Complexities of Antifungal Therapy Made Simple

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Presenter Disclosure

Christine Kubin, PharmD, BCPS-AQID, BCIDP

There are no relationships to disclose related to this presentation.

Unlabeled/unapproved uses of antifungal drugs will be discussed.

Objectives

Pharmacists:

1. Discuss differences in antifungal spectrums of activity for the most commonly used antifungals.

2. Differentiate the antifungals based on their adverse effect profile.

3. Explain the need for antifungal therapeutic drug monitoring and apply this knowledge to clinical practice.

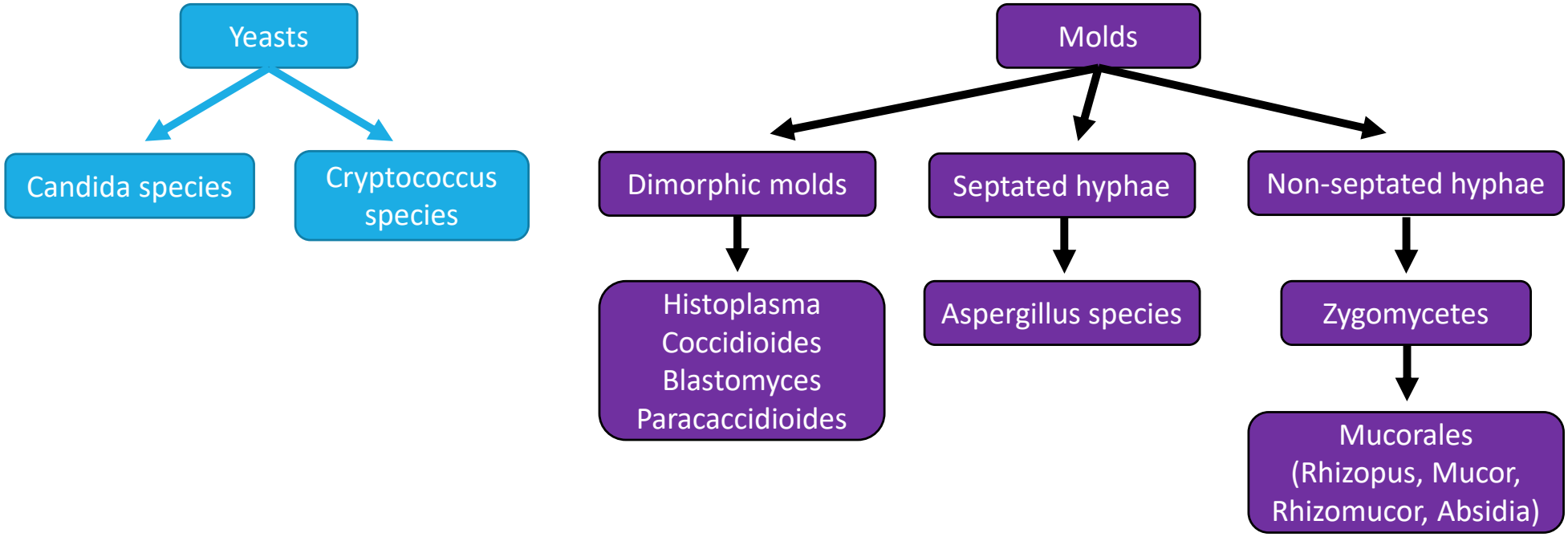
Technicians:

1. Recognize the different classes of antifungal agents.

2. Describe the adverse effects of antifungal agents.

3. Explain the need for antifungal therapeutic drug monitoring.

Fungal Classification



The Big Five

Candida sp.

Aspergillus sp.

Zygomycetes

Cryptococcus neoformans

~~*Pneumocystis jirovecii*~~

Risk Factors for Fungal Infections

Age
Corticosteroids
Recent or current use of antibiotics
Central venous catheters
Diabetes
Renal replacement therapy
TPN
Malnutrition
Abdominal surgery

Fungal colonization
Prolonged mechanical ventilation
Prolonged ICU stay
High disease severity

Immunosuppression
Chemotherapy/radiation
Mucositis
Prolonged neutropenia

Muskett, et al. Crit Care 2011; 15(6): R287.
Kullberg BJ, et al. N Engl J Med 2015; 373: 1445-56.

Invasive Fungal Infections (IFIs) in the ICU

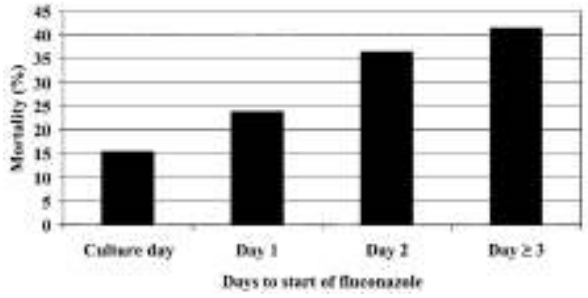
Extended Prevalence of Infection in Intensive Care (EPIC II)

- 19% of isolated pathogens were fungi → 88% Candida

Candida sp. 3rd most common cause of bloodstream infections in the ICU (10%)

Attributable mortality of candidemia 5-71%

- Candidemia associated with ↑ LOS and hospital costs
- Delays in therapy associated with ↑ mortality

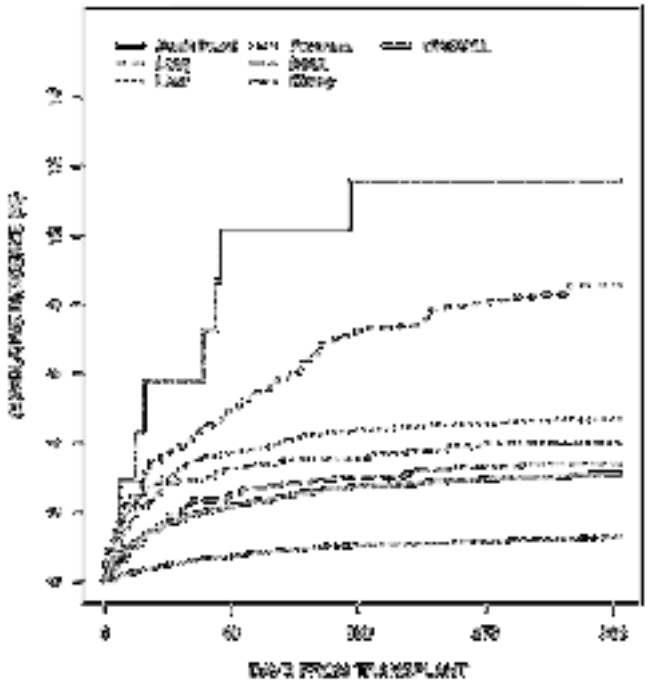


Vincent, et al. JAMA 2009; 302(21): 2323-9.
Wisplinghoff, et al. Clin Infect Dis 2004; 39: 309-17.
Pfaller, et al. Clin Micro Rev 2007; 20: 133-63.
Garey, et al. Clin Infect Dis 2006; 43: 25-31.

IFIs in Solid Organ Transplant

Table 2. No. (%) of Invasive Fungal Infection (IFI) Cases in the Surveillance Cohort, by Transplant Type

IFI type	Kidney (*n* = 332)	Liver (*n* = 378)	Pancreas (*n* = 128)	Lung (*n* = 248)	Heart (*n* = 99)	Small bowel (*n* = 22)
Candidiasis	164 (49)	265 (69)	97 (76)	56 (23)	48 (49)	19 (85)
Aspergillosis	47 (14)	42 (11)	6 (5)	109 (44)	23 (23)	0 (0)
Zygomycosis	8 (2)	9 (2)	0 (0)	8 (3)	3 (3)	0 (0)
Other mold	10 (3.0)	9 (2.4)	4 (3.1)	49 (19.8)	7 (7.1)	0 (0.0)
Unspecified mold	7 (2.1)	8 (2.1)	0 (0.0)	7 (2.8)	2 (2.0)	0 (0.0)
Cryptococcosis	49 (15)	24 (6)	6 (5)	6 (2)	10 (10)	1 (5)
Endemic mycoses	33 (10)	17 (5)	8 (6)	3 (1)	3 (3)	0 (0)
Pneumocystosis	5 (1)	0 (0)	1 (1)	4 (2)	3 (3)	0 (0)
Other yeast	6 (1.8)	9 (2.4)	5 (3.9)	0 (0.0)	0 (0.0)	1 (5)
Unspecified yeast	3 (0.9)	5 (1.3)	1 (0.8)	6 (2.4)	0 (0.0)	1 (5)



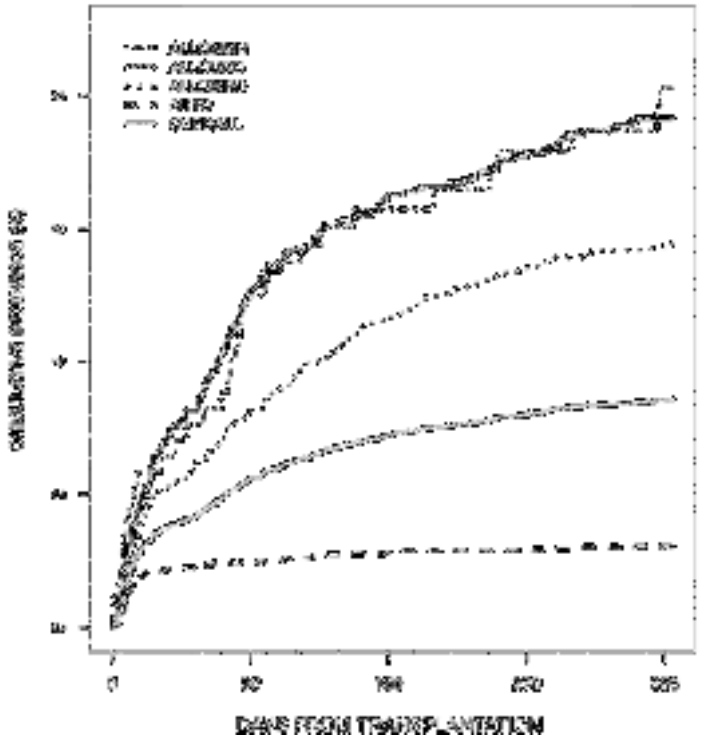
Pappas, et al. Clin Infect Dis 2010; 50: 1101-11.
Andes, et al. Transpl Infect Dis 2016;18(6):921-931.

IFIs in Stem Cell Transplant

43% invasive aspergillosis
- Median onset 99 days

28% invasive candidiasis
- Median onset 61 days

8% mucormycosis



Kontoyiannis, et al. Clin Infect Dis 2010; 50: 1091-1100.

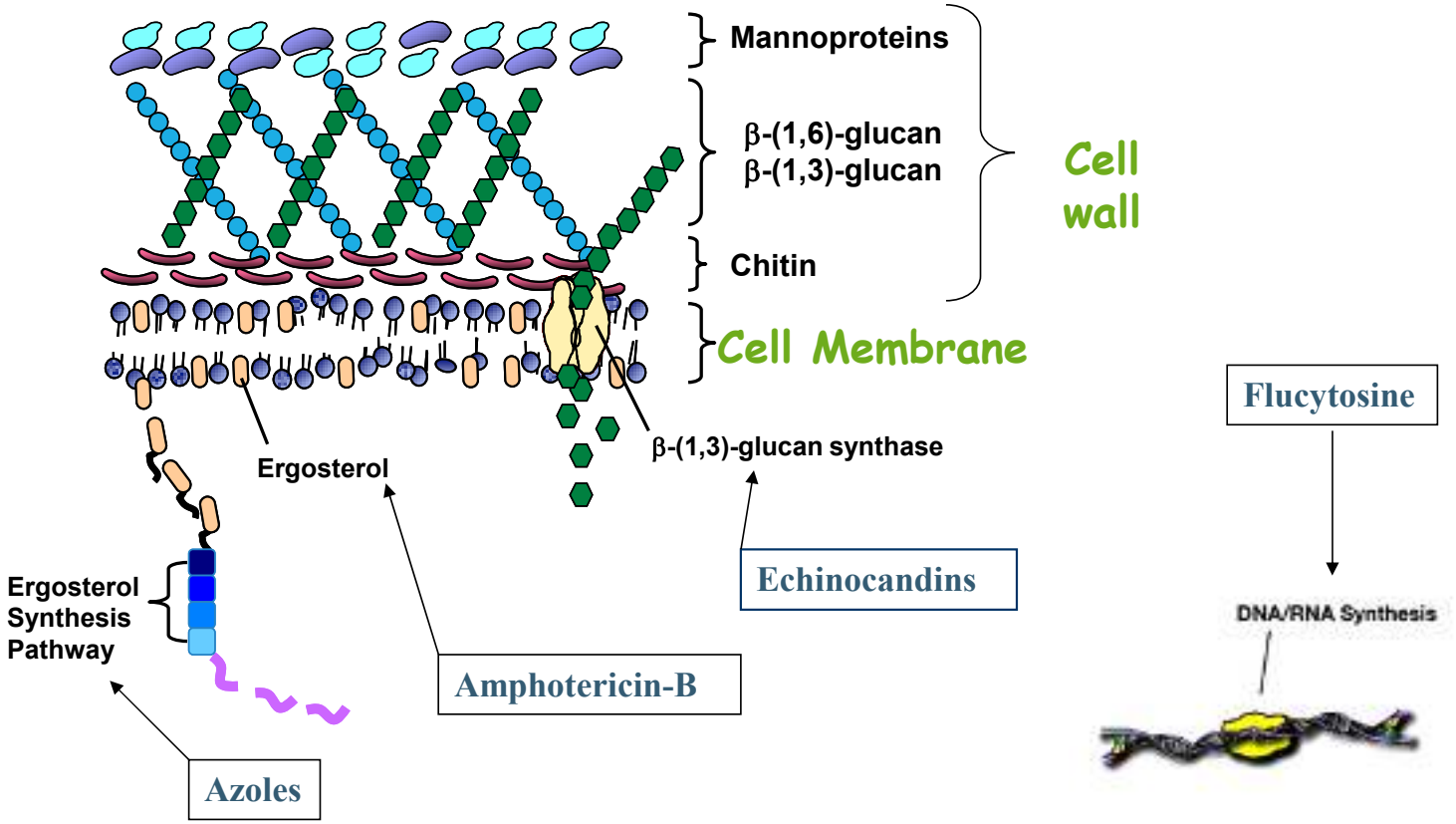
Choosing an Antifungal

Spectrum

Toxicities

Dose

Fungal Cell Membrane and Cell Wall



Slide adapted from R. Lewis; posted at www.doctorfungus.org.

Activities of Antifungal Agents against *Candida* species

Species	Fluconazole	Itraconazole	Voriconazole	Posaconazole	Isavuconazole	Amphotericin B	Echinocandins
C. albicans	S	S	S	S	S	S	S
C. tropicalis	S	S	S	S	S	S	S
C. parapsilosis	S	S	S	S	S	S	S to R
C. glabrata	S-DD to R	S-DD to R	S-DD to R	S-DD to R	S-DD to R	S to I	S
C. krusei	R	S-DD to R	S	S	S	S to I	S
C. lusitaniae	S	S	S	S	S	S to R	S
C. auris	R	R	R	R	R	S to R	S to R

S: susceptible; S-DD: susceptible dose-dependent; I: intermediate; R: resistant

Pappas, et al. Clin Infect Dis 2009; 48: 503-35.
Nett, et al. Infect Dis Clin N Am 2016; 51-83.

Activity of Antifungals against non-*Candida* Species

Fungus	Fluconazole	Itraconazole	Voriconazole	Posaconazole	Isavuconazole	Amphotericin B	Echinocandins
Aspergillus spp.	X	✓	✓	✓	✓	✓ (not A. terreus)	✓
Fusarium	X	X	✓ (breakthrus)	Conflicting data	X	✓ occas R	X
Scedosporium	X	+/-	✓	+/-	+/-	✓ occas R	X
Zygomycetes	X	X	X	✓	✓	✓	X
Cryptococcus	✓	✓	✓	✓	✓	✓	X

X = no in vitro activity
✓ = in vitro activity
R = resistance

Adapted from Arikan & Rex. *Manual of Clinical Microbiology, eighth edition.* 2003, p. 1859.
Nett, et al. Infect Dis Clin N Am 2016; 51-83.

Choosing an Antifungal

Spectrum 

Toxicities

Dose

Adverse Reactions

Type of toxicity	AmB	ABCD	ABLC	LAB	Flu	Itr	Vor	Pos	Anidulafungin	Caspofungin	Micafungin	Flucytosine
Hepatic	++	++	++	++	+	+	+	+	+	+	+	++
Nephrotic	++++	+++	+++	++	–	–	–	–	–	–	–	–
Hematologic	+	+	+	+	NR	NR	NR	NR	NR	+	+	+++
Infusion-related	+++	+++	+++	++	–	–	–	NA	+	+	+	NA
Electrolyte abnormalities[a]	+++	++	++	++	NR	+	+	NR	+	+	NR	+

Amphotericin B
- Renal toxicity
- Electrolyte abnormalities
- Infusion-related reactions

Azoles
- **Hepatotoxicity**: itraconazole >> voriconazole >> posaconazole, isavuconazole > fluconazole
- **QTc prolongation**: all, EXCEPT isavuconazole
- **CNS effects**: voriconazole
- **Photosensitivity/Skin**: increased risk with voriconazole

Flucytosine
- Bone marrow suppression
- Hepatotoxicity

Dodds Ashley. Clin Infect Dis 2006; 43: S28–39.

Beware of Added Toxicities

Hepatotoxicity

- Terbinafine combination, macrolides, anti-mycobacterial therapy

QTc

- Psychotropics, macrolides, quinolones

Renal toxicity

- Vancomycin, aminoglycosides, TMP/SMX, colistin/polymyxin B, calcineurin inhibitors (post-transplant)

Rondeau, et al. Eur Respir J. 2012 ;39:782-4.
Lewis RE. Mayo Clin Proc. 2011; 86: 805–817.
Mourad et al. J Antimicrob Chemother. 2018;73(suppl 1):i26-i32.

Long Term Safety?

Voriconazole associated with most data

- Squamous cell carcinomas and melanomas (3.1-39.5%)
- Periostitis (10%)
- Peripheral neuropathies (9%)

Peripheral neuropathies also reported with itraconazole (17%), posaconazole (1 case), isavuconazole (1 case)

Squamous cell carcinoma reported in 2 cases with isavuconazole

Mourad et al. J Antimicrob Chemother. 2018;73(suppl 1):i26-i32.
Baxter et al. J Antimicrob Chemother. 2011;66(9):2136-9.
DiPippo et al. Clin Infect Dis. 2019 Mar 7. doi: 10.1093/cid/ciz159.

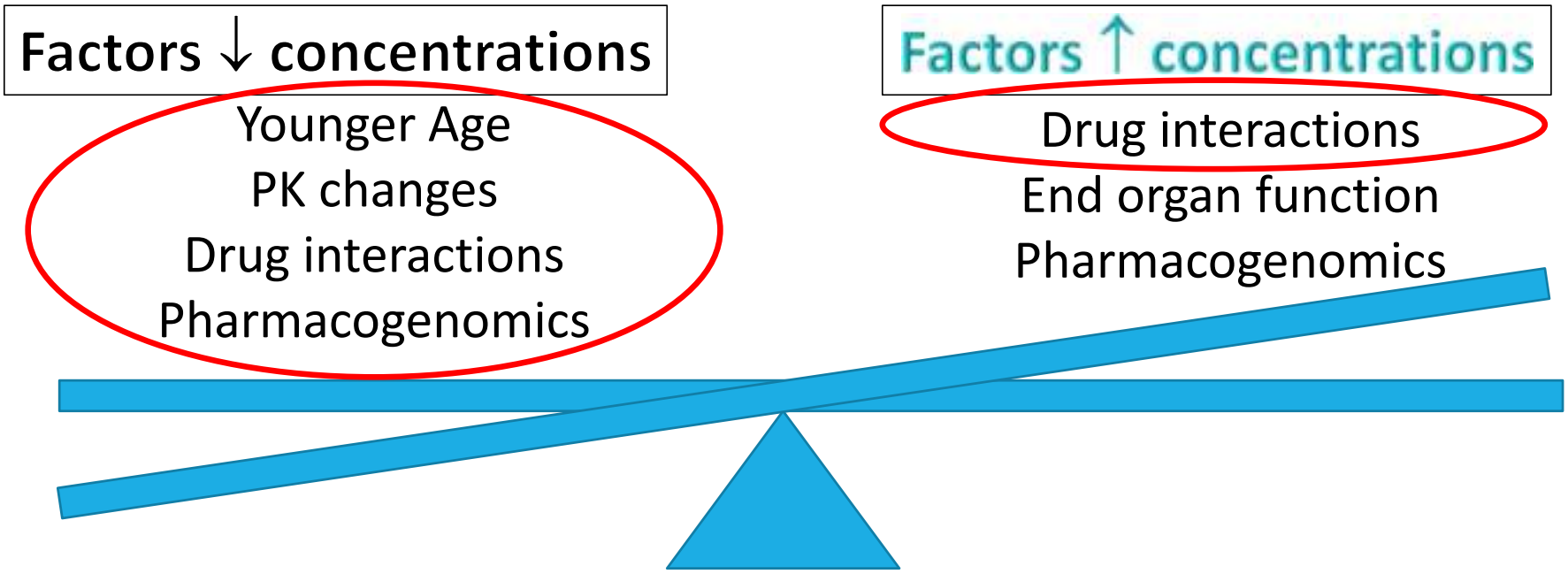
Choosing an Antifungal

Spectrum 

Toxicities 

Dose

Getting the Dose Right



Pharmacokinetics

	Fluconazole	Itraconazole	Voriconazole	Posaconazole	Isavuconazole	Amphotericin B	Echinocandins	Flucytosine
Oral bioavailability	>90%	30% (caps) 50% (soln)	>90%	8-47% (dose-dependent)	98%	<5%	<5%	80%
Protein binding	10%	>99%	58%	>98%	98%	>95%	85-99%	4%
Food effect	↓ Absorption	↑ Absorption (caps) ↓ Absorption (soln)	↓ Absorption	↑ Absorption	None	n/a	n/a	n/a
CSF penetration	> 52%	<1%	60%	5-22%	<1%	<1%	<1%	75%
Urine penetration	90%	1-10%	<2%	<2%	<1%	≤5%	<2%	90%
Metabolism	Minor hepatic (CYP3A4)	Hepatic (CYP3A4)	Hepatic (CYP2C19/2C9)	Hepatic (UDP glucuronidation)	Hepatic (CYP3A4)	Minimal	None Hepatic	Minor intestinal
Elimination	Renal	Hepatic	Renal	Feces	Feces	Minor	Urine Feces	Renal

Lewis R. Mayo Clin Proc 2011; 86: 805-817.
Barde et al. Antimicrob Agents Chemother 2019; 63:e01184-19.
Dodds Ashley E. J Fungi (Basel) 2019; 5: 97.

PK Challenges

Absorption

- Itraconazole: dependent on formulation, food, pH
- Voriconazole: dependent on age (↓50% in children), patient population (lung transplant *F*24-63%)
- Posaconazole: saturable absorption, dependent on food, pH
  - Oral solution: needs fatty supplement
  - Oral delayed-release tabs: ↑50% with fatty meal, not affected by pH

Elimination

- Voriconazole: non-linear PK in adults (↑dose 1.7-fold → ↑ AUC 3.1-fold)

Genetic Polymorphisms

CYP2C19 impacts voriconazole metabolism and concentrations

Table 1. Proposed nomenclature for polymorphic CYP2C19.

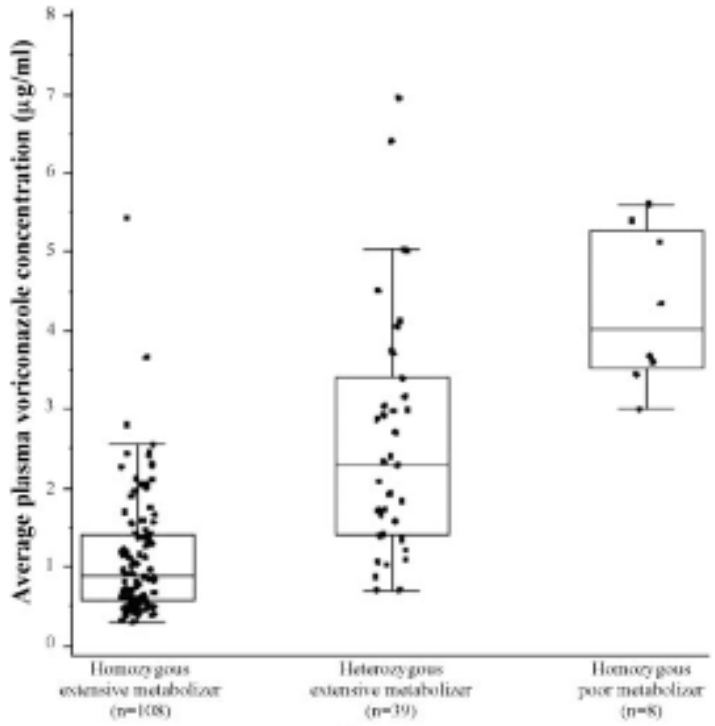
Proposed CYP2C19 phenotype	Required alleles	Allele numbering example(s)
Ultrarapid metabolizer (UM)	2 increased-function	*17/*17
Rapid metabolizer (RM)	1 normal function **and** 1 increased-function	*1/*17
Normal metabolizer (NM)	2 normal function	*1/*1
Intermediate metabolizer (IM)	1 normal function **and** 1 no-function **OR** 1 no-function **and** 1 increased-function	*1/*2, *1/3 OR *2/*17
Poor metabolizer (PM)	2 no-function	*2/*2, *2/*3, *3/*3

Ultrarapid (2-5%)/rapid metabolizers (30%)
↑prevalence in Europeans, Africans
UM/RMs: troughs decreased by 50%

Intermediate (18-45%)/poor metabolizers (2-15%)
↑prevalence in Japanese, Asian, Pacific islanders
PMs: concentrations 3-4x higher than normal

Amsden, et al. Expert Opin Drug Metab Toxicol 2017; 13(11): 1135-46.
Meletiadis, et al. Clin Microbiol Rev 2006; 19:763-87.

Voriconazole Concentrations

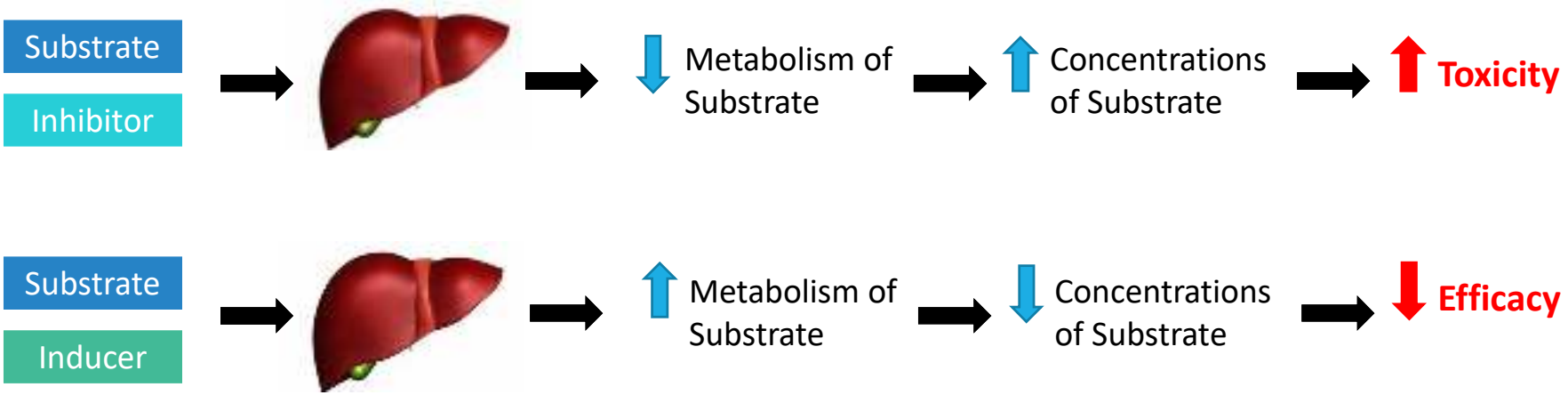


Meletiadis, et al. Clin Microbiol Rev 2006; 19:763-87.

CYP450 Drug Interactions

Cytochrome P450 most common drug metabolizing enzymes

Substrates: drug metabolized by CYP450 enzyme



Azoles as Inhibitors and Substrates

	Fluconazole	Itraconazole	Voriconazole	Posaconazole	Isavuconazole
Inhibitor					
CYP2C19	+	-	**+++**	-	-
CYP2C9	++	+	**++**	-	-
CYP3A4	++	**+++**	**++**	**+++**	++
P-glycoprotein	-	**yes**	-	-	yes (mild)
Substrate					
CYP2C19	-	-	**+++**	-	-
CYP2C9	-	-	**+**	-	-
CYP3A4	+	+++	+	-	**+++**
P-glycoprotein	yes	yes	-	yes	-

Dodds-Ashley et al. Clin Infect Dis. 2006;43(suppl 1):S28-S39.

Clinical Implications of Interactions

Azoles as TARGETS of drug interactions

- Itraconazole, voriconazole, isavuconazole

Azoles as the CAUSE of drug interactions

- Fluconazole, itraconazole, voriconazole, posaconazole

Heightened vigilance with rifamycins, antiepileptics, immunosuppressants, psychotropics, statins, warfarin, HIV antiretrovirals

Dodds-Ashley et al. Clin Infect Dis. 2006;43(suppl 1):S28-S39.
Grasemann H. N Engl J Med. 2017;377: 2085-2088.

Children

Fluconazole

- ↑ clearance → half-life 20 hrs vs 30 hrs in adults
- Children require 6-12 mg/kg/d for similar adult exposure

Voriconazole

- Linear PK
- Exposure most affected by weight
- 7 mg/kg q12h comparable to 4 mg/kg q12h in adults

Echinocandins

- ↑CL and shorter half-life compared to adults
- Caspofungin: BSA dosing
- Micafungin: CL inversely related to age (premature infants require 3-fold higher dosing than adults)

Cohen-Wollkowiez, et al. Curr Opin Infect Dis 2009; 22(6): 553-558.
Watt, et al. Early Hum Dev 2011; 87 (suppl 1): S61-5.

Azole Therapeutic Drug Monitoring

	Pharmacokinetic variability	TDM range defined	Narrow therapeutic window
Itraconazole	√	√	√
Voriconazole	√	√	√
Posaconazole	√	√	?
Isavuconazole	√	X	?

Voriconazole

- TDM range: 2-6 mcg/mL (troughs)
- Troughs >6 mcg/mL associated with hallucinations, hepatotoxicity, neurotoxicity

Posaconazole

- TDM range: >1 mcg/mL (troughs)

Smith et al. Ther Drug Monit. 2008 Apr;30(2):167-72.
John et al. Expert Opin Drug Metab Toxicol. 2019 Sep 25. doi: 10.1080/17425255.2019.

Therapeutic Drug Monitoring

J.R. is a 27 yo woman (wt 50 kg) with CF, s/p lung transplant who is initiated on voriconazole 300 mg PO q12h x 2 doses, then 200 mg PO q12h for *Aspergillus fumigatus* on a respiratory culture. Five days after starting therapy a voriconazole trough level is checked and returns at 0.9 mg/L. The nurses have been administering the voriconazole on an empty stomach. Her LFTs are within normal range.

What are best next steps for her voriconazole therapy?

A. Continue voriconazole at current dose

B. Stop voriconazole and check a QTc

C. Increase voriconazole dose to 300 mg PO q12h

D. Decrease voriconazole dose to 150 mg PO q12h

Choosing an Antifungal

Spectrum ✓

Toxicities ✓

Dose ✓

Candidiasis

T.R. is a 58 yo man with short gut syndrome requiring chronic TPN, DM with chronic renal insufficiency admitted with new fever, chills, hypotension. WBC 22,000. SCr 2.7 mg/dL.

Likely line infection

Blood cx +yeast x2

Which of the following would be the most appropriate empiric antifungal therapy?

A. Fluconazole

B. Voriconazole

C. Micafungin

D. Liposomal amphotericin B

IDSA Guidelines for Candidiasis

"**Fluconazole or an echinocandin is recommended as initial therapy (AI)**. The Expert Panel favors an echinocandin for patients with moderately severe to severe illness or for patients who have had recent azole exposure (A-III)".

For infection due to *Candida glabrata,* an echinocandin is preferred (B-III).

For infection due to *Candida parapsilosis,* treatment with fluconazole is recommended (B-III).

Therapy = source control and early initiation of effective systemic antifungal therapy

Pappas, et al. CID 2009;48:503- 535.

Fluconazole vs Echinocandins

IV vs PO, species, site of infection, toxicity drive treatment choice

Distribution:

Fluconazole		Echinocandins
CSF levels >60% serum levels		<5%
90% excreted unchanged in the urine		<2% excreted unchanged in the urine
Aqueous & vitreous humor levels ≥ 70% serum		0%

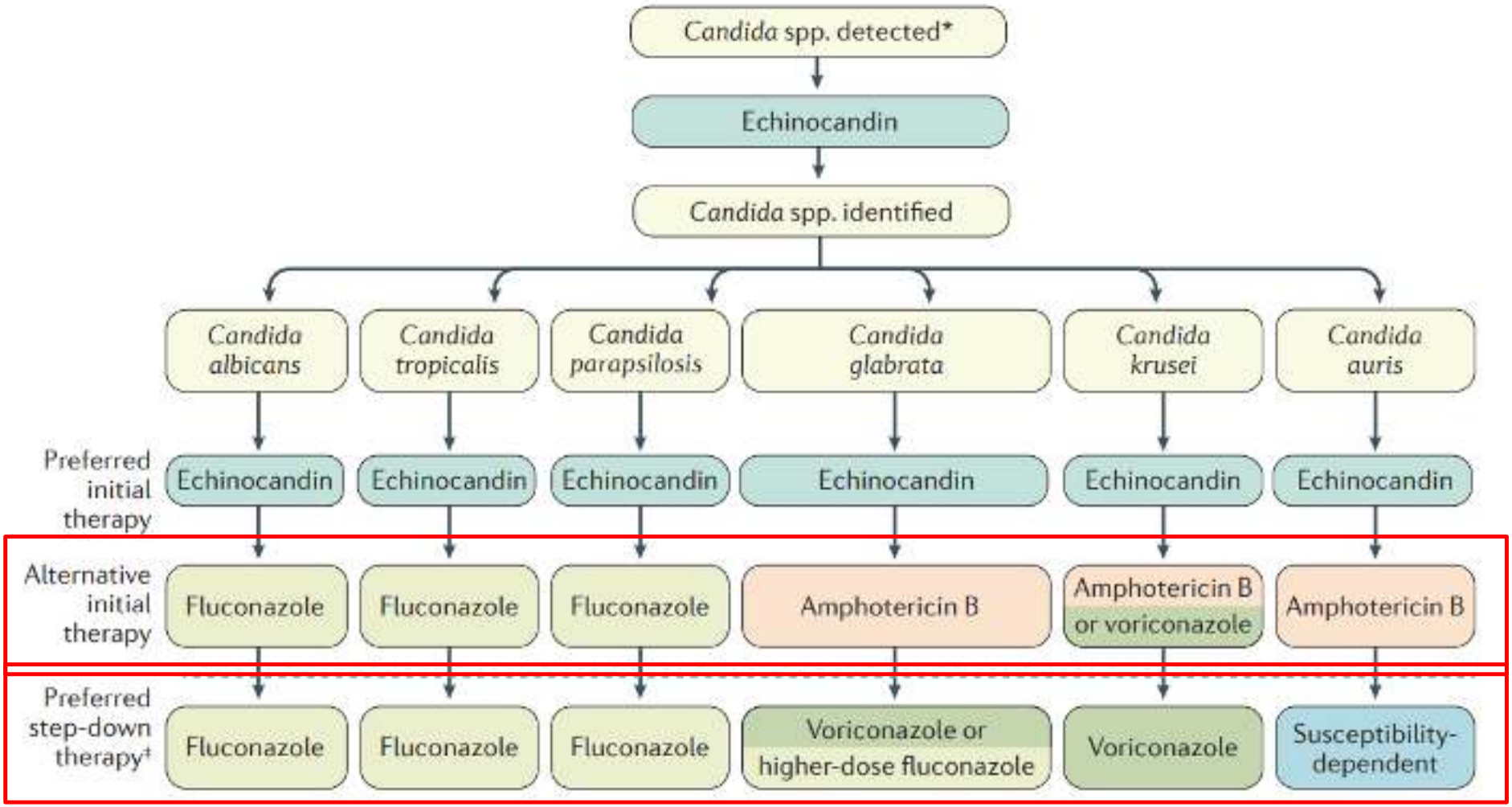
Dodds-Ashley. Clin Infect Dis 2006; 43: S28–39.
Riddell, et al. Clin Infect Dis 2011; 52: 648-53.

Activities of Antifungal Agents against *Candida* species

Species	Fluconazole	Itraconazole	Voriconazole	Posaconazole	Isavuconazole	Amphotericin B	Echinocandins
C. albicans	S	S	S	S	S	S	S
C. tropicalis	S	S	S	S	S	S	S
C. parapsilosis	S	S	S	S	S	S	S to R
C. glabrata	S-DD to R	S-DD to R	S-DD to R	S-DD to R	S-DD to R	S to I	S
C. krusei	R	S-DD to R	S	S	S	S to I	S
C. lusitaniae	S	S	S	S	S	S to R	S
C. auris	R	R	R	R	R	S to R	S to R

S: susceptible; S-DD: susceptible dose-dependent; I: intermediate; R: resistant

Pappas, et al. Clin Infect Dis 2009; 48: 503-35.
Nett, et al. Infect Dis Clin N Am 2016; 51-83.



Pappas, et al. Nat Rev Dis Primers 2018; 4: 18026.

Candidiasis

T.R's blood culture is identified as Candida parapsilosis. He was empirically started on Micafungin, his line was removed/replaced, and he was de-escalated to fluconazole 200 mg PO daily. Five days into his fluconazole course, his QTc increased from 480 msec to 537 msec (normal QRS).

What is the best option to complete T.R.'s antifungal therapy?

A. Continue fluconazole PO

B. Change back to micafungin IV

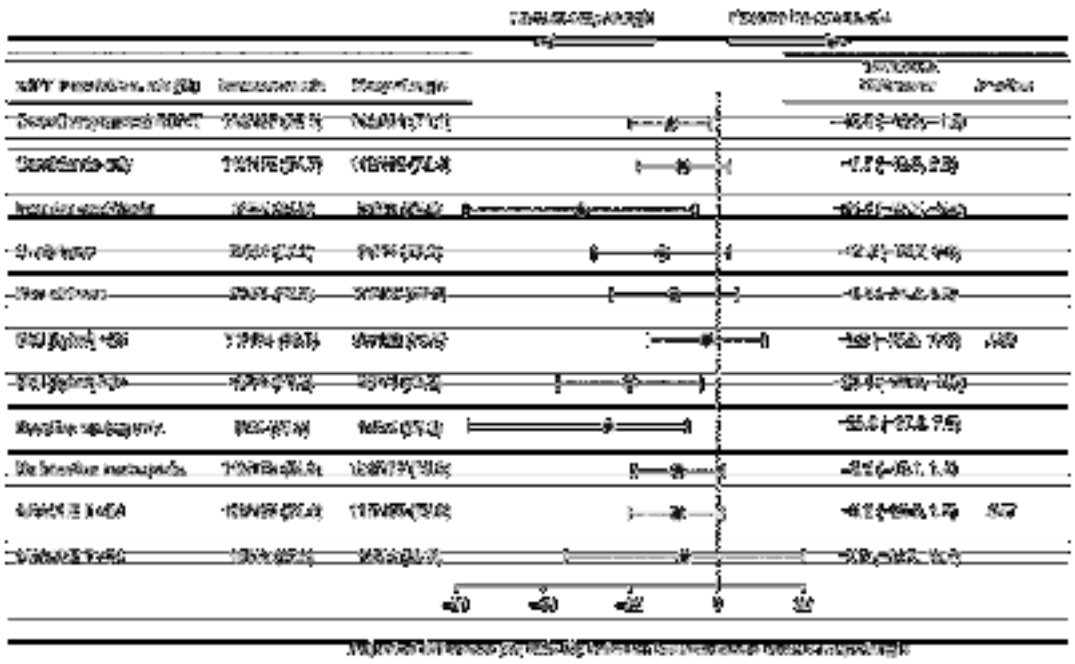
C. Change to isavuconazole PO

D. Change to voriconazole PO

Isavuconazole Versus Caspofungin in the Treatment of Candidemia and Other Invasive Candida Infections: The ACTIVE Trial

Isavuconazole did not meet non-inferiority criteria

- Overall response at EOIVT: successful outcome 60.3% in isavuconazole group vs. 71.1% in caspofungin group (adjusted difference: -10.8%; 95% CI -19.9–-1.8)
- Overall response rates at 2 weeks after EOT and mortality were similar



Invasive Aspergillosis

Risk factors

- Profound and persistent neutropenia
- Repeated cycles of prolonged neutropenia
- Corticosteroids
- GVHD
- HSCT (allo > auto)
- Hematologic malignancies
- SOT (lung > liver > heart)
  - Reoperation/retransplant
  - Rejection
  - CMV infection
  - Renal failure (especially requiring hemodialysis)
  - Aspergillus colonization

Most common species

- A. fumigatus
- A. flavus
- A. niger
- A. terreus

Invasive Aspergillosis

A.F. is a 67 yo woman with AML. She is neutropenic on broad-spectrum antimicrobials, with fever and new respiratory symptoms. A CT scan is obtained and is suggestive of invasive fungal infection with a halo-sign. Invasive aspergillosis is strongly suspected.

Based on the IDSA guidelines, which antifungal regimen should be initiated in A.F.?

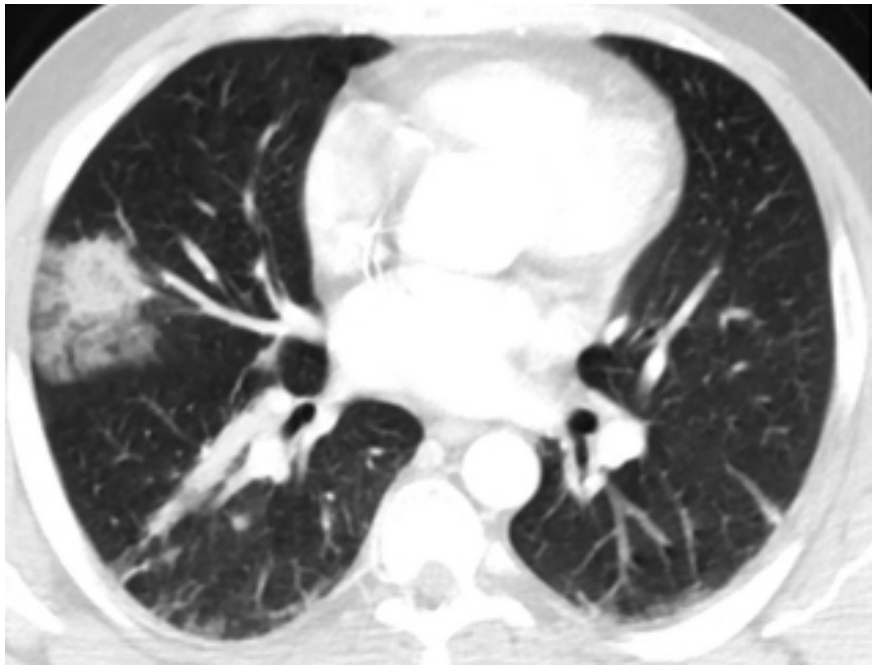
A. Liposomal amphotericin B

B. Fluconazole

C. Voriconazole

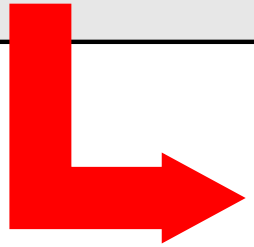
D. Micafungin

E. Voriconazole plus anidulafungin



IDSA Treatment Guidelines - IA

Primary	Alternatives
Voriconazole 6 mg/kg q12h x2, then 4 mg/kg q12h	• **L-AMB 3-5 mg/kg/d, isavuconazole** • ABLC 5 mg/kg/d • Caspofungin • Micafungin • Posaconazole • Itraconazole



	Voriconazole (144)	Amphotericin B (133)
12-week survival (%)	70.8	57.9
12-week complete/partial response (%)	52.8	31.6
Treatment duration (days)	77	10

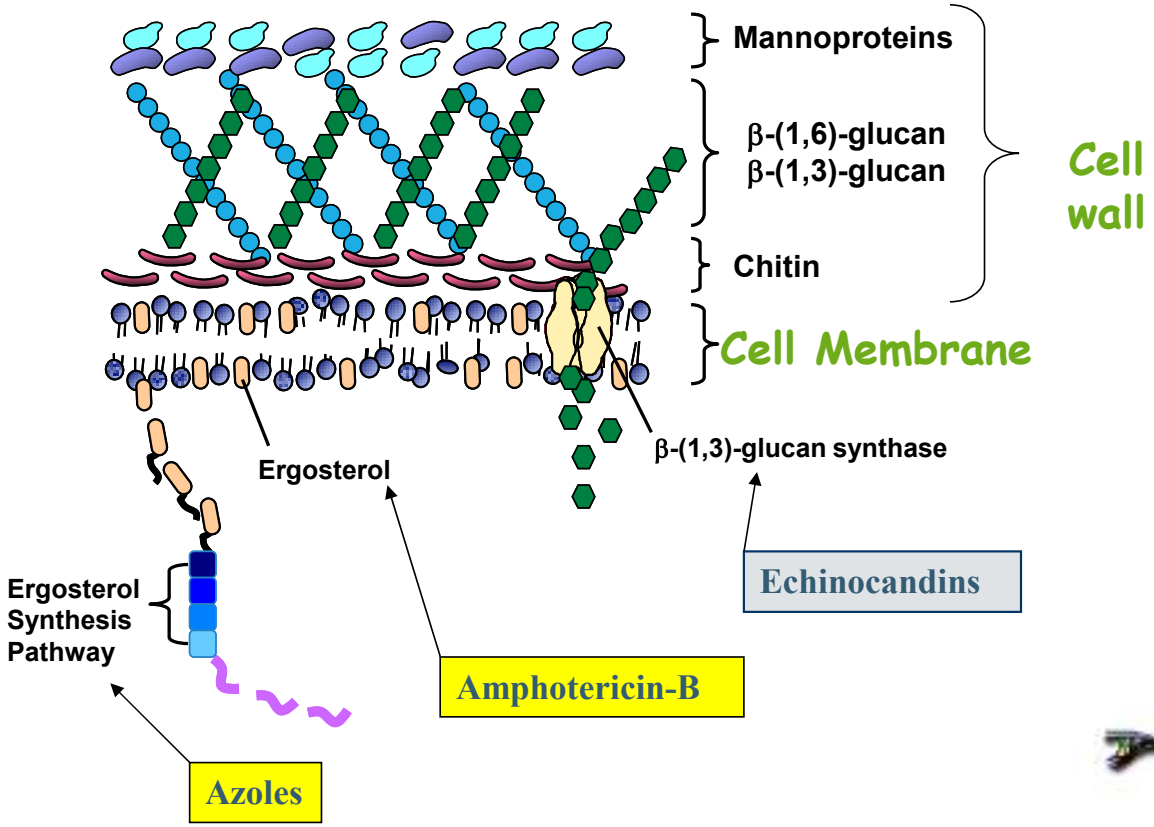
Patterson, et al. Clin Infect Dis 2016; 63: e1-60.
Herbrecht, et al. NEJM 2002; 347: 408-15.

IDSA Treatment Guidelines - IA

Primary	Alternatives	Comments
Voriconazole 6 mg/kg q12h x2, then 4 mg/kg q12h	• **L-AMB 3-5 mg/kg/d, isavuconazole** • ABLC 5 mg/kg/d • Caspofungin • Micafungin • Posaconazole • Itraconazole	Primary combination therapy is not routinely recommended based on lack of clinical data; addition of another agent or switch to another drug class for salvage therapy may be considered in individual patients

Patterson, et al. Clin Infect Dis 2016; 63: e1-60.
Herbrecht, et al. NEJM 2002; 347: 408-15.

Combination Therapy



Slide adapted from R. Lewis; posted at www.doctorfungus.org.

Initial Combination Therapy

Study	Population	Sample size	Design	Regimen-Combo	Regimen-Monotherapy	Outcome measure	Outcome
Kontoyiannis, et al (Cancer 2005)	Heme Malignancy	112 (11 C, 101 M)	Cohort	Lipid ampho + Itra IV/PO	Lipid ampho	Favorable response (EOT)	**NO BENEFIT** 0% combo vs. 10% mono (p=ns)
Singh, et al (Transplantation 2006)	Solid Organ Transplant	87 (40 C, 47 M)	Cohort	Vori + Caspo	Lipid ampho	Mortality (3 mos)	**NO BENEFIT** 68% combo vs. 51% mono (p=0.117) • *Beneficial in subset with renal failure or A. fumigatus infection*
Upton, et al (CID 2007)	HSCT	405 (33 C, 372 M)	Cohort	Vori + Caspo (33)	Voriconazole (58) (Ampho or Lipid Ampho)	Mortality	**NO BENEFIT** Unadj HR 2.3 (0.6-9.4; p=0.23)
Raad, et al (Leukemia 2008)	Heme Malignancy	143 (38 C, 105 M)	Cohort	Lipid ampho (≥ 7.5 mg/kg/d) + caspo (38)	Posaconazole (53)	Favorable Response (EOT or 3 mos) Mortality (3 mos)	**BENEFIT** 11% combo vs. 40% mono (p=0.002) 74% combo vs. 43% mono (p=0.004)
Caillot, et al (Cancer 2007)	Heme Malignancy	30 (15 C, 15 M)	Open, RCT	Lipid ampho (3 mg/kg/d) + caspo	Lipid ampho (10 mg/kg/d)	Favorable response (EOT)	**BENEFIT** 67% combo vs. 27% mono (p=0.028)

Combination Vori/Anidulafungin vs. Vori Monotherapy – Primary Therapy

Prospective, randomized double-blind

- Allo-HSCT/heme malignancy patients
- 142 monotherapy vs. 135 combination
- Combination therapy x 2-4 weeks, at 2 weeks could switch to monotherapy

Primary endpoint: survival at 6 weeks

Table 2. Outcomes according to regimen in the modified intent-to-treat population[1]

Outcome	Voriconazole monotherapy	Combination therapy	p value	95% CI
Death (week 6), n (%)	39 (27.5)	26 (19.3)	0.0868	-19, 1.5
Secondary endpoints				
Death (week 12), n (%)	55 (39.4)	39 (29.3)	0.0766	-21.4, 1.09
Death due to IA (week 6), n (%)	33 (23.9)	23 (17.3)	0.2058	-15.9, 3.42
Global response – success, n (%)	61 (43)	44 (32.6)	0.0782	-21.6, 1.15
Complete response	17 (12)	8 (5.9)		
Partial response	44 (31)	36 (26.7)		
Stable response	19 (13.4)	26 (19.3)		
Failure	7 (4.9)	8 (5.9)		
Death, probable IA, n (%)[2]	39 (27.9)	24 (18.2)	0.0504	-20.1, 0.3
Death, probable IA – GM only[3]	30 (27.3)	17 (15.7)	0.0372	-22.7, -0.4

[1]p values based on two-sided Z test for the difference in response rates, adjusted for randomization strata, using the normal approximation to the binomial distribution; [2]Calculated from 272 patients with probable IA; [3]Calculated from 218 patients with probable IA based on positive GM only

CI, confidence interval; GM, galactomannan; IA, invasive aspergillosis

Take home → combination therapy may be of benefit in patients with clinical symptoms *plus* galactomannan positive AND combination therapy may only be necessary for 2 weeks

Marr, et al. Ann Intern Med 2015;162(2):81-9.

Isavuconazole vs. Voriconazole for IA

Primary treatment

Primary endpoint: no difference in all-cause mortality at day 42 in ITT population

- 19% in isavuconazole groups vs. 20% in voriconazole group (adjusted treatment difference –1.0%, 95% CI −7.8 to 5.7)

Less treatment emergent adverse events in isavuconazole group

- Lower frequency of hepatobiliary disorders, eye disorders, and skin/subcutaneous tissue disorders

No altered/TDM dosing of voriconazole

	Isavuconazole	Voriconazole	Adjusted treatment difference (95% CI)*
DRC-assessed response (mITT population)			
Overall response at EOT§	143	129	
Success	50 (35%)	47 (36%)	1·6% (−9·3 to 12·6)
Complete	17 (12%)	13 (10%)	..
Partial	33 (23%)	34 (26%)	..
Failure¶	93 (65%)	82 (64%)	..
Stable	42 (29%)	33 (26%)	..
Progression	51 (36%)	49 (38%)	..
Clinical response at EOT§	85/137 (62%)	73/121 (60%)	0·4% (−10·6 to 11·5)
Mycological response at EOT§	54/143 (38%)	53/129 (41%)	3·8% (−7·4 to 15·1)
Radiological response at EOT§	41/141 (29%)	42/127 (33%)	5·7% (−4·9 to 16·3)

Posaconazole vs. Voriconazole for IA

Primary treatment

Primary endpoint: no difference in all-cause mortality at day 42 in ITT population

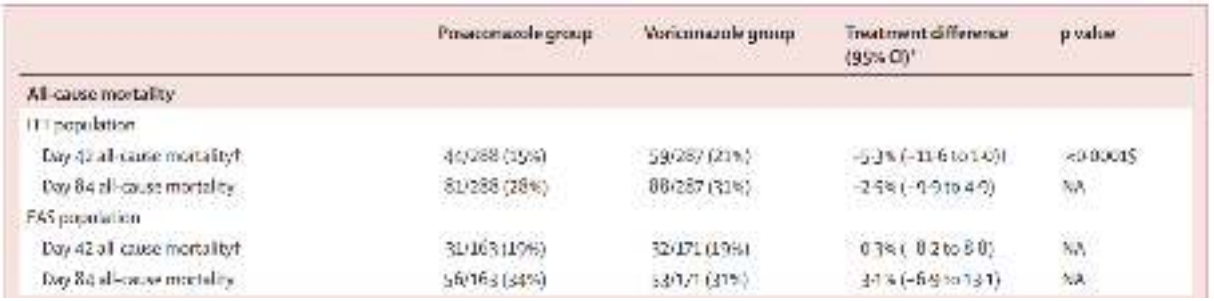
- 15% for posaconazole group vs. 21% for voriconazole group (treatment difference −5.3%, 95% CI −11.6 to 1.0)

Fewer drug-related adverse events with posaconazole

- Eye disorders, psychiatric disorders

More hypokalemia and decreased appetite with Posaconazole

No altered/TDM dosing of voriconazole



	Posaconazole group	Voriconazole group	Treatment difference (95% CI)*	p value
All-cause mortality				
ITT population				
Day 42 all-cause mortality†	46/288 (15%)	59/287 (21%)	−5.3% (−11.6 to 1.0)	<0.0001§
Day 84 all-cause mortality	81/288 (28%)	88/287 (31%)	−2.9% (−9.9 to 4.0)	NA
PAS population				
Day 42 all-cause mortality†	31/163 (19%)	32/171 (19%)	0.3% (−8.2 to 8.8)	NA
Day 84 all-cause mortality	56/163 (34%)	53/171 (31%)	3.1% (−6.5 to 13.1)	NA

Zygomycetes

Manifestations: rhinocerebral, pulmonary, gastrointestinal, cutaneous, and disseminated

Most common species
- Rhizopus
- Rhizomucor
- Mucor
- Absidia

Aggressive, fast growing, non-septate molds
- Tissue necrosis common

Risk factors
- Hematologic malignancy
- Prolonged and profound neutropenia
- Poorly controlled diabetes mellitus
- Prolonged corticosteroid use
- Iron overload
- Malnutrition
- Illicit intravenous drug use
- Premature birth

Mortality 44% in DM, 35% in patients with no underlying conditions, and 66% in patients with malignancies
- 96% mortality with disseminated infections

Petrikkos, et al. Clin Infect Dis 2012:54:S23-34.

Zygomycetes

Zygomycetes Antifungal Therapy

Liposomal amphotericin B (5-10 mg/kg/d)

- Improved survival rate compared to conventional amphotericin B (67% vs. 39%)
- Liposomal > ABLC
- Limited by nephrotoxicity

Isavuconazole

- Compared to historical amphotericin B data
- Day-42 crude all-cause mortality 33% of 21 isavuconazole cases similar to 39% of 33 amphotericin B-treated matched controls
- Limited by small sample size, external control matching

Posaconazole

- Not considered first-line
  - Posaconazole relatively ineffective in pre-clinical animal models
  - Breakthroughs during posaconazole prophylaxis
- Limited to salvage therapy (~60% response rate)

Spellberg, et al. Curr Infect Dis Rep. 2010; 12(6): 423–429.
Dannaoui, et al. J Antimicrob Chemother 2003; 51:45–52.
Marty, et al. Lancet Infect Dis 2016;16(7):828-837.
van Burik, et al. Clin Infect Dis 2006; 42:e61–e65.

Cryptococcus neoformans

Encapsulated yeast

- Grows naturally in environment
- Found in pigeons nests, droppings

C. neoformans var *neoformans*

- Immunocompromised
- Mortality rate 12-28% overall

Pulmonary and disseminated/CNS diseases most common

Cryptococcus neoformans

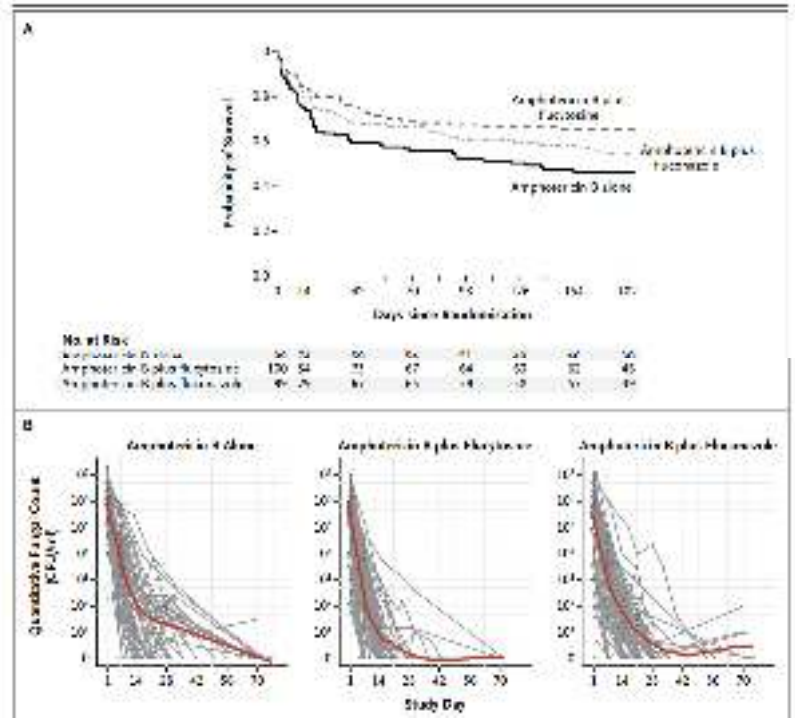
Amphotericin B = main therapy

Combination with flucytosine

- Combination most potent fungicidal regimen with faster CSF sterilization and fewer relapses, lower attributable mortality

Fluconazole

- Substitute for flucytosine
- Fungistatic effect on *Cryptococcus* sp.
- Associated with increased mortality
- Monotherapy in consolidation and maintenance therapy



Maziarz, et al. Infect Dis Clin North Am 2016; 30(1): 179–206.
Day, et al. N Engl J Med 2013; 368: 1291.

Flucytosine

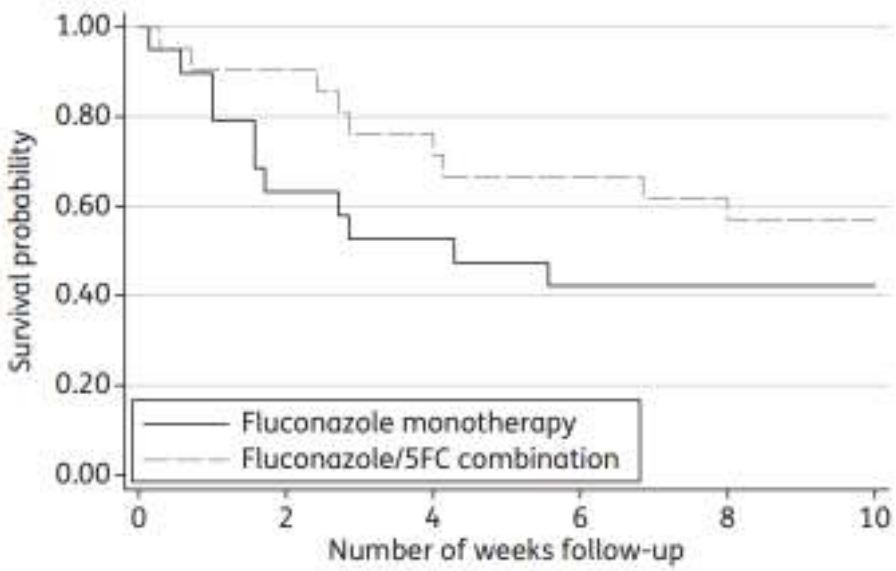
Synthesized in 1957 as an anti-tumor agent

Active against *Candida* sp and *Cryptococcus* sp.

Mechanism: converted to 5-FU which causes RNA miscoding and inhibits DNA synthesis

Significant bone marrow suppression

- Prolonged high serum levels >100 mg/L
- 75-100 mg/kg/d
- Renal elimination, often used with ampho B
- Check 2-hr post dose level: goal 30-80 mg/L



Nussbaum, et al. Clin Infect Dis 2010; 50(3): 338–344.
Perfect, et al. Clin Infect Dis 2010;50(3):291-322.
Vermes, et al. Chemotherapy 2000;46(2):86-94.

Antifungal Stewardship

Delays in diagnosis and appropriate therapy → poorer outcomes

Increased antifungal utilization especially ICUs and transplant centers

Emerging antifungal resistance

Opportunities

- Diagnostics
- De-escalation
- Limiting combination therapy
- Therapeutic drug monitoring
- Drug-drug interaction management
- Guidelines / Education
- IV to PO conversion

Hamdy, et al. Virulence 2017; 8(6): 658–672.
Johnson, et al. J Infect Dis 2020;222(Suppl 3):S175-S198.

Summary

Appropriately assess risk factors for fungal disease in at-risk populations

Choice of antifungal agents based on likely pathogens, pharmacokinetics, toxicity and drug interaction potential

Optimize dosing based on therapeutic drug monitoring

Explore opportunities for antifungal stewardship

Assessment Question #1

Which of the following azole antifungals is not associated with QTc-prolongation?

A. Fluconazole

B. Voriconazole

C. Posaconazole

D. Isavuconazole

Assessment Question #2

Which of the following infusion-related adverse effects to you most expect to see while monitoring a patient receiving intravenous amphotericin B?

A. Anemia

B. Fever and chills

C. Hypokalemia

D. Diarrhea

Assessment Question #3

Which of the following antifungals causes clinically significant drug-drug interactions through inhibition of CYP2C9 or CYP2C19?

A. Micafungin

B. Isavuconazole

C. Voriconazole

D. Posaconazole

Assessment Question #4

Which of the following *Candida* species is notable for its resistance to azole antifungals, persistence in the environment, and association with healthcare-associated infections?

A. *Candida albicans*

B. *Candida lusitaniae*

C. *Candida glabrata*

D. *Candida auris*

Assessment Question #5

Minimal drug interactions and side effects with limited clinical utility in genitourinary and central nervous system fungal infections best characterizes which of the following antifungal classes?

A. Azoles
B. Polyenes
C. Echinocandins
D. Allylamines

Complexities of Antifungal Therapy Made Simple

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