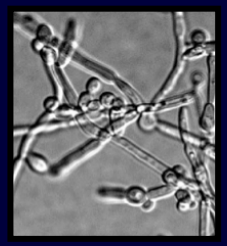
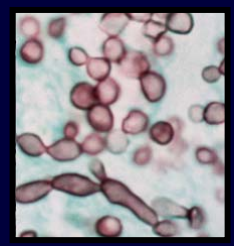
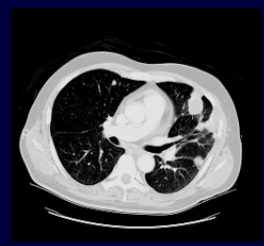
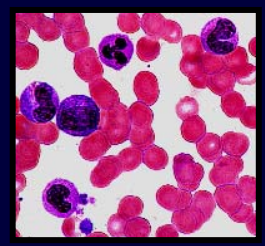


Management Strategies For Invasive Mycoses: An MD Anderson Perspective

Dimitrios P. Kontoyiannis, MD, ScD, FACP, FIDSA

Professor of Medicine

Director of Mycology Research Program

M. D. Anderson Cancer Center

Adjunct Professor

University of Houston

Houston, Texas

Antifungal prophylaxis-

Minimal "standard of care"

Autologous transplant, Acute leukemia → fluconazole 400 mg/day
itraconazole?

Low-risk allogeneic → fluconazole 400 mg/day or

High-risk leukemic
(older patients with AML/MDS, persistent neutropenia, prior history of IA) → voriconazole 200 mg BID or caspofungin 50 mg/day…
posaconazole?

Antifungal prophylaxis-

Minimal "standard of care"

High-risk allogeneic

(cord blood transplants, haploidentical, alemtuzumab recipients or prior history of fungal infection)

→ voriconazole 200 mg BID or caspofungin 50 mg/day or posaconazole? +/- aerosolized AMB-d

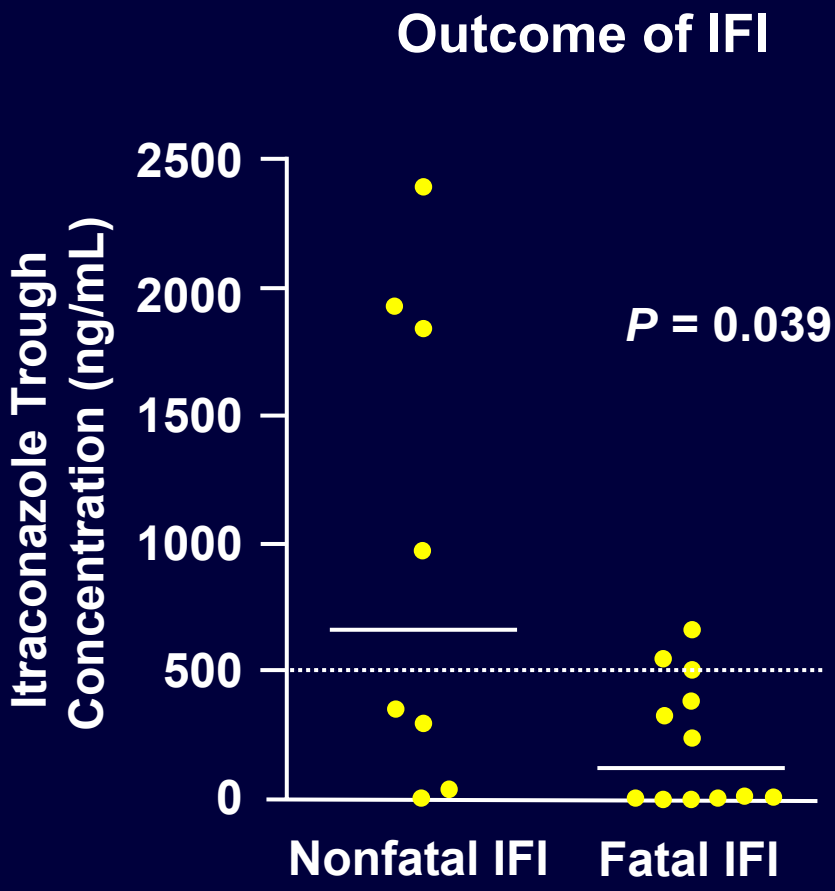
aGvHD with steroids

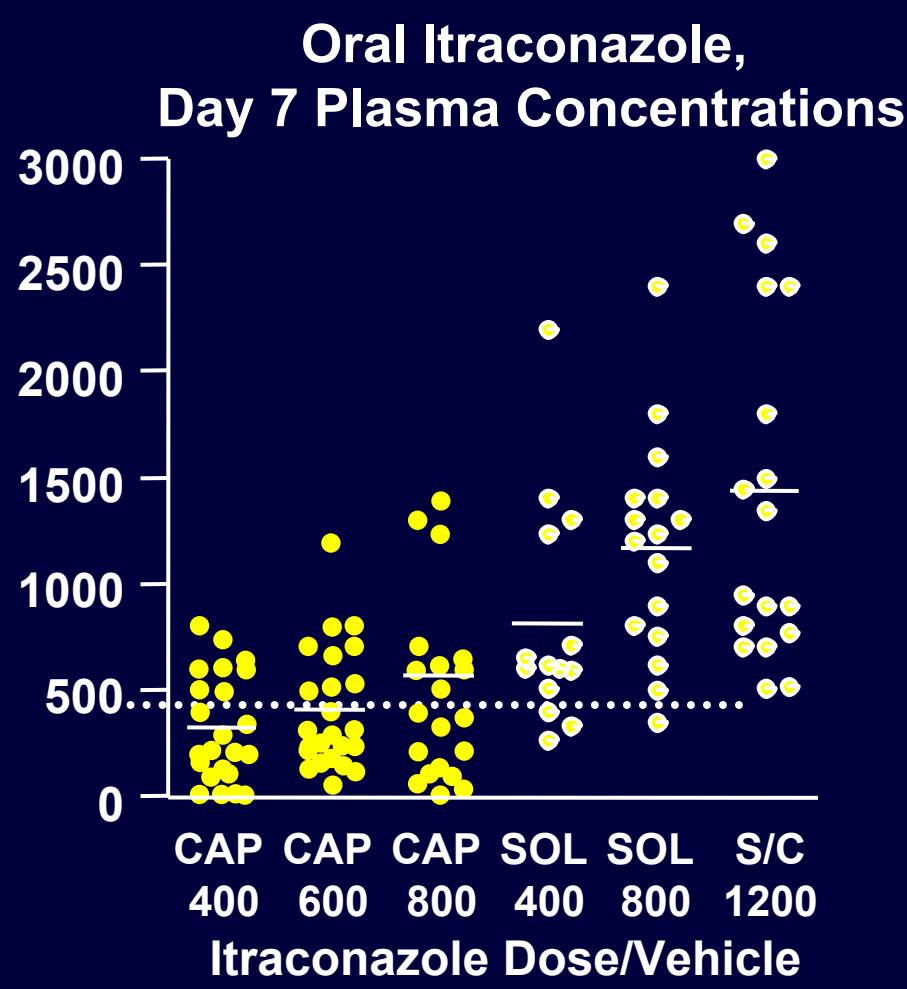
→ voriconazole 200 mg BID or POSA 200mg TID or caspofungin 50 mg/day (inpatient)

Liver function abnormalities

→ caspofungin 50 mg/day (inpatient) or posaconazole

Itraconazole
The Past as Prologue….

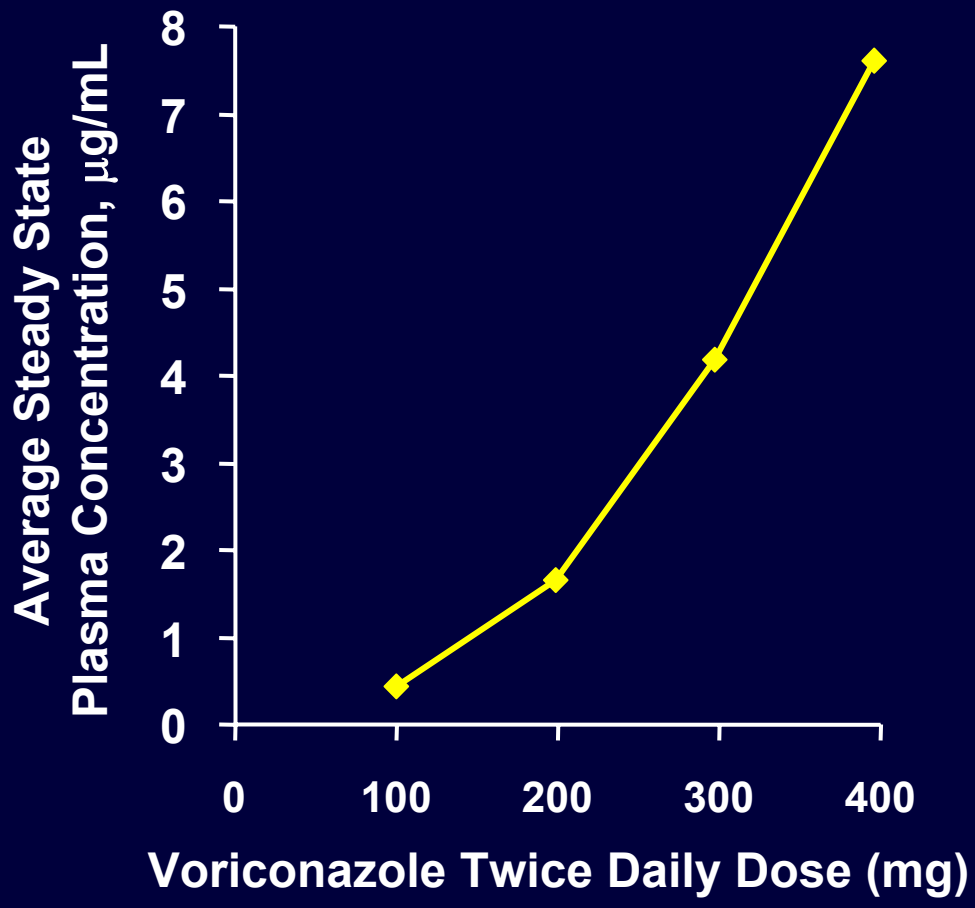




Glasmacher et al. *Mycoses*. 1996;39:249-58.
Glasmacher et al. *Mycoses*. 1999;42:443-51.

Voriconazole Nonlinear Pharmacokinetics

- Due to saturation of metabolism (Michaelis-Menten kinetics)
- Greater than proportional increase in exposure with increasing dose
- On average, 1.5-fold oral dose escalation from 200 mg q12h to 300 mg q12 h will lead to a 2.5-fold increase in exposure
- Considerable inter-patient variability (100-fold) in PK due to CYP2C19 genotype, drug inter-actions, age, weight (≤ 40 kg)



Voriconazole Therapeutic Drug Monitoring
A Retrospective Analysis (2002–2005)

- 28/188 Patients treated with voriconazole serum drug levels
  - Patient dose: 200 mg BID after loading dose
  - Indication: disease progression (17), toxicity (11)
- A significant ($P < 0.025$) relationship between disease progression and drug concentration was described:
  - Random voriconazole concentrations > 2.05 µg/mL
    - 100% (10/10) clinical response
  - Random voriconazole concentrations < 2.05 µg/mL
    - 44% 8/18 (44%) patients with disease progression

Smith et al. *Antimicrob Agents Chemother* 2006;50:1570-72.

Correlation of Posaconazole Plasma Drug Concentrations With Breakthrough IFIs?

- Efficacy: evidence of a "threshold" therapeutic concentration…
  - Effective prophylactic plasma concentration 3–5 hours after oral dose < 700 ng/mL
  - Dose response in treatment seen up to 1000–1500 ng/mL

CAS as primary prophylaxis in patients with stem cell transplant: MDACC

- Retrospective analysis, 2002-2006
- 123 patients, most with liver and/or renal dysfunction
- 117 patients with allogeneic BMT
- Median time to engraftment: 12 days
- 50 pts (41%) with GvHD and systemic corticosteroids
- Median duration of CAS prophylaxis: 73days
- Breakthrough IFIs by day 100: 9 (7%)
  - 6 molds (2 *Aspergillus*, 1 *Rhizopus*, 1 Exserohilum, 1 unspecified)
  - 3 yeasts (*Cryptococcus*, *C. glabrata*, *C tropicalis*)
- Median time to IFI: 65 days, only 1 during neutropenia
- No CAS-related AEs

Chou L & Kontoyiannis DP. Pharmacotherapy. 2008

Why Did Breakthrough IFIs Occur?

- Suboptimal pharmacokinetics (e.g., low ITC, VRC, POS levels)?
- High inoculum of fungus?
- Host related (e.g., polymorphisms in innate-immunity genes)?
- Azole-resistant fungus (primary or breakthrough infection)?
- Do not forget catheters as a cause of breakthrough bloodstream IFI !

Multi-triazole (ITC, VRC, POS, RAVU)-Resistant *Aspergillus*

- Netherlands survey: 0/114 patients (170 *A fumigatus* isolates) from 1945–1998 vs. 10/81 patients (13 isolates) from 2002–2006 ($P < 0.001$)[1]
- No clonality, but unique mechanism of resistant (L98H in CYP51a) in 12/13 isolates[1]
- Some isolates came from patients not previously exposed to azoles[1]
  - Role of OTC and agricultural use of azoles?[2]

dlb6

1. Verweij et al. *N Engl J Med*. 2007; In press.
2. Kontoyiannis & Lewis. *Lancet*. 2001;

dlb6

Kontoyiannis/Lancet/2001: ref not found on PubMed. Query?
Verweij : query... still not found in Pub Med. Ck still in press?
D Balog; 26.03.2007

dlb10

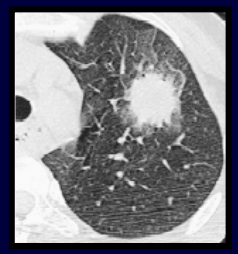
Empiric Antifungal Therapy in Neutropenic High-Risk Patients

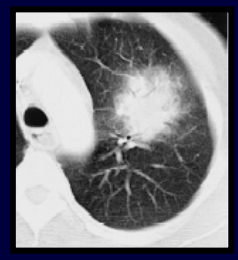
- Empiric antifungal therapy is still an accepted practice in view of suboptimal early diagnosis of IFI, but this might change soon
- Empiric antifungal therapy should not substitute for careful clinical evaluation
- Antifungals should start after 3–7 days of persistent fever[1]
- Risk stratification for the background rate of IFIs, toxicity, and cost of antifungal are important
- Several options, no clear drug of choice, decisions should be individualized
- Caspofungin, L-AmB, voriconazole (high-risk and lower-risk patients) are the most attractive

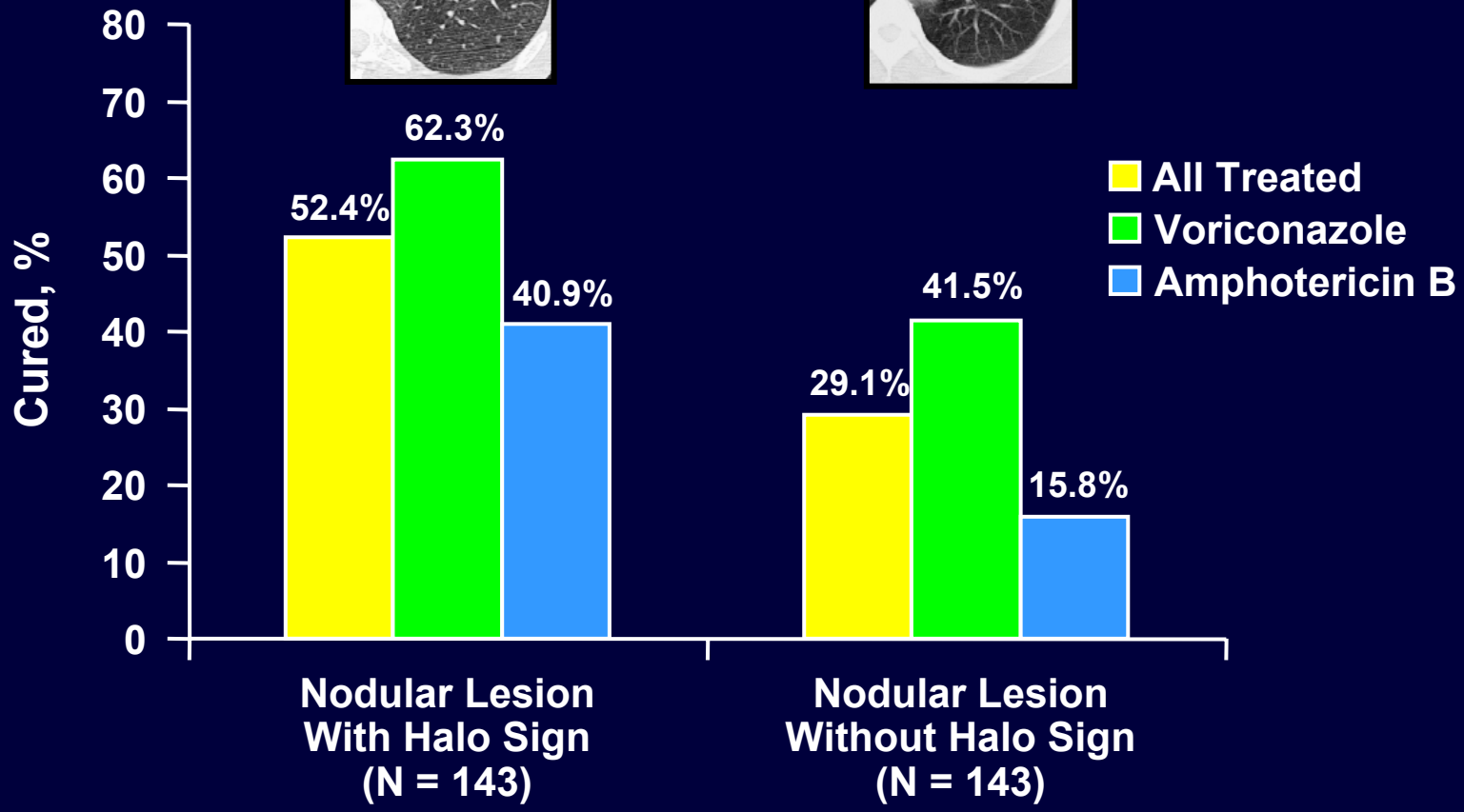
Slayt 11

dlb10 Need a reference citation for bullet 3 - there is a ref attached?
D Balog; 26.03.2007

Treatment Success for Aspergillosis: Importance of Early CT and Early Therapy

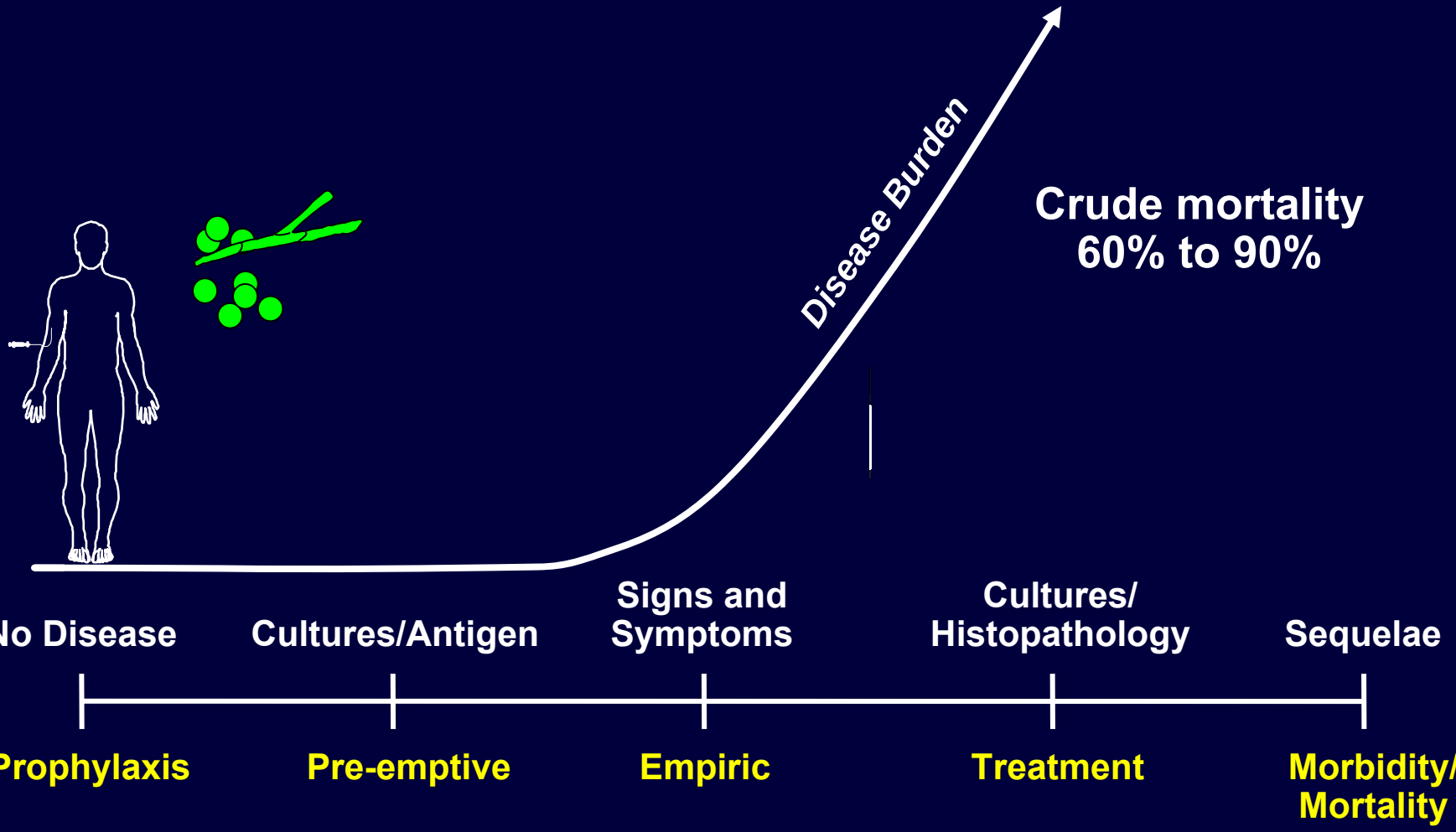






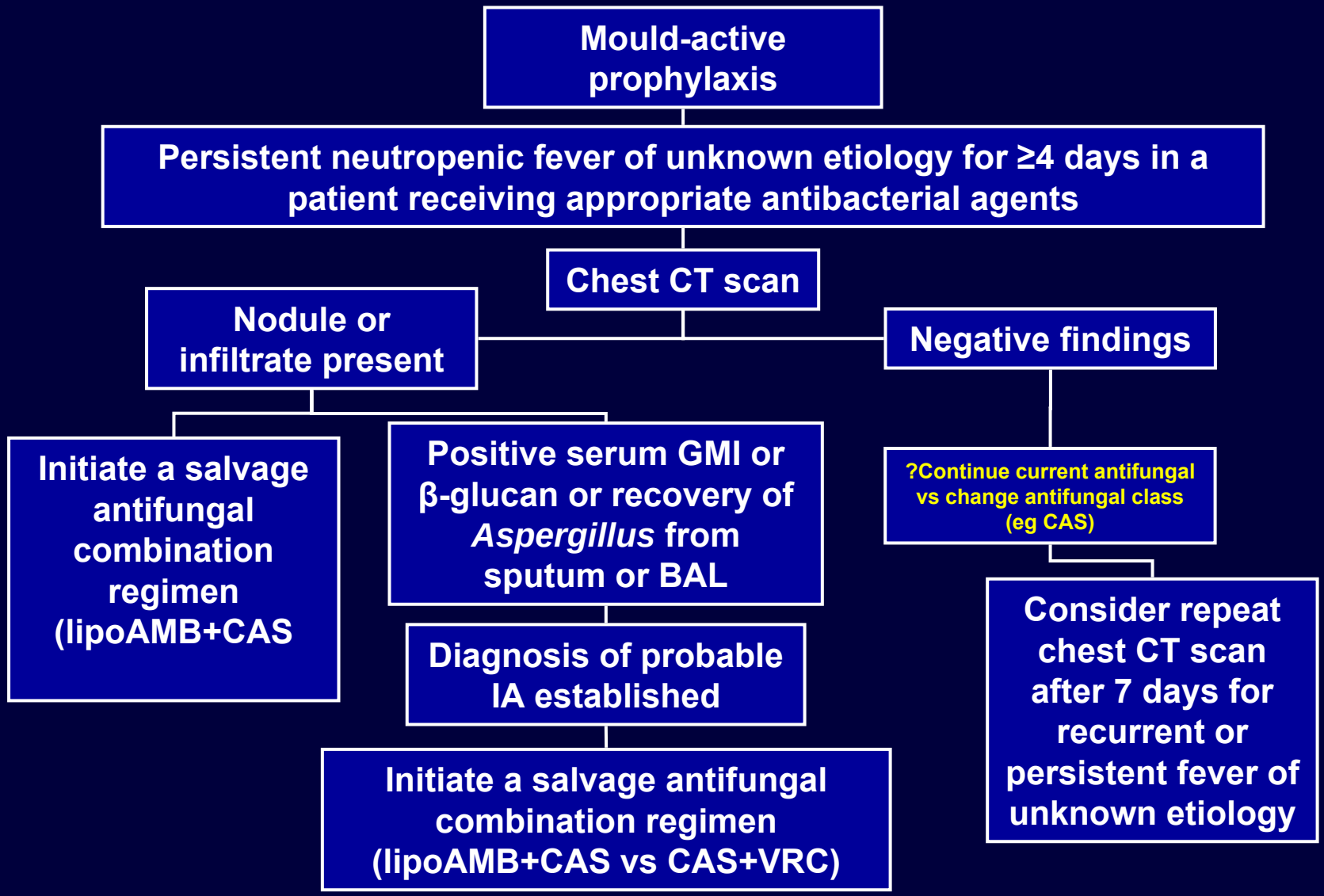
Greene et al. *Clin Infect Dis*. 2007;44:373-379.

Strategies in the Management of IFIs

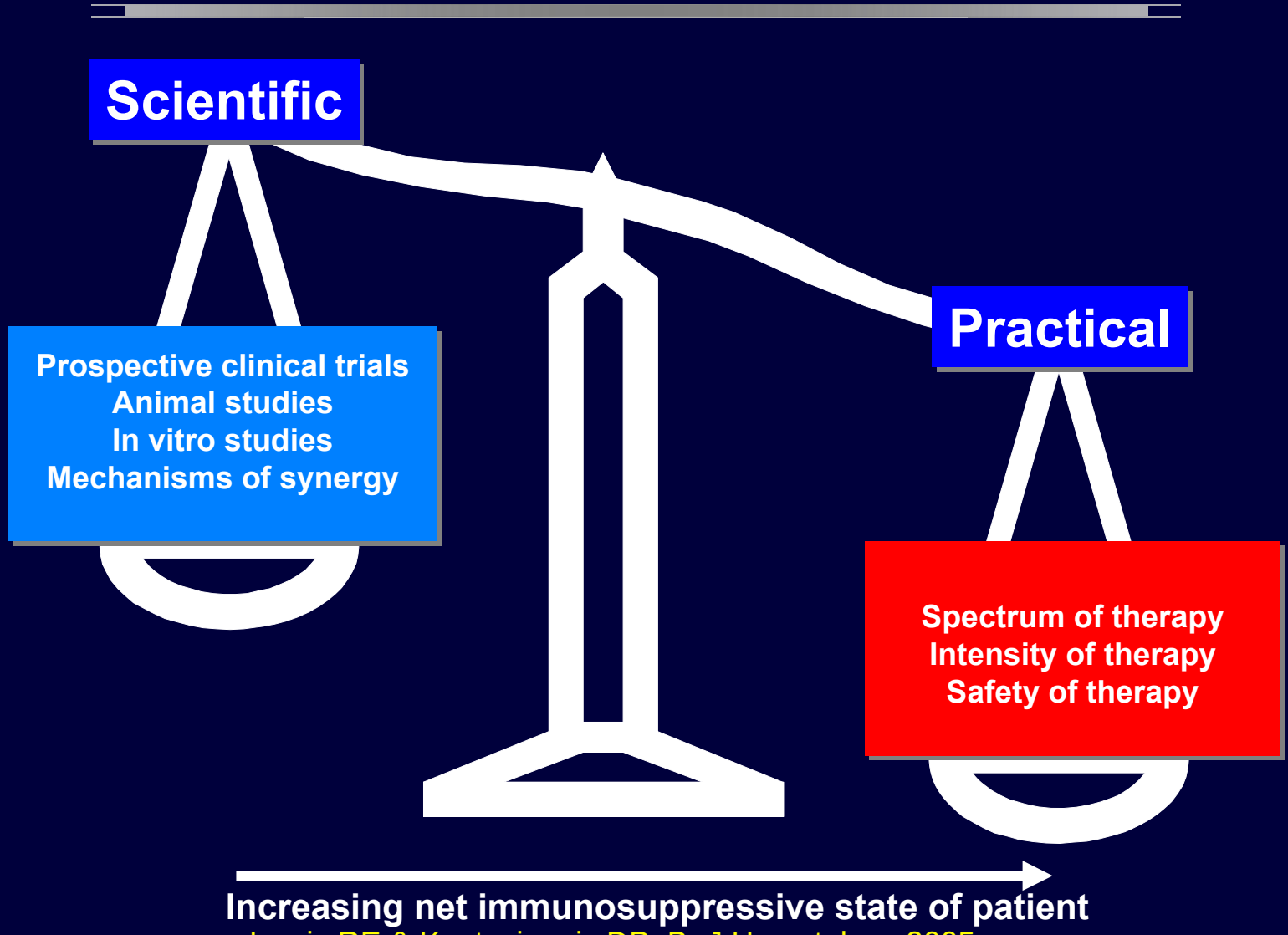


Perfect et al. *Oncology*. 2004;18:5-14.

Suggested Algorithm



Pragmatism vs. Science and Decisions to Use Combination Therapy

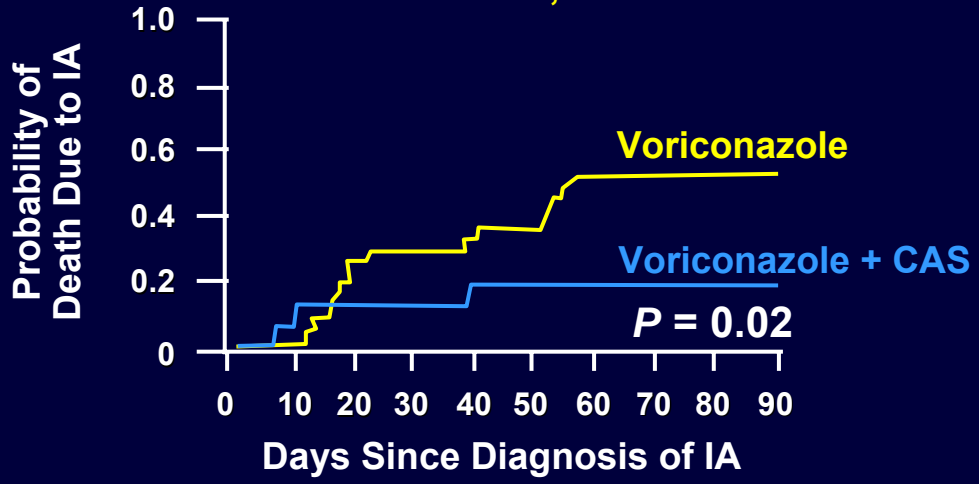


Lewis RE & Kontoyiannis DP. Br J Hematology 2005

dlb8

Combination Therapy for IA
Accumulating Evidence for Benefit?

Marr KA. *Clin Infect Dis.* 2004;39:797-802.

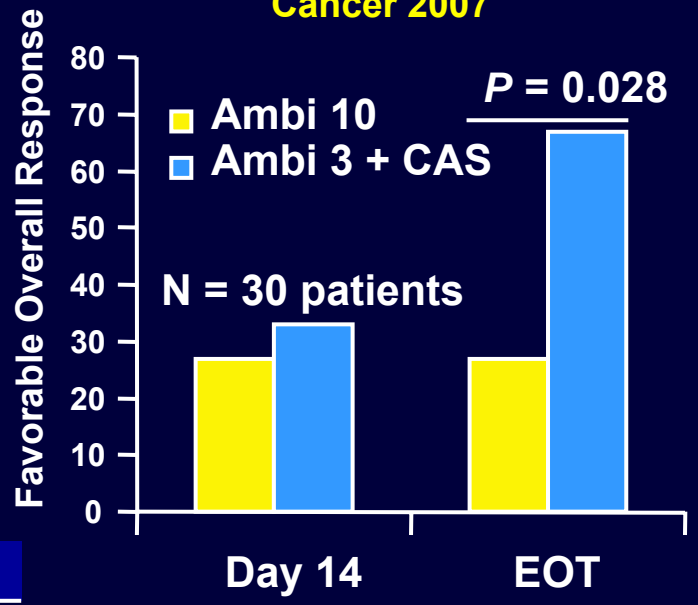


Singh et al. *Transplantation.* 2006;81:320-26.

Variable	Odds Ratio	95% CI	*P* Value
Treatment with VRC + CAS	0.419	0.139–1.263	0.12
Renal failure	2.803	0.946–8.304	0.062
CMV infection	4.340	1.443–13.057	0.009

When controlled for renal failure and CMV infection, patients in the study group were 2.4 times less likely to die within 90 days compared to the control group (OR = 0.419, 95% CI, 0.14–1.3). The difference however, was not statistically significant (*P*= 0.12).

Caillot et al. Combistrat. Cancer 2007



Retrospective salvage data of L-AmB + CAS in IA: ? benefit (Alief et al. *Cancer*. 2003; Kontoyiannis et al. *Cancer*. 2003.)

dlb8

For the lower right citations, I found no matches for Alief nor Kontoyiannis - are the references correct - year / journal?

D Balog; 26.03.2007

Echinocandins-Ideal Antifungals For Candidiasis?

Advantages

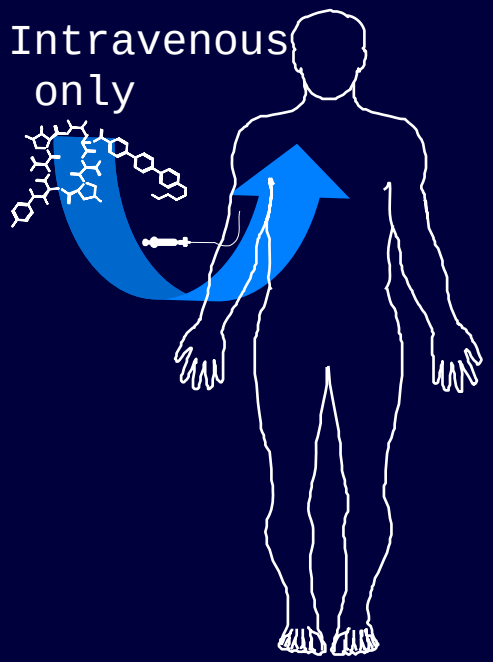
- Excellent in vivo *Candida* efficacy
- No cross resistance among azole-resistant *Candida* species
- Predictable pharmacokinetic profile
- Excellent safety at efficacious doses
- Low theoretical risk of drug interactions or antagonism of other antifungals

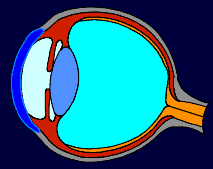
Disadvantages

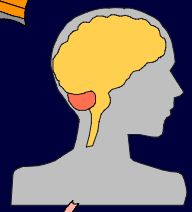
- Notable holes in spectrum for other yeasts (e.g., *Trichosporon*, *Cryptococcus*)
- No oral formulation
- Not distributed in anatomically priveleged sites (e.g.,CNS, eye)

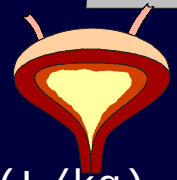
Echinocandin Pharmacokinetics-

Drug distribution precludes use in some forms of candidiasis

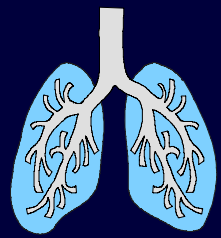


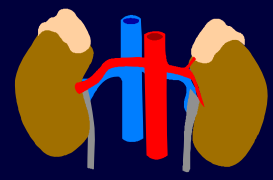

Eye


Brain/ CSF

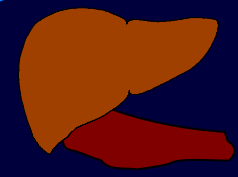

Urine/ Bladder


Esophagus


Lung

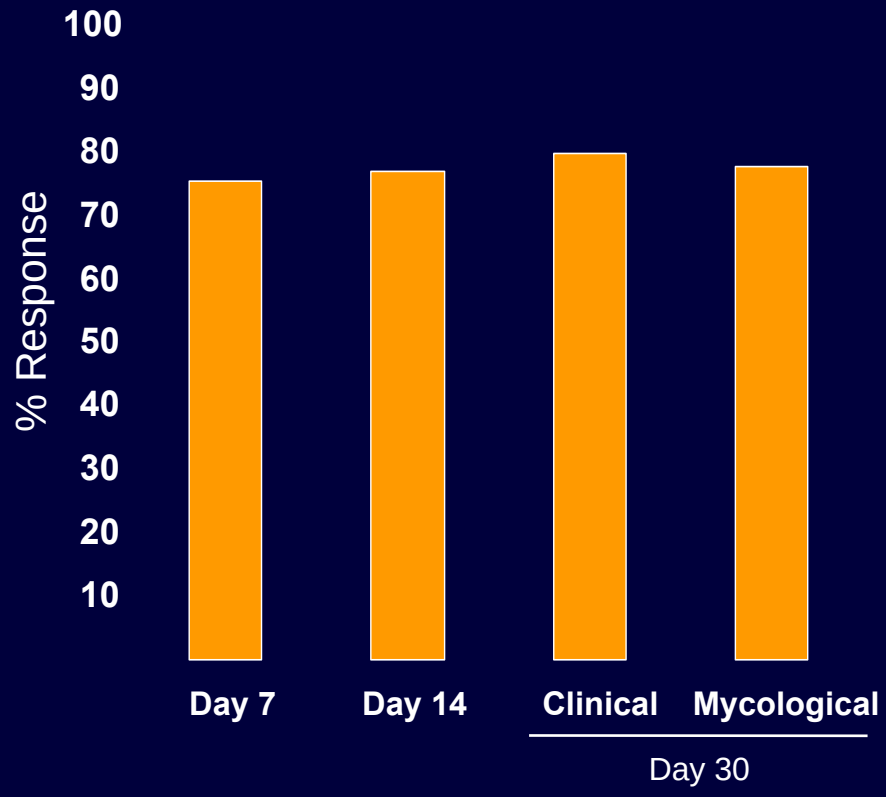

Kidneys

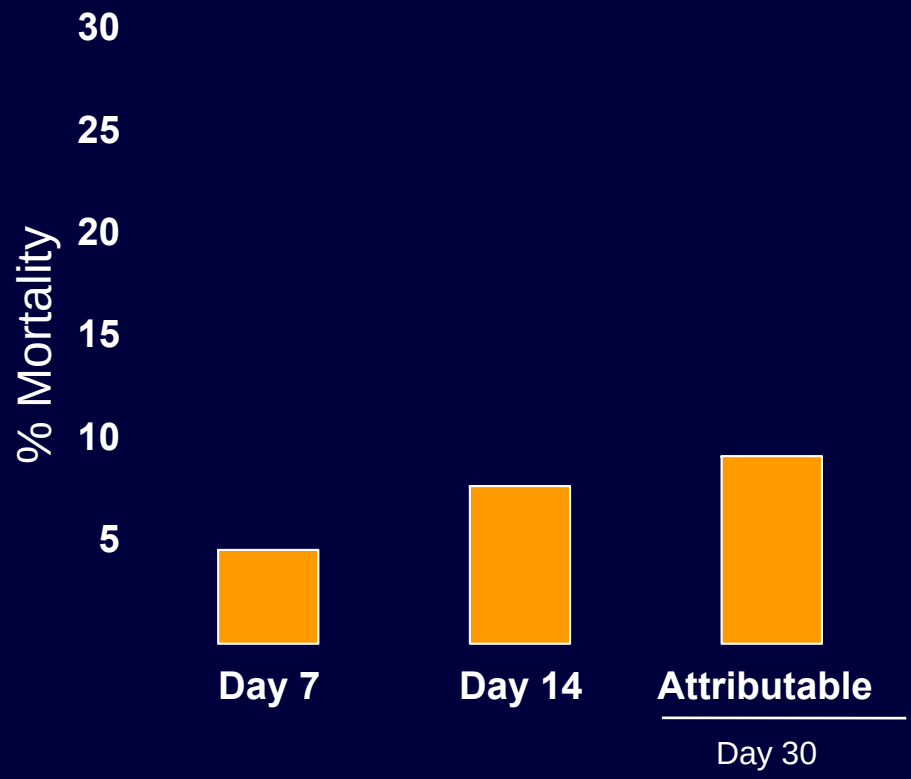

Gut and Gall bladder


Liver & Spleen

Volume of distribution (L/kg)
Caspofungin 0.14
Micafungin 0.24
Anidulafungin 0.5

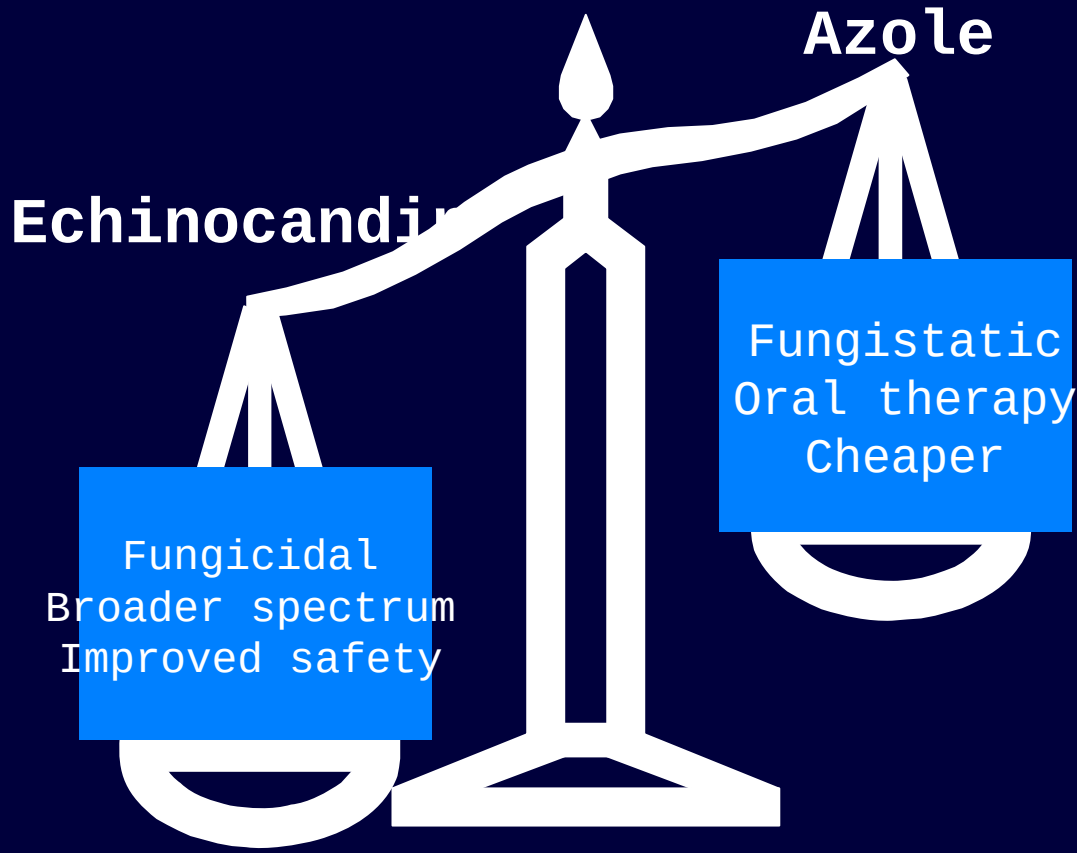
Caspofungin monotherapy treatment outcome at MDACC, 2001-2006 (n=64 patients)





Sipsas & Kontoyiannis. Submitted.

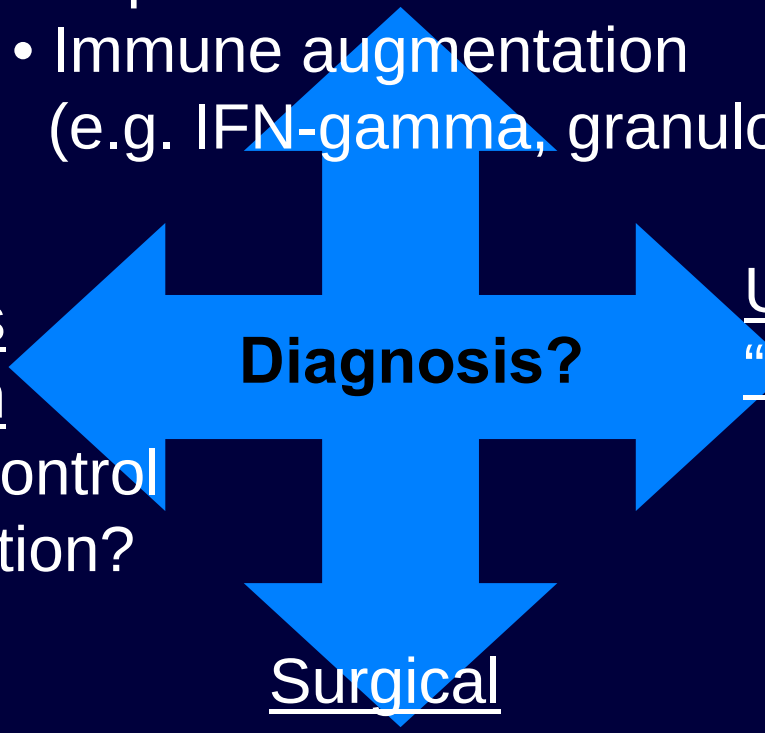
Always start
h an echinocandin in candidemic patie



We now have some data to address this question

Fungus-Specific Empiric Strategies for Progressing mycosis

Host immune suppression
- Taper steroids
- Immune augmentation
  (e.g. IFN-gamma, granulocyte transfusions)



Glucose/
Electrolytes
Malnutrition
- Glucose control
- Iron chelation?

Undiagnosed
"resistant" pathogen
- switch therapy
- combination therapy
- dosage escalation

Surgical
- Debulking

Summary

- Empiric and pre-emptive therapy should take into account the limitation of diagnostics, local epidemiology, and spectrum of antifungals
- Every attempt for diagnosis should be made, and when cultures are available susceptibility testing should be considered
- Targeted antifungal therapy should take into account the spectrum and pharmacokinetic limitations of drugs and unique host-related issues, especially co-morbidities

Highly immunosuppressed patients with IFIs:
Complex decision-making, individualized treatment plans

Thank you!