

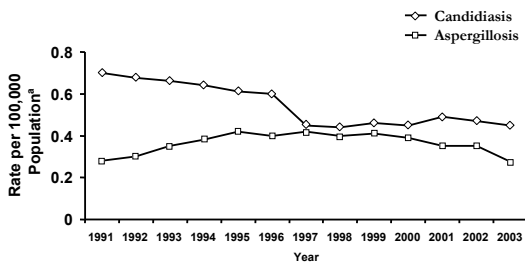
Invasive Candidiasis: What the Pharmacist Needs to Know

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What We're Going to Cover

- Epidemiology overview
- Susceptibility issues
- Issues with diagnostics
- Where do the antifungal classes stand?
 - Azoles
 - Polyenes
 - Echinocandins
- Species-specific issues in *Candida* spp. infections

Crude Mortality in the U.S.



Pfaller, Diekema. *Clin Microbiol Rev.* 2007;20:133-163.

The Impact of Candidemia

- Fourth most common blood stream isolate
- Leading fungal pathogen in US hospitals
- 14.5% attributable mortality in adults
- 10.1 day increased length of stay
- \$39,331 increased hospital charges

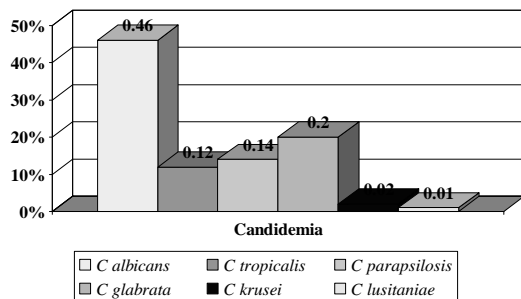
Zaoutis TE, et al. *Clin Infect Dis* 2005;41:1232.
Weinberger M, et al. *J Hosp Infection* 2005;61:146.

Invasive Candidiasis: Who is at Risk?

- >3 days in the ICU
- Central lines
- Broad spectrum antibiotics
- Diabetes
- Severity of illness
- Dialysis
- TPN
- GI perforation or surgery
- Immunosuppression (steroids)
- Colonization?

Ostrosky-Zeichner. *Eur J Clin Micro Infect Dis* 2004;23:739

Not Just *Candida albicans*



Pappas DG, et al. *Clin Infect Dis* 2003;37:634-643.

“Although the susceptibility of *Candida* to the currently available antifungal agents is generally predictable if the species of the infecting isolate is known, individual isolates do not necessarily follow this general pattern.”

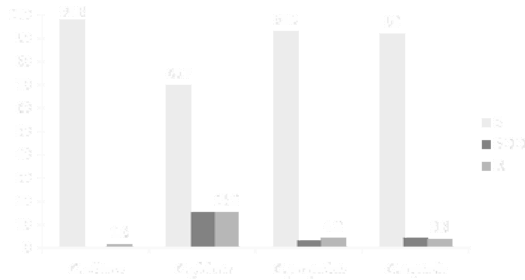
Infectious Diseases Society of America
 2009 Guidelines for Management of Candidiasis
 (*Clin Infect Dis* 2009;48:503-35)

General Susceptibility Patterns of *Candida* spp.

	Flu	Itra	Vori	Posa	Candins	AmB
<i>C. albicans</i>	S	S	S	S	S	S
<i>C. glabrata</i>	S-DD to R	S-DD to R	S-DD to R	S-DD to R	S	S to I
<i>C. tropicalis</i>	S	S	S	S	S	S
<i>C. parapsilosis</i>	S	S	S	S	S to R	S
<i>C. krusei</i>	R	S-DD to R	S	S	S	S to I

Pappas PG, et al. *Clin Infect Dis* 2009;48:503-35

Fluconazole Susceptibility by Species



Pfäler MA, et al. *J Invasive Fungal Infect* 2007;1:74-92.

The Problem with Diagnostics

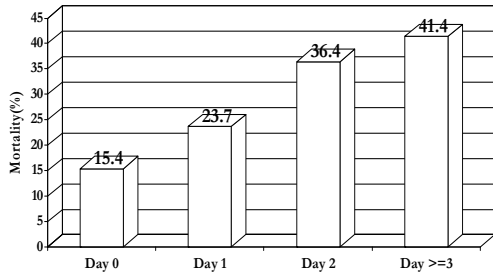
- The “gold standard”
 - Positive culture from sterile site
 - Histopathology
- Blood cultures – only 50-70% sensitive
- β -D-glucan assay
 - Sensitive but how specific?
 - Gram positive organism interference
- Real time PCR – “home brews” no commercial system

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

Pickering JW, et al. *J Clin Micro* 2005;43(12):5957.

Masai M, et al. *J Clin Micro* 2006;44(1):143.

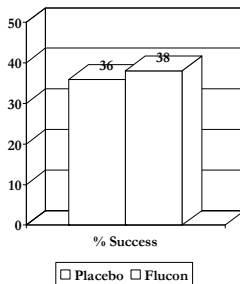
THINK FUNGUS!! – Time to Initiation of Therapy and Mortality



Garvey KW, et al. *Clin Infect Dis* 2006;43:25-31

Prophylaxis in the ICU: Where do we Stand?

- Decreased infections?
- Decreased mortality?
- Resistance issues
- Tolerability issues
- Cost



1. Golan Y, et al. *Ann Intern Med* 2005;143:857.

2. Wenzel RP, et al. *Clin Infect Dis* 2005;41:S389.

3. Cruciani M, et al. *Intensive Care Med* 2005;31:1479.

4. Shorr AF, et al. *Crit Care Med* 2005;33:1928.

5. Ostrosky-Zeichner L, et al. *Crit Care Med* 2006;34:857

6. Schuster MG, et al. *Ann Intern Med* 2008;149:83.

The Drugs

Azole Antifungals

- Inhibit CYP450 lanosterol 14- α demethylase
- *Candida* sp.: Slow killing - considered “static”
- CYP450 drug interactions
- Oral formulations
- Tolerability?

Boucher HW, et al. *Drugs* 2004;64:1997.

Fluconazole

- The most used systemic antifungal
- Benefits
 - Lack of toxicity
 - Oral bioavailability is excellent
 - Extremely active against many *Candida* sp.
- Limitations
 - Spectrum, often under-dosed

Rex J, et al. *NEJM* 1994;331:1325.

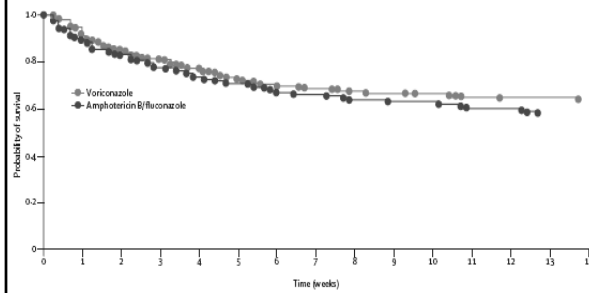
Fluconazole in 2009

- More *C. glabrata*
- Was it as good as ampho or ampho + flu?
- What about that anidulafungin data?
- Where does it fit?
- *C. parapsilosis*?

1.Pappas DG, et al. *Clin Infect Dis* 2003;37:634-643.
 2.Rex J, et al. *NEJM* 1994;331:1325.
 3.Rex J, et al. *Clin Infect Dis* 2003;36:1221.

4.Reboli A, et al. *NEJM* 2007;356:2472-82
 5.Spellberg BG, et al. *Clin Infect Dis* 2006;42:244

Voriconazole in Candidemia



Kullberg et al. *Lancet* 2005;366:1435.

“Voriconazole for Candidosis: An Important Addition?”

Flu Resistant Species	% Vori Resistant
<i>C. albicans</i> (n=1289)	62.9%
<i>C. glabrata</i> (n=2456)	59.5%
<i>C. tropicalis</i> (n=457)	68.7%

- “...patients may have been heavily pre-exposed to fluconazole... for these patients I fear that any triazole might have limited value” – JR Graybill
- Put the azole down and back away slowly!

Pfaller MA, et al. *J Clin Micro* 2007;45:1735.
 Graybill JR. *Lancet* 2005;366:1413.

What about Ampho?

- Still the “gold standard” comparator
- Issues with AmB deoxycholate
- Toxicity limitations
- Steadily declining use
- Wallet toxicity issues with lipid forms and... its still ampho!

Ostrosky-Zeichner L, et al. *Clin Infect Dis* 2003;37:415.

What do We Know About Ampho for Candidemia?

- Rex 1: Ampho vs fluconazole
- Rex 2: Ampho + flu vs fluconazole alone
- Mora Duarte: Ampho vs Caspofungin
- Kullberg: Ampho/flu vs Vori
- Take homes...
- More real world? Lipo AmB vs Micafungin

1. Rex J, et al. *NEJM* 1994;331:1325. 4. Kullberg et al. *Lancet* 2005;366:1435.
 2. Rex J, et al. *Clin Infect Dis* 2003;36:1221 5. Kuse ER et al. *Lancet* 2007; 369: 1519.
 3. Mora-Duarte J, et al. *N Engl J Med* 2002;347:2020.

The Echinocandins: PK

	Caspo	Mica	Anidula
Cmax (µg/ml)	50mg = 9	100mg = 10	100mg = 9
T1/2	10.6 hours	11-17 hours	40 hours
Protein binding	96%	99.8%	98%?
Urine concentration	1.4%	0.7%	<0.1%
% Plasma in CSF	Low	Low	Low

Denning. *Lancet* 2003;362:1142-51
 Caspofungin PI, Micafungin PI, Anidulafungin PI

Echinocandins: Strengths

- Fungicidal (against many *Candida* sp.)
- Tolerability
- Pharmacokinetics
- Few drug-drug interactions
- No cross-resistance with azoles

Echinocandins: Weaknesses

- Limited spectrum (*Candida* sp., *Aspergillus* sp.)
- Endemic mycoses (Histo, Coccidioidomycosis)?
- Not effective against *C. neoformans*, Zygomycetes
- Oral formulations not available
- Cost???

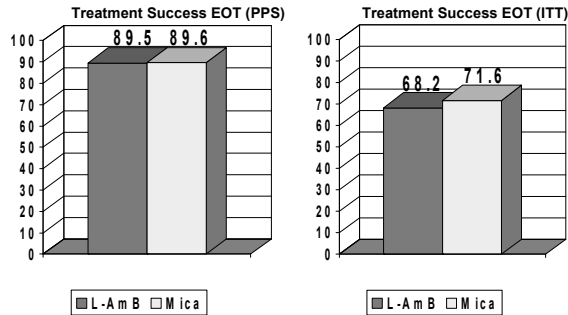
The Clinical Data: Favorable Responses to Therapy

	Caspofungin (n=88)	Amphotericin B (n=97)
End of IV Therapy (MITT)	73.4%	61.7%

MITT=modified intention to treat.

- However...
- Toxicity = Failure
- 3 in the caspofungin arm, 19 in the amphotericin arm ($P = 0.03$)
- Take home...

Micafungin Vs. L-AmB



Kuse ER et al. *Lancet* 2007; 369: 1519-27

Adverse Events

	Micafungin N=264	L-AmB N=267	P ≤ 0.05
Therapy D/C	4.9%	9.0%	=0.087
Infusion rxn	17.0%	28.8%	X
Back pain	0.4%	4.5%	X
LFTs	4.2%	1.9%	
Hypokalemia	6.8%	12.0%	
Creatinine ↑	10.3%	29.9%	X

Kuse ER et al. *Lancet* 2007; 369: 1519-27

Mica vs Caspo: Results

- Overall success
 - Mica 100mg = 76.4%
 - Mica 150mg = 71.4%
 - Caspo = 72.3%

Success by Sp.	Mica 100 (%)	Caspo 70/50 (%)
<i>C. albicans</i>	71/92 (77.2)	61/83 (73.5)
<i>C. glabrata</i>	24/28 (85.7)	22/33 (66.7)
<i>C. tropicalis</i>	21/31 (67.7)	24/32 (75.0)
<i>C. kerusei</i>	6/8 (75.0)	3/4 (75.0)
<i>C. parapsilosis</i>	22/29 (75.9)	27/42 (64.3)

Pappas PG, et al. *Clin Infect Dis* 2007;45:883-93.

Anidulafungin in Candidemia: % Success MITT Population

Timepoint	Anidula (N=127)	Flucon (N=118)	Delta, %	95% CI
End of IV Therapy	75.6	60.2	15.4	3.9-27.0
2 Week Follow up	64.6	49.2	15.4	3.1-27.7
6 Week Follow up	55.9	44.1	11.8	-0.6-24.3

Reboli A, et al. *NEJM* 2007;356:2472-82

More Anidula vs. Flu

- More immunosuppressed pts in Flu arm
- 25.4% *C. glabrata* in flu arm
- More persistence in Flu arm (17 vs. 8. P = 0.055)
- Flu better for *C. parapsilosis* but with small N
- Trend toward improved survival in anidula arm (P=0.1)

Reboli A, et al. *NEJM* 2007;356:2472-82

Echinocandins: What We Know

- They work well for *Candida* sp. infections
- The new gold standard?
- Prices have dropped considerably
- They are safe & well tolerated
- Minimal drug interactions

Mora-Duarte J, et al. *N Engl J Med* 2002;347:2020.
 Kuse ER et al. *Lancet* 2007; 369: 1519-27
 Pappas PG, et al. *Clin Infect Dis* 2007;45:883-93.
 Anidulafungin Prescribing Information Revised March 2006

Where Does this Leave Us?

- “In a gravely ill patient such as this one, starting with an echinocandin might be preferred...”¹
- “most experts recommend using a fungicidal agent...that covers all the *Candida* species ...for a critically ill patient”²
- It is critical to note though...

1) Bennett JE. *N Engl J Med* 2006;355:1154-9
2) Ostrosky *Crit Care Med* 2006;34(3):857-863
3) Lipsett PA. *Crit Care Med* 2006; 34:S215-S224
4) Sanford Guide 2008 ed.

Conclusions

- *Candida* spp. in the ICU – a moving target
- The role of prophylaxis
- Which drugs when?
- A changing of the guard?
- What about ampho?
