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PEARLS OF LABORATORY MEDICINE

Pearls of Antifungal Agents

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Epidemiology

- Invasive fungal infections (IFIs):
  - Significant public health concern
  - Prevalence continues to increase due to:
    - Rise in use of immunosuppressive agents/transplants
    - Neoplastic & immune modifying agents
    - Prosthetic devices/grafts/catheters
    - Broad-spectrum antimicrobials
    - Surgery
  - True burden underestimated due to difficulty in diagnosis/recognition

Oren I, et al. *Clin Microbiol Infect.* 2014;20(6):1-4.

Epidemiology

- Yeasts – candidiasis/candidemia
  - *Candida* spp. most common cause of invasive fungal infection
  - Shift from *C. albicans* to more azole-resistant non-*C. albicans spp.*
    - *C. glabrata, C. auris*
  - Risk factors: neutropenia, mucosal barrier breakdown, broad spectrum antibiotic use
  - 30-40% mortality
- Molds – aspergillosis and mucormycosis
  - *Aspergillus spp.* and *Rhizopus spp., Zygomycetes*
  - Risk factors: prolonged neutropenia, solid organ transplant (SOT) and hematopoietic stem cell transplant (HSCT), chronic immunosuppression, diabetes mellitus
  - 40-90% mortality

Oren I, et al. *Clin Microbiol Infect.* 2014;20(6):1-4.
Schmalreck AF, et al. *Mycoses*. 2012;55(3):e124-37.

Current Management Paradigm

- Improved non-culture based diagnostic tools
  - Molecular techniques (PCR, T2Candida)
  - Antigens ((1,3)-β-D-glucan, galactomannan)
- More effective preventative measures/prophylaxis
  - Venous and urinary catheters
- Understanding of antifungal resistance
  - Whole genome sequencing
- New antifungal agents and novel pipeline compounds

Sanguinetti M, et al. *J Antimicrob Chemother*. 2019;74(Supplement_2):ii27-ii37.
Arvanitis M, et al. *Clin Microbiol Rev*. 2014;27(3):490-526.
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Rauseo AM, et al. *Open Forum Infect Dis*. 2020;7(2):ofaa016.

Antifungal Agents

Polyenes	Triazoles	Echinocandin	5-fluorocytosine
Amphotericin B	Fluconazole Itraconazole* Voriconazole* Posaconazole* Isavuconazole*	Caspofungin Micafungin Anidulafungin	Flucytosine

**mold-active triazoles*

Nett JE, et al. Infect Dis Clin North Am. 2016;30(1):51-83.

Spectrum of Activity

Organism	Fluconazole	Itraconazole	Voriconazole	Posaconazole	Isavuconazole
Aspergillus spp.	-	+	+	+	+
C. albicans	+	+	+	+	+
Non-C. albicans	+/-	+/-	+	+	+
Cryptococcus spp.	+	+	+	+	+
Coccidioides spp.	+	+	+	+	+
Blastomycetes	+	+	+	+	+
Histoplasma spp.	+	+	+/-	+	+/-
Fusarium spp.	-	-	+	+	+/-
Scedosporium	-	+/-	+	+	+/-
Zygomycetes	-	-	-	+	+

Ashley ESD, et al. *Clin Infect Dis.* 2006;43(Suppl 1):S28-S39.
Kullberg BJ, et al. *Clin Infect Dis.* 2019;68(12):1981-1989.
Nett JE, et al. Infect Dis Clin North Am. 2016;30(1):51-83.

Spectrum of Activity

Fungus	Amphotericin B	Micafungin	Caspofungin	Anidulafungin
Aspergillus spp.*	+	+	+	+
C. albicans	+	+	+	+
Non-C. albicans	+	+	+	+
Cryptococcus spp.	+	-	-	-
Coccidioides spp.	+	-	-	-
Blastomycetes	+	-	-	-
Histoplasma spp.	+	-	-	-
Fusarium spp.	+/-	-	-	-
Scedosporium	+/-	-	-	-
Zygomycetes	+	-	-	-

*In vitro activity only

Ashley ESD, et al. *Clin Infect Dis.* 2006;43(Suppl 1):S28-S39.
Nett JE, et al. Infect Dis Clin North Am. 2016;30(1):51-83.
Patterson TF, et al. *Clin Infect Dis*. 2016;63(4):e1-e60.

Pharmacokinetic/Pharmacodynamic Parameters

	C_{max} (ug/mL)	AUC (mg x h/L)	Protein Binding (%)	Metabolism	Elimination	Half-life (hours)	PK/PD Index and Target
Amphotericin B deoxycholate	0.5-2	17	>95	Hepatic (minor)	Feces	50	Cmax:MIC 4-10 or AUC:MIC>100
Amphotericin B liposomal	83	555	>95	Unknown	Unknown	100-150	Cmax:MIC>40 or AUC:MIC>100
Fluconazole	6-20	400-800	10	Hepatic	Renal	27-34	AUC:MIC 25-50
Itraconazole	0.5-2.3	29.2	>95		Feces	30	AUC:MIC 25-50
Voriconazole	3.0-4.6	20.3	58		Feces	6	AUC:MIC 25-50
Posaconazole	1.5-2.2	8.9	99		Feces	20	AUC:MIC 25-50
Isavuconazole	7.5	120	>99		Feces	80-120	AUC:MIC 25-50

Lepak AJ, et al. *Cold Spring Harb Perspect Med.* 2014;5(5):a019653-a.
Bellmann R, et al. *Infection*. 2017;45(6):737-79.

Pharmacokinetic/Pharmacodynamic Parameters

	C_{max} (ug/mL)	AUC (mg x h/L)	Protein Binding (%)	Metabolism	Elimination	Half-life (hours)	PK/PD Index and Target
Caspofungin	8-10	119	97	Hepatic	Urine	30	Cmax:MIC >10 or AUC:MIC>20
Micafungin	10-16	158	99	Hepatic	Feces	15	Cmax:MIC >10 or AUC:MIC>20
Anidulafungin	6-7	99	84	Chemical degradation	Feces	26	Cmax:MIC >10 or AUC:MIC>20
Flucytosine	30-40	30-62	4	Hepatic	Renal	3-4	Time>MIC 20-40%

Lepak AJ, et al. *Cold Spring Harb Perspect Med.* 2014;5(5):a019653-a.
Bellmann R, et al. *Infection*. 2017;45(6):737-79.

Therapeutic Drug Monitoring

Antifungal	Goal/Rationale	Target	
Itraconazole	Confirm absorption	Prophylaxis	Trough: >0.5-1 mcg/mL
		Treatment	Trough: >0.5-1 mcg/mL
Voriconazole	High intrasubject variability, drug interactions, toxicity	Prophylaxis	Trough: 2-5.5 mcg/mL
		Treatment	Trough: 2-5.5 mcg/mL
Posaconazole	High intrasubject variability	Prophylaxis	Trough: >0.7 mcg/mL
		Treatment	Trough: >1 mcg/mL
Isavuconazole	Minimize gastrointestinal toxicities	Prophylaxis	Trough: 2.5-5 mcg/mL
		Treatment	Trough: 2.5-5 mcg/mL
Flucytosine	Minimize hematologic toxicities	Prophylaxis	n/a
		Treatment	Trough: 20-40 mcg/mL Peak: <100 mcg/mL

Ashbee HR, et al. *J Antimicrob Chemother*. 2014;69(5):1162–1176.
Furfaro E, et al. *J Antimicrob Chemother*. 2019;74(8):2341-2346.
Patterson TF, et al. *Clin Infect Dis*. 2016;63(4):e1-e60.
Stott KE, et al. *J Antimicrob Chemother*. 2017;72(suppl_1):i12-i18.

Amphotericin B

Mechanism of Action	Binds to ergosterol in the fungal cell membrane, disrupting cell permeability and results in rapid cell death
Clinical Indications	Candidiasis, candidemia, *Cryptococcus neoformans, Aspergillus* spp., *Histoplasma* spp., *Blastomycetes, Zygomycetes*
Formulations	Deoxycholate, liposomal (LAMB), lipid complex
Dosing	Deoxycholate: 1-1.5 mg/kg Other: 3-5 mg/kg
Toxicities	Nephrotoxicity, infusion-related reactions and electrolyte abnormalities higher with AmB

Nett JE, et al. *Infect Dis Clin North Am*. 2016;30(1):51-83.
Amphotericin B lipid complex (Abelcet®) for injection (package insert).
Amphotericin B liposome (AmBisome®) for injection (package insert).
Amphotericin B Cholesteryl Sulfate Complex (Amphotec®) for Injection (package insert).
Amphotericin B for Injection (package insert).

Clinical Pearls

- Deoxycholate formulation should only be used for urinary tract infections
- Liposomal formulations are nephrotoxic but not renally cleared
  - Dose should not be adjusted for renal dysfunction
- Lower doses of LAMB (1-3 mg/kg) may have equal efficacy
- Higher doses of LAMB (>5 mg/kg) do not improve outcomes

Hamill RJ. *Drugs*. 2013;73(9):919-34.
Steimbach LM, et al. *Mycoses*. 2017;60(3):146-154.
Felton T, et al. *Clin Microbiol Rev*. 2014;27(1):68-88.

Fluconazole

Mechanism of Action	Block the demethylation of lanosterol, inhibiting ergosterol synthesis
Clinical Indications	Candidiasis, candidemia, *Cryptococcus*
Formulations	Capsules, injection, suspension
Dosing	400-800 mg/day (up to 12 mg/kg/day)
Toxicities	Headache, alopecia, transaminitis
Drug-drug Interactions	Moderate 3A4, 2C9, 2C19 inhibitor

Nett JE, et al. *Infect Dis Clin North Am*. 2016;30(1):51-83.
Fluconazole tablet (package insert)
Pappas PG, et al. *Clin Infect Dis*. 2016;62(4):e1-50.

Itraconazole

Mechanism of Action	Block the demethylation of lanosterol, inhibiting ergosterol synthesis
Clinical Indications	Histoplasmosis, blastomycosis
Formulations	Capsules, solution
Dosing	200-400 mg/day
Toxicities	Nausea, vomiting, hypertriglyceridemia, hypokalemia, transaminitis, skin rash, headache, decreased cardiac output, QTC prolongation
Drug-drug Interactions	Strong 3A4 inhibitor P-gp substrate and inhibitor

Nett JE, et al. *Infect Dis Clin North Am*. 2016;30(1):51-83.
Itraconazole capsules (package insert).
Itraconazole oral solution (package insert).

Voriconazole

Mechanism of Action	Block the demethylation of lanosterol, inhibiting ergosterol synthesis
Clinical Indications	Candidiasis, aspergillosis
Formulations	Injection, suspension, tablets
Dosing	• Weight-based: 6 mg/kg IV/PO every 12 hours x 2 doses then 4 mg/kg IV/PO every 12 hours • Standard: 200-300 mg every 12 hours
Toxicities	Visual disturbances, altered mental status, hepatoxicity, QTc prolongation
Drug-drug Interactions	Strong 3A4 inhibitor Moderate 2C19 and weak 2C9 inhibitor

Nett JE, et al. *Infect Dis Clin North Am*. 2016;30(1):51-83.
Voriconazole (Vfend®) (package insert).

Posaconazole

Mechanism of Action	Block the demethylation of lanosterol, inhibiting ergosterol synthesis
Clinical Indications	Aspergillosis, mucormycosis
Formulations	Injection, delayed-release tablet, suspension
Dosing	• Suspension: 200 mg 3-4 times daily • Tablet/injection: 300 mg twice daily x 2 doses, then 300 mg daily
Toxicities	Nausea, vomiting, hepatoxicity, QTC prolongation
Drug-drug Interactions	Strong 3A4 inhibitor

Nett JE, et al. *Infect Dis Clin North Am*. 2016;30(1):51-83.
Posaconazole (Noxafil®) (package insert).

Isavuconazole

Mechanism of Action	Block the demethylation of lanosterol, inhibiting ergosterol synthesis
Clinical Indications	Aspergillosis, mucormycosis
Formulations	Capsules, injection
Dosing	200 mg every 8 hours x 6 doses then 200 mg once daily
Toxicities	Hepatoxicity, QTc shortening
Drug-drug Interactions	Moderate 3A4 inhibitor 3A4 substrate

Fontana L, et al. *Clin Infect Dis*. 2020;70(5):723-730.
Isavuconazonium sulfate (Cresemba®) (package insert).
Kullberg BJ, et al. *Clin Infect Dis*. 2019;68(12):1981-1989.
Miceli MH, et al. *Clin Infect Dis*. 2015;61(10):1558-1565.
Nett JE, et al. *Infect Dis Clin North Am*. 2016;30(1):51-83.
Townsend R, et al. P0216. ECCMID Congress 2015.

Clinical Pearls

- Itraconazole absorption is highly dependent on formulation, food, and acidic environment
- Voriconazole:
  - Demonstrates non-linear PK and significant intra- and inter-patient variability
    - Due in part to CYP2C19 polymorphisms
  - Many drug-drug interactions
- Posaconazole is first line for prophylaxis of IFIs in patients with certain hematologic malignancies
  - Tablets can be given without regard to food or gastric acid suppressants
- Isavuconazole has less toxicities and drug-drug interactions than other mold-active triazoles

Maertens JA, et al. *J Antimicrob Chemother.* 2018;73(12):3221-3230.
Lee CH, et al. *Antimicrob Agents Chemother.* 2018;62(8):e00355-18.

Echinocandins

Mechanism of Action	Interfere with (1, 3)-β-D-glucan synthase inhibiting cell membrane formulation
Clinical Indications	Candidiasis
Formulations	Injection
Dosing	• Caspofungin: 70 mg x 1, then 50 mg daily • Micafungin: 100-150 mg daily • Anidulafungin: 200 mg x 1, then 100 mg daily
Toxicities	Generally well tolerated

Nett JE, et al. *Infect Dis Clin North Am*. 2016;30(1):51-83.
Anidulafungin (Eraxis®) for injection (package insert).
Caspofungin acetate (caspofungin®) for injection (package insert).
Micafungin (Mycamine®) for injection (package insert).

Clinical Pearls

- Unreliable in vivo activity against molds
- Have demonstrated improved outcomes over azoles for candidiasis/candidemia in several Phase 3 trials
- IDSA recommends as initial therapy for candidiasis/candidemia

Pappas PG, et al. *Clin Infect Dis*. 2016;62(4):e1-50.

Flucytosine

Mechanism of Action	Converted to 5-fluorouracil inside the cell and interferes with DNA formation
Clinical Indications	*Cryptococcal meningitis, Candida cystitis*
Formulations	Capsules
Dosing	• 25 mg/kg every 6 hours ○ Renal dose adjustment required
Toxicities	Nausea, vomiting, bone marrow suppression

Nett JE, et al. *Infect Dis Clin North Am*. 2016;30(1):51-83.
Flucytosine capsule (package insert).

Summary

- IFIs contribute to morbidity, mortality, and excess healthcare costs
- Prevalence of infections due to non-albicans *Candida* continue to increase, and are more azole resistant
- Amphotericin B is most broad spectrum antifungal
  - Liposomal formulation less toxic
- Azole antifungals each have unique pharmacologic properties, clinical indications, and adverse effects
- Isavuconazole is the newest mold-active triazole with less toxicities and drug-drug interactions
- Echinocandins are safe and may be more efficacious than azoles for invasive candidiasis

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Disclosures/Potential Conflicts of Interest

Upon Pearl submission, the presenter completed the Clinical Chemistry disclosure form. Disclosures and/or potential conflicts of interest:

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