pancytopenia) Hepatotoxicity	NEVER give as monotherapy (rapid development of resistance) Dose adjustments based on renal function, toxicity, and TDM

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