

## “There’s Fungus Among Us” 2008

Kara L. Birrer, Pharm.D.  
Clinical Pharmacist, Trauma/General Surgery  
Orlando Regional Medical Center

## Objectives

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

2

## 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

3

## 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 2<sup>nd</sup> most common cause of fungal infections in cancer patients

4

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

## Risk Factors

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

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

5

## Risk Factors

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

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

6

## 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

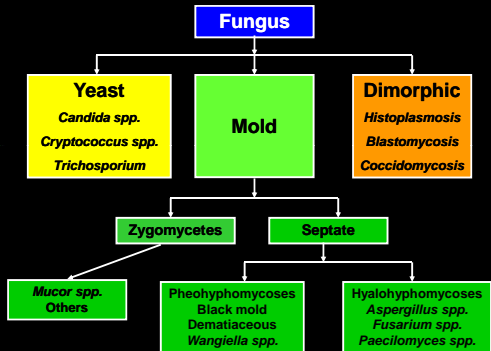
7

## Types of Invasive Fungal Infections

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

8

## Emerging Fungal Pathogens



Ashley ESD. An update on antifungal therapy. FSHP 2006

9

## Yeast – *Candida spp.*

- Most common fungal pathogen
- Opportunistic pathogens
- 4<sup>th</sup> 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.

10

## 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

11

## 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](http://www.asm.org/Division/c/fungi.htm)

12

## 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

13

## Yeast – *Candida spp.* Treatment

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

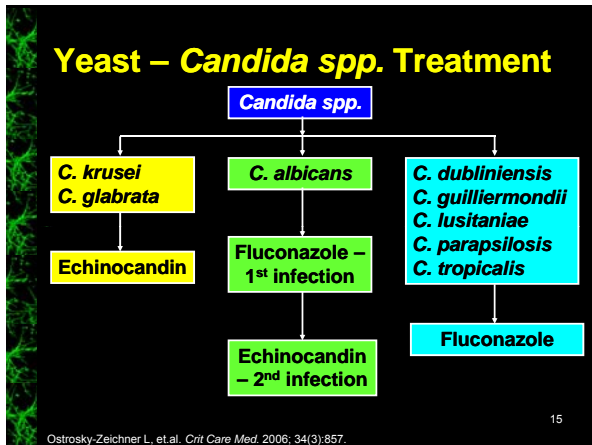
| Species                | Frequency (%) | Common Susceptibility Patterns |        |                              |  |                           |
|------------------------|---------------|--------------------------------|--------|------------------------------|--|---------------------------|
|                        |               | Amphotericin B                 | 5-FC   | Fluconazole and Itraconazole | Voriconazole and Posaconazole <sup>2</sup> | Echinocandin <sup>2</sup> |
| <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 <sup>3</sup>                    | 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 <sup>4</sup>       |
| <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.

<sup>2</sup>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. <sup>3</sup>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).

14

Ostrosky-Zeichner L, et al. Crit Care Med. 2006; 34(3):857.



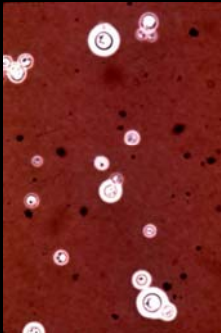
## Patient Case - DB

- 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

16

## Yeast – *Cryptococcus spp.*

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



17

Sobel JD, et al. Contemporary Diagnosis & Management of Fungal Infections, 2003, pp.123.

## 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

18

Sobel JD, et al. Contemporary Diagnosis & Management of Fungal Infections, 2003, pp.123.

## **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.

19

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

20

## **Aspergillus spp. Treatment**

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

**? 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.

21

## **Aspergillus spp. Treatment**

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

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

22

## **Fusarium spp.**

- Ubiquitous fungus found in the soil
- 2<sup>nd</sup> 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.

23

## **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.

24

## Mucor spp.

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

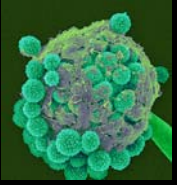


<http://www.doctorfungus.org/thefungi/mucor.htm>  
[www.sci.muni.cz/mikrobi/Miniatlas/muc.htm](http://www.sci.muni.cz/mikrobi/Miniatlas/muc.htm)

25

## 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](http://pathmicro.med.sc.edu/mycology/mycology-1.htm)

26

## 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

27

## Special Populations

- Burns:
  - 1<sup>st</sup> 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.

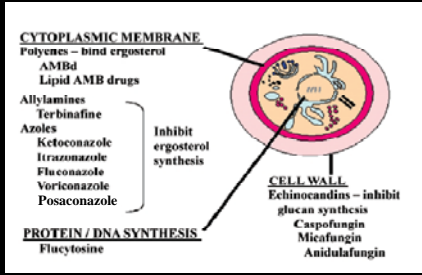
28

## 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

29

## 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.

30

## 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

31

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®) |
|-----------------------------------|------------------------|---|--------------------------------------|
| <b>Dose</b>                       | 0.7-1.5 mg/kg IV daily | 3-5 mg/kg IV daily                      | 3-7 mg/kg IV daily                   |
| <b>Infusion-related reactions</b> | ++                     | ++                                      | +                                    |
| <b>Nephrotoxicity</b>             | +++                    | ++                                      | ++                                   |
| <b>CSF Penetration</b>            | +                      | ++++                                    | +                                    |

32


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®)

33

<https://www.epocrates.com/pillimages/A1055050.jpg>  
[http://www.drug3k.com/imo/abelcet\\_12206\\_1.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



34

[www.gallowaypharmacy.com/products.php?cat=19](http://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

35

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

## Azole Anti-fungals

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


36

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]

37

## 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]

38

## 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]

39

## 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]

40

## 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]

41

## 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]

42

## 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]

43

## 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]

44

## Azole Antifungal Summary

- Fluconazole – 1<sup>st</sup> 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]

45

## 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]

46

## 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]

47

|                             | Caspofungin   | Micafungin   | Anidulafungin   |
|-----------------------------|---|--|---|
| <b>Spectrum of Activity</b> | <i>C. albicans</i><br><i>C. glabrata</i><br><i>C. krusei</i><br><i>C. lusitanae</i><br><i>C. tropicalis</i><br><i>C. guilliermondii</i><br><i>Aspergillus spp.</i>  | <i>C. albicans</i><br><i>C. glabrata</i><br><i>C. krusei</i><br><i>C. lusitanae</i><br><i>C. tropicalis</i><br><i>C. guilliermondii</i>                                      | <i>C. albicans</i><br><i>C. glabrata</i><br><i>C. krusei</i><br><i>C. lusitanae</i><br><i>C. tropicalis</i><br><i>C. guilliermondii</i>   |
| <b>Indications</b>          | <ul style="list-style-type: none"> <li>• Neutropenic fever</li> <li>• Candidemia</li> <li>• Intra-abd. abscess</li> <li>• <i>Candida</i> peritonitis</li> <li>• Pleural infections</li> <li>• Esophageal candidiasis</li> <li>• Refractory invasive <i>Aspergillus</i></li> </ul> | <ul style="list-style-type: none"> <li>• Candidemia</li> <li>• Invasive candidiasis</li> <li>• Stem-cell transplant prophylaxis</li> <li>• Esophageal candidiasis</li> </ul> | <ul style="list-style-type: none"> <li>• Candidemia</li> <li>• Invasive candidiasis</li> <li>• Intra-abdominal abscess</li> <li>• <i>Candida</i> peritonitis</li> <li>• Esophageal candidiasis</li> </ul> |
| <b>Dosage</b>               | 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   |
|--------------------------|--|---|---|
| <b>Pharmacokinetics</b>  | <ul style="list-style-type: none"> <li>Hepatic metabolism</li> <li>Fecal elimination</li> </ul>  | <ul style="list-style-type: none"> <li>Hepatic metabolism</li> <li>Fecal elimination</li> </ul>   | <ul style="list-style-type: none"> <li>Spontaneous degradation</li> <li>30% Fecal elimination</li> </ul>                      |
| <b>ADR</b>               | <ul style="list-style-type: none"> <li>Phlebitis/thrombophlebitis</li> <li>↑ LFTs</li> <li>Possible histamine-mediated symptoms</li> </ul> | <ul style="list-style-type: none"> <li>Infusion-site reactions</li> <li>↑ LFTs</li> <li>Possible histamine-mediated symptoms</li> </ul> | <ul style="list-style-type: none"> <li>Possible histamine-mediated symptoms</li> <li>Hypokalemia</li> <li>Diarrhea</li> </ul> |
| <b>Drug Interactions</b> | <ul style="list-style-type: none"> <li>Phenytoin</li> <li>Tacrolimus</li> <li>Cyclosporine</li> </ul>                                      | <ul style="list-style-type: none"> <li>Nifedipine</li> <li>Sirolimus</li> </ul>   | <ul style="list-style-type: none"> <li>Cyclosporine</li> </ul>  |
| <b>Special Notes</b>     | <ul style="list-style-type: none"> <li>dose-adjust for hepatic failure</li> </ul>  |   | <ul style="list-style-type: none"> <li>Made w/ 20% alcohol – disulfiram-like reactions</li> </ul>                             |

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