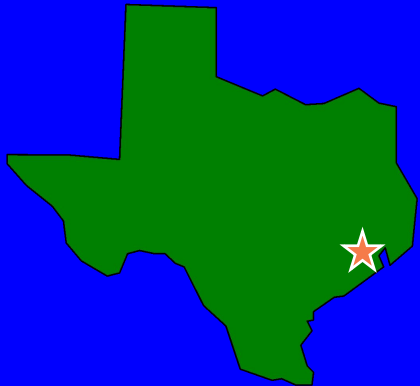

Combination Antifungal Therapy



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The Past as Prologue

What can we learn from prior work on
antibacterial combinations?

History lessons: Stay alert!

- Combinations can be **GOOD**
 - *Enterococcus*: PCN (or amp or vanc) + gent
 - » Good in endocarditis. **But**, not clearly so at other sites
- Combinations can be **BAD**
 - PCN \pm chloro in pneumococcal meningitis
 - » Adding chloro decreased survival from 79 to 21%
- Assessing all this in vitro is **TRICKY**
 - Technical: *Enterococcus*, PCN, & gent
 - » Checkerboard is not reliable—must use time-kill
 - Some interactions (e.g., metabolic) not seen

About those words...

Less than expected Same as expected More than expected

Loewe Antag. Additive Synergy

Bliss Antag. Independent Synergy

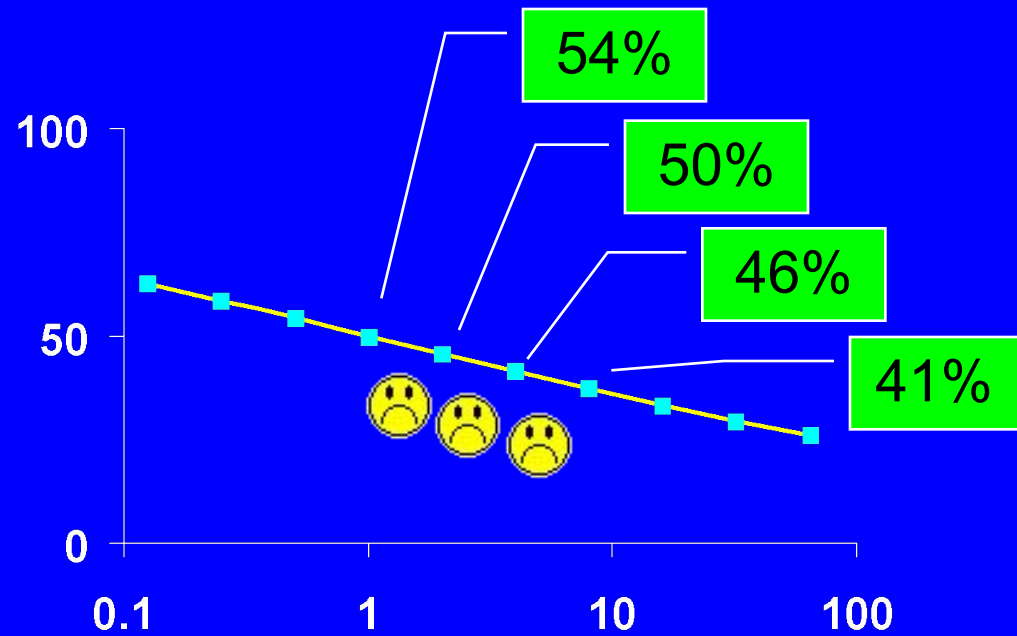
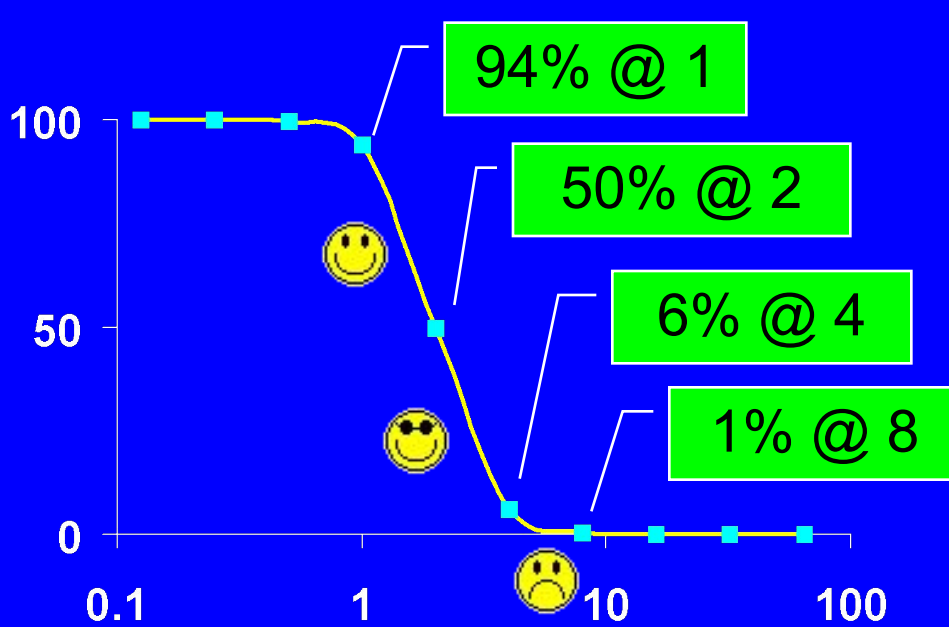
- The word additive can be confusing
 - It really means that a drug added to itself produces the expected sum of effects
 - It does **not** imply effects **greater than expected**
- “**Indifferent**” has no clear definition

About those numeric scores...

- What about FICIs and other numbers?
 - FICI = 1 is the null point
 - Other values are parsed infinitely
 - » ≤ 0.5 = synergism
 - » 0.5 to 4 = additive or indifferent or other phrases
 - » > 4 = antagonistic
- All is arbitrary and highly technique driven
 - I am going to be looking at mostly in vivo data
 - I will lump into positive, neutral, & negative

Bug-, drug-, and & model-dependence

- A thought experiment: Add a drug to itself
 - $1 \mu\text{g/ml} + 1 \mu\text{g/ml} = 2 \mu\text{g/ml}$, right?
 - Dose-response curve: shape & location...



Antifungal Combinations

With all that in mind, what about the antifungal agents?

My focus will be on combinations where we can currently shown some clinical utility

Drugs & Abbreviations

- Amphotericin B (AmB): Membrane effects
- 5-Flucytosine (5FC): DNA/RNA synthesis
- Ergosterol pathway: azoles & allylamines
 - FLU, ITR, KETO, VOR, RAV, POS
 - Terbinafine (TERB)
- Glucan synthesis: The candin/fungins
 - CFG, MFG, AFG
- Chitin synthesis: Nikkomycin Z (NikZ)

5-Flucytosine plus various things

Generally favorable

5FC + Things



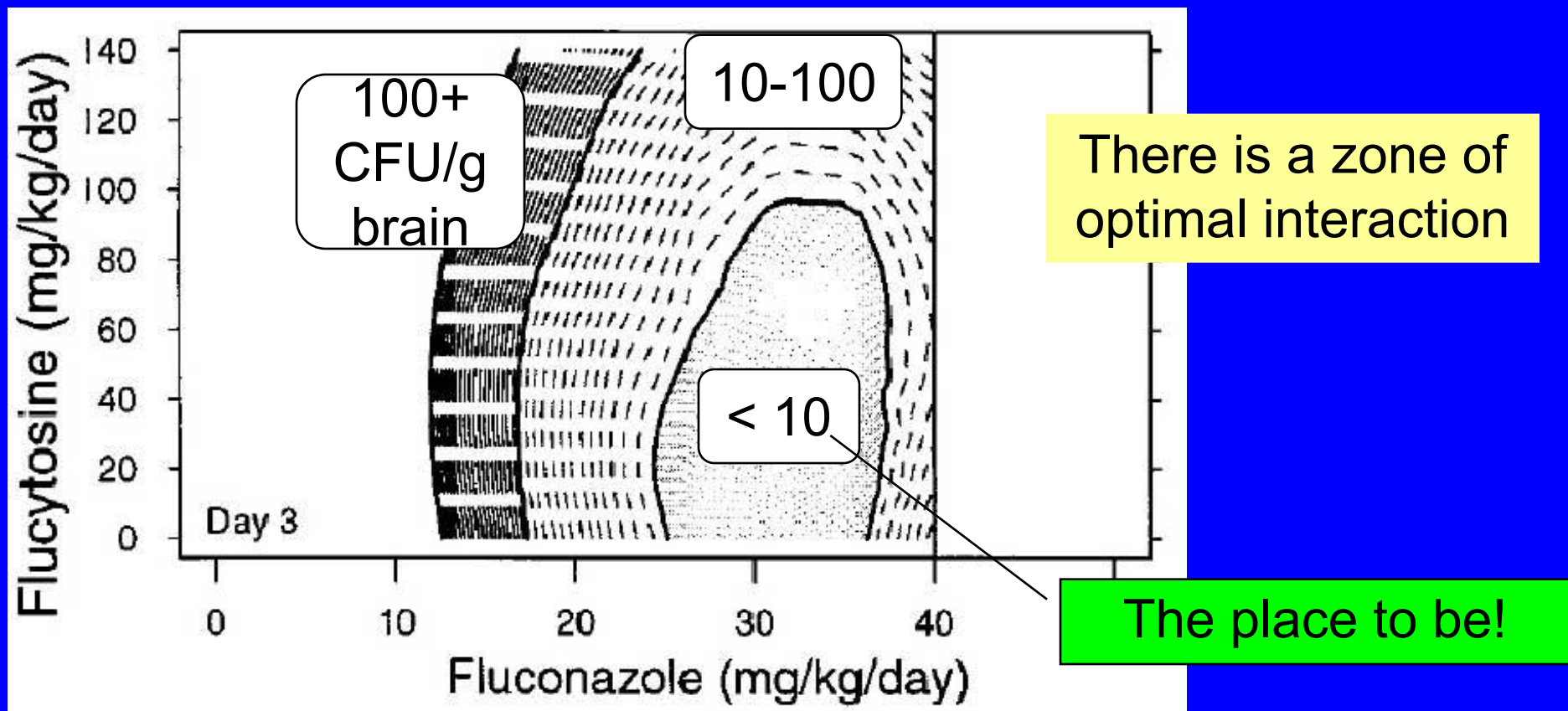
Cryptococcal meningitis

- » ↑ success, ↑ rate CSF sterilized
- » ↓ AmB dose & thus nephrotoxicity
- » ↓ relapse rates (HIV)

- Other fungi: Not obviously good or bad
 - *Candida*: ?in vitro antag, but OK in case series
 - *Aspergillus* et al.: OK in vitro & tiny case series
 - » Te Dorsthorst ICAAC '02, M-850: +AmB is good, +ITR is bad

Useful lesson: Dose matters!

- Murine models of cryptococcal meningitis
 - FLU + 5FC is **generally** quite favorable



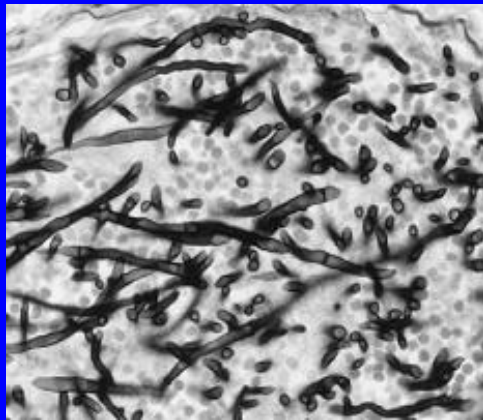
Candins plus various things

A hot topic at present!

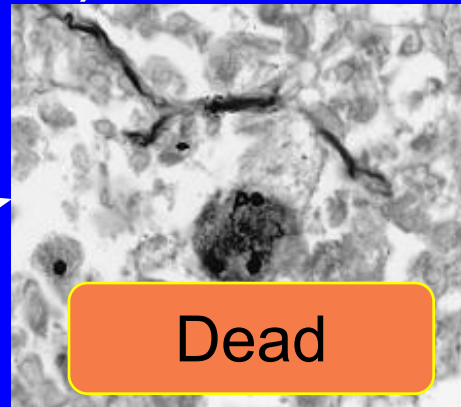


Aspergillus: Not quite dead (1)

- Rabbit model, Ara-C, **persistent neutropenia**
 - Anidulafungin (AFG), intratracheal inoculation



Control lung section
6.5 d survival



Dead

AmB, 1 mg/kg/d
~1.5 log ↓
CFU/g



Not quite

AFG, 10 mg/kg/d
No ↓ CFU/g



Aspergillus: Not quite dead (2)

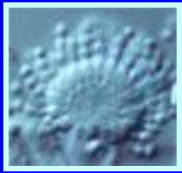
- Anidulafungin, murine model, cyclophos
 - Model produced transient neutropenia
 - IV infection with *Aspergillus* conidia

Lung CFU/g # Survivors

Control	310	0/10
AmB 2 mg/kg/d	90	7/10
AFG 10 mg/kg/d	60	8/10

Verweij et al., AAC 42:873, 1998

Now we see a
CFU drop



For *Aspergillus*,

- Echinocandins alone do not completely kill
 - Persistent neutropenia: tissue **may not** clear
 - Transient neutropenia: tissue **is** cleared
- So, the candin needs a helping hand
 - Second agent could be a **neutrophil**
 - Or a drug!



In vivo data are supportive

- Most data show strong positive interactions
 - Candin plus AmB
 - » CFG: (Flattery, ICAAC #J-61, '98)
 - Value seen in DBA2/N mice, but not pancytopenic mice
 - » MFG: (Kohno, ICAAC #1686, '00); (Nakajima, ICAAC #1685, '00)
 - Candin plus azole
 - » VOR + CFG: (Kirkpatrick, AAC 46:2564, '02)
 - » RAV + MFG: (Petraitiene, ICAAC M-857, '02)
- A few differences here and there
 - » MFG + AmB: Neutral (Capilla-Luque, ICAAC J-1834, '01)
 - » Cilofungin + AmB: Negative (Denning, AAC 35:1329, '91)



Human Data?

- Really scant so far.
 - An anecdote
 - » *A. flavus* pneumonia & osteo in boy with CGD
 - » CAS + VOR held in check, but VOR alone did not.
 - Open-label or salvage: Hard to interpret
 - » Kontoyiannis, ICAAC '02, M-1820
 - 50 with invasive aspergillosis. CFG+L-AmB
 - » Thiebaut, ICAAC '02, M-859
 - 10 with various IFI. CFG + AmB
 - » Gentina, ICAAC '02, M-860
 - 6 with IA, use of CFG + L-AmB and CFG + VOR

Other Fungi



Cryptococcus

- Candins alone have minimal effects
- CFG + AmB:
 - » Favorable in vitro, but no obvious in vivo advantage



Candida

- In vitro: candins are very potent, combos additive
 - » Bachman ICAAC '02, M-1813: FLU+CAS bad in biofilm?
- CFG + AmB: Favorable in vivo effect
 - » Also reported with cilofungin + AmB

Candin Combinations: Bottom Line

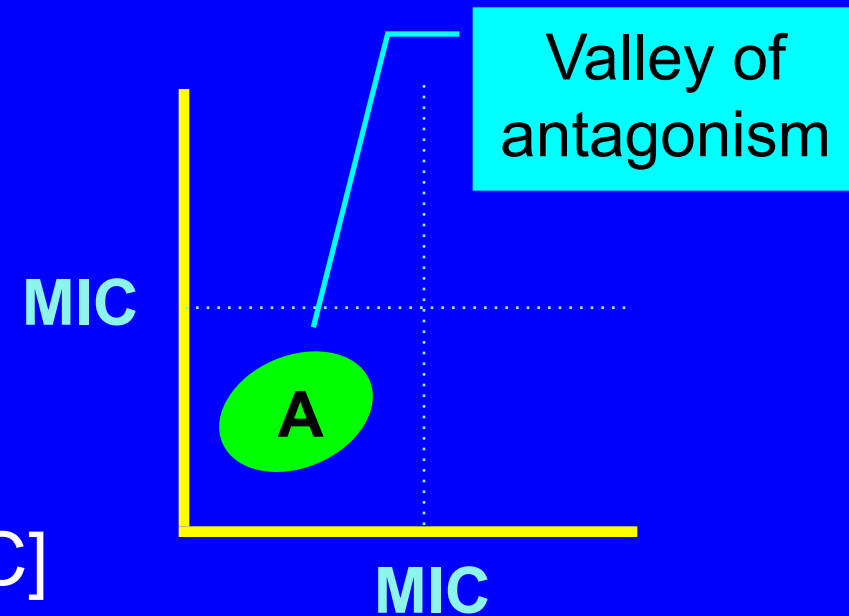
- I'd rate this as *very* interesting
- *Aspergillus* data are especially powerful
 - These data really make sense based on our understanding of the relative drug effects
 - A serious clinical study is in order!
- The other fungi?
 - Not so obvious why you should do it
 - But, you *can* do it without ill-effect, should you need a combination to get a broader spectrum

Polyenes plus azoles

The really confusing one

Azoles + AmB: In vitro

- In theory
 - Azole depletes ergosterol, AmB needs ergosterol
- Thought experiment
 - If azole works, who cares?
 - Always at least azole effect?
- In practice...
 - AmB first? No negative effect
 - Together? Negative at [sub-MIC]
 - Azole first? Often negative, especially w/ ITR, KETO





Aspergillus: Any answer you want...

- KETO first, AmB second: **Bad** in rat model
- ITR and AmB together
 - Series of murine disseminated disease models
 - » Mostly no interaction, occasionally slightly negative
 - » POS+AmB: neutral (Najvar, ICAAC '02, M-1818)
 - Murine CNS aspergillosis model
 - » Combination trended towards better survival than either alone. **Not negative, for sure!**
- Key: Result is model-, drug-, site-specific

Note color coding: blue for FLU, yellow for AMB

Continued variation



Cryptococcus: GOOD

- Murine model: FLU + AmB gave best results!
 - » But, FLU first was bad



Histoplasma: BAD

- Higher lung & spleen CFU with FLU + AmB



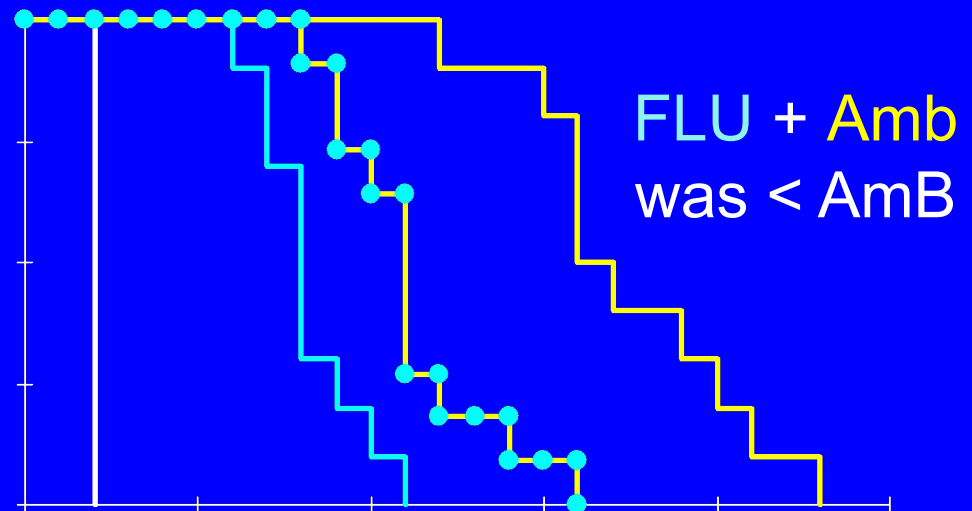
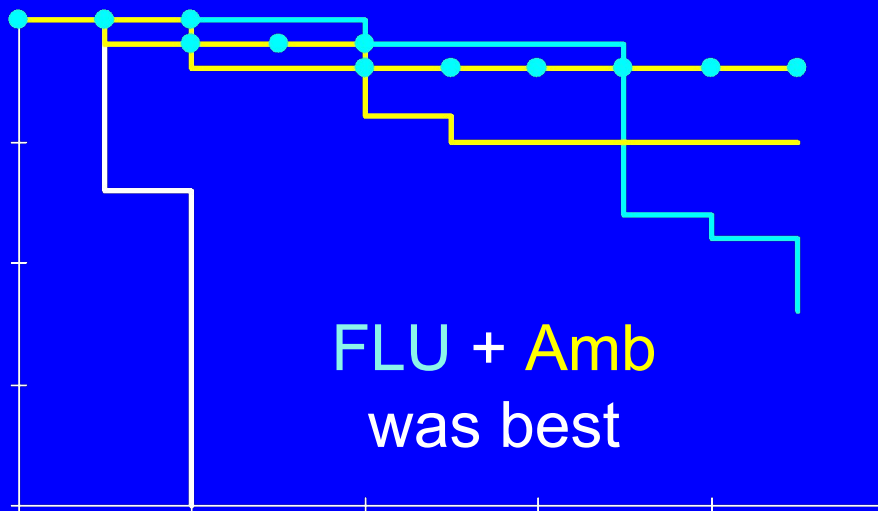
Trichosporon: GOOD

- FLU + AmB was better than AmB alone
 - » And, FLU + AmB + levofloxacin was best of all!



Candida: We have some data

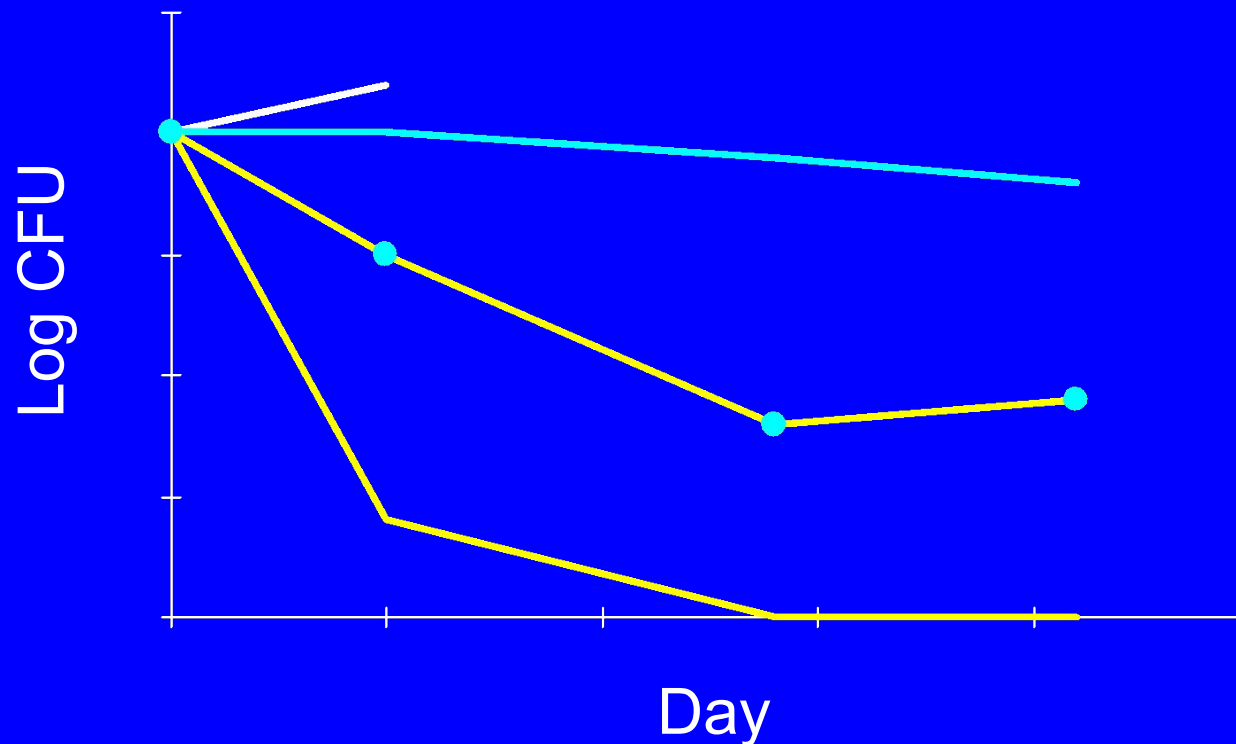
- All possible results seen. The azole matters
 - **AmB** + Pos: Combo best (Cacciapuoti ICAAC '02 M-1814)
 - **AmB** + ITR: Combo < AmB (? 2° toxicity)
 - FLU, two murine models, *C. albicans*





Candida: A caveat

- Louie et al. AAC 43:2831, '99
 - Clearance of heart valves (rabbits, *C. albicans*)



FLU + Amb was intermediate between FLU and AmB alone

Human Data: *Non-Candida*

- Mostly a lot of anecdotes, mostly OK
 - Anecdotal use of AmB+5FC+FLU for crypto
 - AIDS/Histo, crypto: alternate azole & AmB use
 - Stray anecdotes
 - » ITR + L-AmB cured skull base aspergillosis
 - » ITR + L-AmB failed in in two cases of aspergillosis
 - » ITR + L-Amb used without comment (!)
- And, we've got a serious trial in *Candida*...



FLU + AmB for Candidemia

- Study Arms
 - FLU+Placebo: FLU 800 mg/day plus MVI
 - FLU+AmB: FLU 800 mg/day + 0.7 mg/kg dAmB
- Placebo/AmB x 3-8 days & was **blinded!**
- Results: FLU + AmB...
 - Was favored overall (P = 0.04 to 0.08)
 - » Was more nephrotoxic (no surprise)
 - **Gave lowest rate persistent +BC ever seen!**
 - » 7% vs. 17%: this is better than ANY previous study
 - And, as for antagonism...



Prior Therapy: % Success (N)

Group	FLU+Placebo	FLU+AmB
No prior therapy	61% (46)	69% (39)
FLU only	56% (48)	67% (55)
AmB only	17% (6)	73% (11)
FLU & AmB	50% (4)	50% (2)
Any drug	52% (58)	68% (68)

A good number of cases.
Not even a *hint* of in vivo antagonism.
No antagonism in vitro, either.

AmB + Azoles: Bottom Line

- Yow! Very confusing
 - Many negative trends, but many surprises
- *Cryptococcus*: Combination often positive
- *Candida*: A wild range of results
 - The one human trial was NOT negative
 - Can do if needed. This strategy pursued to get better spectrum. Candins should render moot.
- *Aspergillus*
 - Start w/AmB, switch to azole, **may overlap**

Further Afield

Terbinafine + Azoles

- A sequential one-two attack
 - TERB: squalene epoxidase, upstream of
 - Azoles: 14- α -demethylase
- In vitro is almost entirely favorable
 - *Candida*: FLU, ITR, POS, VOR, AmB
 - *A. fumigatus*: FLU, ITR
 - » Unfavorable with AmB, 5FC
 - Zygomycetes: AmB, VOR
 - & more: *Scopulariopsis*, *Pythium*, *Trichosporon*



Terbinafine + Azoles: *Candida*

- Clinical anecdote
 - OPC unresponsive to FLU at 200/d x 2 weeks
 - FLU MIC of 32 $\mu\text{g/ml}$
 - FLU 200/d + TERB 250/d: Clears completely
- Clinical study Flu-refractory OPC in HIV
 - TERB 1000-1500/d alone: 15-17% response
 - TERB with 200/d FLU: 23% response
 - Right direction, just not very strong



Terbinafine + Azoles: *Pythium*

- *Pythium* is an aquatic near-fungus
 - Causes “swamp cancer” in horses
 - Unremitting tissue destruction
 - Responds poorly drugs – surgery is key
- A 2-year-old had deeply invasive infection
 - Surgery not an option
 - In vitro, TERB + ITR favorable (esp. for MLC)
 - Responds completely to 1 year of ITR + TERB!
 - » This is really *quite* striking

Others: Too many to discuss!

- NikZ + candin or azole
- Azoles + quinolones (yes, quinolones)
 - FLU + trova = AmB in murine *Rhizopus* model
 - » Quin effect might include immune enhancement
- Rifampin, azithromycin, tetracycline
 - Protein synth. Inhibitors: Often positive in vitro
- Cyclosporine plus azoles or candins
 - Makes azoles cidal in endocarditis models!

And, at this meeting

- At least 25 presentations on combinations
 - Poster session at noon today (11-12:30)
 - Slide session with mini-lecture Monday AM
- Some highlights
 - Sophisticated in vitro models
 - Cotrimoxazole as a co-agent
 - Lots of candin-based work
 - Interesting terbinafine-based data

Summary

*Your head is round so that your
thinking can change direction...*

Clinical Implications for Today

- *Cryptococcus*
 - Adding 5FC is generally good. +FLU is better?
- *Candida*
 - Can combine fluconazole with AmB
 - » But, probably should avoid in endocarditis
 - » Candins may render this idea moot
- *Aspergillus*
 - Candin-based combos look like the way to go
- Keep terbinafine-based combos in mind

Thank you!

You've been very patient!

That was a lot of stuff!

... and your head is also round so that it can spin!