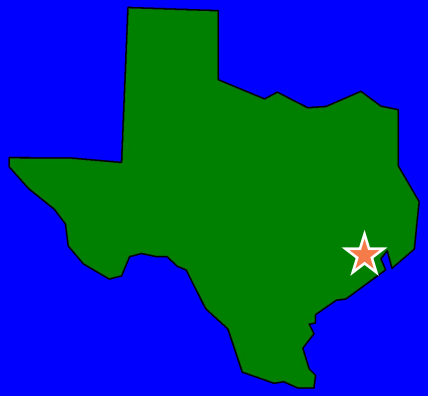
Combination Antifungal Therapy



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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 ± 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

Greco WR et al. Pharmacol Rev 1995;47:331

About those words…

	Less than expected	Same as expected	More than expected
Loewe	Antag.	Additive	Synergy
Bliss	Antag.	Independent	Synergy

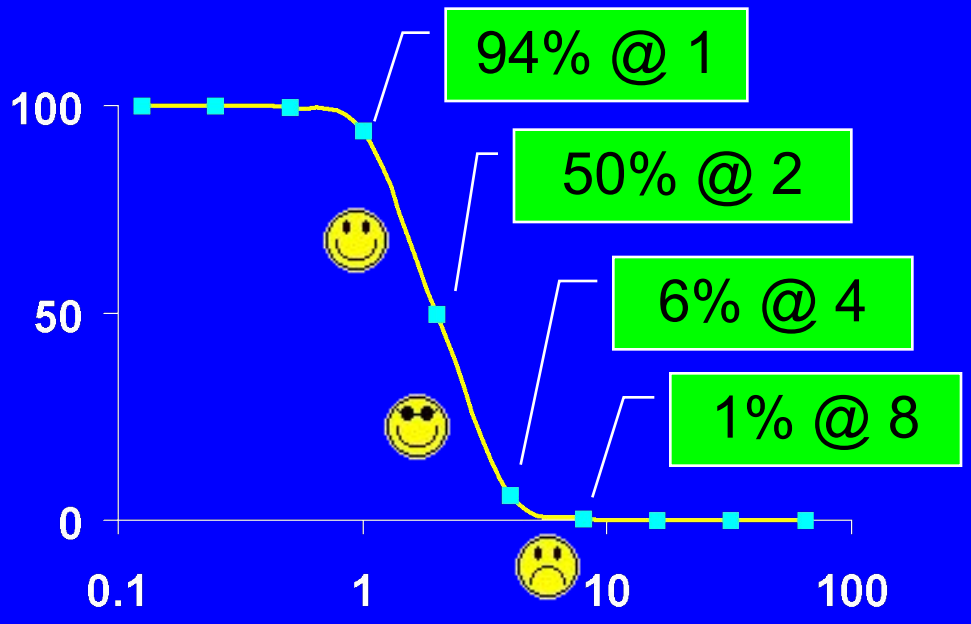
- The word additive can be confusing
  - It really means that a drug added to itself produces the expected sum of effects
  - It does not imply effects greater than expected
- "Indifferent" has no clear definition

About those numeric scores…

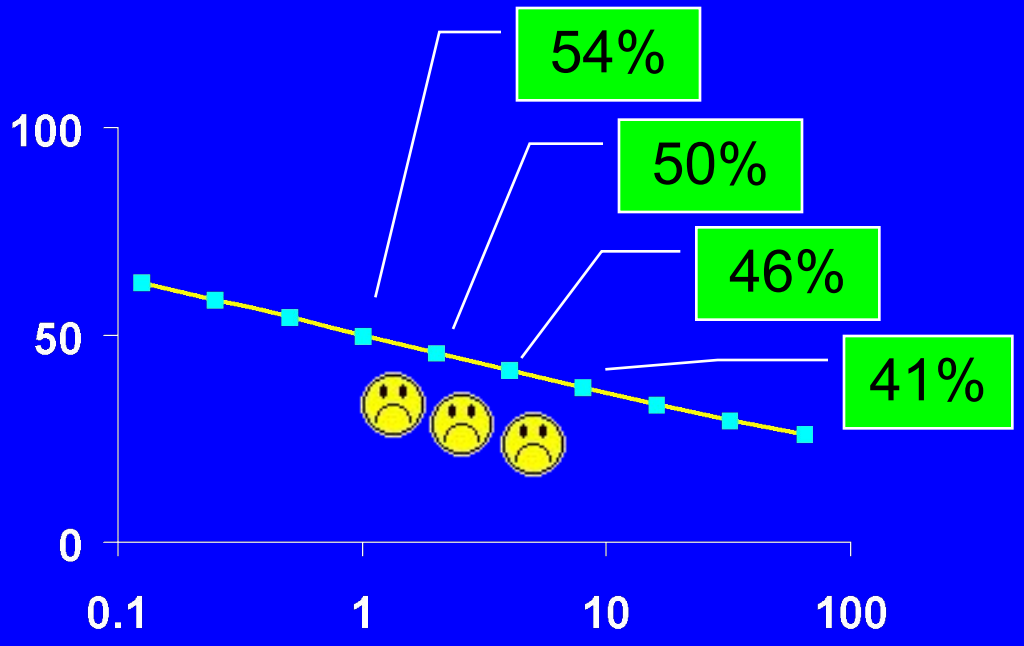
- What about FICIs and other numbers?
  - FICI = 1 is the null point
  - Other values are parsed infinitely
    - » ≤ 0.5 = synergism
    - » 0.5 to 4 = additive or indifferent or other phrases
    - » > 4 = antagonistic
- All is arbitrary and highly technique driven
  - I am going to be looking at mostly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

Bug-, drug-, and & model-dependence

- A thought experiment: Add a drug to itself
  - 1 μg/ml + 1 μg/ml = 2 μg/ml, right?
  - Dose-response curve: shape & location…



Hill Slope = 4



Hill Slope = 0.25

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

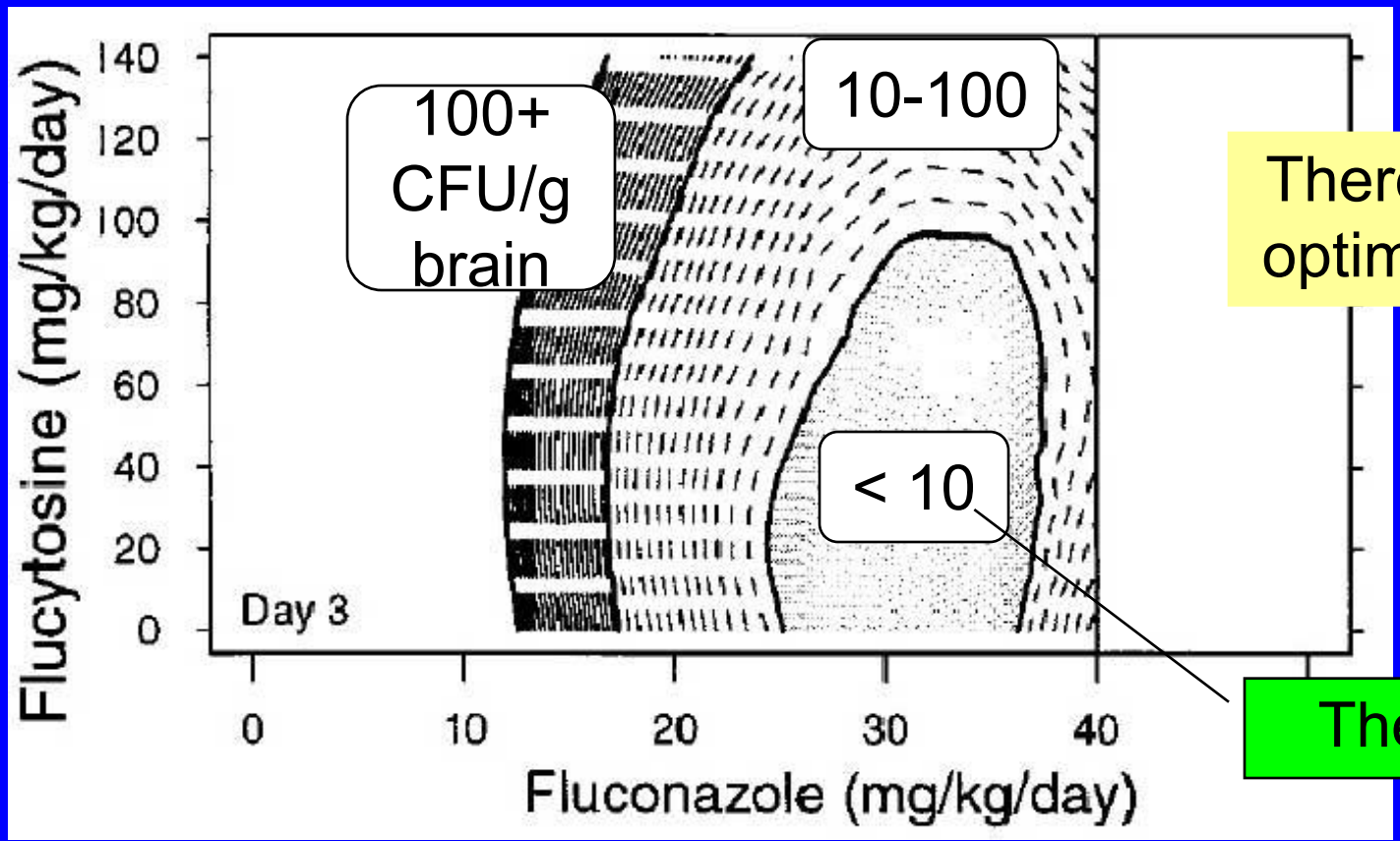
- Cryptococcal meningitis
  - » ⇑ success, ⇑ rate CSF sterilized
  - » ⇓ AmB dose & thus nephrotoxicity
  - » ⇓ relapse rates (HIV)
- Other fungi: Not obviously good or bad
  - – *Candida*: ?in vitro antag, but OK in case series
  - – *Aspergillus* et al.: OK in vitro & tiny case series
    - » Te Dorsthorst ICAAC '02, M-850: +AmB is good, +ITR is bad

Block Proc Soc Exp Biol Med 142;476, '73; Te Dorsthorst AAC 46:2982, '02; Bennett NEJM 301:126, 1979; van der Horst NEJM 337:15, '97; Saag CID 28:291, '99; Saag CID 30:710, '00; Te Dorsthorst AAC 46:2982, '02; Martin AAC 38:1331, '94; Barbaro Chest 110:1507, '96; Polak Chemotherapy 33:381, '87; Verweij Infection 22:81, '94; SIlling Mycoses 42 (S2):101, '99; Denning RID 12:1147, '90

Ding AAC 41:1589, ’97; Allendoerfer AAC 35:726, ’91; Barchiesi AAC 44:2435, ‘00

Useful lesson: Dose matters!

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

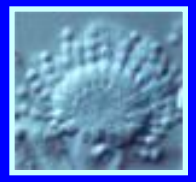


There is a zone of optimal interaction

The place to be!

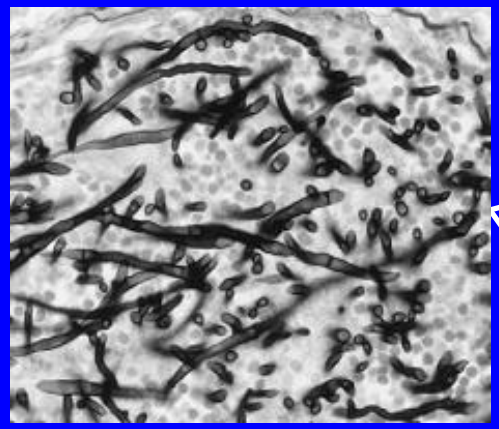
Candins plus various things

A hot topic at present!

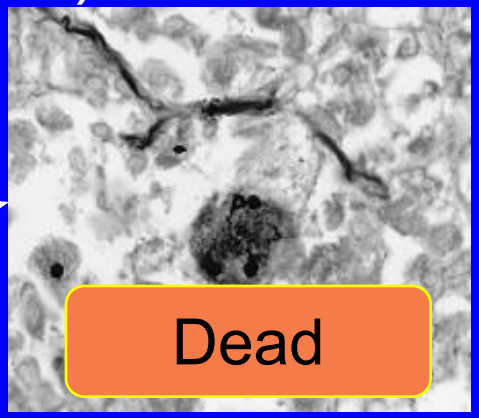


Aspergillus: Not quite dead (1)

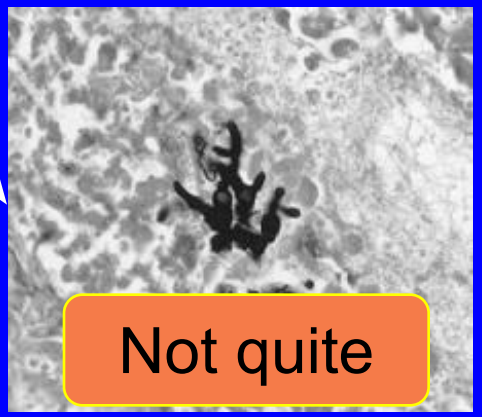
- Rabbit model, Ara-C, persistent neutropenia
  - Anidulafungin (AFG), intratracheal inoculation



Control lung section
6.5 d survival

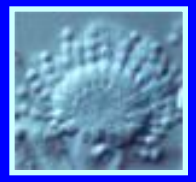


AmB, 1 mg/kg/d
~1.5 log ↓ CFU/g



AFG, 10 mg/kg/d
No ↓ CFU/g

Petraitis et al., AAC 42:2898, 1998



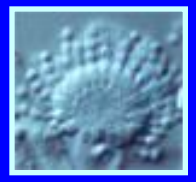
Aspergillus: Not quite dead (2)

- 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

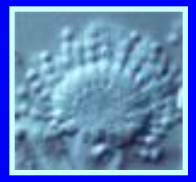
Verweij et al., AAC 42:873, 1998

Now we see a CFU drop



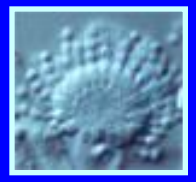
For *Aspergillus*,

- 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

Franzot AAC 41:331, ’97; Flattery ICAAC #J-61, ’98; Smith EJCMID 10:588, ’91; unpublished data (Rex); Sugar AAC 35:2128, ’91; Roling DMID 43:13, ‘02

Candin Combinations: Bottom Line

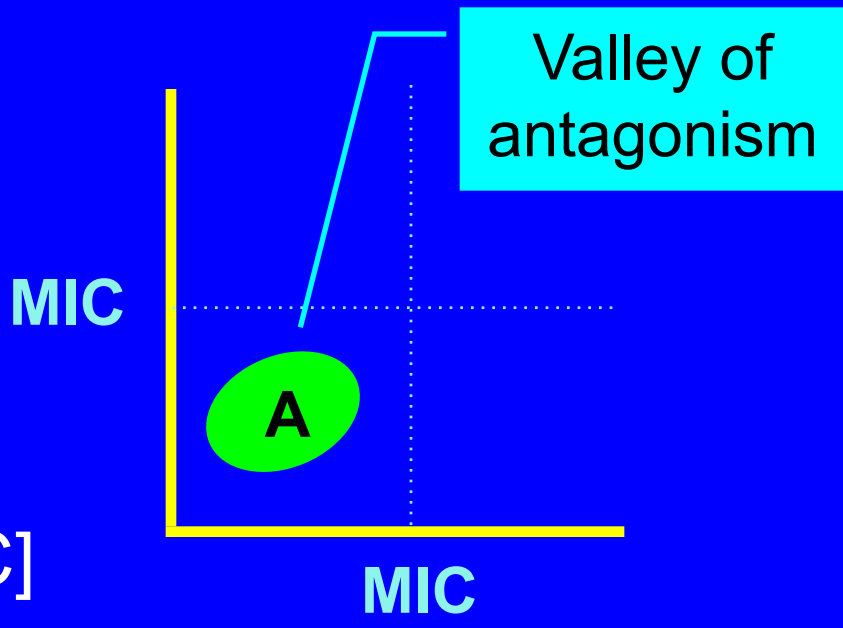
- I'd rate this as *very* interesting
- *Aspergillus* data are especially powerful
  - These data really make sense based on our understanding of the relative drug effects
  - A serious clinical study is in order!
- The other fungi?
  - Not so obvious why you should do it
  - But, you *can* do it without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

Polyenes plus azoles

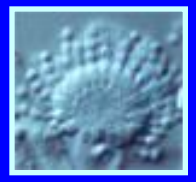
The really confusing one

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



Scheven AAC 39:1779, ’95, Scheven Mycoses 38 (S1):14, ‘95



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 then either alone. Not negative, for sure!
- Key: Result is model-, drug-, site-specific

Schaffner JID 151:902, '85; Polak Chemotherapy 33:381, '97; Chiller ICAAC #J-1615, '01.

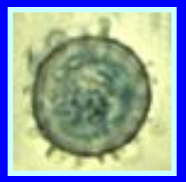
Note color coding: blue for FLU, yellow for AMB

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

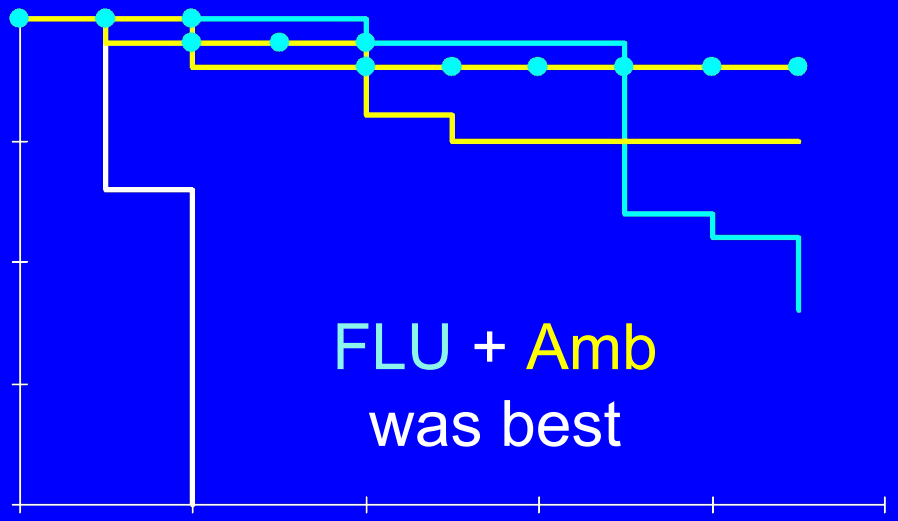
– FLU + AmB was better than AmB alone

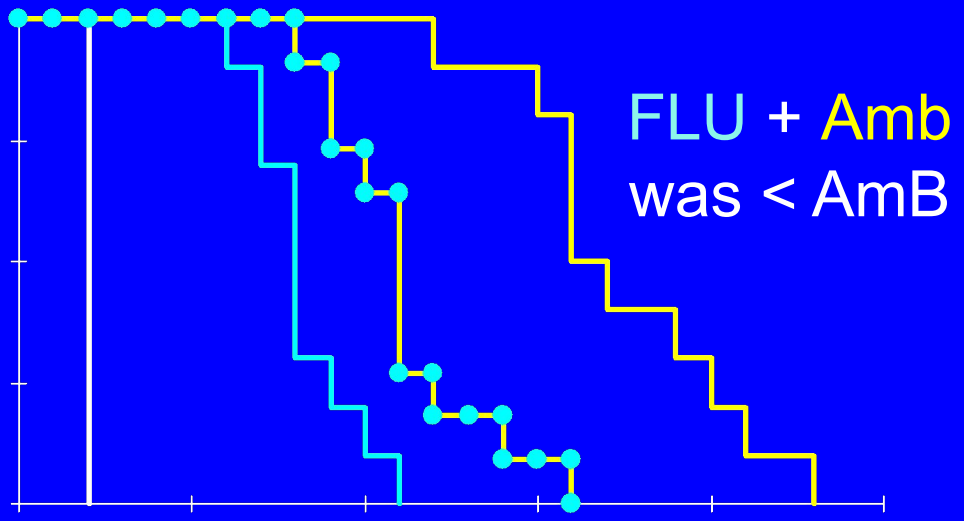
» And, FLU + AmB + levofloxacin was best of all!

Barchiesi AAC 44:2435, ’00; LeMonte JID 182;545, ’00; Louie ICAAC J-1619, ‘01

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*

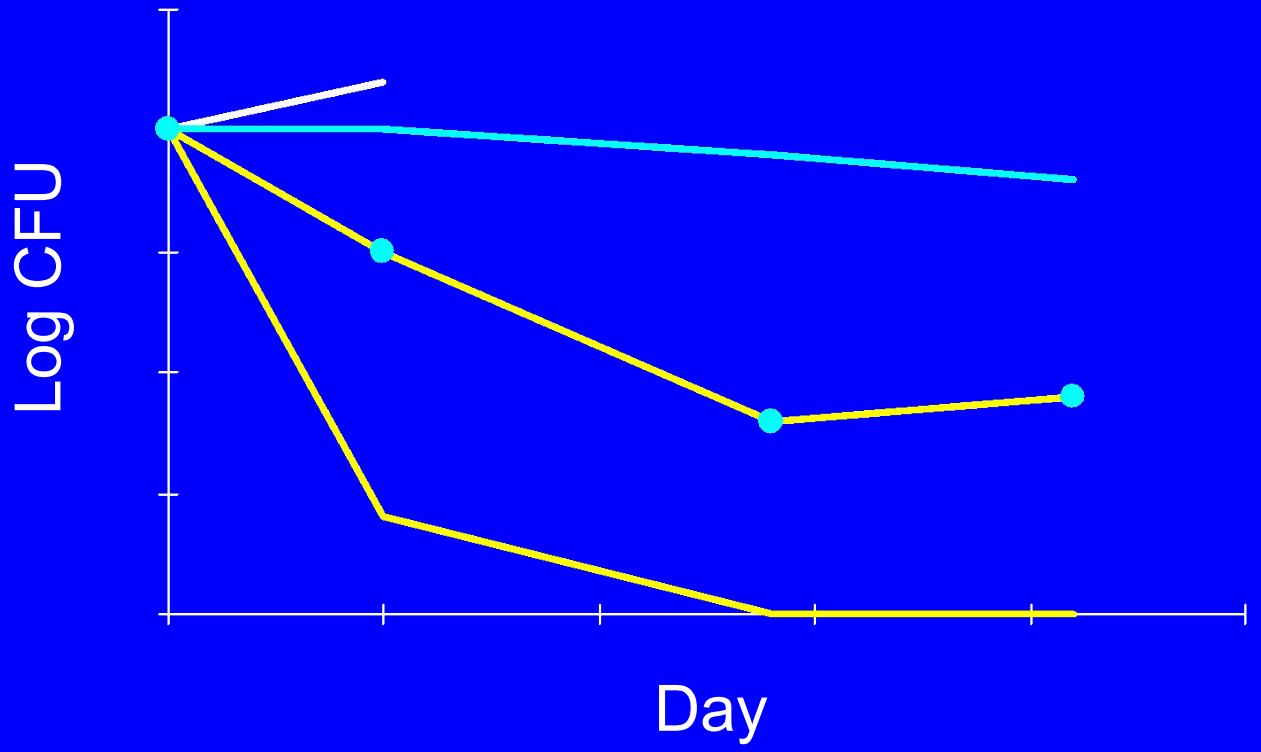




Sugar JID 177:1660, ’98; Sugar AAC 38:371, ’94; Sugar AAC 39:598, ’95; Louie AAC 43:2841, ‘99

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…*

Streppel Ann Otol Rhinol Laryngol 108:205, '99; Bajjoka Pharmacotherapy 19:118, '99; Caillot JCO 15:139, '97

ICAAC 2001, #J681a

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*

Brachiesi JAC 41:59, ’98 & AAC 41:1812, ’97; Perea JCM 40:1831, ’02; Mosquera 40:189, ’02; Dannaoui AAC 46:2708, ’02; Ryder Mycoses 42 (Suppl. 2): 115, ‘99

Terbinafine + Azoles: *Candida*

- Clinical anecdote
  - OPC unresponsive to FLU at 200/d x 2 weeks
  - FLU MIC of 32 μg/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

Ghannoum Clin Diag Lab Immunol 6:921, '99; Vazquez ICAAC 2000 (Toronto), #1418

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

Shenep CID 27:1388, ‘98

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!

Chiou AAC 45:3310, ’01; Li AAC 43: 1401, ’99; Capilla-Luque ICAAC #J-1834, ’01; Sugar AAC 44:2004, ’00; Sugar AAC 41:2518, ’97; Shalit 46:2442, ’02; Arroyo AAC 11:21, ’77; Clancy AAC 42:509, ‘98; Clancy JAC 41:127, ’98; Ernst RID 5:S626, ’83; Graybill RID 5:S620, ’83; Hughes AAC 25:560 & 26:837, ’84; Huppert AAC 5:473, 1974; Kitahara JID 133:633, 1976; Marchetti AAC 44:2373, ’00; Marchetti AAC 44:2932, ’00; Heitman EMBO J 21:546, ‘02

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!