

The role of new antifungal agents in the surgical patient

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There are a lot of references in these slides. Don't worry about copying them down, as you'll be able to get a copy from www.doctorfungus.org soon after the meeting.

Focus for today

- The focus is on Candida
 - It is certainly the most common & arguably the most important
 - We've also have accumulated a large amount of data on therapeutic choices over the past 10 years
 - And, we have a new class (the echinocandins) with a strong focus here
- Beyond candidiasis? Will discuss briefly, but expert consultation is advised
 - Therapy for Aspergillus & other moulds is complex and evolving

Data Sources

For more background

- IDSA guidelines cite **data on fluconazole & ampho**: Pappas et al. Clin Infect Dis 38:161-189, 2004.
- Spellberg gives a **current overview**. Clin Infect Dis 42:244-251, 2006
- Chandrasekar reviews **micafungin**. Clin Infect Dis 2006;42:1171-1178.
- Vazquez reviews **anidulafungin**. Clin Infect Dis 43:215-222, 2006.
- McCormack reviews **caspofungin**. Drugs 65:2049-68, 2005.
- Ashley compares **PK, tox, & more**: Clin Infect Dis 2006;43 (Suppl. 1):S28-S39

- 2006 Nijmegen Mycology Consensus
 - European Expert Panel on Management of Invasive Candidiasis
- 2004 IDSA candidiasis guidelines
- Key recent publications
 - Caspofungin v. amphotericin B (AmB)
 - Mora-Duarte. NEJM 347:2020-2029, 2002
 - Anidulafungin v. fluconazole
 - Reboli. ICAAC 2005, M-718
 - Micafungin v. liposomal AmB
 - Ruhnke. ICAAC 2005, M-722c
 - Voriconazole v. AmB followed by flu
 - Kullberg. Lancet 366:1435-42, 2005
 - Susceptibility
 - Pfaller. Clin Microbiol Rev 19:435-447, 2005

Principles (1): Drug activity & *Candida* species

This used to be easy!

But, the array of new agents has made it more complex. Sorry about that, but having the new drugs is certainly worth the confusion.

In this context, **reliable** means that > 95% of isolates appear susceptible and that clinical data are consistent with this.

- Amphotericin B (all forms)
 - Reliable for everything
 - Occasional exceptions: *lusitaniae*, *guilliermondii*, *inconspicua*, *sake*, *kefyr*, and *rugosa*
- Fluconazole and itraconazole
 - No: *krusei*
 - Maybe: *glabrata*
- Voriconazole & posaconazole
 - Maybe: *krusei* (70% vori salvage rate)
 - Often: *glabrata*. MICs rise, but responds
- Echinocandins
 - Reliable for (nearly) everything
 - Resistance issues slowly emerging

Principles (2): The echinocandin class

Dosages for invasive candidiasis (IC) and esophageal (EC)

- Caspofungin: 70 mg load then 50 mg/d
- Anidulafungin: 200 mg load then 100 mg/d (IC); 100/50 for EC
- Micafungin: 50 mg/d (EC). Not approved yet for IC; dose likely 100/d

- The three sisters. All are IV only
 - Caspofungin
 - Anidulafungin
 - Micafungin
- Mostly similar
 - Safety: Consistently very clean
 - Non-renal clearance (no adjust in renal fail)
 - Hepatic failure:
 - ◆ A: None for any severity
 - ◆ M: None for moderate, no data for severe
 - ◆ C: 35 mg/d for moderate, no data for severe
 - Drug interactions: More with caspofungin
 - P450 inducers: No effect (A, M), some ↓ (C)
 - Cyclosporine: No effect (A, M), caution (C)
 - Tacrolimus: No effect (A, M), some ↑ (C)

Echinocandins: No cross-resistance

This AIDS patient failed fluconazole, amphotericin B, and itraconazole...



Baseline



After caspofungin

Principles (3): The azoles

Dosages for invasive candidiasis (IC) and esophageal (EC)

- Flu: 100-200 mg/d (EC) and 400/d (IC). Load with 2x daily dose.
- Vori: Load with 6 mg/kg q12h x 2 doses. Then, 3-4 mg/kg qd (IC). Oral is 200 mg q12h x 2 dose then 200/d (IC & EC).

- Fluconazole
 - Renal clearance (dose per creatinine)
 - IV and PO: forms are interchangeable
- Voriconazole
 - Hepatic clearance (↓ dose 50% with mild to moderate failure, no data in severe)
 - IV uses cyclodextrin carrier that is cleared by kidneys. Avoid in renal failure
- Safety: Both are quite good
 - Hepatic injury is main risk
- Drug interactions
 - Both have typical range of P450/cytochrome azole problems
 - Voriconazole is more difficult

Principles (4): The amphotericin name game

Why does this matter?

Some patients tolerate one but not another

The deoxycholate form is *lethal* at lipid amphotericin B doses: Mohr Pharmacotherapy 25:426-428, 2005 describe a very sad case of this.

- The amphotericins
 - Amphotericin B deoxycholate
 - Fungizone™
 - Liposomal amphotericin B
 - AmBisome™
 - Amphotericin B lipid complex
 - ABLC, Abelcet™
 - Amphotericin B colloidal dispersion
 - ABCD, Amphocil™, Amphotec™
- The names matter
 - Side-effects & dosages are different
 - “Lipid ampho B” does not describe anything at all! Avoid this phrase!

Principles (5): Development of resistance during therapy

What about susceptibility testing?

MIC testing is as yet only meaningful for *Candida* spp. vs. fluconazole and perhaps voriconazole.

High echinocandin MICs by current methods do not reliably predict failure.

- Amphotericin B: Very rare
- Azoles: Common and of concern
 - *C. krusei* is often R
 - *C. glabrata* readily becomes R
 - Others only rarely become R
 - R in *C. albicans* in setting of HIV and OPC is a special case
- Echinocandins
 - Definitely occurs, but rare as yet
 - Only caspofungin has had wide use as yet
 - So, all reports focus on this candin
 - *C. parapsilosis* seems most problematic
 - Worth a case report if you see this

Typical scenarios with the surgical patient

So, we'll next review

Choice of treatments for proven candidiasis

The great catheter debate

- Proven deep-site infection
 - Candidemia is most common
 - Other proven (esp. intra-abdominal)
 - Data are from: Candidemia studies
- Presumptive
 - Fever, Candida from non-sterile sites, multiple risk factors (antibacterial antibiotics, TPN)
 - Treat as for proven deep-site
- Intravascular catheters
- Other settings
 - Endocarditis, devices: Expert consultation advised

Proven invasive candidiasis: Choice of therapy

Limitations of the datasets

Mostly (90-100%) non-neutropenic patients

Mostly (90-100%) candidemia

- At a high level:
 - Amphotericin B, fluconazole, voriconazole, and all three 3 candins have similar efficacy
 - This is even true despite various resistance issues
 - *C. krusei* is rare
 - *C. glabrata* does respond to azoles in non-neutropenic patients
- But, there are still differences to be discerned
 - Azoles
 - Mostly fungistatic; IV & PO; lesser spectra
 - AmB & candins
 - Mostly fungicidal; IV only; better spectra

Core strategy for *Candida*

This is a consensus strategy

Advice is consistent with Spellberg 2006, IDSA 2004, and Nijmegen 2006 (unpublished).

For a flowchart view, see Ostrosky-Zeichner. Crit Care Med 2006;34:857-863

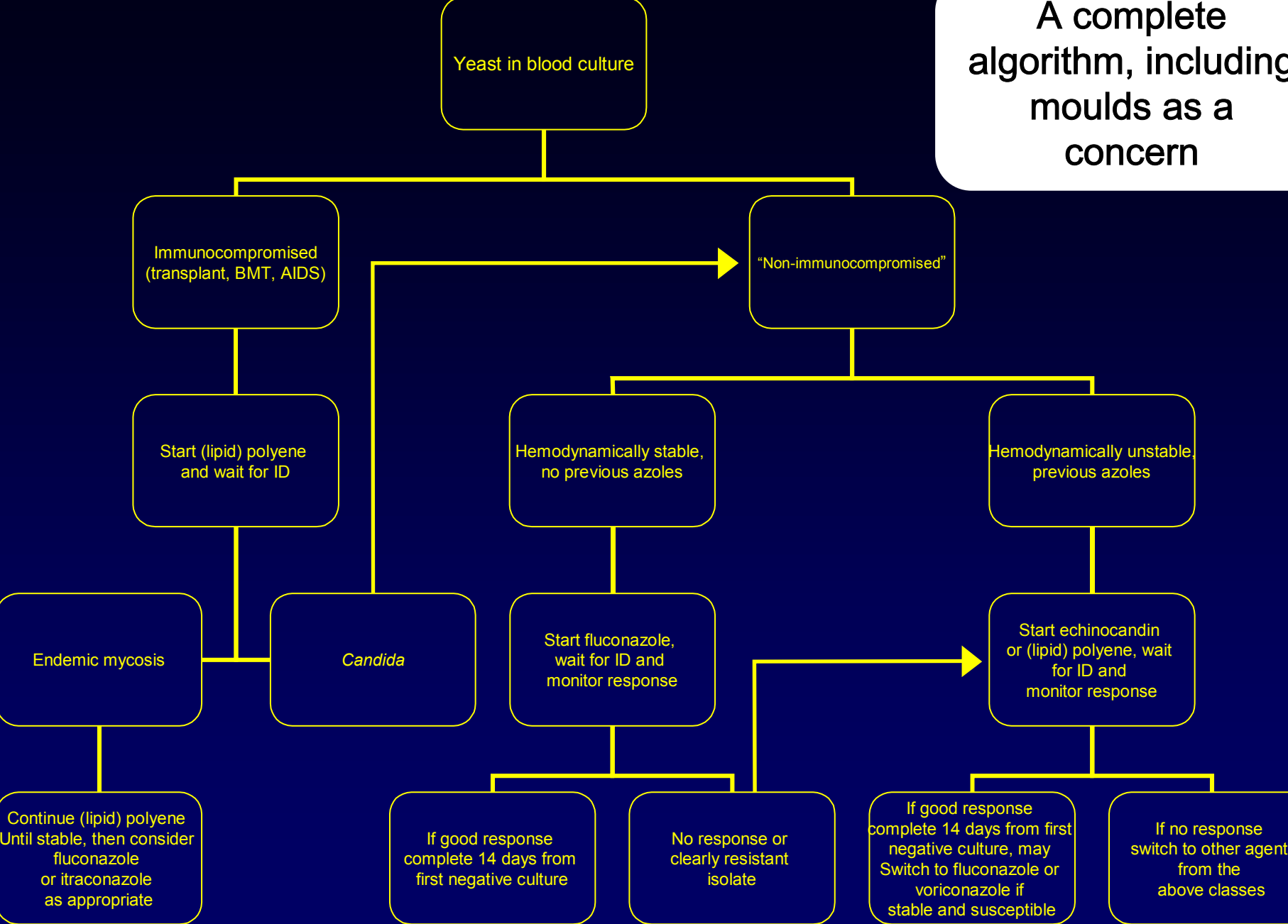
Pediatrics? See Steinbach WJ Antifungal agents in children. Pediat Clin N Amer 2005;52:895-915, VIII.

This is the *Candida* strategy

The algorithm is different if a mould is possible!

- Lower risk setting
 - Non-neutropenic. Not very sick. Community-hospital epidemiology.
 - First choice: Fluconazole is fine
 - Lots of experience here
- Higher risk setting
 - Neutropenia. Risk of *C. krusei*. Prior azole exposure. Septic shock.
 - First choice: An echinocandin
 - Second choice: An amphotericin
- Twists & turns
 - Renal dysfunction? Avoid AmB
 - Ready for PO? Flu or voriconazole (use vori especially for *C. glabrata* & *krusei*)
 - Pediatrics? Same drugs. See Steinbach

A complete algorithm, including moulds as a concern



Other points

Can you safely give amphotericin B?

Classic AmB deoxycholate (Fungizone) is a tough drug. You can soften the blow by using an array of tricks described by Gallis. *Rev Infect Dis* 1990;12:308-329. In short, give lots of fluids, watch K⁺, Mg⁺⁺, and creatinine closely.

But, this still doesn't really make it safe. See Ullmann *Clin Infect Dis* 43:E29-E38, 2006 for a European set of data showing the advantage of AmBisome in terms of reduced nephrotoxicity, length of stay, and mortality.

- Which echinocandin?
 - There is little that separates them
- Which amphotericin?
 - Preferred choice? Avoid entirely
 - Must use: AmBisome appears safest
- Itraconazole:
 - Is active (Tuil, *Critical Care* 2003;7 (Suppl 2):S63), but oral PK is unreliable, IV uses cyclodextrin carrier, and spectrum is no better than fluconazole
- Posaconazole
 - Strength is extended mould spectrum
 - Rather like voriconazole for *Candida*
 - Also, it lacks an IV formulation

Making good guesses: Catheters!

In truth, what would you really do?

- A patient has candidemia & a 10-day-old subclavian catheter. The most useful way to decide if the catheter should be removed is:
 - A. Obtain differential venous and trans-catheter blood cultures
 - B. Order a PET scan
 - C. Palpate and inspect the site
 - D. Ask a friendly surgeon if it should come out
 - E. Forget about tests -- just pull it out

Some General Papers

Nucci & Anaissie Revisiting the source of candidemia: Skin or gut? Clin Infect Dis 2001;33:1959-1967.

Nucci & Anaissie: Should vascular catheters be removed from all patients with candidemia? An evidence-based review. Clin Infect Dis 2002;34:591-599.

The Gaur paper does not focus on *Candida* (only one case), but it makes a good argument about advantages of time to growth (quicker, works even if CFU/ml are high in both samples).

■ * All have (at least some) merit

A. Differential cultures: CFU or time

- *CFU*: Telenti, Mayo Clin Proc 1991;66:1120-1123
- *Time*: Gaur, Clin Infect Dis 2003;37:469-475

B. Order a PET scan

- Girmenia, CID Clin Infect Dis 1996;23:506-514
- [18F]Fluorodeoxyglucose scans showed a hot spot even w/ neutropenia (series of 6 patients)

C. Site inspection: Of course!

D. Ask microbiology to tell you the species of the blood isolate

- *C. parapsilosis* just loves plastic
- Girmenia, CID Clin Infect Dis 1996;23:506-514

E. Forget about tests -- just pull it out

- Time is not on your side. Take it out. Take them *all* out -- I've seen every possible type of catheter be infected

Speaking of time: You don't have any to waste

Data are from these two studies of candidemia and mortality:

Morrell et al. Antimicrob Ag Chemother 49:3640-5, 2005.

Garey et al. Clin Infect Dis 43:25-31, 2006

To make the pattern easier to see, I report averaged and rounded figures at right

- Time to initiation of effective therapy for candidemia matters
 - Morrell (one hospital) and Garey (four hospitals) are quite similar
 - Mortality if therapy begins on
 - Day positive blood culture taken: ~15%
 - 24h later: ~25%
 - 48h later: ~35%
 - 72h later: ~40%
- Admittedly, you have to be something of a mentalist to start therapy on day of culture
 - But, that's the point. Go ahead and start therapy if *Candida* is creeping into your thoughts

Thank You!

Any solution to a problem changes the problem.

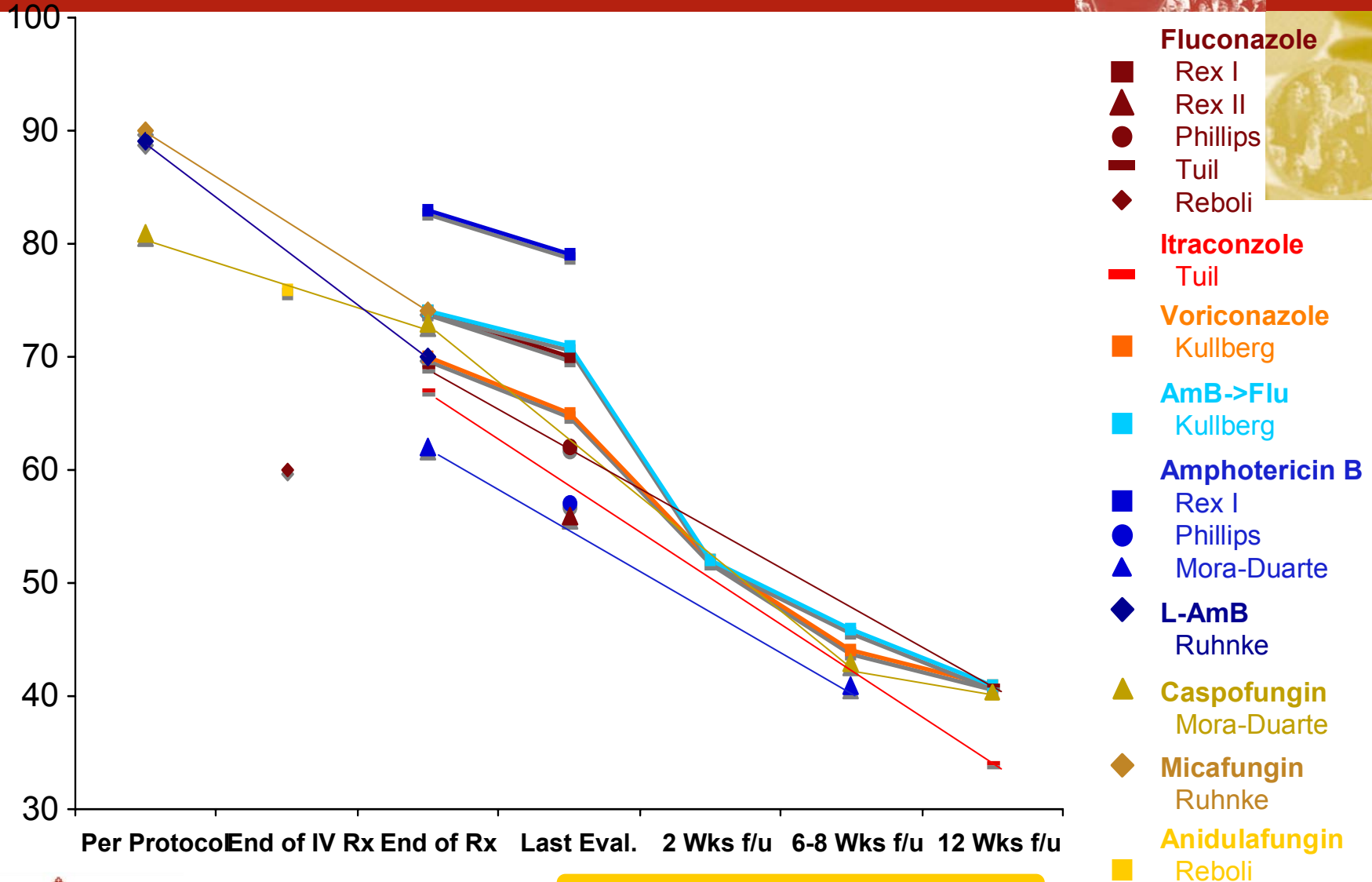
— R. W. Johnson

Life would otherwise be boring, no?

Our heads are round so that our thinking can change direction!

Backup slides

Reported success rates depend on endpoint definition



Susceptibility

Ostrosky-Zeichner et al.
Antifungal susceptibility
survey of 2,000
bloodstream *Candida*
isolates in the United
States. *Antimicrob Agents
Chemother* 2003;47:3149-
3154.

Ostrosky-Zeichner et al.
Voriconazole salvage
treatment of invasive
candidiasis. *Eur J Clin
Microbiol Infect Dis*
2003;22:651-655.

ICAAC 2004: Treating isolates with ↑ Vori MICs

M-218: Buckland et al. Vori
MIC of 2.5 required equiv.
of human dose of 400 bid in
a murine invasive model

- Susceptibility to one azole predicts susceptibility to all:
 - B. False**
- There is a good correlation, but
 - There are enough differences that testing each agent is worthwhile.
 - Especially with vori & (likely) posa
 - As FLU MICs rise, so do these but,
 - ◆ Not always so much and not always to “untreatable” levels
 - ◆ E.g., vori data suggests at least some activity vs. *C. krusei*
 - 7/10 (70%) salvage response rate
 - Relevance of vori MICs uncertain

Vori & Flu MICs: Similar but not identical

| | | VORI MIC | | | | | | | |
|---------|------|----------|------|------|-----|----|----|----|-----|
| | | 0.06 | 0.13 | 0.25 | 0.5 | 1 | 2 | 4 | ≥ 8 |
| FLU MIC | 0.13 | 196 | 1 | 1 | | 1 | 1 | | |
| | 0.25 | 383 | 3 | 2 | 2 | 2 | | 1 | 5 |
| | 0.5 | 346 | 9 | 3 | 3 | 2 | 1 | 1 | 5 |
| | 1 | 228 | 26 | 5 | 3 | | 2 | | 8 |
| | 2 | 87 | 20 | 5 | 3 | | 1 | 1 | 5 |
| | 4 | 44 | 43 | 25 | 4 | 4 | | 1 | 4 |
| | 8 | 21 | 55 | 66 | 35 | 5 | 4 | | 1 |
| | 16 | 5 | 8 | 25 | 48 | 35 | 2 | 1 | |
| | 32 | 5 | 4 | 21 | 15 | 27 | 5 | 1 | 3 |
| | ≥ 64 | 21 | 2 | 5 | 16 | 12 | 16 | 18 | 31 |

Susceptibility (a *really* technical question)

- To separate *most clearly* caspofungin S and R *Candida* isolates, you should do MICs by
 - A. NCCLS, but 24h reading, partial inhibition endpoint (MIC₂)
 - B. NCCLS, but 24h reading, complete inhibition endpoint (MIC₀)
 - C. NCCLS, but 48h reading, partial inhibition endpoint (MIC₂)
 - D. NCCLS, but 48h reading, complete inhibition endpoint (MIC₀)
 - E. There is no good way to do this

Susceptibility (a *really* technical question)

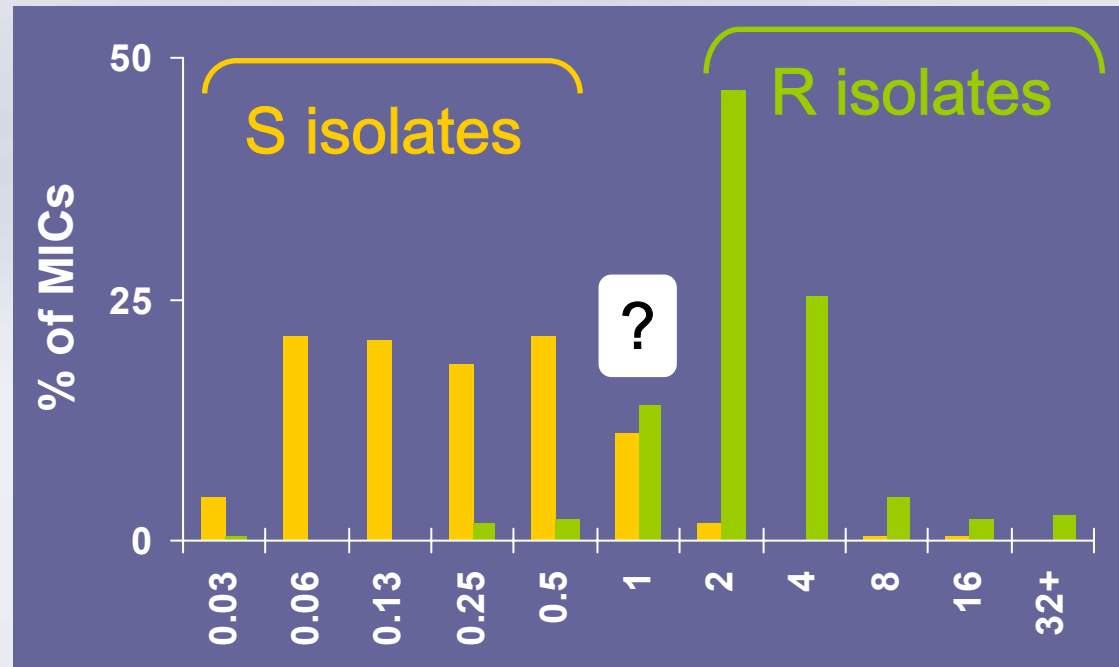
Odds FC et al. Interlaboratory comparison of results of susceptibility testing with caspofungin against *Candida* and *Aspergillus* species. *J Clin Microbiol* 2004;42:3475-82.

Agreement ± 1 dilution was still never better than 73%. Adding 2% glucose, using AM3, and reading with a spec either did not help or made things worse.

AM3, did, however, sharpen the separation between S and R.

See also Pfaller MA et al. *J Clin Microbiol* 42:3117-9, 2004 for further validation of these data

- To separate *most clearly* caspo S and R isolates, you should use
 - A. NCCLS (RPMI), 24h, MIC2 (visual)
 - These conditions give the best inter-laboratory agreement
 - They best separate S and R isolates



Multiple readings on 8 isolates with a molecular basis for reduced susceptibility and 22 with normal susceptibility

Caspofungin susceptibility testing

- Caspofungin susceptibility testing
 - A. Has been clearly proven clinical relevant and you really do need to be testing your isolates
 - B. Has been clearly shown to be complete nonsense, a waste of time, and a waste of money
 - C. Can identify isolates with high MICs, but so far clinical isolates with *really* high MICs are rare and 99% of isolates have MICs that don't seem to relate to failure

Caspofungin susceptibility testing

Pfaller MA et al. J Clin Microbiol 42:3117-9, 2004.

This study used the 24h, partial inhibition endpoint defined by the Odds paper. The two groups of *Candida* spp. Relate to differences in enzyme IC50.

See Mora-Duarte J et al. NEJM 347:2020-2029, 2002 for clinical response data.

As with the voriconazole data, the chief limitation is the small number of cases to date.

- Caspofungin susceptibility testing
 - C. Can identify high MICs, but clinical isolates with *really* high MICs are rare. MICs don't predict failure.
- In 3,314 recent clinical isolates
 - Only 3 isolates (*C. parapsilosis* x 2, *C. guilliermondii* x 1) had MIC ≥ 2 $\mu\text{g/ml}$
 - But, 41 more had MIC = 1 $\mu\text{g/ml}$
 - Still, 99% had MICs < 1 $\mu\text{g/ml}$
 - Summary: Two *Candida* groups
 - i. Albicans, glabrata, tropicalis, kefyr, pelliculosa: MIC90 = 0.06 $\mu\text{g/ml}$
 - ii. Paraps, krusei, lusit, guillier: MIC90 = 0.5
 - But, all species seem to respond equally to therapy in studies to date