

“There’s Fungus Among Us” 2008

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Objectives

- Describe the epidemiology
- Identify risk factors for infection
- Review common fungal infections
- Discuss special high-risk populations
- Differentiate between the various antifungal agents

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Patient Case - DB

- 62yom presents for Ex-lap, colonoscopy, rigid anoscopy, LOA, small bowel resection
- POD# 10 – sepsis, perc-drain RLQ
- Empiric antibiotics:
 - Zosyn 4.5g IV q6
 - Vancomycin 750mg IV q12
 - Fluconazole 800mg IV x1, then 400mg IV q24

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Epidemiology

- Fungal species account for up to 25% of all healthcare-associated blood infections
- *Candida spp.* account for 8-15% of all blood stream infections
- *C. albicans* accounts for 40-60% of the fungal infections
- *Aspergillus spp.* are the 2nd most common cause of fungal infections in cancer patients

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Richardson MD, JAC 2005;56(S1):i5.

Risk Factors

Underlying Conditions	Immune Defects	Iatrogenic Factors
<ul style="list-style-type: none"> • Burns (large ± inhalation inj.) • Cancer • <i>Candida</i> colonization • Cytomegalovirus (CMV) • Diabetes mellitus • Graft versus host disease • Hematological malignancies • HIV • Malnutrition • Organ transplantation 	<ul style="list-style-type: none"> • Granulocytopenia • Neutropenia • T-cell defects 	<ul style="list-style-type: none"> • Broad-spectrum antibiotics • Central venous catheters • Chemotherapy • High-dose steroids • Immunosuppressive therapy • Intra-abdominal surgery • Total parenteral nutrition

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Richardson MD, JAC 2005;56(S1):i5.
Sobel JD, et al. Contemporary Diagnosis & Management of Fungal Infections, 2003, pp.135.

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Sobel JD, et al. Contemporary Diagnosis & Management of Fungal Infections, 2003, pp.135.

Diagnosis

- Culture – single best tool
- Smear of body fluids and/or tissues
- Skin test – coccidioidin antigen
- Histopathology or special stains of biopsy specimens
- Serology – only moderately helpful

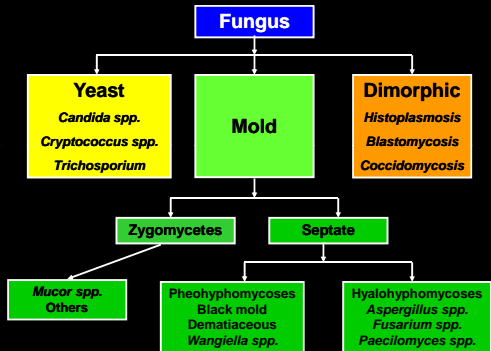
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Types of Invasive Fungal Infections

- Yeasts
 - *Candida spp.*
 - *Cryptococcus neoformans*
- *Aspergillus spp.*
- *Fusarium spp.*
- *Mucor spp.*
- Other fungi

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Emerging Fungal Pathogens



Ashley ESD. An update on antifungal therapy. FSHP 2006

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Yeast – *Candida spp.*

- Most common fungal pathogen
- Opportunistic pathogens
- 4th most common nosocomial bloodstream infection
- Portals of entry:
 - Gastrointestinal tract
 - Central venous catheters
- *C. albicans* versus non-*C. albicans*

Bustamante CL. *Cur Opin Infect Dis.* 2005; 16:490.

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Yeast – *Candida spp.*

- Most common types of infections
 - Mucosal candidiasis (thrush)
 - *Candida* esophagitis
 - *Candida* pneumonia
 - Candidemia
 - 25-50% of nosocomial candidiasis
 - 20% associated with central venous catheters

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Yeast – *Candida spp.*

- *C. albicans* = 80-90% of oropharyngeal colonization
- Also common fecal normal flora
- *C. albicans* & *C. glabrata* account for 70% of all *Candida* infections
- Drug of Choice (DOC): *Candida spp.* dependant



www.asm.org/Division/c/fungi.htm

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Yeast – *Candida spp.*

- At ORMC (July 2006 – June 2007 Sterile Sites):
 - 52% *C. albicans*
 - 48% *C. non-albicans*
- Other *Candida spp* concerns:
 - Biofilm formation on indwelling catheters
 - *C. albicans* resistance to fluconazole

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Yeast – *Candida spp.* Treatment

Table 2. Epidemiological distribution and common susceptibility patterns of *Candida* species

Species	Frequency (%)	Common Susceptibility Patterns				
		Amphotericin B	5-FC	Fluconazole and Itraconazole	Voriconazole and Posaconazole ²	Echinocandin ²
<i>C. albicans</i>	40-60	S	S	S	S	S
<i>C. glabrata</i>	20-30	S to I	S	S to I	S to S-DDI	S
<i>C. krusei</i>	5-10	S to I	I to R	R	S to S-DDI ³	S
<i>C. lusitanae</i>	0-3	R	S	S	S	S
<i>C. parapsilosis</i>	10-20	S	S	S	S	S to I ⁴
<i>C. tropicalis</i>	20-30	S	S	S	S	S

S, 5-FC, S: susceptible; I, intermediate; S-DDI, susceptible dose-dependent (dose needs to be increased to achieve therapeutic efficacy); R, resistant.
 Although voriconazole and posaconazole are active *in vitro*, *in vivo*, and in early clinical experience against *C. glabrata* and *C. krusei*, their efficacy against these classically azole-resistant organisms hasn't been clearly established. Minimum inhibitory concentrations of the echinocandins are higher for *C. parapsilosis* than for other *Candida* species. Clinical trials have shown similar response rates for *C. parapsilosis* as compared with other species, but the full clinical significance of these findings is unknown. Table is adapted from several sources (6, 13, 16, 25, 36, 47).

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Yeast – *Candida spp.* Treatment

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    graph TD
      Root[Candida spp.] --> Group1[C. krusei  
C. glabrata]
      Root --> Group2[C. albicans]
      Root --> Group3[C. dubliniensis  
C. guilliermondii  
C. lusitanae  
C. parapsilosis  
C. tropicalis]
      Group1 --> Echinocandin[Echinocandin]
      Group2 --> Fluconazole1[Fluconazole - 1st infection]
      Fluconazole1 --> Echinocandin2[Echinocandin - 2nd infection]
      Group3 --> Fluconazole2[Fluconazole]
    
```

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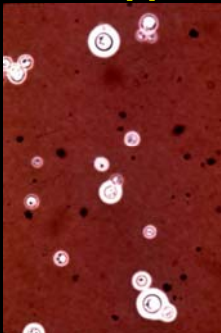
Patient Case - DB

- RLQ Abscess Cx: (results available POD#15)
 - *Candida (Torulopsis) glabrata*
 - *Candida tropicalis*
- Is the fluconazole enough? Concerns?
- POD# 15 –
 - Discontinue fluconazole
 - Caspofungin 70mg IV x 1, then 50mg IV daily

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Yeast – *Cryptococcus spp.*

- Cryptococcus neoformans*
- Source – soil contamination with pigeon droppings
- Portal of entry – inhalation
- Primarily infects the central nervous system – meningoencephalitis



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Yeast – *Cryptococcus spp.*

- Nearly always associated with an immunocompromised state
 - 6-10% of HIV+ patients in the US will develop
- Treatment:
 - Amphotericin B + Flucytosine x 2 weeks
 - Followed by Fluconazole 400mg po daily x 6 weeks

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Aspergillus spp.

- *Aspergillus spp.* are widespread in the environment
- *Aspergillus spp.* are moulds
- Air = primary route of transmission in hospitals
- *Aspergillus fumigatus* – most frequent pathogen




<http://www.asm.org/Division/c/photo/asp1.JPG>
Sobel JD, et al. Contemporary Diagnosis & Management of Fungal Infections, 2003, pp.135.

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Aspergillus spp.

- Invasive infection associated with immunodeficiency
- Primary sites of infection:
 - Lungs
 - Central Nervous System
 - Sinuses
- Infections can be local or invasive
- Definitive diagnosis → tissue biopsy



Aspergillus fumigatus

http://www.primidi.com/images/aspergillus_fumigatus.jpg
Sobel JD, et al. Contemporary Diagnosis & Management of Fungal Infections, 2003, pp.135.

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Aspergillus spp. Treatment

High Risk	Low Risk
<ul style="list-style-type: none">• Neutropenia• Febrile• Lung infiltrates• Isolation of <i>Aspergillus</i> in sputum cultures	<ul style="list-style-type: none">• Solid organ transplant• Malignancy• Chronic granulomatous disease• HIV (+)

? Start Treatment:

- **High Risk** → start empiric therapy
- **Low Risk** → await biopsy results

Sobel JD, et al. Contemporary Diagnosis & Management of Fungal Infections, 2003, pp.135.

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Aspergillus spp. Treatment

- DOC: Voriconazole (VFend®)
- Alternative Treatments:
 - Caspofungin (Cancidas®) – refractory disease
 - Amphotericin B – also 1st line, high failure rate
 - Itraconazole – oral only
 - Posaconazole – oral only

Sobel JD, et al. Contemporary Diagnosis & Management of Fungal Infections, 2003, pp.135.

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Fusarium spp.

- Ubiquitous fungus found in the soil
- 2nd most common cause of invasive mycotic infections
- Can also superficial skin infections
- May be confused with *Aspergillus spp* in the lab

Sobel JD, et al. Contemporary Diagnosis & Management of Fungal Infections, 2003, pp.135.

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Fusarium spp.


- Diagnosis –
 - Easily recovered from blood cultures
 - 60-70% of patients with fusariosis will have (+) blood cultures
- Treatment –
 - Frequently resistant to amphotericin B, azoles, & flucytosine
 - DOC: Voriconazole (VFend®)
 - Alternate: Posaconazole (oral only)

Sobel JD, et al. Contemporary Diagnosis & Management of Fungal Infections, 2003, pp.135.

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Mucor spp.

- Included in the zygomycosis group of infections
- Environmental mold
- Transmission through inhalation or ingestion of spores
- Risk Factors:
 - DKA
 - Immunosuppression
 - Others

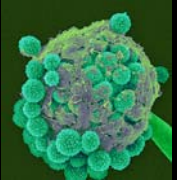


<http://www.doctorfungus.org/thefungi/mucor.htm>
www.sci.muni.cz/mikrobi/Miniatlas/muc.htm

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Mucor spp.

- Treatment:
 - Early diagnosis is key
 - Surgical debridement or resection if possible
 - Antifungal therapy: Voriconazole (VFend®)
 - Reverse immunosuppression if possible



<http://www.doctorfungus.org/thefungi/mucor.htm>
pathmicro.med.sc.edu/mycology/mycology-1.htm

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Treatment Principles

- Special population considerations
- Source control
- Antifungal class review
 - Mechanism of action
 - Spectrum of activity
 - Dosing
 - Adverse reactions
- Antifungal resistance issues
- Duration of therapy

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Special Populations

- Burns:
 - 1st line treatment: Surgical debridement
 - Adjuvant systemic antifungal therapy
- Critically Ill Patients –
 - Hypothermia/Hyperthermia
 - Isolation of yeast/mold from any culture with risk factors
- Solid Organ Transplant
 - Time since transplant
 - Type of transplant dictates risk

Horvath EE, et al. *Ann Surg*. 2007; 245:978
 Holzheimer RG, et al. *Eur J Med Res*. 2002; 7(5):200.

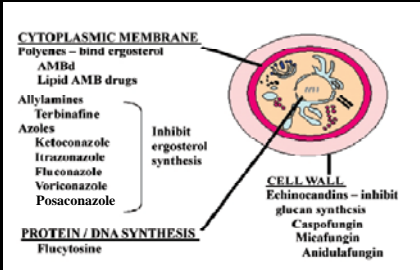
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Treatment

- Surgical debridement
- Removal of invasive devices (if possible)
 - Central venous lines (new stick)
 - Drains, pumps, etc
- Antifungal therapy
 - Polyenes/Amphotericin B Products
 - Flucytosine
 - Azoles
 - Echinocandins

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Sites of Action



CYTOPLASMIC MEMBRANE
 Polyenes – bind ergosterol
 AMBd
 Lipid AMB drugs

Allylamines
 Terbinafine

Azoles
 Ketoconazole
 Itraconazole
 Fluconazole
 Voriconazole
 Posaconazole

Inhibit ergosterol synthesis

CELL WALL
 Echinocandins – inhibit glucan synthesis
 Caspofungin
 Micafungin
 Anidulafungin

PROTEIN / DNA SYNTHESIS
 Flucytosine

AMBd = Amphotericin B deoxycholate
 AMB = Amphotericin B

Dismukes WE. *Clin Infect Dis*. 2006; 42(9):1289.

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Amphotericin B (Polyenes)

- MOA: Bind ergosterol in cell membrane causing disruption and cell death
- Lipophilic antifungal
- Spectrum of Activity:
 - *Candida spp.*
 - *Aspergillus spp.*
 - *Cryptococcus spp.*
 - Others

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Sobel JD, et al. *Contemporary Diagnosis & Management of Fungal Infections*. 2003, pp.11.

Amphotericin B (Polyenes)


	Amphotericin B	Amphotericin B Lipid Complex (Abelcet®)	Liposomal Amphotericin B (Ambisome®)
Dose	0.7-1.5 mg/kg IV daily	3-5 mg/kg IV daily	3-7 mg/kg IV daily
Infusion-related reactions	++	++	+
Nephrotoxicity	+++	++	++
CSF Penetration	+	++++	+

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Micromedex. © 2008. [Accessed 13-Mar-2008].

Amphotericin B (Polyenes)

- Adverse Reactions:
 - Infusion-related reactions
 - Nephrotoxicity
 - LFT abnormalities
- Drug Interactions:
 - Digoxin (↑ levels)
 - Tacrolimus (↑ toxicity)
 - Cyclosporine (↑ toxicity)



Amphotericin B deoxycholate




Amphotericin B lipid complex (Abelcet®)

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<https://www.epocrates.com/pillimages/A1055050.jpg>
http://www.drug3k.com/imo/abelcet_12206_1.jpg

Flucytosine

- MOA: converted to 5-fluoruracil in the fungal cell and then disrupts RNA & protein synthesis
- Spectrum of Activity:
 - *Candida spp.*
 - *Cryptococcus spp.*
- Rapidly develops resistance



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www.gallowaypharmacy.com/products.php?cat=19
 Sobel JD, et al. *Contemporary Diagnosis & Management of Fungal Infections*. 2003, pp.20.

Flucytosine

- Dose: 100-150 mg/kg/day PO divided q6
- Pharmacokinetics:
 - 75-90% bioavailable
 - CSF levels = 60-100% of blood levels
 - 75-90% excreted unchanged in urine
- Adverse reactions:
 - Myelosuppression (22%)
 - Renal insufficiency
 - Nausea/Vomiting/Diarrhea

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Sobel JD, et al. *Contemporary Diagnosis & Management of Fungal Infections*. 2003, pp.20.

Azole Anti-fungals


- MOA: inhibition of CYP450-dependant inosterol 14- α -demethylase → inhibition of ergosterol synthesis
- Specific Agents:
 - Fluconazole (Diflucan®)
 - Itraconazole (Sporonox®) – oral only
 - Voriconazole (VFend®)
 - Posaconazole (Noxafil®) – oral only

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Sobel JD, et al. *Contemporary Diagnosis & Management of Fungal Infections*. 2003, pp.20.
 Micromedex. © 2008. [Accessed 05-May-2008].

Fluconazole (Diflucan®)

- Spectrum of Activity:
 - *Candida spp* (except *C. krusei*)
 - *Cryptococcus neoformans*
 - *Histoplasma capsulatum*
 - *Blastomyces dermatitidis*
 - Others
- Good empiric anti-fungal choice
- Dose:
 - 800mg IV on Day #1, then 400mg IV/PO q24
 - Adjust for renal dysfunction




Sobel JD, et al. Contemporary Diagnosis & Management of Fungal Infections. 2003, pp.20. Micromedex. © 2008. [Accessed 05-May-2008]

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Fluconazole (Diflucan®)

- >90% oral bioavailability
- Drug Interactions:
 - Amiodarone
 - Warfarin (↑ INR)
 - Phenytoin (↓ levels)
 - Glyburide/Glipizide (mask hypoglycemia)
- Adverse reactions:
 - Rash (~10%)
 - Increased LFTs (~10%)




Sobel JD, et al. Contemporary Diagnosis & Management of Fungal Infections. 2003, pp.20. Micromedex. © 2008. [Accessed 05-May-2008]

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Voriconazole (Vfend®)

- Spectrum of Activity:
 - *Aspergillus spp.*
 - *Candida spp.*
 - *Fusarium spp.*
 - *Histoplasma capsulatum*
 - *Blastomyces dermatitidis*
 - Others
- DOC: *Aspergillus spp.*
- Dose:
 - IV/PO: 6 mg/kg q12 x 2 doses, then 4mg/kg q12




Sobel JD, et al. Contemporary Diagnosis & Management of Fungal Infections. 2003, pp.20. Micromedex. © 2008. [Accessed 05-May-2008]

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Voriconazole (Vfend®)

- IV excipient accumulates in renal failure – use for loading dose only
- Drug Interactions:
 - Amiodarone
 - Warfarin (↑ INR)
 - Digoxin (↑ levels)
 - Glyburide/Glipizide (mask hypoglycemia)
- Adverse Reactions:
 - Transient visual disturbances (24%)
 - Rash (6%)
 - Increased LFTs (4-20%)



Sobel JD, et al. Contemporary Diagnosis & Management of Fungal Infections. 2003, pp.20. Micromedex. © 2008. [Accessed 05-May-2008]

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Itraconazole (Sporonox®)

- Spectrum of Activity:
 - *Candida spp.*
 - *Aspergillus spp.*
 - *Histoplasma capsulatum*
 - *Blastomyces dermatitidis*
 - Others
- Dosage:
 - Serious infections: 200mg po q12
 - Oral *Candida* infections: 200mg po daily x 14 days



Sobel JD, et al. Contemporary Diagnosis & Management of Fungal Infections. 2003, pp.20. Micromedex. © 2008. [Accessed 05-May-2008]

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Itraconazole (Sporonox®)


- Bioavailability:
 - Capsules – increased with food
 - Solution – must take on empty stomach
- Drug Interactions:
 - Antacids (↓ absorption of itraconazole)
 - Digoxin (↑ levels)
- Adverse Reactions:
 - Nausea, vomiting, diarrhea
 - Hypertension, ↓ K, edema

Sobel JD, et al. Contemporary Diagnosis & Management of Fungal Infections. 2003, pp.20. Micromedex. © 2008. [Accessed 05-May-2008]

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Posaconazole (Noxafil®)

- Spectrum of Activity:
 - *Candida spp.*
 - *Aspergillus spp.*
 - *Fusarium spp.*
 - *Cryptococcus neoformans*
 - Others
- Dose:
 - 400mg po q12
 - Ophthalmic: 10mg/0.1mL to affected eye q1h (+ PO)



Sobel JD, et al. Contemporary Diagnosis & Management of Fungal Infections. 2003, pp.20. Micromedex. © 2008. [Accessed 05-May-2008]

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Posaconazole (Noxafil®)

- Increased absorption when given with food
 - Must be taken with a fatty meal
- 77% fecal excretion
- Drug Interactions:
 - Phenytoin (↑ levels)
 - Midazolam (↑ sedation)
 - Others
- Adverse Reactions:
 - Hypotension (~40%)
 - Rash (2% of HIV patients)



Sobel JD, et al. Contemporary Diagnosis & Management of Fungal Infections. 2003, pp.20. Micromedex. © 2008. [Accessed 05-May-2008]

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Azole Antifungal Summary

- Fluconazole – 1st line for *Candida albicans*
- Itraconazole – almost no place in therapy
- Voriconazole – DOC for *Aspergillus spp*
- Posaconazole – place in therapy to be determined

Sobel JD, et al. Contemporary Diagnosis & Management of Fungal Infections. 2003, pp.20. Micromedex. © 2008. [Accessed 05-May-2008]

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Echinocandins

- Synthetic, lipopeptide antifungals derived from *Zalernon arboricola*
- MOA: non-competitive inhibition of the synthesis of the enzyme glucan synthase
- Specific Agents:
 - Caspofungin (Cancidas®)
 - Micafungin (Mycamine®)
 - Anidulafungin (Eraxis®)

Sobel JD, et al. Contemporary Diagnosis & Management of Fungal Infections. 2003, pp.20. Micromedex. © 2008. [Accessed 05-May-2008]

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Echinocandins

- Advantages:
 - No adjustment for renal dysfunction
 - Well tolerated
 - Effective against *Candida* biofilms

Sobel JD, et al. Contemporary Diagnosis & Management of Fungal Infections. 2003, pp.20. Micromedex. © 2008. [Accessed 05-May-2008]

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	Caspofungin	Micafungin	Anidulafungin
Spectrum of Activity	<i>C. albicans</i> <i>C. glabrata</i> <i>C. krusei</i> <i>C. lusitanae</i> <i>C. tropicalis</i> <i>C. guilliermondii</i> <i>Aspergillus spp.</i>	<i>C. albicans</i> <i>C. glabrata</i> <i>C. krusei</i> <i>C. lusitanae</i> <i>C. tropicalis</i> <i>C. guilliermondii</i>	<i>C. albicans</i> <i>C. glabrata</i> <i>C. krusei</i> <i>C. lusitanae</i> <i>C. tropicalis</i> <i>C. guilliermondii</i>
Indications	<ul style="list-style-type: none"> • Neutropenic fever • Candidemia • Intra-abd. abscess • <i>Candida</i> peritonitis • Pleural infections • Esophageal candidiasis • Refractory invasive <i>Aspergillus</i> 	<ul style="list-style-type: none"> • Candidemia • Invasive candidiasis • Stem-cell transplant prophylaxis • Esophageal candidiasis 	<ul style="list-style-type: none"> • Candidemia • Invasive candidiasis • Intra-abdominal abscess • <i>Candida</i> peritonitis • Esophageal candidiasis
Dosage	70mg IV x 1, then 50mg IV q24	100mg IV daily	200mg IV daily, then 100mg IV daily

Sobel JD, et al. Contemporary Diagnosis & Management of Fungal Infections. 2003, pp.20. Micromedex. © 2008. [Accessed 05-May-2008]

	Caspofungin	Micafungin	Anidulafungin
Pharmacokinetics	<ul style="list-style-type: none"> Hepatic metabolism Fecal elimination 	<ul style="list-style-type: none"> Hepatic metabolism Fecal elimination 	<ul style="list-style-type: none"> Spontaneous degradation 30% Fecal elimination
ADR	<ul style="list-style-type: none"> Phlebitis/thrombophlebitis ↑ LFTs Possible histamine-mediated symptoms 	<ul style="list-style-type: none"> Infusion-site reactions ↑ LFTs Possible histamine-mediated symptoms 	<ul style="list-style-type: none"> Possible histamine-mediated symptoms Hypokalemia Diarrhea
Drug Interactions	<ul style="list-style-type: none"> Phenytoin Tacrolimus Cyclosporine 	<ul style="list-style-type: none"> Nifedipine Sirolimus 	<ul style="list-style-type: none"> Cyclosporine
Special Notes	<ul style="list-style-type: none"> dose-adjust for hepatic failure 		<ul style="list-style-type: none"> Made w/ 20% alcohol – disulfiram-like reactions

Sobel JD, et al. Contemporary Diagnosis & Management of Fungal Infections. 2003, pp 20. Micromedex. © 2008. [Accessed 05-May-2008]

Anti-Fungal Resistance

- Initially described in HIV population
- Mechanisms:
 - Clinical failure – the drug cannot eradicate the fungi
 - Cellular resistance (decreased response)
 - Intrinsic – fungi is always resistant
 - Acquired – fungi is initially susceptible & develops resistance
- Management:
 - Speciation of *Candida* isolates
 - Removal of invasive devices (biofilm source)
 - Aggressive dosing or alternative agents

Kuhn DM, et al. Antimicrob Agents Chemother. 2002; 46(6):1773-80. Rodriguez D, et al. Clin Microbiol Infect. 2007; 13:788-93

Duration of Therapy

- Candidemia
 - Repeat blood cultures 3-5 days into therapy
 - Continue systemic anti-fungal agent for 14 days **AFTER** negative blood cultures
- Candiduria
 - Change catheter or remove if possible
 - If candiduria persists after catheter change - treat 7-14 days
- Other fungal infections –
 - Duration based on clinical judgment or wound status
 - (Or ID consult recommendations)

Brief Review

- Fungi account for 25% of all healthcare-related infections
- Multiple risk factors – including ICU stay, broad-spectrum antibiotics, CVLs, steroids, & diabetes
- Most common organisms: *Candida spp.*
- Burn, critically ill, & transplant patients at highest risk
- Choose antifungal agent based on most likely organism