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Vancouver Coastal Health

IDSA Treatment Guidelines for Candidiasis and Invasive Aspergillosis

Out with the old and in with the new!

Dr. Dawn Warkentin
 B.Sc (Pharm), PharmD
 Pharmacotherapeutic Specialist Heme/Onc
 CSU Pharmaceutical Sciences, VGH
 Clinical Associate Professor,
 Faculty of Pharmaceutical Sciences, UBC
 Dawn.warkentin@vch.ca



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IDSA Treatment Guidelines for Candidiasis and Invasive Aspergillosis: Out with the old and in with the new!

Learning Objectives:

1. To discuss changes in the IDSA treatment guidelines for the treatment of candidiasis and aspergillosis.
2. To discuss implications of these treatment guidelines changes on clinical practice.
3. Compare and contrast available antifungal agents and data to support their use in invasive mycosis.

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IDSA Treatment Guidelines for Candidiasis and Invasive Aspergillosis: Out with the old and in with the new!

Outline:

1. Review significant changes in guidelines in treatment of invasive aspergillus and candidiasis
 - Supporting evidence
 - Diagnostic testing
 - Therapeutic drug monitoring
2. Review available antifungal agents
 - Differences in activity
 - Differences in pharmacokinetics

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The Old...

Practice Guidelines for Diseases Caused by *Aspergillus*

From the Society of Infectious Disease Specialists and the Infectious Diseases Society of America

Enoch A. Smerdis,^{1,2,3,4} Virginia L. Kline,^{5,6} Mark A. Jenkins,^{7,8} V. Bal G. Subramanian,^{9,10} Joseph D. Tenover,¹¹ David M. Fleming,¹² John H. Burdick,¹³ Thomas J. Walsh,¹⁴ Thomas F. Patterson,¹⁵ and George A. Pankey,¹⁶

Clinical Infectious Diseases 2000;30:694-709

ISDA GUIDELINES

Guidelines for Treatment of Car

Peter G. Pappas,¹ John H. Rex,² Jack D. Sobel,³ Scott C. Fisher,⁴ William E. Dismukes,⁵ Thomas J. Walsh,⁶ and John E. Edwards,⁷

Division of Infectious Diseases, University of Alabama at Birmingham, Alabama; ²San Diego Pharmaceutical, Menlo Park, California; ³Wayne State University School of Medicine, Detroit, Michigan; ⁴Yale University School of Medicine, New Haven, Connecticut; ⁵University of California San Diego School of Medicine, San Diego, California; ⁶University of Michigan Medical Center, Ann Arbor, Michigan; ⁷University of Washington School of Medicine, Seattle, Washington

Clinical Infectious Diseases 2004;38:161-89

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Quality of Evidence

Table 1. Infectious Diseases Society of America–United States Public Health Service grading system for ranking recommendations in clinical guidelines.

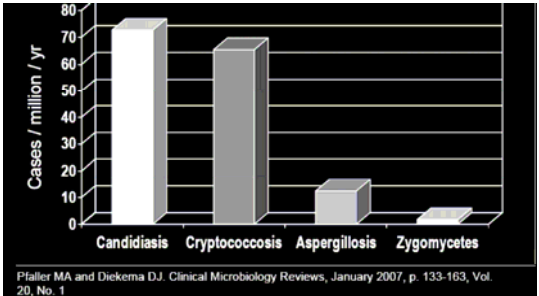
Category, grade	Definition
Strength of recommendation	
A	Good evidence to support a recommendation for use
B	Moderate evidence to support a recommendation for use
C	Poor evidence to support a recommendation
Quality of evidence	
I	Evidence from ≥1 properly randomized, controlled trial
II	Evidence from ≥1 well-designed clinical trial, without randomization, from cohort or case-controlled analytic studies (preferably from >1 center), from multiple time-series; or from dramatic results from uncontrolled experiments
III	Evidence from opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees

IDSA Guidelines for Aspergillosis • CID 2008;46 (1 February) • 329

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Incidence of Invasive Mycosis

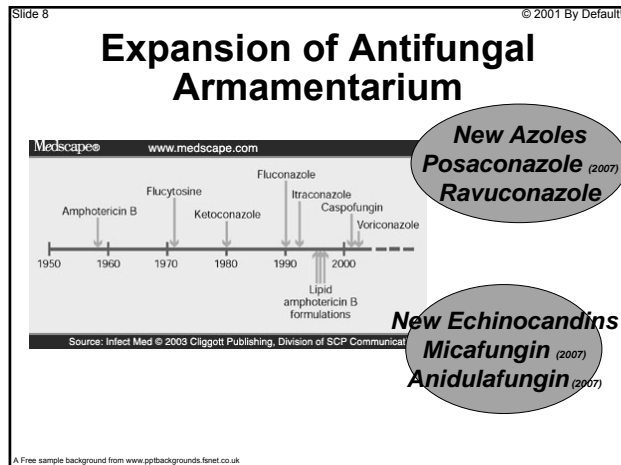
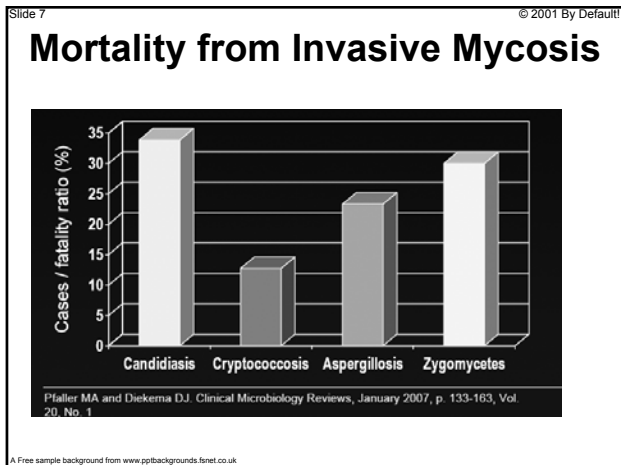


Mycosis	Incidence (Cases / million / yr)
Candidiasis	~75
Cryptococcosis	~65
Aspergillosis	~15
Zygomycetes	~5

Pfaller MA and Diekema DJ. Clinical Microbiology Reviews, January 2007, p. 133-163, Vol. 20, No. 1

US National Hospital Discharge Survey statistics
 Candida species is 4th leading cause of nosocomial bloodstream infections

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- Slide 9 © 2001 By Default!
- ## 2008 IDSA Guidelines: Management of Invasive Aspergillosis (IA)
- Invasive pulmonary aspergillosis
 - Diagnosis
 - Available antifungal agents
 - Therapeutic drug monitoring
 - Primary therapy
 - Salvage therapy
 - Prophylaxis
 - Combination therapy
 - Adjunctive therapy
 - Surgery
 - Immunomodulation
 - Extrapulmonary aspergillosis
 - Chronic, saprobitic, and allergic forms
- Walsh et al. Treatment of Aspergillosis: Clinical Practice Guidelines of the Infectious Disease Society of America. CID 2008;46:327-60.
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- ## Advances in diagnosis of IA
- Diagnosis should be aggressively pursued whenever possible
 - EORTC definition (European Organization for Research in Treatment of Cancer – Invasive Fungal Infection Cooperative Group)
 - Diagnostic imaging
 - Halo sign and air-crescent sign by CT
 - Non-culture based diagnosis
 - Galactomannan Antigen EIA
 - Used in combination with CT findings for early initiation of therapy and to assess response
 - Not HC approved
 - Promising but remains investigational
 - Surrogate marker
 - Be aware of false positive results
-
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- ## Recommended approach for therapeutic drug monitoring (TDM)
- Rationale:
 - Evidence shows patient to patient variability in pharmacokinetics of triazoles
 - Absorption (itra and posa), drug interactions (all), and pharmacogenetics (vori).
 - Not enough data to generate consensus or specific recommendations
-
- Recommend TDM when evaluating reasons for therapeutic failure or toxicity (B-III)
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- ## Therapeutic Drug Monitoring (TDM)
- What the guidelines say:
 - Itraconazole:
 - Measure levels to document absorption (B-II)
 - Limited evidence but >250ng/ml – more favorable outcome
 - Voriconazole
 - Measure levels especially with oral therapy
 - Potential toxicity
 - Document adequate response (B-III)
 - Posaconazole
 - Limited data, one study observed an association between concentration and response in salvage invasive aspergillosis
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Other recent publications of TDM

	Target Range	Comment
Itraconazole	Trough >0.5 mcg/mL	After 7days on therapy to ensure absorption
Voriconazole	Trough >2mcg/mL Peak <6mcg/mL Avg. 1.25mcg/mL	After 7days on therapy Efficacy, toxicity
Posaconazole	Level TBD	Average >1.25 mcg/mL assoc with response
Flucytosine	<100 mcg/mL	Obtain 2hr after oral dose; toxicity seen with >100mcg/mL

TDM not recommended for amphotericin B, fluconazole, or echinocandins

Dodds Ashley ES, et al. Clin Infect Dis 2006;43:S28-39. Goodwin ML, et al. Antimicrob Chemother 2007;61:17-25.


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Voriconazole TDM

Fungus Testing Laboratory
University of Texas Health Science Center
7703 Floyd Curl Drive
San Antonio, Texas 78284
Contact: Gennethel Pennick
ph-210-567-4131
pennick@uthscsa.edu

Focus Technology
5785 Corporate Ave.
Cypress, California 90630
Contact: Dr. Howard Engler
ph-714-220-2065
fax-714-484-1296
email:hengler@focusanswers.com



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Recommended approach for primary therapy of IA


Early initiation of therapy (A-I)

Voriconazole IV (A-1)

Dose:

- 6mg/kg IV q12h X 2 then 4mg/kg IV q12h
- Step down to 200mg PO BID (maximize oral dose by using 4mg/kg)

Consider drug interactions, ADR's, dosing issues, renal function with IV




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Voriconazole vs Amphotericin B for Primary Therapy of Invasive Aspergillosis

Herbrecht R et al. N Engl J Med 2002;347:408-15.



Definite or probable aspergillosis

Voriconazole 6mg/kg IV BID X1 day
then 4mg/kg IV BID X ≥7 days
then 200mg PO BID

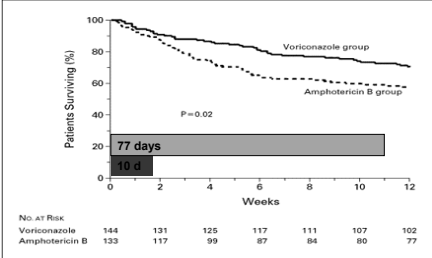
Amphotericin B
1-1.5mg/kg/day

Randomized, unblinded, MC trial

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Voriconazole vs Amphotericin B for Primary Therapy of Invasive Aspergillosis



Survival at 12 wk in MITT group
Vori: 70.8%
AmB: 57.9%

Authors conclusions: This study shows the superiority of voriconazole over amphotericin B as initial therapy for invasive aspergillosis, in terms of response rate, survival rate, and safety

Herbrecht R et al. N Engl J Med 2002;347:408-15.

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What is an alternate agent for primary therapy?

- Lipid formulation of amphotericin B (A-I)
 - Dose: 3-5mg/kg/day IV

Randomized trial looking at two doses of L-amphotericin B

- 3 mg/kg/day was as effective and less toxic than 10mg/kg/day for first 14 days*

e.g. patients where there is contraindication to voriconazole

* Cornely OA, et al. Liposomal amphotericin B as initial therapy for invasive mold infection: a randomized trial comparing a high-loading dose regimen with standard dosing. Clin Infect Dis 2007;44:1289-97.


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What is another alternate agent for primary therapy?

Resource-limited settings

- “Amphotericin B deoxycholate may be the only agent and should be considered standard of care”
- \$53/day




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Recommended approach for salvage therapy of IA

- Include the following:
 - Lipid formulations of amphotericin B (LFAB)
 - Itraconazole
 - Posaconazole
 - Caspofungin
 - Micafugin
- Refractory to Voriconazole?
 - Paucity of data
- Change of class of agents and/or combination



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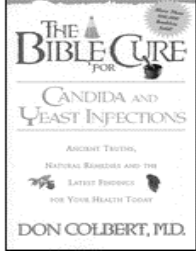
Recommended approach for combination therapy in IA

- Not well-controlled clinical trials for routine administration for primary therapy
 - potential role in salvage therapy
- Paramount is reversal of immunosuppression or recovery from neutropenia

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2008 Proposed IDSA Guidelines: Management of Candida Infections



Pappas PG et al. 2007 IDSA Annual Meeting

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Recommended approach for treatment of candidemia/invasive candidiasis

Uncomplicated
Non-neutropenic
Hemodynamically stable
No recent azole exposure
Not colonized with *C. glabrata* or *krusei*

↓

Start IV fluconazole
800mg IV x1 → 400mg IV qday → PO

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Recommended approach for treatment of candidemia/invasive candidiasis

Complicated
Neutropenic
Hemodynamically unstable
Recent azole exposure
Colonized with *C. glabrata* or *krusei*

↓

Start Echinocandin

- Caspo 70mg LD → 50mg IV qday or
- Mica 100mg IV qday or
- Anidula 200mg LD → 100mg IV qday

OR LFAB 3mg/kg/day


Transition to PO fluco/vori only if sensitivities known

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Which agent to use for invasive candida - Echinocandins


- MIC and pharmacokinetic differences small
- More experience with Caspofungin
- Micafungin dose is determined (100mg)
- Caspo/mica equivalent
- No future studies likely
- Consider all three therapeutically equivalent



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What is about in resource-limited settings when echinocandins or LFAB are unavailable?



- "Amphotericin B deoxycholate 0.5-1.0mg/kg/day should be considered standard of care"
- Transition to fluconazole when you have an isolate with predictable sensitivities

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Recommended approach for treatment of candidemia/invasive candidiasis


- Voriconazole
 - Offers little advantage over fluconazole as primary therapy
 - Limited to transition to PO in selected cases (e.g.. *C. krusei*)
- Intravenous catheter removal recommended
- Duration of therapy
 - Candidemia: at least 2 weeks after last positive culture and resolution of symptoms
 - Candidiasis: not studied

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When are the echinocandins NOT the drug of first choice?

- Sanctuary Sites
 - Endophthalmitis?
 - Endocarditis?
 - CNS infections?
 - Candiduria
- C. Parapsilosis in complicated situations such as endocarditis or osteomyelitis



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Quality Improvement Measures

- Fundoscopic exam on all patients with proven invasive candidiasis
- Start antifungal agents within 24 hours of positive culture
- Confirmatory negative cultures (i.e.. get follow up cultures to document clearance)

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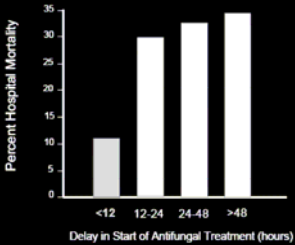
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Time to therapy-does it matter?

134 patients with *Candida* bloodstream infections over 4 years (2001-2004)

Only 5.7% received antifungal treatment within 12 hours of 1st blood sample

Delayed empiric antifungal treatment 12 hours after a positive blood sample is associated with greater hospital mortality



Delay in Start of Antifungal Treatment (hours)	Percent Hospital Mortality
<12	~10
12-24	~30
24-48	~32
>48	~35

Morrell M, et. Antimicrob Agents Chemother. 2005;49:3640-5.

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2008 Proposed IDSA Guidelines: Management of Candida Infections

- Major changes from 2004
 - Emphasis on fluconazole and echinocandins as the "preferred choices" for proven/suspected cases
 - De-emphasis on AmB and LFAB under most circumstances
 - Concept of step-down therapy is strongly encouraged
 - Voriconazole generally advised as step-down therapy for selected isolated (e.g. *C. krusei* and other isolates with known susceptibility data)
 - More emphasis on species identification and susceptibility

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2008 Proposed IDSA Guidelines: Management of Candida Infections

- Major changes from 2004
 - Little distinction made between echinocandins
 - Fluconazole prophylaxis in neonatal units limited to high risk sites
 - Consideration of resource-limited environments

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Review of Currently Available antifungal agents

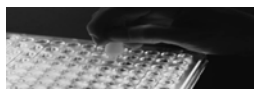
Availability	PO	IV
Azoles		
itra, fluco, vori	+	+
posaconazole	+	-
Polyenes		
amphotericin B deoxycholate and lipid formulations of amphotericin B (LFAB)	-	+
Echinocandins		
casprofungin, micafungin, anidulafungin	-	+

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Recent advances in susceptibility testing for *Aspergillus* sp.

- Development of standardized susceptibility testing for *Aspergillus* species.
- Aspergillus* spp. sent to reference lab in Edmonton
 - Some clinical correlation with azoles and amphotericin
- Interpretive breakpoints not established for any antifungal agents against filamentous fungi.
- Non-aspergillus molds difficult to interpret MIC data
- Often data from animal models do not correlate clinically



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Recent advances in susceptibility testing for *Candida* sp.

- Clinical and Laboratory Standards Institute (CLSI) has developed reproducible standardized testing of azoles against *Candida* spp.
 - Clinical correlation best for patients with oropharyngeal/esophageal candidiasis and *C. albicans*
 - Not as good correlation with systemic infections and other yeasts
- CLSI developed standardized testing and determined MIC's for echinocandins but poor clinical correlation

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Spectrum of Activity

Table 1. Antifungal spectrum of activity against common fungi.

Organism	Antifungal agent								
	AmB ^a	Flu	tr	vor	pos	Anidulafungin	Caspofungin	Micafungin	Fluocytosine
<i>Aspergillus</i> species	+	—	+	+	+	+	+	+	—
<i>A. fumigatus</i>	+	—	+	+	+	+	+	+	—
<i>A. niger</i>	+	—	+	+	+	+	+	+	—
<i>A. terreus</i>	—	—	+	+	+	+	+	+	—
<i>Candida</i> species	+	+	+	+	+	+	+	+	+
<i>C. albicans</i>	+	+	+	+	+	+	+	+	+
<i>C. glabrata</i>	+	+	+	+	+	+	+	+	+
<i>C. krusei</i>	+	+	+	+	+	+	+	+	+
<i>C. lusitanae</i>	—	+	+	+	+	+	+	+	+
<i>C. parapsilosis</i>	+	+	+	+	+	+	+	+	+
<i>C. tropicalis</i>	+	+	+	+	+	+	+	+	+
<i>Cryptococcus neoformans</i>	+	+	+	+	+	+	+	+	+
<i>Cryptosporidium</i> species	+	+	+	+	+	+	+	+	+
<i>Blastoschizum</i> species	+	+	+	+	+	+	+	+	+
<i>Histoplasma</i> species	+	+	+	+	+	+	+	+	+
<i>Pneumocystis carinii</i>	+	+	+	+	+	+	+	+	+
<i>Sporothrix schenckii</i>	+	+	+	+	+	+	+	+	+
<i>Sporothrix brasiliensis</i>	+	+	+	+	+	+	+	+	+
<i>Dermoglyphis</i>	+	+	+	+	+	+	+	+	+

NOTE: Flu (+) indicates that the antifungal agent has activity against the organism specified. Flu (-) indicates that the antifungal agent does not have activity against the organism specified. Flu (+/-) indicates that the agent has variable activity against the organism specified. AmB, amphotericin B; Flu, fluconazole; tr, terbinafine; pos, posaconazole; vor, voriconazole. Data are derived from [2, 3].

^a Includes lipid formulations.

^b In vivo data show that the echinocandins, specifically, micafungin may have variable activity against the dimorphic fungi, depending on whether they are in the mycelial or yeast-like form. In this, there has been one case report of successful therapy with casprofungin for *C. immitis* infection.

S30 • CID 2006:43 (Suppl 1) • Dodds Ashley et al.

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Spectrum of Activity: Echinocandins

Activity	Species
Highly Active Low MIC, fungicidal	<i>C. albicans, glabrata, tropicalis, krusei, kefyr</i> <i>P. jirovecii</i>
Very Active Low MIC without fungicidal activity mostly	<i>C. parapsilosis, guilliermondii, lusitanae</i> <i>A. fumigatus, flavus, terreus</i>
Some Activity Might have therapeutic potential (?combination)	<i>Coccidioides immitis, B. dermatitidis, Scedosporium spp, P. variotii, H. capsulatum</i>
Inactive	<i>Zygomycetes, Cryptococcus neoformans, Fusarium, Trichosporon</i>


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- ## Echinocandin's spectrum of activity - summary
- No consistent relevant differences between echinocandins
 - MIC's in vitro studies vary depending on center and medium
 - *C. parapsilosis* - ↑ MIC in all 3 but ? clinical relevance
 - For candida and aspergillus infections: choice of agent is not species driven
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Pharmacokinetic considerations

Table 3. Suggested dose modifications for antifungal agents, by type of organ dysfunction.



Type of organ dysfunction	Antifungal agent											
	AmB	ABCD	ABLC	LAB	Flu	Itr	Vor	Pos	Anidulafungin	Caspofungin	Micafungin	Flucytosine
Hepatic	None	None	None	None	None	None	Decrease dose for mild-to-moderate cirrhosis	None	None	Decrease dose for moderate inefficiency	None	None
Renal	None	None	None	None	Increase dose	Caution with iv preparation for ClCr <30 mL/min	Caution with iv preparation for ClCr <50 mL/min	None	None	None	None	Increase dose

NOTE: ABCD, amphotericin B colloid dispersion; ABLC, amphotericin B lipid complex; AmB, amphotericin B; ClCr, creatinine clearance; Flu, fluconazole; Itr, itraconazole; LAB, liposomal amphotericin B; Pos, posaconazole; Vor, voriconazole. Data are derived from [37, 41, 45, 47, 54, 80, 81, 90, 92].

Pharmacology of Systemic Antifungal Infections • CID 2006:43 (Suppl 1) • S33

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Drug Interactions - Azoles

Table 4. Summary of azole-mediated cytochrome P450 drug-drug interactions.

Drug mechanism	Drug			
	Flu	Itr	Pos	Vor
Inhibitor	2C19			+++
	2C9	+		++
	3A4	++	+++	+++
Substrate	2C19			+++
	2C9			+
	3A4	+++		+

NOTE: Plus signs indicate degree of activity: +, minimal activity; ++, moderate activity; and +++, strong activity. Flu, fluconazole; Itr, itraconazole; Pos, posaconazole; Vor, voriconazole. Data are derived from [37, 41, 45, 95, 96].

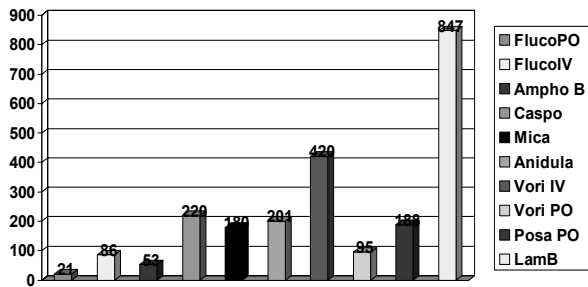
Pharmacology of Systemic Antifungal Infections • CID 2006:43 (Suppl 1) • S33

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- ## Drug Interactions - Echinocandins
- Caspofungin**
- ↑ Caspo by CSA (33%) – controversial
 - ↓ AUC tacrolimus by 20%
 - ↓ Caspo by P450 inducers such as rifampin, phenytoin, carbamazepime, nelfinavir, efavirenz
 - (↑ dose from 50 mg to 70mg/day)
- Micafungin**
- ↑ AUC of nifedipine and sirolimus
- Anidulafungin**
- No interactions reported
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- ## Common Drug Toxicities
- Amphotericin B and LFAB**
- Nephrotoxicity
 - Electrolyte abnormalities
 - Infusion-related reactions
- Azoles**
- LFT elevations, rash
 - Itra: GI disturbance
 - Vori: visual changes and hallucinations
- Echinocandins**
- Generally well tolerated
 - No major or significant difference between three drugs
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Relative "Econotoxicities"



Daily acquisition cost (\$) for treatment of invasive fungal infections

In conclusion....



- IDSA Primary treatment of IA
 - Voriconazole or LFAB
 - Resource limited: Amphotericin B deoxycholate
- IDSA Primary treatment of IC or candidemia
 - Stable patient: fluconazole
 - Unstable patient: echinocandin or LFAB
 - Resource limited: Amphotericin B deoxycholate

Consider: species and location of infection, organ function, pharmacokinetics, ADR's and drug interactions