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When is failure failure?

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The ICU patient with candidemia

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- Female, 39 years old
- Multiple abdominal surgeries for Crohn's disease
- Total parenteral nutrition via Hickman catheter
- Wednesday: admission with sepsis syndrome
  Temperature 39.8° and chills for 3 days
- Start piperacillin-tazobactam
- Catheter not removed

- Persisting fever 40°
- Friday afternoon: blood cultures grow yeasts
- Started on fluconazole 400 mg (800 mg loading)
- Hickman catheter removed

Friday afternoon again 1 week later

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- Blood cultures: *C. albicans*
  MIC Flu 0.125; Amb 0.25
- Clinically stable, wants to go home
- Daily fever, peaking to 41°C (now for 12 days)
- CRP 300
- Blood cultures taken on days 1, 3 & 4 under fluconazole still positive
- Echocardiography & Doppler subclavia normal

What should we do?

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1. Additional diagnostics
2. Continue Fluconazole (400 or 800mg)
3. Fluconazole + 5-fluorocytosine
4. Amphotericin B (conventional or liposomal)
5. Caspofungin or Anidulafungin
6. Voriconazole

PET scan

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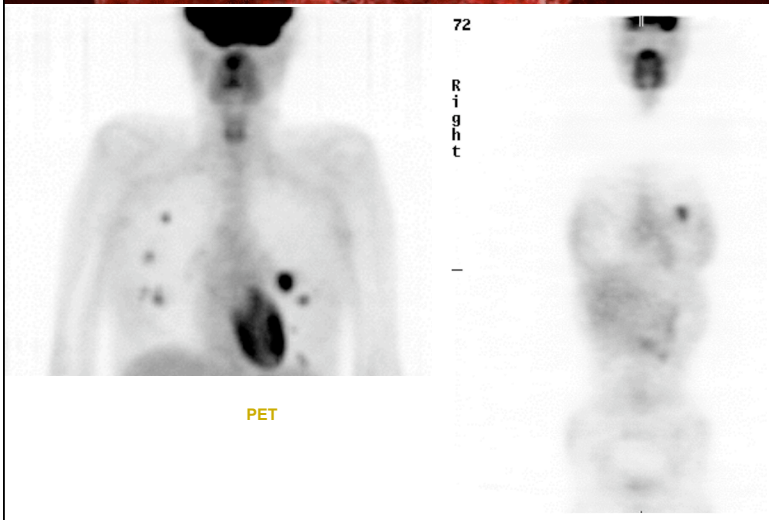

PET

Pt 8671269 / 05-12-2003

CT

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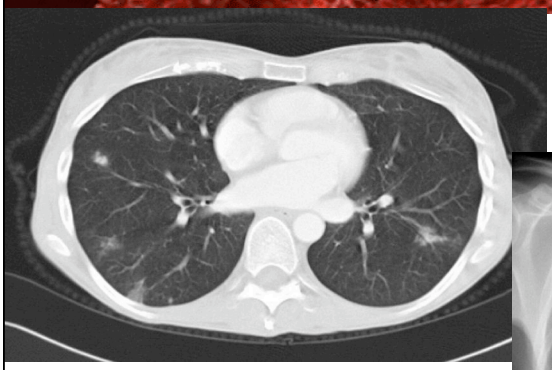

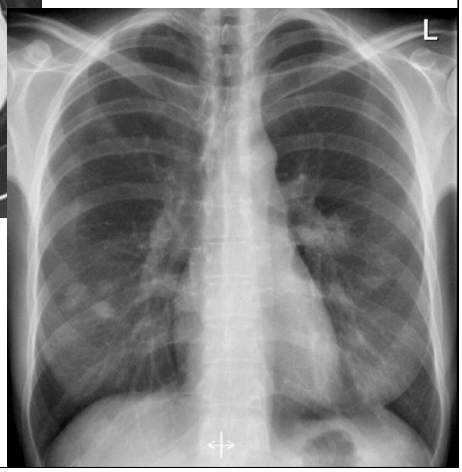

Persistent candidemia

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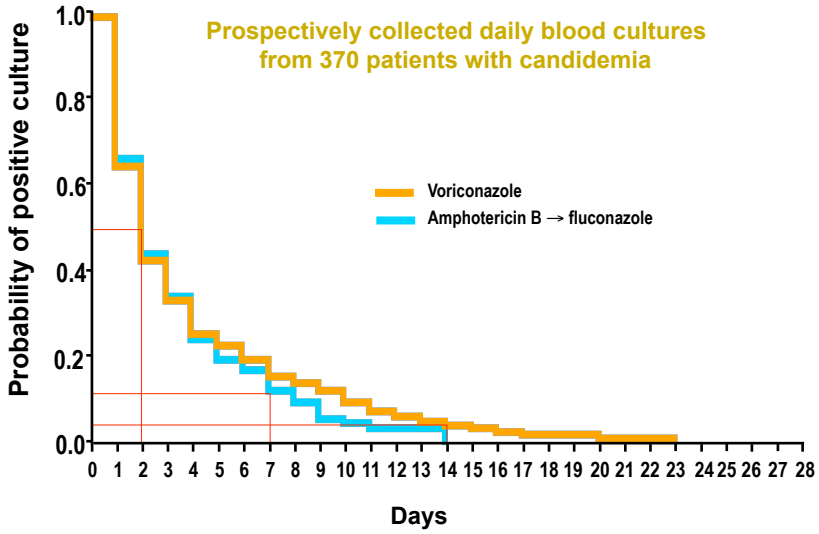

Kullberg et al. Lancet 2005; 366: 1435-42

Persistent candidemia

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36 / 370 patients had persistent candidemia ≥ 7 days (10%)

N = 370	Pos. BC ≥ 7 days N = 36	Pos. BC < 7 days N = 334	P-value
Age (range)	56 (15-87)	53 (13-90)	0.4
Man	61%	58%	0.73
APACHE II-score (median, range)	16 (15.5, 2-30)	14 (13, 0-41)	0.024
Not surgical	56%	49%	0.62
Abdominal surgery	31%	39%	
Non-abdo surgery	14%	13%	
ICU	61%	47%	0.12
Ventilated	39%	37%	0.78
R/ Voriconazole	72%	67%	0.49
R/ Amfo B/fluconazole	28%	33%	0.49

Persistent candidemia

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- No significant effect of catheter management on persistent candidemia in this study
- Disseminated candidiasis
  More frequent than in controls, p=0.014
- Mortality
  Greater than in controls, p=0.0041
- *Candida* contributory to death
  More often than in controls, p=0.005

Persistent candidemia as a prognostic factor

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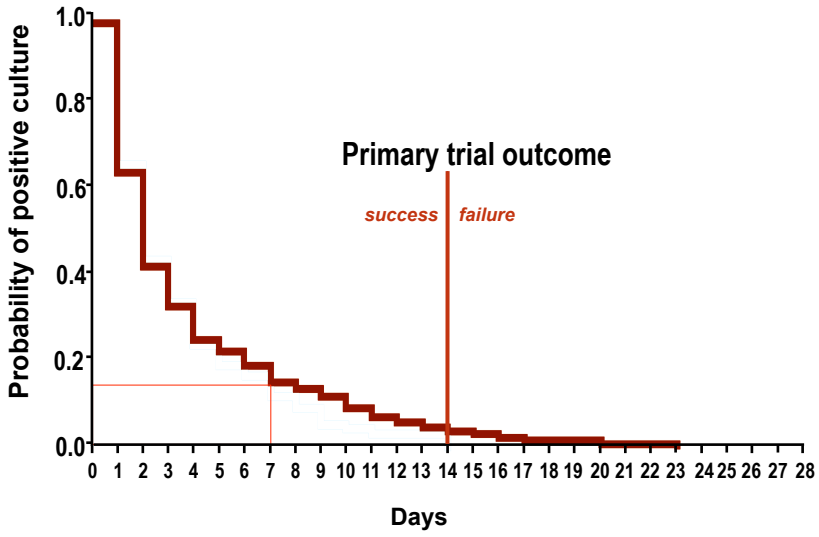

Patient management

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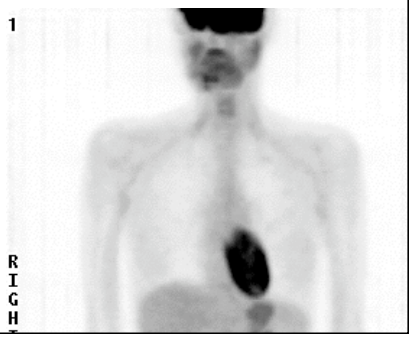
- Radiological progression of metastatic foci after 7 days of fluconazole
- Persistently positive blood cultures at least until Day 4 of fluconazole (… and ongoing until Day 7)
- R/ caspofungin 70/50mg iv x 2 wks
- Temperature and CRP normalized
- Another 4 wks of oral fluconazole after discharge



Is this a failure?

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- Radiological progression of metastatic foci after 7 days of fluconazole
- Persistently positive blood cultures until Day 7
- Temperature and CRP normalized after switch of antifungal

Clinical definition of success

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- **Survival (within n weeks of observation)**
- **Candidemia: *cure*, i.e., documented (or presumed) clearance (not necessarily sterilization)**
- **Cryptococcosis: *successful control of disease* i.e., absence of relapse, despite microbiological persistence**
- **Invasive aspergillosis: *partial response* i.e., survival, improvement in symptoms, radiological improvement, reduction of fungal burden (cultures, antigen)**

Invasive Aspergillosis

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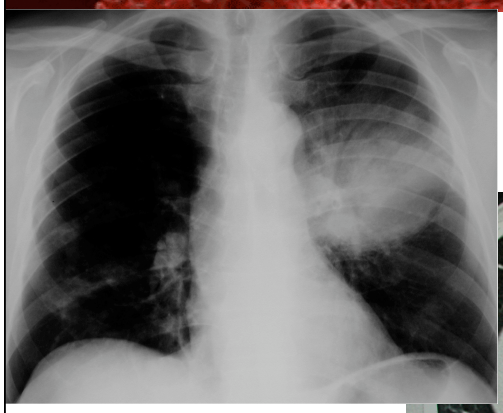

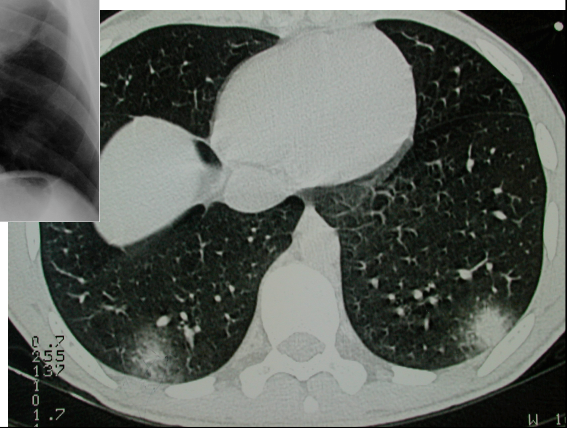

Invasive Aspergillosis in neutropenic patients

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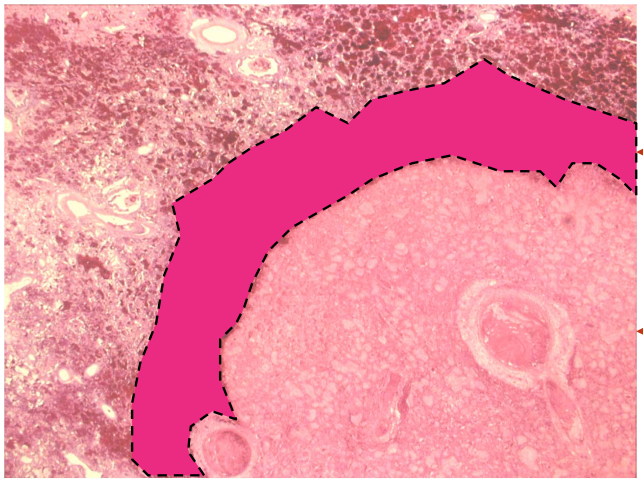

HR CT scan: Halo Sign

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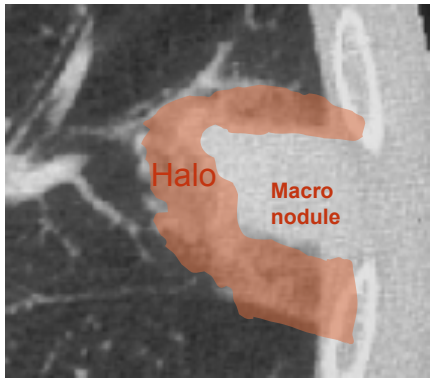
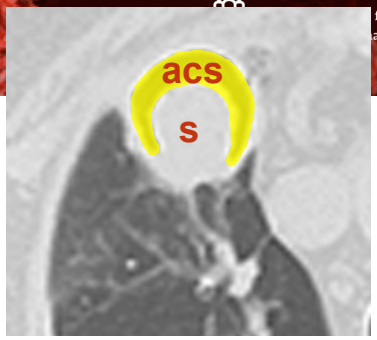
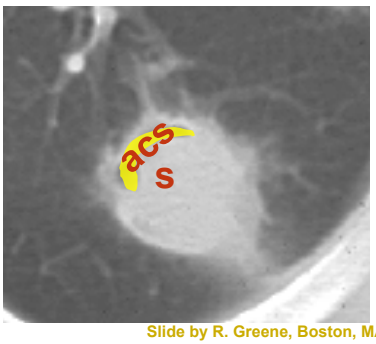
- ✓ Solid Macronodule
- ✓ Translucent ground glass halo



Air Crescent Sign

Crescent of gas
surmounting a necrotic, retracting
soft tissue sequestrum





Slide by R. Greene, Boston, MA

Evolution of CT changes during neutropenia

25 patients with proven invasive aspergillosis

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Findings (% present)	Day 0	Day 3	Day 7	Day 14
Halo	96	68	22	19
Non-specific changes	0	31	50	18
Air-crescent sign	0	8	28	63
Volume cm^3	11	37	47	34

Caillot et al. J Clin Oncol 2001; 19: 253

Invasive Aspergillosis in neutropenic patients

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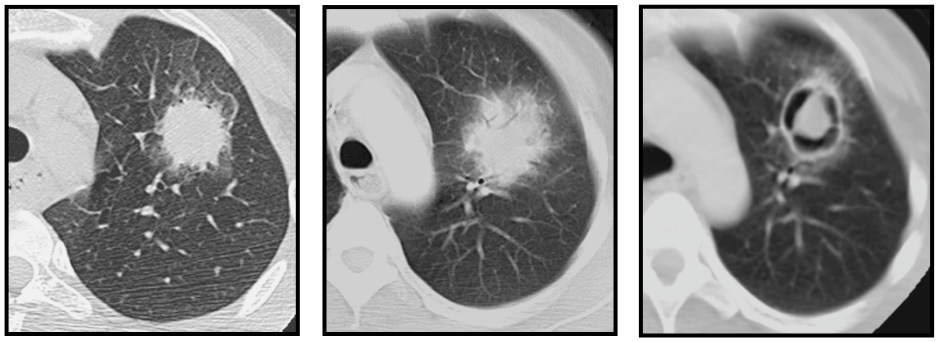

day 0 day 3 day 10

Caillot et al. J Clin Oncol 2001

Natural course of invasive Aspergillosis

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- **Neutrophil influx (diffuse infiltrate)**
- **Peripheral hemorrhage (halo sign) & hemoptysis**
- **Coagulation necrosis**
- **Liquefaction necrosis (cavatation, air crescent sign)**

3-Dimensional lesions on 2-D scan:

- **2x diameter → 8x volume**
- **1.25x diameter → 2x volume**

Is it a failure?
Impact on salvage therapy studies

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Findings (% present)	Day 0	Day 3	Day 7	Day 14
Halo	96	68	22	19
Non-specific changes	0	31	50	18
Air-crescent sign	0	8	28	63
Volume cm^3	11	37	47	34

"Salvage therapy should be started after ≥7 days of standard antifungal therapy in case of radiological worsening"

Caillot et al. J Clin Oncol 2001; 19: 253

Galactomannan as a surrogate marker for success

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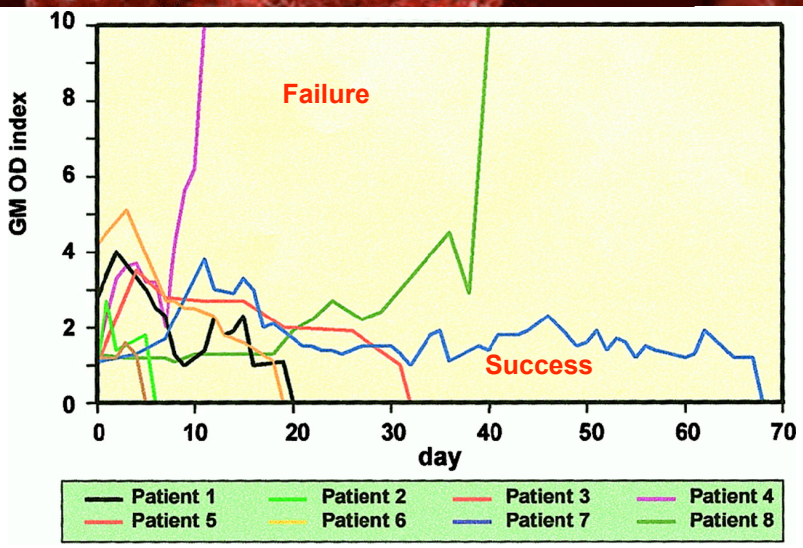

Maertens J et al. Blood 2001

Understanding Candidemia trials

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- choice of comparator
- equivalence vs. superiority
- control of confounders
- definition of endpoints (time point / MITT)
- time to negative blood culture

Anidulafungin Candidemia Study

Global Success at EIV Rx by Pathogen

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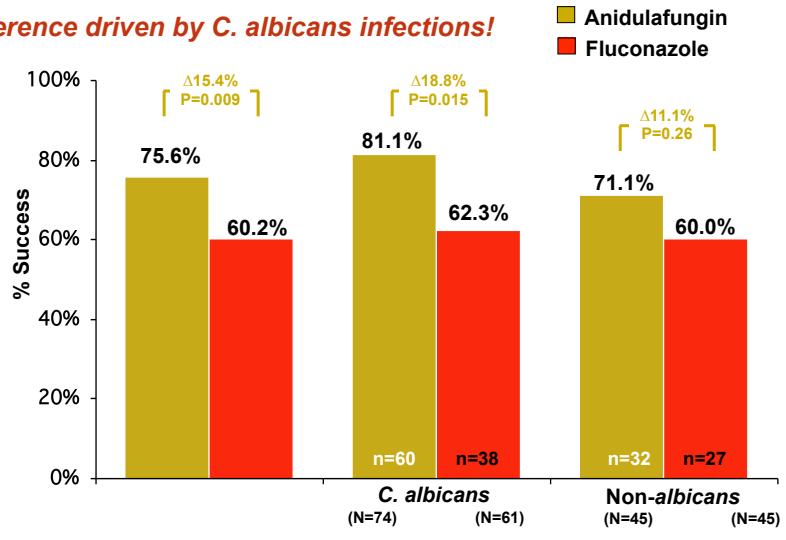
Difference driven by C. albicans infections!



* Patients with a single baseline pathogen

Reboli et al. N Engl J Med 2007

What we learned

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- In previous trials, all arms were equivalent in efficacy but not in toxicity

- Equivalent - Two possibilities:

  ✓ Either the classes are really equally effective

  OR

  ✓ Studies unable to show differences

Fungal Persistence at End of Therapy

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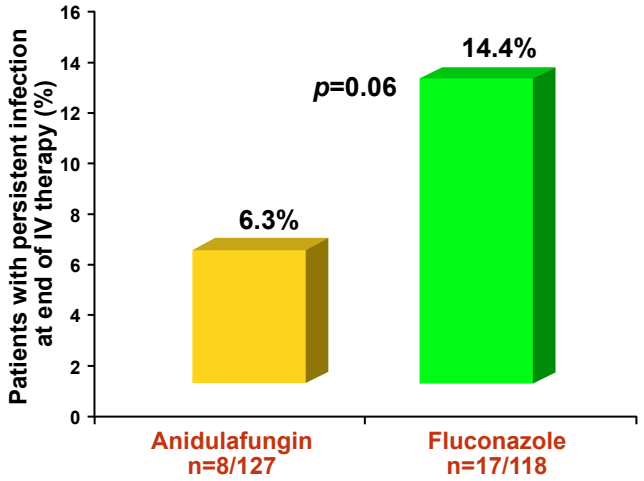

Based on:
Reboli et al. N Engl J Med 2007

Equivalence?

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- **Is initial therapy with fluconazole as effective as candidacidal antifungals?**
  - ✓ **Rex trials (Flu vs AmB; Flu vs. AmB+Flu): Yes**
  - ✓ **Anidula trial (Flu vs. Anid): Probably not…**
- **Is fluconazole as effective as comparators in patients with *C. glabrata*?**
- ~~***"In our study, outcome with fluconazole for C. glabrata was not significantly different from that with broadspectrum comparator drug"***~~
  - ✓ **Subsets with *C. glabrata* cases were small**
  - ✓ **Studies have not been powered to demonstrate equivalence (or inferiority) for *C. glabrata***
- **To prove equivalence (i.e., rule out that success rate with fluconazole is ≥15% lower), 318 *C. glabrata* patients are required**
  - ***There is not such a thing as subgroup equivalence***

Understanding Candidemia trials

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- **choice of comparator**
- **equivalence vs. superiority**
- **control of confounders**
- **definition of endpoints (time point / MITT)**
- **time to negative blood culture**

Antifungal Therapies Compared
MITT; End of Treatment

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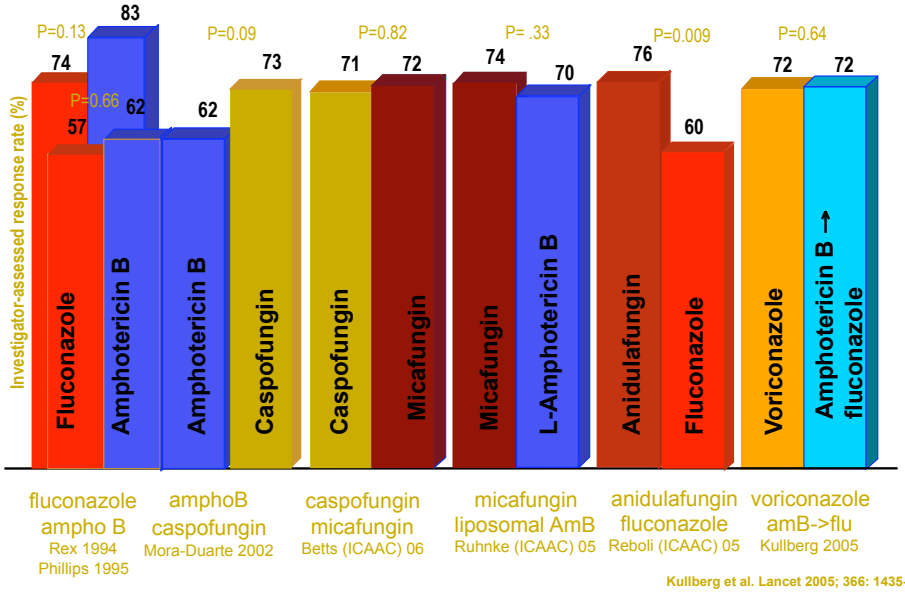

fluconazole ampho B — Rex 1994, Phillips 1995

amphoB caspofungin — Mora-Duarte 2002

caspofungin micafungin — Betts (ICAAC) 06

micafungin liposomal AmB — Ruhnke (ICAAC) 05

anidulafungin fluconazole — Reboli (ICAAC) 05

voriconazole amB->flu — Kullberg 2005

Kullberg et al. Lancet 2005; 366: 1435-42

Definition of endpoints

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- **Early:** End of i.v. study drug therapy (EOT)
- **Variable:** Last evaluable post-End of Treatment visit
- **Fixed:** 6-8 weeks after End of Treatment
- **Fixed:** 12 weeks after End of Treatment
  sustained successes 12 wks post EOT only

Kullberg et al. Lancet 2005; 366: 1435-42

Voriconazole success rate
MITT Population

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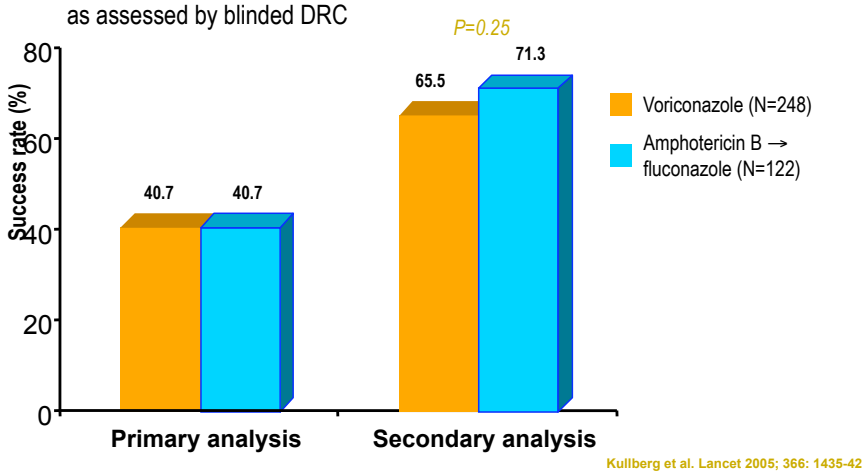
Primary analysis
- *Sustained successes* at the 12-week follow-up timepoint only as assessed by blinded DRC

Secondary analysis
- DRC *successes* at the last evaluable follow-up study visit



Kullberg et al. Lancet 2005; 366: 1435-42

Sustained successes at 8–12 wks

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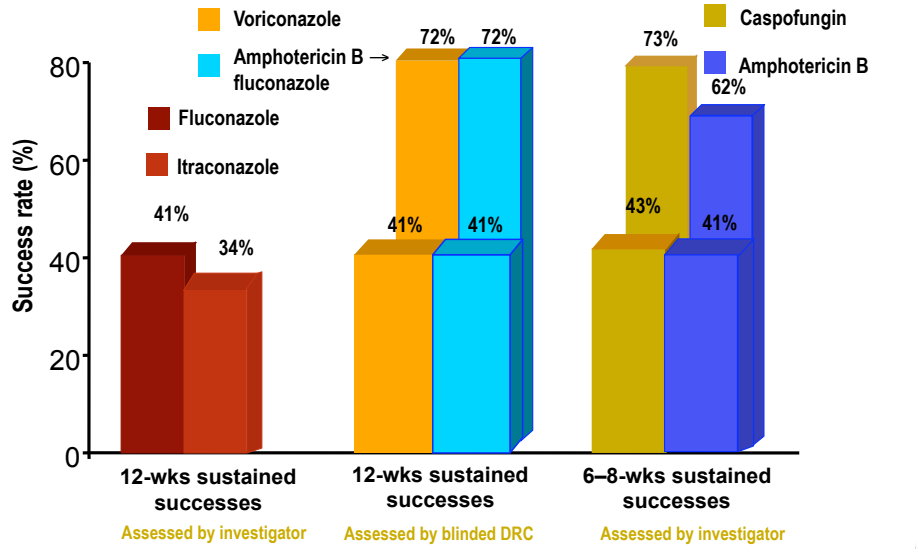

Kullberg et al. Lancet 2005; 366: 1435-42

Hidden failures in trial reports: ITT and MITT vs. PP endpoints

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Intent to Treat:

- All patients entered into the trial,
  even if
  - ✓ Withdrawn/died before/after randomization
  - ✓ Did not have candidemia
  - ✓ Did receive no / incorrect study drug

Modified Intent to Treat:

- All patients randomized, and
  - ✓ Have candidemia
  - ✓ received at least 1 dose of study drug

The Per-Protocol endpoint

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Not *Intent-to-Treat*

e.g., Patients who completed 5 days of study drug

Exclude:

- Patients with <5 days of study drug
  - ✓ Early deaths due to candidemia despite study Rx
  - ✓ Patients taken off due to acute toxicity
  - ✓ Patients withdrawn by investigator

Evaluation starts with "100% success" on Day 5

Further reading…

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VIEWPOINTS

Defining Responses to Therapy and Study Outcomes in Clinical Trials of Invasive Fungal Diseases: Mycoses Study Group and European Organization for Research and Treatment of Cancer Consensus Criteria

Brahm H. Segal,[1] Raoul Herbrecht,[22] David A. Stevens,[9,10] Luis Ostrosky-Zeichner,[4] Jack Sobel,[7] Claudio Viscoli,[28,29] Thomas J. Walsh,[12] Johan Maertens,[30] Thomas F. Patterson,[5] John R. Perfect,[2] Bertrand Dupont,[23] John R. Wingard,[8] Thierry Calandra,[21] Carol A. Kauffman,[6] John R. Graybill,[5] Lindsey R. Baden,[15] Peter G. Pappas,[11] John E. Bennett,[13] Dimitrios P. Kontoyiannis,[3] Catherine Cordonnier,[24] Maria Anna Viviani,[27] Jacques Bille,[26] Nikolaos G. Almyroudis,[1] L. Joseph Wheat,[14] Wolfgang Graninger,[25,26] Eric J. Bow,[16] Steven M. Holland,[13] Bart-Jan Kullberg,[18,19] William E. Dismukes,[11] and Ben E. De Pauw[17]

[1]Department of Medicine, Roswell Park Cancer Institute, Buffalo, New York; [2]Duke University Medical Center, Durham, North Carolina; [3]The University of Texas M. D. Anderson Cancer Center and [4]University of Texas Health Science Center at Houston and [5]Department of Medicine, University of Texas Health Science Center, San Antonio; [6]University of Michigan, Veterans Administration Ann Arbor Healthcare System, Ann Arbor, and [7]Wayne State University School of Medicine, Detroit, Michigan; [8]University of Florida College of Medicine, Gainsville; [9]Santa Clara Valley Medical Center, San Jose, and [10]Stanford University Medical School, Stanford, California; [11]Department of Medicine, University of Alabama at Birmingham; [12]Pediatric Oncology Branch, National Cancer Institute, and [13]Laboratory of Clinical Infectious Diseases, National Institute of Allergy and Infectious Disease, National Institutes of Health, Bethesda, Maryland; [14]MiraVista Diagnostics/MiraBella Technologies, Indianapolis, Indiana; [15]Division of Infectious Diseases, Brigham and Women's Hospital, Dana-Farber Cancer Institute, Harvard Medical School, Cambridge, Massachusetts; [16]CancerCare Manitoba, University of Manitoba, Winnipeg, Manitoba, Canada; [17]University Medical Center St. Raboud, [18]Department of Medicine, Nijmegen University Medical Center, and [19]Raboud University Nijmegen Medical Center, Nijmegen, The Netherlands; [20]Institute of Microbiology University Hospital and [21]Infectious Disease Service/Department of Medicine, Centre Hospitalier Universitaire Vaudois and University of Lausanne, Lausanne, Switzerland; [22]Department of Hematology and Oncology, Hospital de Hautepierre, Strasbourg, [23]Maladies Infectieuses et Tropicales, Hospital Necker, Paris, and [24]Henri Mondor Hospital APHP and Paris 12 University, Creteil, France; [25]Medical University of Vienna and [26]Division of Infectious Diseases, University Hospital Vienna, Vienna, Austria; [27]Universita degli Studi, Department of Public Health, Microbiology, and Virology, Section of Public Health, Milan, [28]University of Genova, and [29]Division of

Segal et al. Clin Infect Dis 2008: 47; 674-83