# Top Papers on Invasive Fungal Disease Management 2014-15

**Souha S. Kanj, MD, FACP, FIDSA**

Professor and Head, Division of Infectious Diseases
American University of Beirut Medical Center, Beirut, Lebanon
Consultant Professor, Duke University Medical Center, NC, USA

April 26, 2015

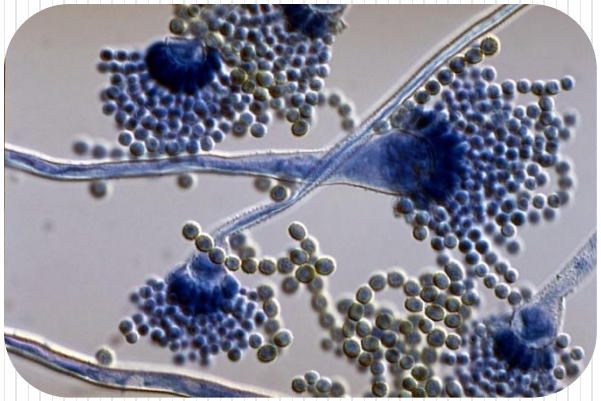
# Disclosure

**Grants**

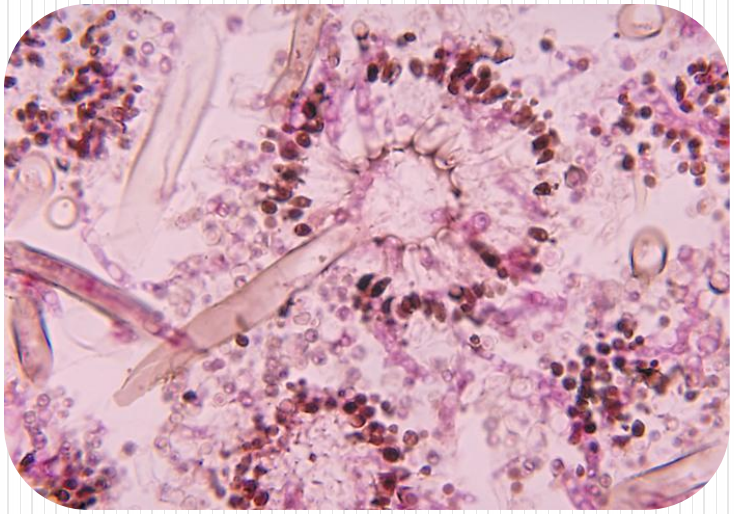
- Astellas

**Speaker**

- Pfizer
- MSD
- AstraZeneca
- Biologix
- Aventis Pasteur



# Invasive Aspergillosis (IA)



# Invasive Aspergillosis (IA)

- Associated with poor outcome in pts with hematologic malignancies (HM) and hematopoetic stem cell transplantation (HCT)
- Small *in vitro* studies, animal models, and clinical series suggest a role for combination antifungal therapy
- 2 studies published this year addressing this issue


Petraitis V, et al. Antimicrob Agents Chemother 2009;53:2382

Marr KA, et al. Clin Infect Dis 20114;39:797

Dowell JA, et al. J Clin Pharmacol 2005;45:1373

Singh N, et al. Transplantation 2006; 81:320

Annals of Internal Medicine

ORIGINAL RESEARCH

# Combination Antifungal Therapy for Invasive Aspergillosis

## A Randomized Trial

Kieren A. Marr, MD; Haran T. Schlamm, MD; Raoul Herbrecht, MD; Scott T. Rottinghaus, MD; Eric J. Bow, MD, MSc; Oliver A. Cornely, MD; Werner J. Heinz, MD; Shyla Jagannatha, PhD; Liang Piu Koh, MBBS; Dimitrios P. Kontoyiannis, MD; Dong-Gun Lee, MD; Marcio Nucci, MD; Peter G. Pappas, MD; Monica A. Slavin, MD; Flavio Queiroz-Telles, MD, PhD; Dominik Selleslag, MD; Thomas J. Walsh, MD; John R. Wingard, MD; and Johan A. Maertens, MD, PhD

- Compares the safety and efficacy of voriconazole + anidulafungin to voriconazole monotherapy
- Randomized, double-blind, placebo-controlled multicenter
- 93 international sites in 24 countries

Marr KA et al. Ann Intern Med 2015 Jan;162:81

# Enrolled Patients

- Designed by the PI and Pfizer in consultation with an international steering committee coordinated by MSG
- 454 pts with HM or HCT pts (≥ 16 y) with possible, probable, or proven IA

Marr KA et al. Ann Intern Med 2015 Jan;162:81

# Exclusion Criteria

- Progressive HM not likely to respond to treatment
- Antifungal drugs for > 96 hrs
- Severe liver dysfunction
- Karnofsky score < 20
- Non infectious death anticipated within 30 days
- Mechanical ventilation
- Pregnancy
- Lactation
- Receiving drugs that might interact
- Allergy to azoles or echinocandins

# Combination Therapy in IA?

- Different design than prior studies
  - Primary outcome
  - Patients enrolled
- **Primary outcome**
  - 6-week all cause mortality (Kaplan Meier)
- **Secondary outcomes**
  - 12-week all cause mortality
  - 6 week-mortality in major subgroups
  - Safety

Marr KA et al. Ann Intern Med 2015 Jan;162:81

# Methods

- Randomly assigned at 1:1 ratio and stratified according to
  - Allo HCT
  - Pulmonary versus disseminated
  - Region

# Methods

- IV voriconazole: 6 mg/kg on day 1, then 4 mg/kg (every 12 hours) for the first week
- Possible switch to oral (300 mg every 12 hours) to complete 6 weeks
  - Dose adjusted according to clinical response, AEs, or plasma level
- Anidulafungin 200 mg on day 1, then 100 mg daily or placebo for the first 2 weeks up to a maximum of 4 weeks

Marr KA et al. Ann Intern Med 2015 Jan;162:81

# Blinded External Data Review Committee

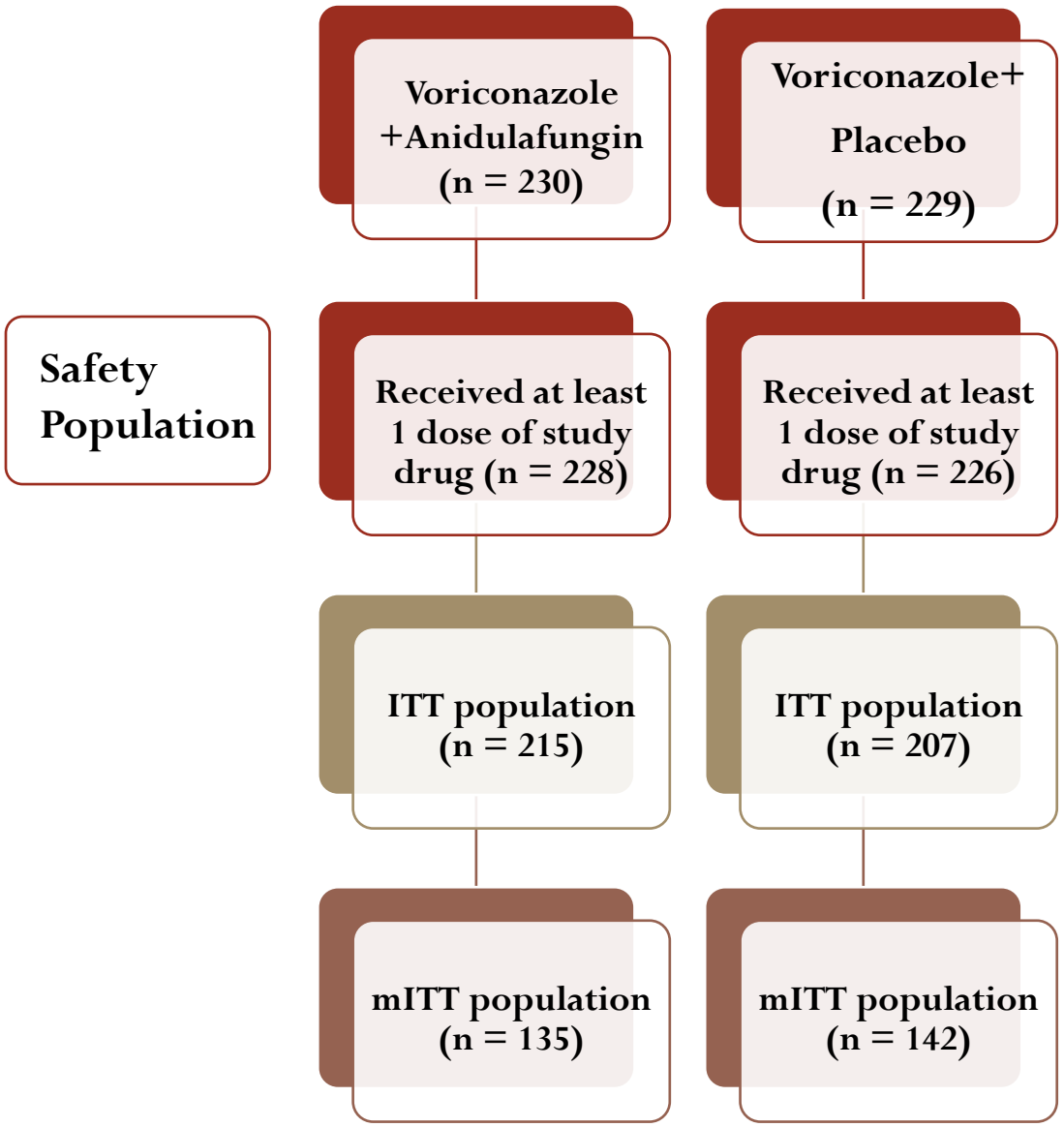
- **Complete response**
  - Resolution of all signs and symptoms
  - More than 90 % radiographic improvement
- **Partial response**
  - Clinical improvement and >50 % radiographic improvement
- **Stable disease**
  - No change from baseline or < 50% radiographic improvement
- **Failure**
  - Progression of disease

# Data Monitoring Committee

- Safety  data quarterly
- Mortality data
- At the second interim  analysis had the option to recommend increase sample size

Marr KA et al. Ann Intern Med 2015 Jan;162:81

# n=459


Voriconazole +Anidulafungin (n = 230)
Voriconazole+ Placebo (n = 229)
Safety Population
Received at least 1 dose of study drug (n = 228)
Received at least 1 dose of study drug (n = 226)
ITT population (n = 215)
ITT population (n = 207)
mITT population (n = 135)
mITT population (n = 142)

# Baseline Characteristics

Similar in both groups

- Underlying conditions
- IA diagnoses
- 20% ≥ 65 y
- Acute leukemia was the most likely diagnosis
- 30 % HCT
- 60% neutropenic at study entry
- 7.6 % were on mold active prophylaxis

Marr KA et al. Ann Intern Med 2015 Jan;162:81

# Diagnoses

- 80% of pts had DRC diagnosis of confirmed or probable IA
  - Radiographic findings+ galactomannan Ag in serum or BAL

- 51/272 (19 %) of probable IA had positive cultures
- *A. fumigatus*:61%
- Sp. not identified: 24%

# Treatment

- Median duration of
  - Combination:14 days (1-29)
  - Voriconazole:42 days (1-48)

  - Dose of voriconazole reduced in 20 % of pts because of AEs or level

Marr KA et al. Ann Intern Med 2015 Jan;162:81

# Results

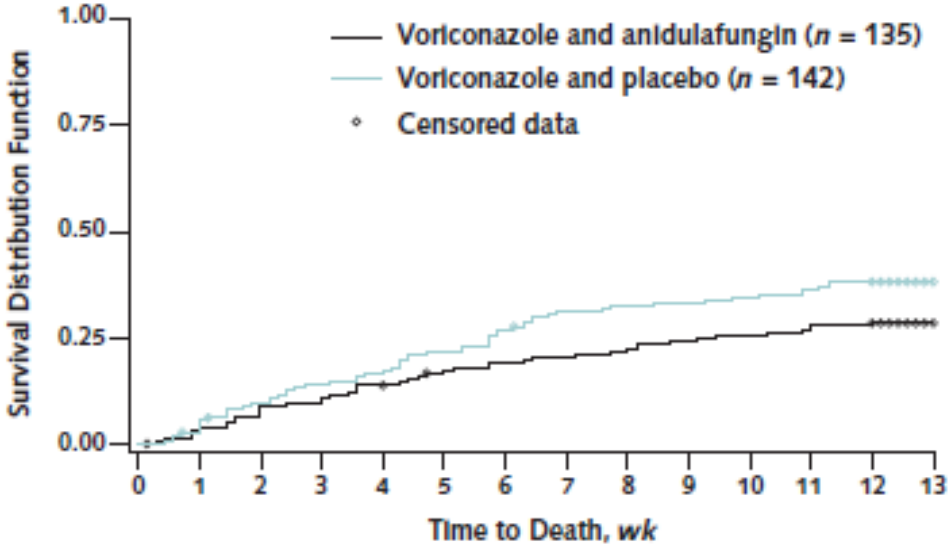
- Mortality rates at 6 weeks in mITT
  - 19.5% for combination
  - 27.8% for monotherapy

  (P = 0.087, 95 % CI-19.0 to 1.5)

- Mortality at 12 weeks:
  - 29.3% vs 39.4 %

  (P= 0.077 CI,-21.4 to 1.1)

- In the ITT mortality similar in both groups (20.3 & 23.5 % )




**Non significant but clinically meaningful**

Marr KA et al. Ann Intern Med 2015 Jan;162:81

# Mortality Outcomes in the MITT

| Variable | Deaths, *n/N (%)** | | Treatment Difference (95% CI), *percentage points*† |
|---|---|---|---|
| | Monotherapy | Combination Therapy | |
| **Overall** | 39/142 (27.8) | 26/135 (19.5) | −8.3 (−19.0 to 1.5) |
| **Overall 12-wk mortality** | 55/142 (39.4) | 39/135 (29.3) | −10.1 (−21.4 to 1.1) |
| **Allogeneic HCT** | | | |
| Yes | 12/42 (28.6) | 10/44 (22.7) | −5.9 (−24.3 to 12.6) |
| No | 27/100 (27.5) | 16/91 (17.9) | −9.6 (−21.5 to 2.2) |
| Reduced-intensity conditioning | 5/15 (33.3) | 4/19 (21.1) | −12.2 (−42.4 to 17.8) |
| Non-reduced-intensity conditioning | 7/27 (25.9) | 6/25 (24.0) | −1.9 (−25.5 to 21.6) |
| HLA-matched/related donor | 7/17 (41.2) | 2/14 (14.3) | −26.9 (−56.6 to 2.8) |
| HLA-mismatched/unrelated donor | 5/25 (20.0) | 8/29 (27.6) | 7.6 (−15.0 to 30.2) |
| High-dose corticosteroids‡ | 3/6 (50.0) | 3/9 (33.3) | −16.7 (−67.2 to 33.8) |
| **Neutropenia§** | | | |
| Yes | 21/86 (24.4) | 18/77 (23.5) | −0.9 (−14.0 to 12.2) |
| No | 15/47 (33.2) | 7/52 (13.7) | −19.5 (−36.1 to −2.8) |
| **Geographic region** | | | |
| Europe | 21/83 (25.6) | 14/75 (18.9) | −6.7 (−19.6 to 6.3) |
| Asia/Australia | 8/33 (25.0) | 6/33 (18.3) | −6.7 (−26.7 to 13.3) |
| North America | 7/17 (41.2) | 5/20 (25.3) | −15.9 (−46.1 to 14.4) |
| South America/Latin America | 3/9 (33.3) | 1/7 (14.3) | −19.0 (−59.3 to 21.1) |

# Results

- Most deaths up to 6 weeks considered attributable to IA
- Successful global response at 6 weeks was 32.6 and 43%

Marr KA et al. Ann Intern Med 2015 Jan;162:81

# Results

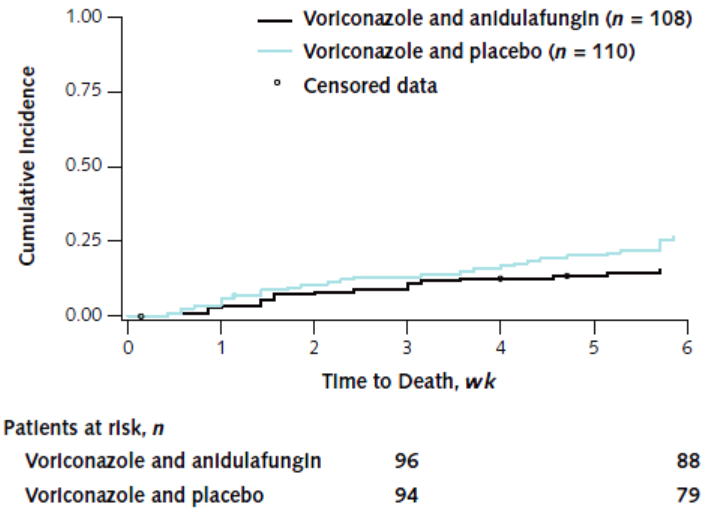
- Post Hoc uni and multivariate analyses identified 3 independent risk factors for mortality at 6 weeks:
  - High serum galactomannan Ag value
  - Low Karnofsky score
  - Low baseline platelet count
- Safety measures, including hepatotoxicity, were not statistically different

Marr KA et al. Ann Intern Med 2015 Jan;162:81

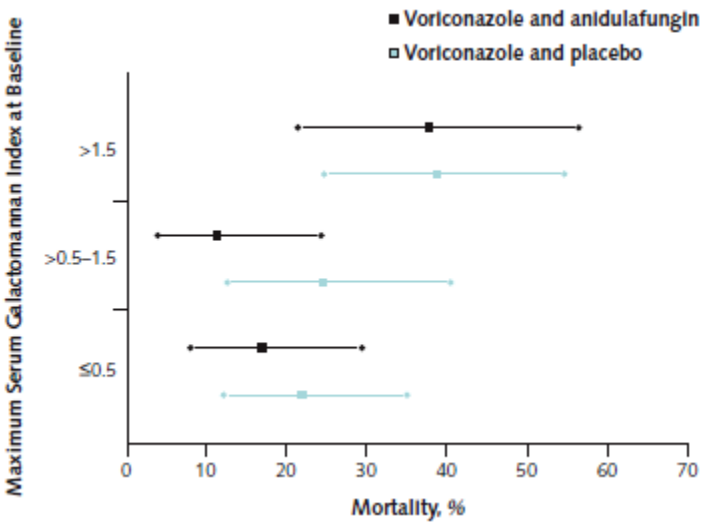
# Outcome in the +ve Galactomannan Group

- All cause mortality
  - 15.7% in the combination
  - 27.3% in monotherapy

**(P=0.037, CI-22.7 to -0.4)**




**Greatest mortality difference in pts with baseline value of 0.5 to 1.5**



# Limitations

- Mortality at 6 weeks higher than expected
- Difference in mortality lower than expected
- Enrollment restricted to HM and HCT
- Study did not address whether longer duration of combination would be beneficial

→***Further studies are necessary to confirm difference in mortality and define the population with the greatest potential benefits***

Marr KA et al. Ann Intern Med 2015 Jan;162:81

# Jeita Grotto, Lebanon

International Journal of Antimicrobial Agents 45 (2015) 283–288

Contents lists available at ScienceDirect

International Journal of Antimicrobial Agents

journal homepage: http://www.elsevier.com/locate/ijantimicag

# Clinical experience of the use of voriconazole, caspofungin or the combination in primary and salvage therapy of invasive aspergillosis in haematological malignancies

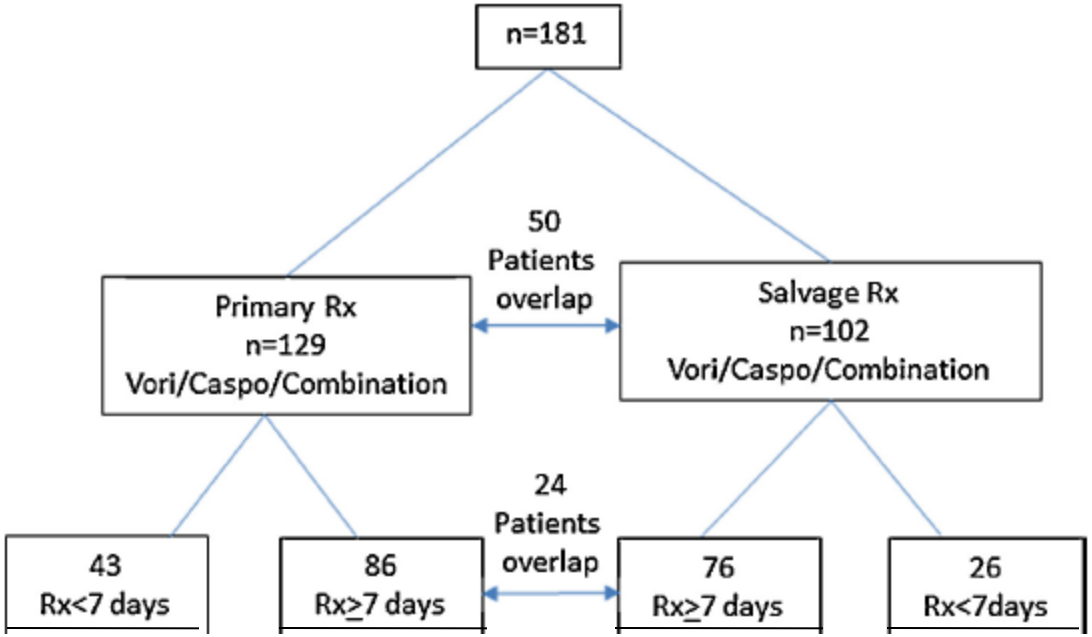
Issam I. Raad*, Aline El Zakhem, Gilbert El Helou, Ying Jiang, Dimitrios P. Kontoyiannis, Ray Hachem

*Department of Infectious Diseases, Infection Control and Employee Health, The University of Texas MD Anderson Cancer Center, 1515 Holcombe Blvd., Houston, TX 77030, USA*

**Raad II et al. Int J Antimicrob Agents 2015 Mar;45:283**

- 12 year **retrospective** study, supported by MSD grant
- 181 pts with HM and IA (proven or probable) who received primary or salvage therapy (for ≥7 days) with:

- Caspofungin
- Voriconazole
- Combination caspofungin and voriconazole



# Patients

- 138 pts treated ≥7 days, 86 primary, 76 salvage (27 after 1ry)
- Duration of therapy: 1-234 days
- **Primary**: 15 caspo, 38 vori, 33 combination
- **Salvage**: 17 caspo, 24 vori, 35 combination

Raad II et al. Int J Antimicrob Agents 2015 Mar;45:283

# Primary Therapy Group

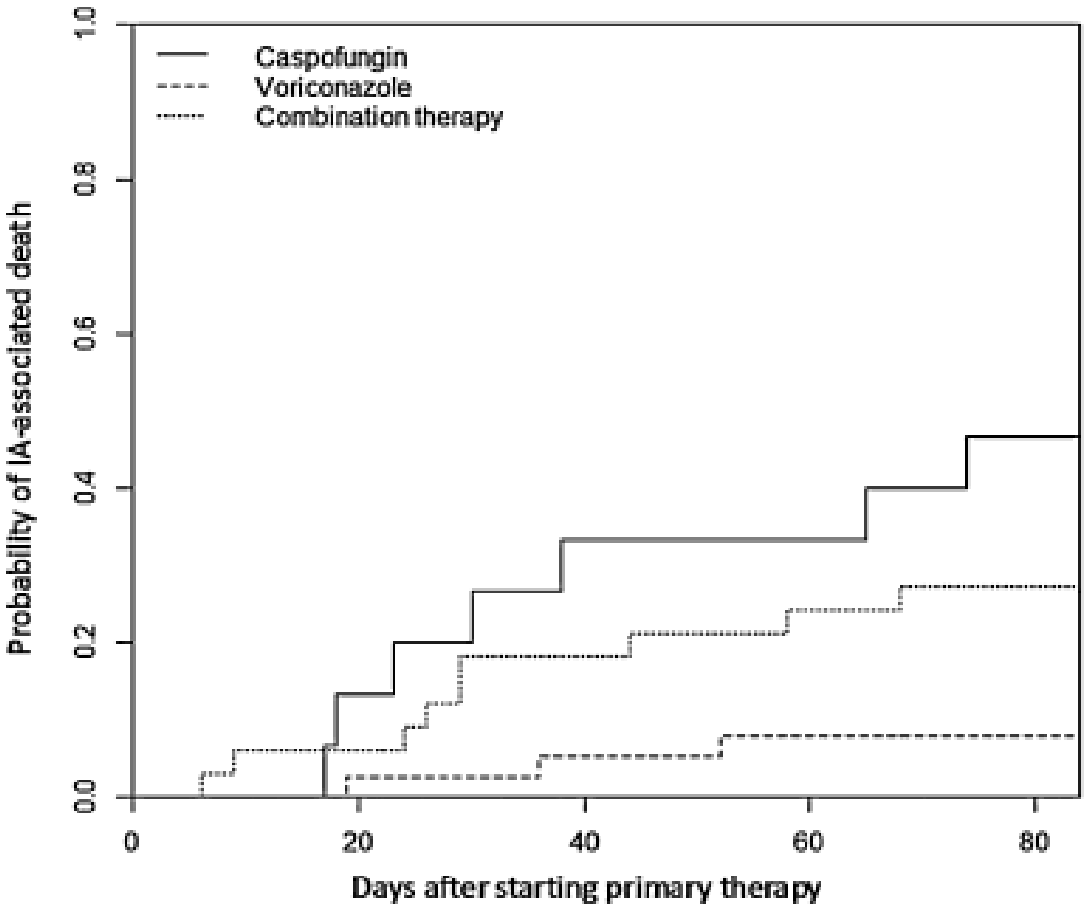
Similar characteristics except

- Caspo and combination more common in leukemia and in transplantation within 1 y
- Caspo more common in pts with mechanical ventilation
- Antifungal prophylaxis

- Response : 27% for caspo, 47 % vori, 55 % combination (P=0.2)
- No difference in AEs

Raad II et al. Int J Antimicrob Agents 2015 Mar;45:283

- Voriconazole was independently associated with lower IA associated mortality (8%) rates than caspofungin (47%), and combination (27%)

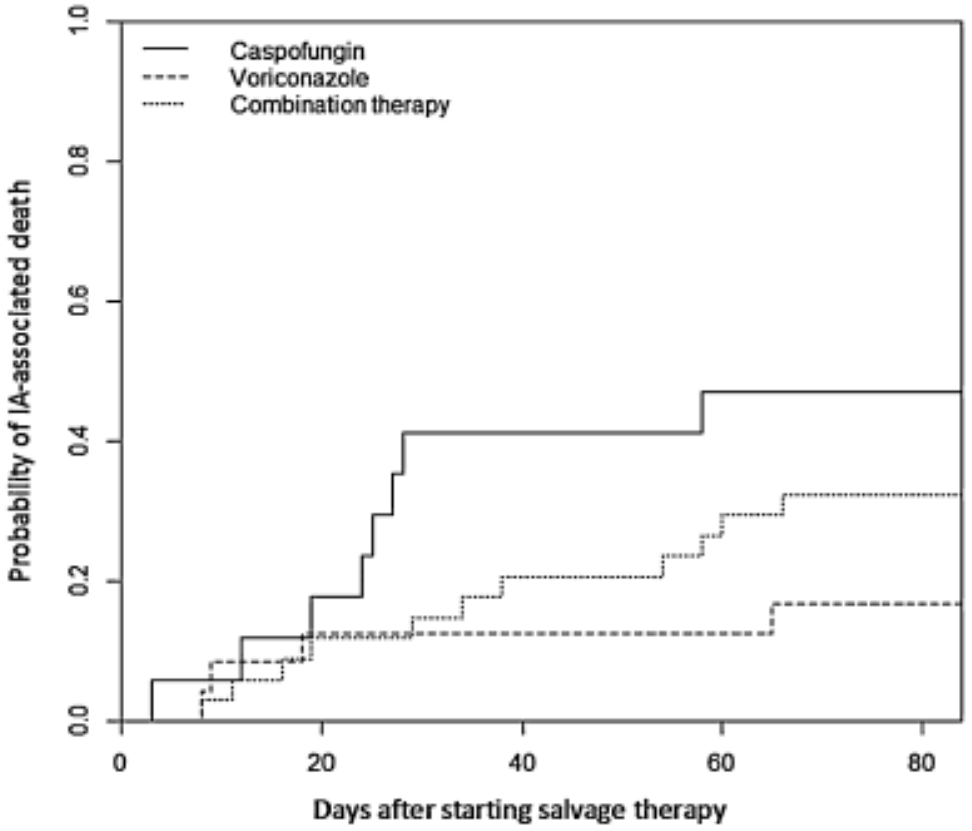


# Salvage Therapy Group

- All 3 groups had similar characteristics except for cancer type
- Response rates:
  - 29% caspo
  - 46% vori
  - 31% combo

  (P= 0.44)

**Mortality: 47 %, 17 % and 34 % (P= 0.11)**




Raad II et al. Int J Antimicrob Agents 2015 Mar;45:283

# Salvage Therapy Group

- ICU admission→only factor independently associated with death

- Adverse events (P= 0.02)
  - 6% for caspofungin
  - 17% for voriconazole
  - 37% For the combination

Raad II et al. Int J Antimicrob Agents 2015 Mar;45:283

# Conclusions

- Voriconazole was associated with lower mortality than caspofungin
- Combination had no advantage in response nor mortality in 1ry nor in salvage
- Higher rate of AEs in salvage group in combination group
- Too few pts with +ve galactomannan → unable to draw conclusions

- Study supports the IDSA guidelines
  - Combination reserved to certain groups for salvage

Raad II et al. Int J Antimicrob Agents 2015 Mar;45:283

# Limitations

- Retrospective
- Single institution
- Small sample size

Raad II et al. Int J Antimicrob Agents 2015 Mar;45:283

# Raouche Rock, Beirut

*J Antimicrob Chemother* 2014; **69**: 3148–3155
doi:10.1093/jac/dku241 Advance Access publication 8 July 2014

Journal of Antimicrobial Chemotherapy

# Invasive aspergillosis caused by *Aspergillus terreus*: an emerging opportunistic infection with poor outcome independent of azole therapy

**Roy Hachem[1]*, Marisa Zenaide Ribeiro Gomes[1], Gilbert El Helou[1], Aline El Zakhem[1], Christelle Kassis[2], Elizabeth Ramos[2], Ying Jiang[1], Anne-Marie Chaftari[1] and Issam I. Raad[1]**

*[1]Department of Infectious Diseases, Infection Control and Employee Health, The University of Texas M. D. Anderson Cancer Center, 1515 Holcombe Blvd, Houston, TX 77030, USA; [2]Division of Infectious Diseases, The University of Texas Health Science Center at Houston, 6431 Fannin, Houston, TX 77030, USA*

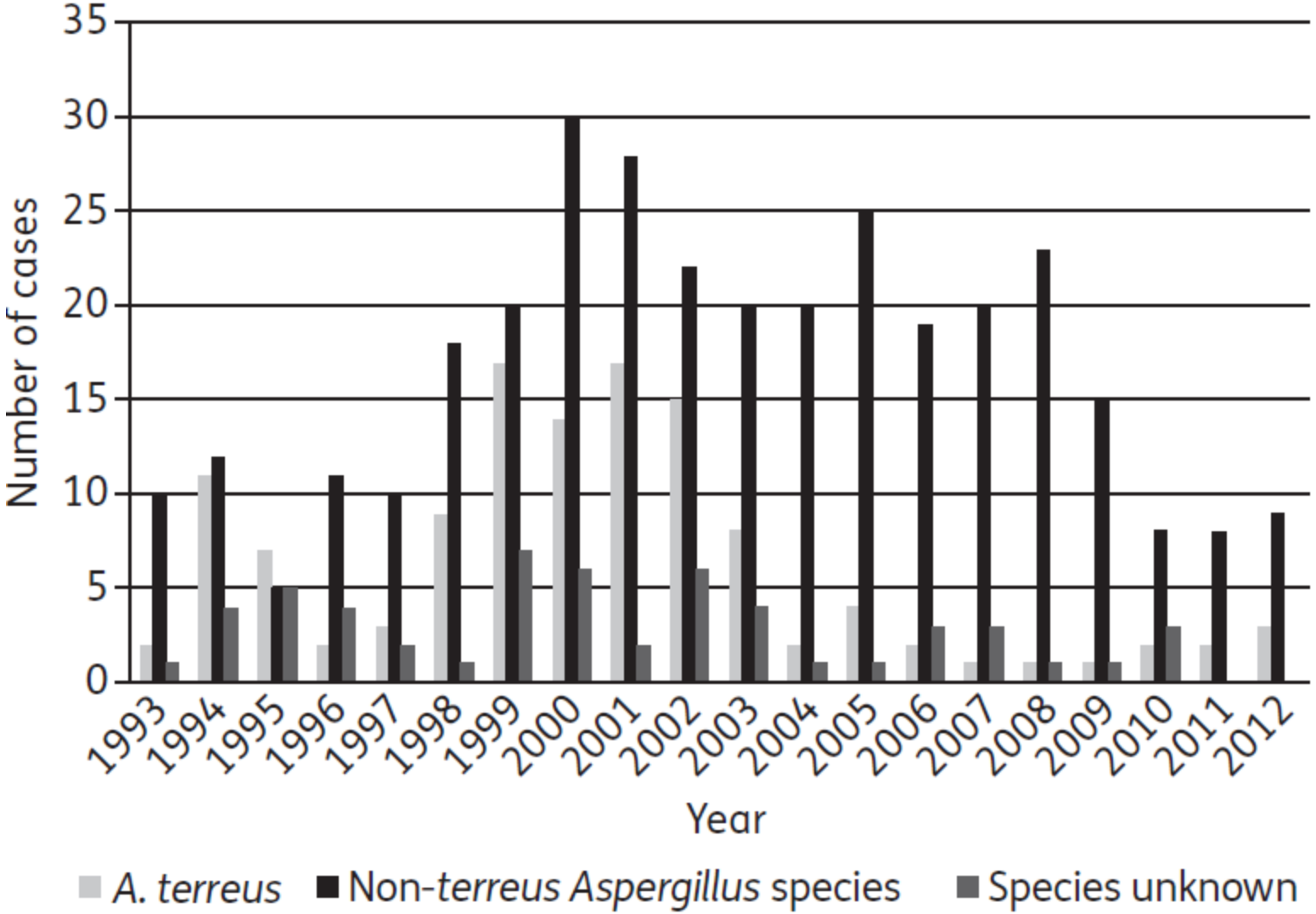
**Compared pts infected with *A. terreus* (n= 96) vs non-terreus *Aspergillus sp.* (n=335)**

# *Aspergillus terreus*

- Has intrinsic or acquired resistance to amphotericin B
- May become more common due to environmental and regional differences
- Some cancer centers: *A. terreus* is 2nd to 3rd after *A fumigatus* (rates 15-23%)

Steinbach WJ et al. J Infet 2012;65:453
Lass_FlorlC et al, J Clin Microbiol 2007;45:2686
Hachem R et al. Cancer 2004;101:1594

# *A. terreus* versus non-terreus *Aspergillus sp.* causing IA in HM patients, 1993–2012



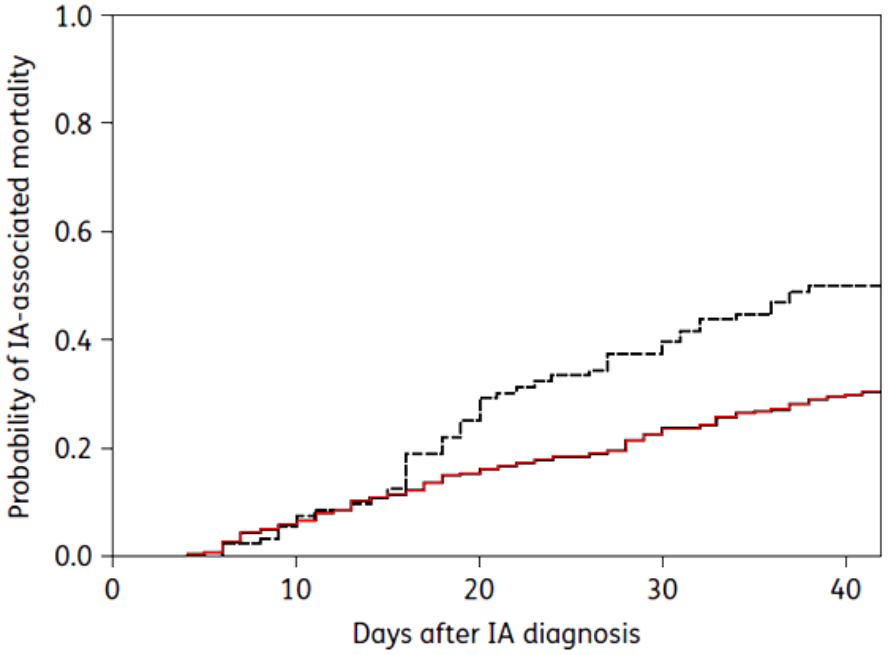
# Infection with *A. terreus*

- *A. terreus* infection was associated with
  - More breakthrough infections 91% vs 77% (P=0.009)
  - Lower rate of final response to antifungal therapy 21% vs 38% (P=0.0015)

Hachem R et al. J Antimicrob Chemother 2014 Nov; 69:3148

# Estimated Cumulative Incidence Curves of IA-Associated Mortality for HM Patients

Higher rate of IA-associated mortality
51% vs 30% (P<0.001)




***Outcomes independent of pts characteristics and Rx choices***

Hachem R et al. J Antimicrob Chemother 2014 Nov; 69:3148

# Patients with *A. terreus*

- Younger
- More likely to have leukemia
- Less likely to have lymphoma
- Longer duration of neutropenia

Hachem R et al. J Antimicrob Chemother 2014 Nov; 69:3148

# Predictive Factors for IA Associated Death

By multivariate competing risk analysis with death due to other causes as a competent event

| Predictive factors | *n* | HR | 95% CI | *P* value |
|---|---|---|---|---|
| Species for IA infection | | | | 0.038 |
| *A. terreus* | 95 | 1.43 | 1.02–2.00 | |
| other *Aspergillus* species | 321 | 1.0 | | |
| Treatment including azoles | | | | <0.0001 |
| yes | 196 | 0.19 | 0.13–0.29 | |
| no | 220 | 1.0 | | |

Hachem R et al. J Antimicrob Chemother 2014 Nov; 69:3148

# Conclusions

- Improved methods for the timely isolation and identification of *A. terreus* are needed
- Important for therapy and prognostic
- Reaffirms the use of voriconazole as first line therapy for IA

Hachem R et al. J Antimicrob Chemother 2014 Nov; 69:3148

# Aspergillus Azole Resistance


**Germany** =>Fischer J. J Antimicrob Chemother. 2014 Jun;69(6):1533

**China and France** =>Wang **DY**. Poult Sci. 2014 Jan;93(1):12

**Japan** => Kikuchi K. J Infect Chemother. 2014 May;20(5):336

**Poland** => Ziołkowska G, Poult Sci. 2014 May;93(5):1106

**Kuwait** => Ahmad S. Environ Res. 2014 Aug;133:20

**Denmark** => Astvad KM. Antimicrob Agents Chemother. 2014 Jun 16. pii: AAC.02855-14

**Tanzania** => Chowdhary A. J Antimicrob Chemother. 2014 Jul 7. pii: dku259

# Antifungal Susceptibility of TR34/L98H and TR46/Y121F/T289A *A. fumigatus sp.*

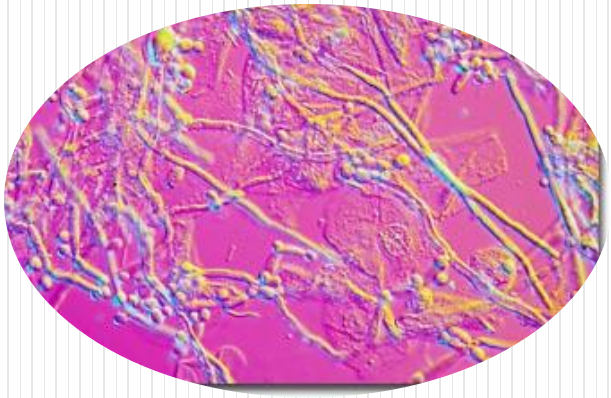
- 2010-2013, 952 *A. fumigatus*
  - 364 azole R strains
    - 225 $TR_{34}$/L98H
    - 98 $TR_{46}$/Y121F/T289A mutation

van Ingen J et al. J Antimicrob Chemother 2015;70:178

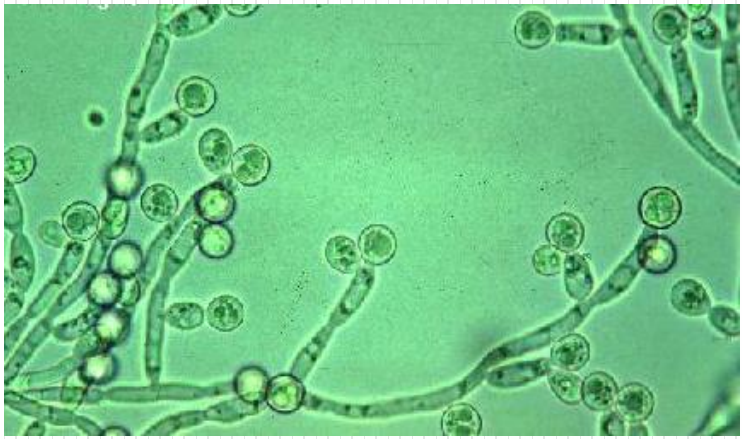
# Antifungal Susceptibility of TR34/L98H and TR46/Y121F/T289A *A. fumigatus sp.*

- TR34/L98H mutation and R to
  - 99.6 % itraconazole (MIC >2 mg/L)
  - 92.4 % voriconazole (MIC >2mg/L)
  - 97.8 % posaconazole (MIC>0.5 mg/L)
- TR46/Y121F/T289A mutation and R to
  - 100 % voriconazole
  - 82.7 % itraconazole
  - 94.9 % posaconazole

van Ingen J et al. J Antimicrob Chemother 2015;70:178



# Invasive Candidiasis (IC)



# Invasive Candidiasis (IC)

- Third most common BSI in the ICU
- Independently associated with mortality
- 3 methodologically sound single-center studies and metaanalysis showed efficacy of IC prophylaxis in ICU settings
  - Fluconazole ↓ the rate of IC in ICU but no improved survival

- No large or multicenter studies
- EORTC/MSG criteria incorporated β-D-glucan as microbiologic support of IC

De Paw B, et al. Clin Infect Dis 2008;46:1813

MAJOR ARTICLE

# MSG-01: A Randomized, Double-Blind, Placebo-Controlled Trial of Caspofungin Prophylaxis Followed by Preemptive Therapy for Invasive Candidiasis in High-Risk Adults in the Critical Care Setting

Luis Ostrosky-Zeichner,[1] Shmuel Shoham,[2] Jose Vazquez,[3] Annette Reboli,[4] Robert Betts,[5] Michelle A. Barron,[6] Mindy Schuster,[7] Marc A. Judson,[8] Sanjay G. Revankar,[9] Juan Pablo Caeiro,[10] Julie E. Mangino,[11] David Mushatt,[12] Roger Bedimo,[13] Alison Freifeld,[14] Minh Hong Nguyen,[15] Carol A. Kauffman,[16] William E. Dismukes,[17] Andrew O. Westfall,[18] Jeanna Beth Deerman,[17] Craig Wood,[19] Jack D. Sobel,[9] and Peter G. Pappas[17]

Ostrosky-Zeichner L et al. Clin Infect Dis 2014 May;58:1219

- Adults who were
  - In the ICU for at least 3 days
  - Ventilated
  - On broad spectrum antibiotics
  - Central line
  - Had 1 additional risk factor
    - Parenteral nutrition
    - Dialysis
    - Surgery
    - Pancreatitis
    - Systemic steroids
    - Other immunosuppressants

Ostrosky-Zeichner L et al. Clin Infect Dis 2014 May;58:1219

# Endpoints

**Primary:** incidence of proven or probable IC in pts with no disease at baseline in the MITT

→Pts with IC allowed to break the blind and receive preemptive therapy with caspofungin

**Secondary**

- Incidence of proven IC
- Time to development of IC
- Initiation of systemic antifungal Rx within 7 days of stopping prophylaxis
- All cause mortality within 7 days of ending prophylaxis
- LOS in the hospital and ICU

Ostrosky-Zeichner L et al. Clin Infect Dis 2014 May;58:1219

# Patients

- 222 adult pts from 15 ICUs in the US
- Non pregnant ≥ 18 y
- Admitted to ICU, expected to stay  for at least 48 hrs
- Meeting conditions of the clinical prediction rule for IC

Ostrosky-Zeichner L  et al. Clin Infect Dis 2014 May;58:1219

# Exclusion criteria

- Allergy
- ANC < 500
- AIDS
- Aplastic anemia
- CGD
- Hepatic insufficiency
- Subjects likely to die within 24 hrs
- Antifungal Rx within 10 d
- Active invasive fungal infection

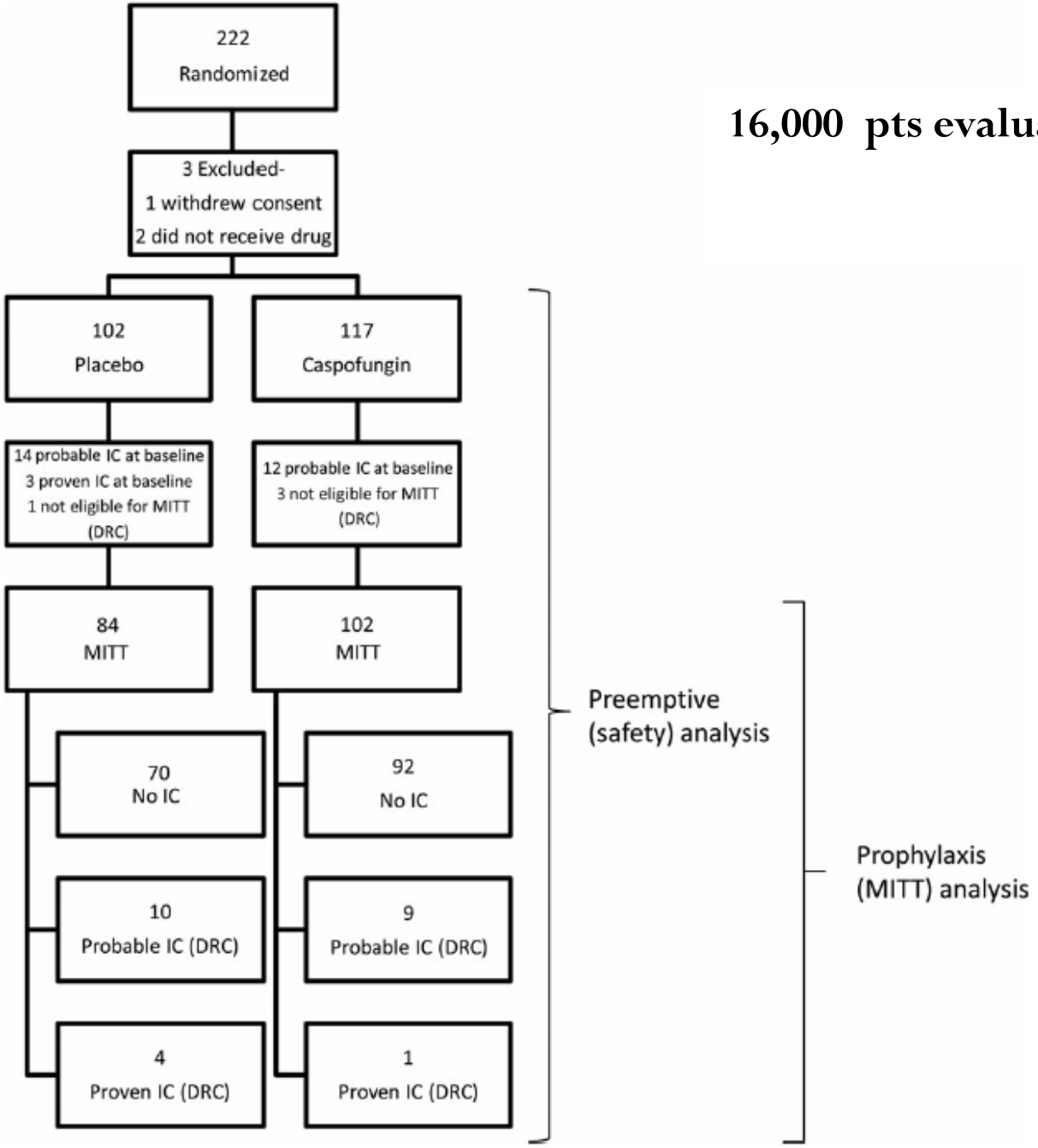
# Intervention

- Randomized to caspofungin (70 then 50 mg /d) vs placebo
- F/U for the duration of ICU stay, up to 28d
- F/U visits at 1 and 2 weeks, and at hospital discharge
- 1,3-β-D-glucan levels monitored twice weekly
- When subjects met the 1ry endpoint→ break the blind

  →Subjects receiving placebo were started on caspo

  → Subjects on caspo were allowed to continue or switch

Ostrosky-Zeichner L et al. Clin Infect Dis 2014 May;58:1219




**16,000 pts evaluated**

# Study Endpoints and Outcomes

## Prophylaxis/MITT Population

| | Caspofungin (n=102) | Placebo (n=84) | P value |
|---|---|---|---|
| Incidence of proven or probable IC by DRC, % | 9.8 | 16.7 | 0.14 |
| Incidence of proven IC by DRC, % | 1.0 | 4.8 | 0.11 |
| Use of antifungals within 7 d EOT, % | 13.7 | 17.9 | 0.35 |
| All-cause mortality within 7 d EOT, % | 16.7 | 14.3 | 0.78 |

Ostrosky-Zeichner L et al. Clin Infect Dis 2014 May;58:1219

# Study Endpoints and Outcomes

## Preemptive/ Safety Population

| | Caspofungin | Placebo | P value |
|---|---|---|---|
| Incidence of proven or probable IC by DRC, % | 18.8 | 30.4 | 0.04 |
| Incidence of proven IC by DRC, % | 0.9 | 6.9 | 0.02 |

Other secondary outcomes were similar in both groups

Ostrosky-Zeichner L et al. Clin Infect Dis 2014 May;58:1219

# Results

- Caspofungin was safe and tended to reduce the incidence of IC when used for prophylaxis
  - but the difference was not statistically significant
- A preemptive therapy approach deserves further study

Ostrosky-Zeichner L et al. Clin Infect Dis 2014 May;58:1219

# Safety

| Events | Caspofungin (n = 117) | Placebo (n = 102) | Total (N = 219) |
|---|---|---|---|
| No. of adverse events | 517 | 372 | 889 |
| Subjects with adverse events | 106 (90.6) | 87 (85.3) | 193 (88.1) |
| No. of severe adverse events | 43 | 33 | 76 |
| Subjects with severe adverse events | 33 (28.2) | 28 (27.5) | 61 (27.9) |
| Severe adverse events related to study drug | 1 (0.9) | 0 | 1 (0.5) |
| Study discontinuations related to study drug | 2 (1.7) | 2 (2) | 4 (1.8) |
| Deaths through end of study | 24 (20.5) | 16 (15.7) | 40 (18.3) |

**Ostrosky-Zeichner L et al. Clin Infect Dis 2014 May;58:1219**

# Conclusions

- Possibly underpowered study for the primary analysis population
- Cases of IC based on 1,3-β-D-glucan positivity were diagnosed earlier than expected
- ?? Lack of statistical significance related to the study being underpowered due to lower than expected incidence of IC in the MITT
- Data from secondary analyses point to an overall +ve effect

***Serves as a proof of concept model for preemptive antifungal Rx based on detection of early infection by 1,3-β-D-glucan***

Ostrosky-Zeichner L et al. Clin Infect Dis 2014 May;58:1219

# Byblos, The Most Ancien City

Research

Original Investigation

# Effect of Fluconazole Prophylaxis on Candidiasis and Mortality in Premature Infants
## A Randomized Clinical Trial

Daniel K. Benjamin Jr, MD, PhD; Mark L. Hudak, MD; Shahnaz Duara, MD; David A. Randolph, MD, PhD; Margarita Bidegain, MD, MHS-Cl
Gratias T. Mundakel, MD; Girija Natarajan, MD; David J. Burchfield, MD; Robert D. White, MD; Karen E. Shattuck, MD; Natalie Neu, MD, M
Catherine M. Bendel, MD; M. Roger Kim, MD; Neil N. Finer, MD; Dan L. Stewart, MD; Antonio C. Arrieta, MD; Kelly C. Wade, MD; David A.
Paolo Manzoni, MD; Kristi O. Prather, MPH; Daniela Testoni, MD, MHS; Katherine Y. Berezny, MPH; P. Brian Smith, MD, MPH, MHS;
for the Fluconazole Prophylaxis Study Team

Invasive candidiasis in premature infants causes death and neuro-developmental impairment

**Benjamin DK Jr et al. JAMA 2014 May;311:1742**

# Methods

- Randomized, blinded, placebo-controlled trial of fluconazole in premature infants
- 361 Infants < 750 g from 32 NICUs in the US
- Received fluconazole (6 m/kg) or placebo twice weekly for 42 d
- Surviving infants were evaluated at 18 to 22 months corrected age for neuro-developmental outcomes

Benjamin DK Jr et al. JAMA 2014 May;311:1742

# Outcomes

- **Primary end point:** composite of death or definite or probable IC prior to study day 49 (1 week after completion of study drug)

- **Secondary and safety outcomes**: IC, liver function, bacterial infection, LOS, intracranial hemorrhage, periventricular leukomalacia, chronic lung disease, patent ductus arteriosus requiring surgery, retinopathy of prematurity requiring surgery, necrotizing enterocolitis, spontaneous intestinal perforation, and neurodevelopmental outcomes

Benjamin DK Jr et al. JAMA 2014 May;311:1742

# Results

- Among infants with a birth weight of less than 750 g, 42 days of fluconazole prophylaxis compared with placebo did not result in a lower incidence of the composite of death or IC

***=> Findings do not support the universal use of prophylactic fluconazole in extremely low-birth-weight infants***

**Benjamin DK Jr et al. JAMA 2014 May;311:1742**

J Antimicrob Chemother
doi:10.1093/jac/dku544

Journal of Antimicrobial Chemotherapy

# Micafungin twice weekly as antifungal prophylaxis in paediatric patients at high risk for invasive fungal disease

**K. Bochennek[1], A. Balan[1,2], L. Müller-Scholden[1], M. Becker[1], F. Farowski[3], C. Müller[4], A. H. Groll[5] and T. Lehrnbecher[1]***

*[1]Pediatric Hematology and Oncology, Johann Wolfgang Goethe-University, Frankfurt, Germany; [2]"Victor Babes" University of Medicine and Pharmacy, Timisoara, Romania; [3]Department I of Internal Medicine, University Hospital of Cologne, Cologne, Germany; [4]Department of Pharmacology, University Hospital of Cologne, Cologne, Germany; [5]Infectious Disease Research Program, Center for Bone Marrow Transplantation and Department of Pediatric Hematology/Oncology, University Children's Hospital Münster, Münster, Germany*

**Bochennek K et al. J Antimicrob Chemother 2015 May; 70:1527**

# Methods

- Analysed safety (primary end-point), efficacy and micafungin serum concentrations (secondary end-points) of children at high risk for IFD
  - 3 and 4 mg/kg twice weekly
- High risk children with ALL, AML, relapsed leukemia, non Hodgkins lymphoma, HCT
  - intolerant or had contraindications to polyenes and triazoles

21 children median age 9

Bochennek K et al. J Antimicrob Chemother 2015 May;70:1527

# Results

- No significant clinical AEs occurred
  - EOT values of renal and hepatic function were not different from baseline
- **Proven or probable breakthrough IFD did not occur in any of the pts**
- In 9/11 pts in whom plasma micafungin concentrations were assessed, the first trough concentration ≥150 ng/mL (effective for prophylaxis)

Bochennek K et al. J Antimicrob Chemother 2015 May;70:1527

# Conclusion

- Micafungin twice weekly at3-4 mg/kg could be convenient, safe and efficient antifungal prophylaxis in children at high risk for IFD
- Has to be validated in larger patient populations

Bochennek K et al. J Antimicrob Chemother 2015 May;70:1527

# Saidon, Lebanon

Vazquez et al. BMC Infectious Diseases 2014, 14:97
http://www.biomedcentral.com/1471-2334/14/97

BMC Infectious Diseases

RESEARCH ARTICLE Open Access

# Evaluation of an early step-down strategy from intravenous anidulafungin to oral azole therapy for the treatment of candidemia and other forms of invasive candidiasis: results from an open-label trial

Jose Vazquez[1], Annette C Reboli[2], Peter G Pappas[3], Thomas F Patterson[4], John Reinhardt[5], Peter Chin-Hong[6], Ellis Tobin[7], Daniel H Kett[8], Pinaki Biswas[9] and Robert Swanson[9*]

# Recommendation To Step Down to Oral Rx

- **IDSA**
  - if pt is stable and blood cultures are negative
- **ESCMID** after 10 d of Rx
  - if pt is stable, tolerates oral Rx and the *Candida Sp*. is susceptible

- Neither have been prospectively studied and the appropriate timing is unclear
- Phase IV, Open label, non-comparative study, in the US (44 centers), and Korea (4 centers)

Vazquez Jet al. BMC Infect Dis 2014 Feb;14:97

# Methods

- Pts with C/IC were treated with IV anidulafungin and after 5 days of IV had the option to step-down to oral azole (fluconazole or voriconazole)
- **Primary endpoint:** global response rate (clinical + microbiological) at EOT in the MITT population (at least one dose of anidulafungin plus positive Candida within 96 hours of study entry)
- **Secondary endpoints:** efficacy at other time points and in predefined pt subpopulations
- Pts who stepped down early (≤ 7 days' anidulafungin) were identified as the "early switch" subpopulation

# Results

- 250 were included in the MITT population
- 40 % remained on anidulafungin (Median IV Rx 12 d)
- 60 %  stepped down to oral (Median IV Rx 6 d)
- MITT global response rate at EOT was 83.7%
- Global response rates at all time points were similar
  - In the early switch subpopulation compared with the MITT population
  - Across multiple *Candida species* *(C. albicans, C. glabrata, and C. parapsilosis)*

**Vazquez Jet al. BMC Infect Dis 2014 Feb;14:97**

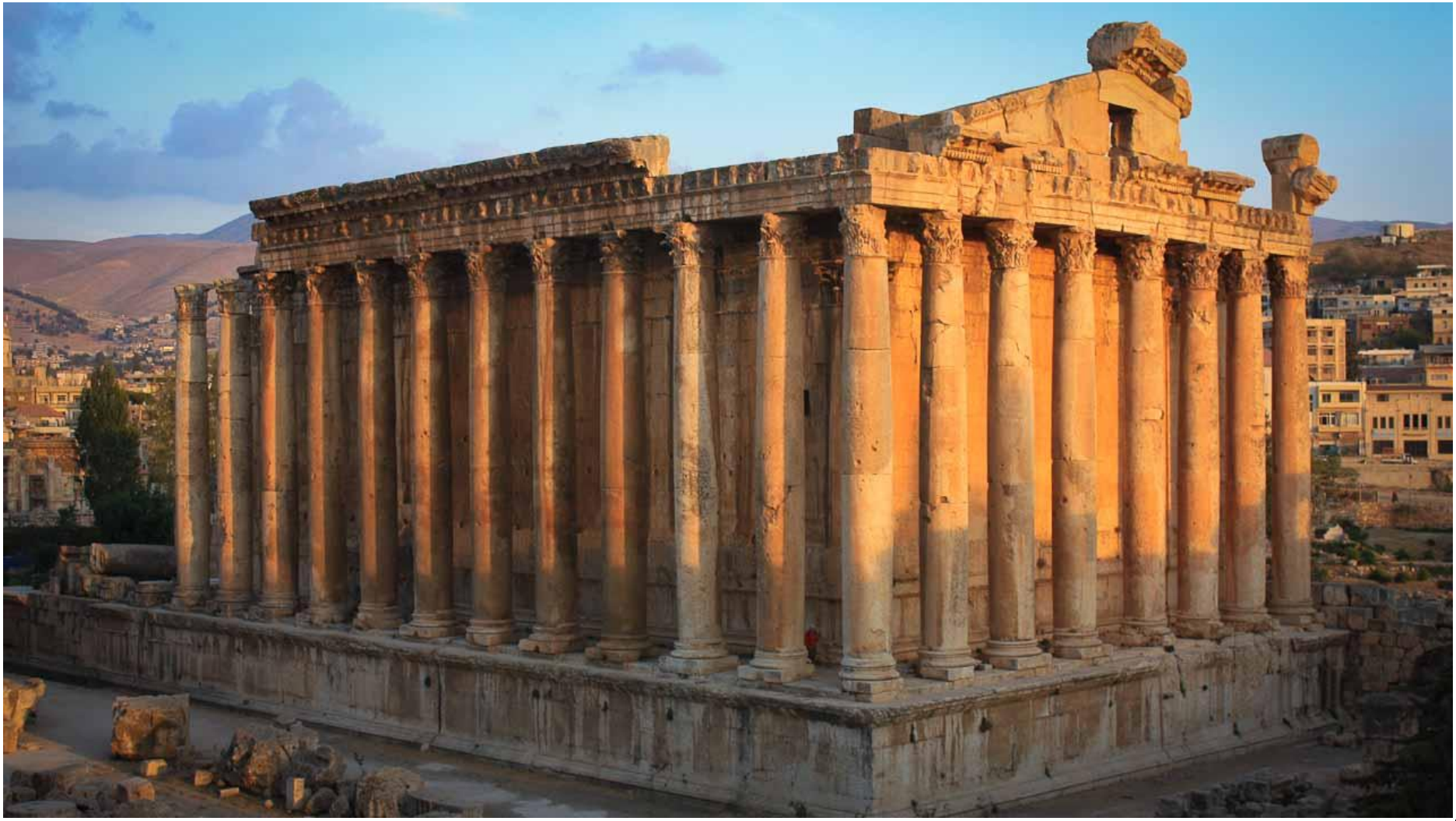
# Discussion

- In general, the early switch subpopulation showed response rates similar to the MITT population and these response rates were maintained through the end of study
  - pts in the early switch subpopulation were less severely ill

***Efficacy of including an early step-down strategy***

Vazquez Jet al. BMC Infect Dis 2014 Feb;14:97

# Baalabek, Lebanon




# Initial Use of Echinocandins Does Not Negatively Influence Outcome in *Candida parapsilosis* Bloodstream Infection: A Propensity Score Analysis

Mario Fernández-Ruiz,[1] José María Aguado,[1] Benito Almirante,[2,3] David Lora-Pablos,[4,5] Belén Padilla,[6] Mireia Puig-Asensio,[2,3] Miguel Montejo,[7] Julio García-Rodríguez,[8] Javier Pemán,[9] Maite Ruiz Pérez de Pipaón,[10] and Manuel Cuenca-Estrella[11]; for the CANDIPOP Project, GEIH-GEMICOMED (SEIMC), and REIPI[a]

**Fernández-Ruiz M et al. Clin Infect Dis 2014 May;58:1413**

# Methods

- Concerns regarding the optimal regimen for *C. parapsilosis* (↓ susceptibility to echinocandins)
- CANDIPOP is a prospective population Study on candidemia in Spain
- Multicenter population-based surveillance program on candida BSI through a 12 month period in 29 Spanish hospitals
  - Identified by DNA sequencing and antifungal susceptibility
- Impact of echinocandin within 72 hrs by a propensity score approach

Fernández-Ruiz M et al. Clin Infect Dis 2014 May;58:1413

# Results

- Among 752 episodes of Candida BSI identified, 200 (26.6%) were due to *C. parapsilosis*
- Predictors for clinical failure were assessed:
  - all-cause mortality between days 3 to 30
  - or persistent candidemia for ≥72 hours after initiation of therapy
- Clinical failure occurred in 32.8% of evaluable episodes

Fernández-Ruiz M et al. Clin Infect Dis 2014 May;58:1413

# Univariate and Multivariate Logistic Regression Analyses of Prognostic Factors for Clinical Failure

| | Univariate Analysis | | | Multivariate Analysis | | |
|---|---|---|---|---|---|---|
| Variable | OR | 95% CI | *P* Value | Adjusted OR | 95% CI | *P* Value[b] |
| Orotracheal intubation at diagnosis | 4.67 | 2.32–9.38 | .000 | 2.81 | 1.19–6.65 | .018 |
| Septic shock | 7.17 | 2.63–19.56 | .000 | 2.91 | .88–9.64 | .081 |
| Hematogenous dissemination | 6.75 | 1.32–34.56 | .016 | 7.42 | .67–82.44 | .103 |
| Early CVC removal (≤48 h) | 0.41 | .20–.86 | .016 | 0.43 | .19–.96 | .040 |
| Initial antifungal therapy | | | | | | |
| Azole-based regimen | 1 | . . . | . . . | 1 | . . . | . . . |
| Echinocandin-based regimen | 1.34 | .60–2.97 | .479 | 1.73 | .66–4.54 | .265 |
| Amphotericin B–based regimen | 0.99 | .40–2.45 | .989 | 0.99 | .34–2.89 | .996 |
| Combination regimen | 0.86 | .31–2.36 | .769 | 1.06 | .33–3.43 | .922 |

***=> The initial use of an echinocandin-based regimen does not seem to negatively influence outcome in C. parapsilosis BSI***

Fernández-Ruiz M et al. Clin Infect Dis 2014 May;58:1413

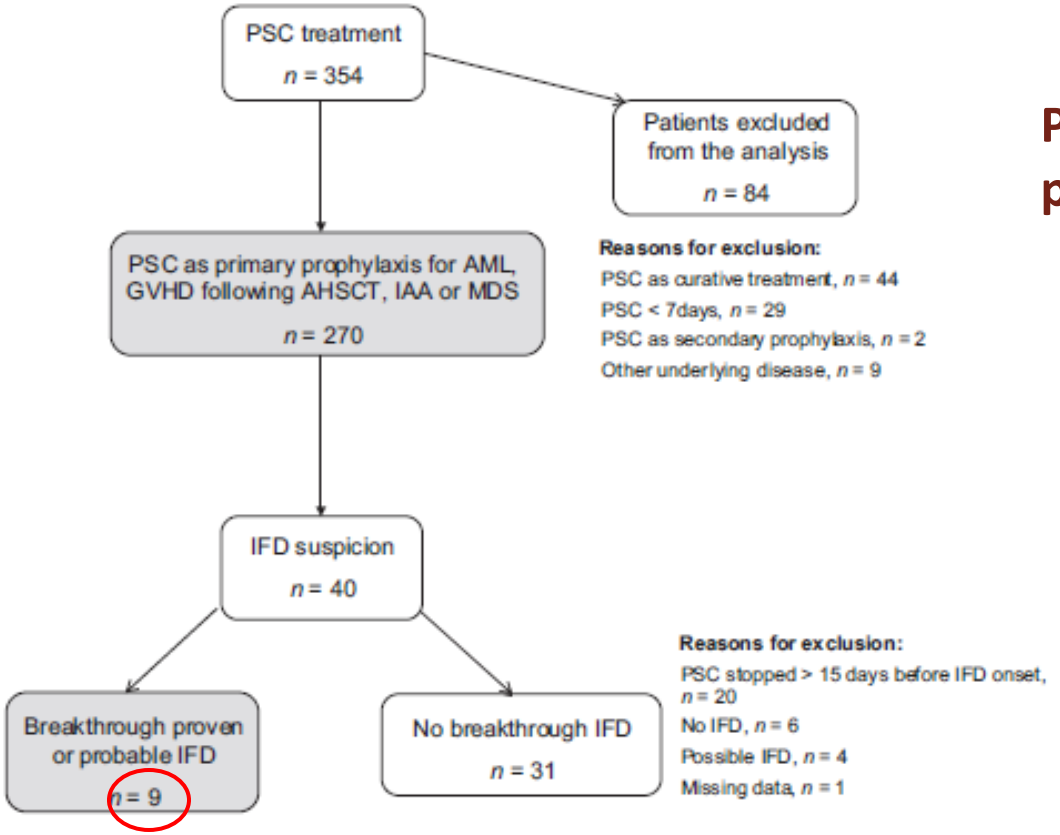
# Beirut Sea shore

# Breakthrough on Posaconazole

- Posaconazole (PSC) is currently recommended as primary prophylaxis in
  - Neutropenic pts with AML
  - Allogenic HCT recipients with GVHD
- Retrospective study of all consecutive pts on PSC prophylaxis
  - from January 2007 to December 2010
- 279 pts (median duration of 1.4 months)

Lorelle N et al. Clin Microbiol Infect 2014 Nov;20:O952

# Breakthrough IFD on Posaconazole




**Proven (n = 6)**

**probable (n = 3)**

- ***Candida glabrata* (n=2)**
- **pulmonary IA (n=3)**
- **disseminated fusariosis (n=2)**
- **pulmonary mucormycosis (n=2)**

Lorelle N et al. Clin Microbiol Infect 2014 Nov;20:0952

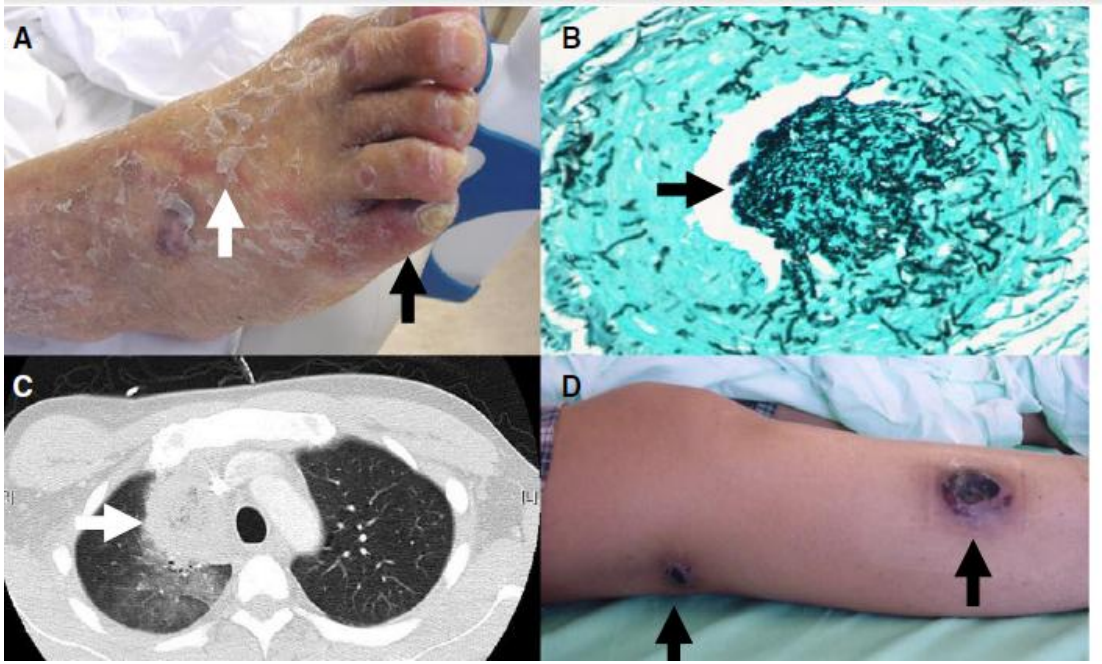
Ann Hematol (2014) 93:493–498
DOI 10.1007/s00277-013-1882-2

ORIGINAL ARTICLE

# Breakthrough invasive fungal diseases during echinocandin treatment in high-risk hospitalized hematologic patients

Thomas S. Y. Chan · Harinder Gill · Yu-Yan Hwang · Joycelyn Sim · Alan C. T. Tse · Florence Loong · Pek-Lan Khong · Eric Tse · Anskar Y. H. Leung · Chor-Sang Chim · Albert K. W. Lie · Yok-Lam Kwong

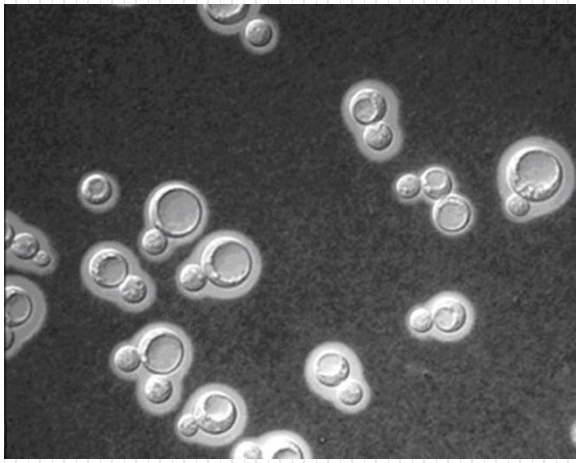
- Retrospectively analyzed 534 hematologic pts treated with echinocandins
  - Caspofungin, N =55
  - Micafungin, N =306
  - Anidulafungin, N =173
- Four proven IFDs were found, caused by
  - *Candida parapsilosis* (N =2)
  - *Candida glabrata* (N =1)
  - *Fusarium species* (N =1)




Chan TS et al. Ann Hematol 2014 Mar; 93:493

# Beirut Down Town

# Cryptococcal Meningitis (CM)



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

# Timing of Antiretroviral Therapy after Diagnosis of Cryptococcal Meningitis

David R. Boulware, M.D., M.P.H., David B. Meya, M.Med., Conrad Muzoora, M.Med., Melissa A. Rolfes, Ph.D., Katherine Huppler Hullsiek, Ph.D., Abdu Musubire, M.Med., Kabanda Taseera, M.Med., Henry W. Nabeta, M.B., Ch.B., Charlotte Schutz, M.B., Ch.B., M.P.H., Darlisha A. Williams, M.P.H., Radha Rajasingham, M.D., Joshua Rhein, M.D., Friedrich Thienemann, M.D., Ph.D., Melanie W. Lo, M.D., Kirsten Nielsen, Ph.D., Tracy L. Bergemann, Ph.D., Andrew Kambugu, M.Med., Yukari C. Manabe, M.D., Edward N. Janoff, M.D., Paul R. Bohjanen, M.D., Ph.D., Graeme Meintjes, M.B., Ch.B., Ph.D., for the COAT Trial Team*

# Early Antiretroviral treatment (ART)

- Shown to reduce AIDS-defining events and death in pts with various opportunistic infections
- And among pts with noncerebral TB
- Did not appear to be beneficial in TB meningitis
- Outcome of CNS infections might differ possibly because of intracranial structures

Zolopa A et al. PloS One 2009;4:e5575
Kambugu A, et al. Clin Infect Dis 2008;46:1694

# Methods

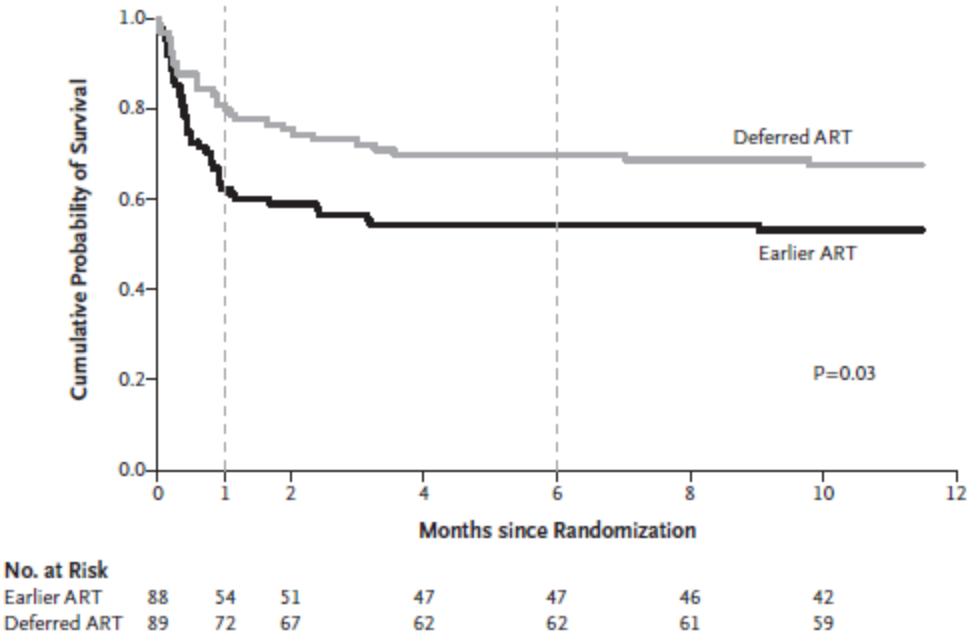
- Assessed survival at 26 weeks among **177 HIV pts** in Uganda and South Africa with
  - Cryptococcal meningitis
  - Not previously on ART
- Randomly assigned study participants to undergo
  1. earlier ART initiation (1 to 2 wks after diagnosis)
  2. deferred ART initiation (5 wks after diagnosis)
- Received Ampho B and fluconazole for 14 d followed by consolidation therapy with fluconazole

Boulware DR et al. Engl J Med 2014 Jun;370:2487

# Overall Survival

- 26-week mortality with earlier ART initiation was significantly **higher** than with deferred ART initiation

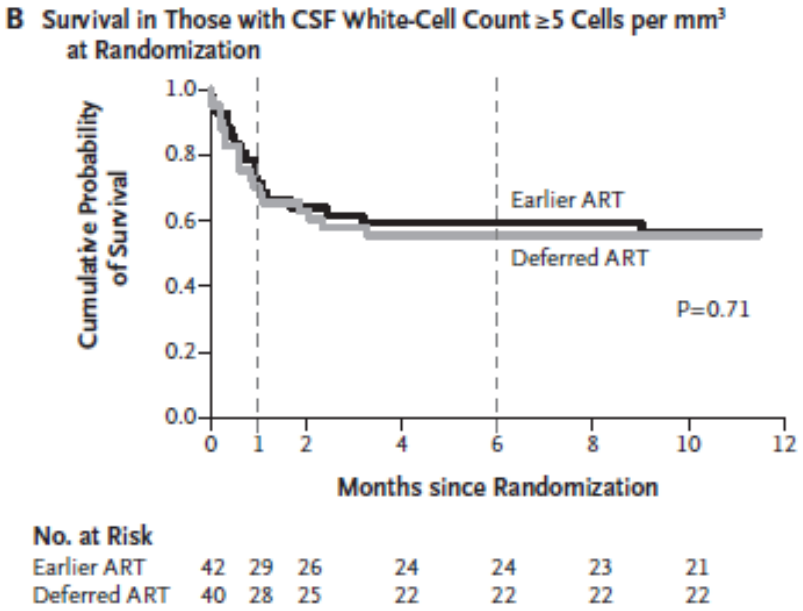
(45% vs. 30%, HR 1.73, CI 1.06-2.82;P=0.03)

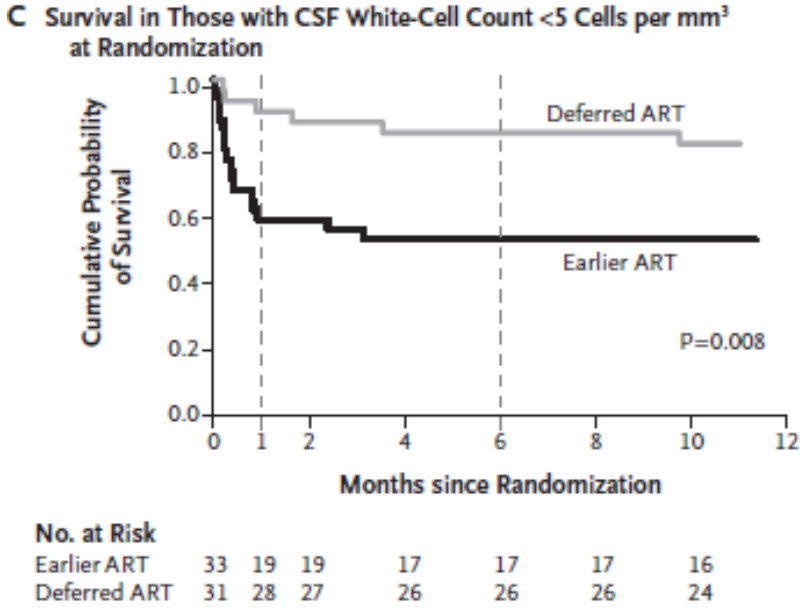



Boulware DR et al. N Engl J Med 2014 Jun;370:2487

# Results

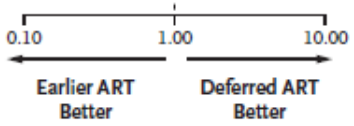
- Among pts with few wbc in CSF, mortality was particularly elevated with earlier ART




**Paucity of wbc →risk factor for immune reconstitution inflammatory syndrome (IRIS)**

| Group | Earlier ART | | Deferred ART | | Hazard Ratio (95% CI) | P Value | P Value for Interaction |
|---|---|---|---|---|---|---|---|
| | *no. of patients* | *no. of deaths* | *no. of patients* | *no. of deaths* | | | |
| **All Patients** | | | | | | | |
| 6-Mo mortality | 88 | 40 | 89 | 27 | 1.73 (1.06–2.82) | 0.03 | |
| Overall mortality | 88 | 41 | 89 | 29 | 1.66 (1.03–2.68) | 0.04 | |
| Days 0–7 | 88 | 12 | 89 | 9 | 1.39 (0.59–3.30) | 0.46 | |
| Days 8–30 | 75 | 21 | 80 | 8 | 3.10 (1.37–7.00) | 0.007 | |
| Days 31–183 | 54 | 8 | 72 | 12 | 0.92 (0.35–2.43) | 0.87 | |
| **Subgroup** | | | | | | | |
| GCS score within 48 hr of randomization | | | | | | | 0.18 |
| 15 | 76 | 30 | 77 | 22 | 1.54 (0.89–2.67) | 0.12 | |
| <15 | 12 | 10 | 12 | 5 | 2.96 (1.00–8.80) | 0.05 | |
| CD4 cell count at randomization | | | | | | | 0.91 |
| ≥50/mm$^3$ | 29 | 13 | 34 | 10 | 1.83 (0.80–4.17) | 0.15 | |
| <50/mm$^3$ | 58 | 26 | 54 | 16 | 1.74 (0.93–3.24) | 0.08 | |
| CSF cryptococcus culture results at meningitis diagnosis | | | | | | | 0.38 |
| ≤100,000 CFU/ml | 29 | 11 | 39 | 12 | 1.37 (0.61–3.11) | 0.45 | |
| >100,000 CFU/ml | 43 | 25 | 36 | 11 | 2.44 (1.20–4.96) | 0.01 | |
| Data excluded (>48 hr after diagnosis) | 16 | 4 | 14 | 4 | 0.87 (0.22–3.47) | 0.84 | |
| CSF cryptococcus culture results at randomization | | | | | | | 0.87 |
| <100 CFU/ml | 30 | 11 | 34 | 6 | 2.37 (0.88–6.41) | 0.09 | |
| 100–10,000 CFU/ml | 28 | 16 | 35 | 14 | 1.57 (0.77–3.22) | 0.22 | |
| >10,000 CFU/ml | 18 | 8 | 10 | 4 | 1.36 (0.41–4.53) | 0.61 | |
| Culture not performed | 12 | 5 | 10 | 3 | 1.62 (0.38–6.80) | 0.51 | |
| CSF white-cell count at meningitis diagnosis | | | | | | | 0.76 |
| <5/mm$^3$ | 36 | 16 | 27 | 6 | 2.34 (0.91–5.99) | 0.08 | |
| ≥5/mm$^3$ | 44 | 21 | 56 | 20 | 1.58 (0.86–2.92) | 0.14 | |
| Cell count not performed | 8 | 3 | 6 | 1 | 2.19 (0.23–21.06) | 0.50 | |
| CSF white-cell count at randomization | | | | | | | 0.02 |
| <5/mm$^3$ | 33 | 16 | 31 | 5 | 3.87 (1.41–10.58) | 0.008 | |
| ≥5/mm$^3$ | 42 | 17 | 40 | 18 | 0.88 (0.46–1.71) | 0.71 | |
| Cell count not performed | 13 | 7 | 18 | 4 | 3.01 (0.87–10.38) | 0.08 | |
| Cryptococcal antigen titer at meningitis diagnosis | | | | | | | 0.47 |
| <1:2000 | 19 | 7 | 25 | 5 | 2.13 (0.67–6.73) | 0.20 | |
| ≥1:2000 | 67 | 31 | 63 | 22 | 1.48 (0.86–2.56) | 0.16 | |



# Discussion

- Timing of ART did not influence any of the secondary end points, even the Incidence IRIS (20% and 30%; P=0.32)
- Nor the rate of crypto clearance (+ cx at 14 d in 37 and 39%)
- Difference in mortality →stopped early

***Conclusion: Deferral of ART for 5 wks after diagnosis of crypto meningitis especially for those with a few wbc in CSF***

# Cedars, Northern Lebanon

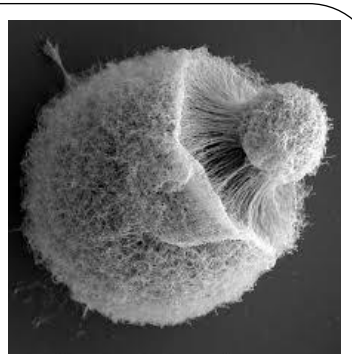
Clinical Infectious Diseases 2014;58(5):736–45

HIV/AIDS MAJOR ARTICLE

# Determinants of Mortality in a Combined Cohort of 501 Patients With HIV-Associated Cryptococcal Meningitis: Implications for Improving Outcomes

**Joseph N. Jarvis,[1,2,3,4,a] Tihana Bicanic,[1,a] Angela Loyse,[1] Daniel Namarika,[5] Arthur Jackson,[5] Jesse C. Nussbaum,[5,6] Nicky Longley,[1,2,4] Conrad Muzoora,[7] Jacob Phulusa,[5] Kabanda Taseera,[7] Creto Kanyembe,[5] Douglas Wilson,[8] Mina C. Hosseinipour,[5] Annemarie E. Brouwer,[9] Direk Limmathurotsakul,[10] Nicholas White,[10,11] Charles van der Horst,[5] Robin Wood,[2] Graeme Meintjes,[4,12,13] John Bradley,[14] Shabbar Jaffar,[14] and Thomas Harrison[1]**

[1]Research Centre for Infection and Immunity, Division of Clinical Sciences, St George's University of London, United Kingdom; [2]Desmond Tutu HIV Centre, Institute of Infectious Disease and Molecular Medicine, University of Cape Town, South Africa; [3]Department of Clinical Research, Faculty of Infectious and Tropical Diseases, London School of Hygiene and Tropical Medicine, United Kingdom; [4]Division of Infectious Diseases and HIV Medicine, Department of Medicine, University of Cape Town, South Africa; [5]University of North Carolina Project, Lilongwe, Malawi; [6]Division of Infectious Diseases, University of California, San Francisco; [7]Mbarara University of Science and Technology, Uganda; [8]Edendale Hospital, Pietermaritzburg, South Africa; [9]St Elisabeth Hospital Tilburg and Radboud University Medical Centre Nijmegen, the Netherlands; [10]Mahidol-Oxford Research Unit, Faculty of Tropical Medicine, Mahidol University, Bangkok, Thailand; [11]Centre for Tropical Medicine, Nuffield Department of Clinical Medicine, University of Oxford, United Kingdom; [12]Institute of Infectious Disease and Molecular Medicine, University of Cape Town, South Africa; [13]Department of Medicine, Imperial College London, United Kingdom; and [14]Faculty of Epidemiology and Population Health, London School of Hygiene and Tropical Medicine, United Kingdom



- Pts prospectively followed for 10 weeks

(Thailand, Uganda, Malawi, and South Africa)

- Factors that predicted acute mortality at 2 weeks
  - Altered mental status
  - CSF fungal burden
  - Older age
  - High peripheral wbc
  - Slow clearance of CSF
  - **Fluconazole based induction regimen**
    - **Mortality in fluconazole treated pts was double than Ampho B at 10 weeks**
- The mean EFA (early fungicidal activity) was greater for amphotericin-based compared with fluconazole-based induction treatment $P < .001$

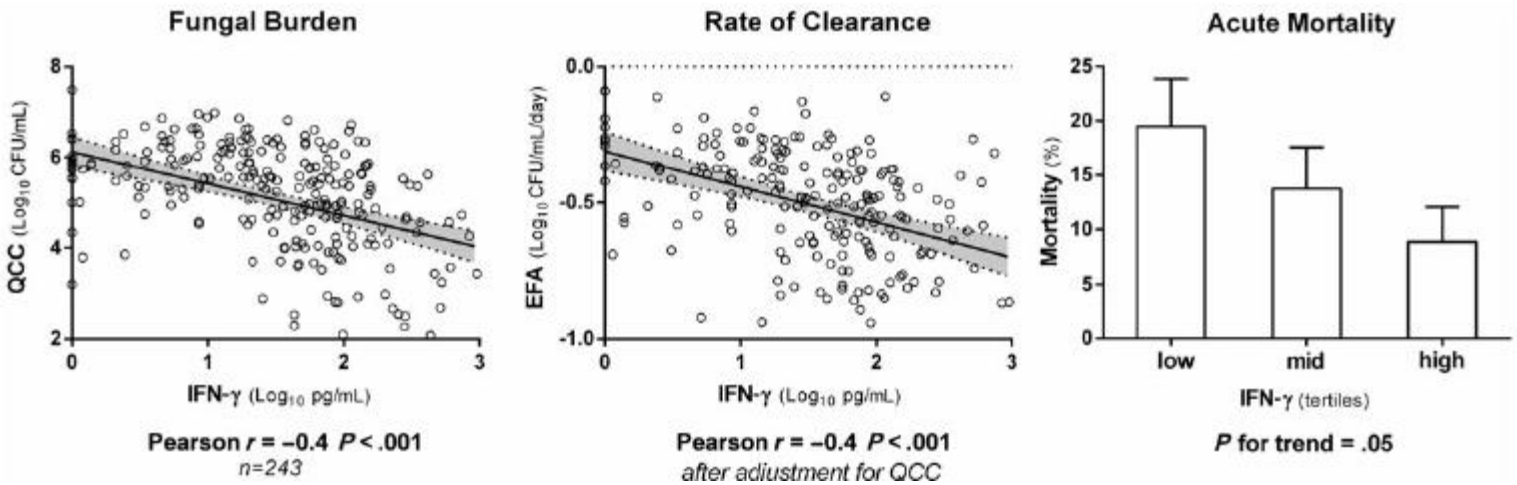
# Association Between Treatment and Mortality

| 2 week mortality | No | Mortality | OR (95% CI), Univariable | P Value | AOR (95% CI), Multivariable | P Value |
|---|---|---|---|---|---|---|
| Fluconazole | 99 | 26%(26) | 1 | 0.005 | 1 | 0.05 |
| Amphotericin | 393 | 14% (56) | 0.5 (.3–.8) | | 0.5 (.3–1.0) | |

| 10 week mortality | No | Mortality | OR (95% CI), Univariable | P Value | AOR (95% CI), Multivariable | P Value |
|---|---|---|---|---|---|---|
| Fluconazole | 99 | 53% (52) | 1 | <0.001 | 1 | 0.02 |
| Amphotericin | 385 | 29% (111) | 0.4 (0.2–0.6) | | 0.5 (0.3–0.9) | |

Jarvis JN et al. Clin Infect Dis 2014 Mar;58:736

- EFA was associated independently with amphotericin-based treatment, baseline organism count, and CSF IFN-γ level




⇒ earlier diagnosis

⇒ more rapidly fungicidal amphotericin-based regimens

⇒ prompt immune reconstitution with ART

…. are priorities for improving outcomes

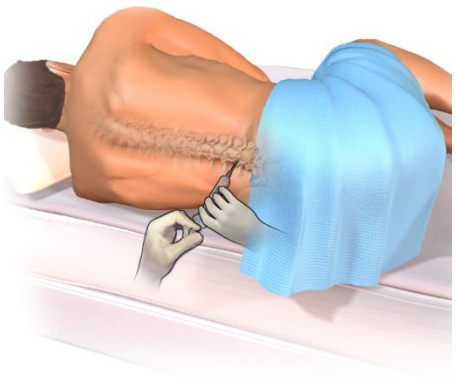
# Zaytouna Bay

MAJOR ARTICLE HIV/AIDS

# The Effect of Therapeutic Lumbar Punctures on Acute Mortality From Cryptococcal Meningitis

**Melissa A. Rolfes,[1] Kathy Huppler Hullsiek,[2] Joshua Rhein,[1,3] Henry W. Nabeta,[3] Kabanda Taseera,[4] Charlotte Schutz,[5] Abdu Musubire,[3] Radha Rajasingham,[1,3] Darlisha A. Williams,[1,3] Friedrich Thienemann,[5] Conrad Muzoora,[4] Graeme Meintjes,[5,6] David B. Meya,[1,3,7] and David R. Boulware[1]**

[1]Department of Medicine, Medical School, and [2]Division of Biostatistics, School of Public Health, University of Minnesota, Minneapolis; [3]Infectious Diseases Institute, Makerere University, Kampala, [4]Internal Medicine, Faculty of Medicine, Mbarara University of Science and Technology, Uganda; [5]Institute of Infectious Disease and Molecular Medicine and Department of Medicine, University of Cape Town, South Africa; [6]Department of Medicine, Imperial College London, United Kingdom; and [7]School of Medicine, College of Health Sciences, Makerere University, Kampala, Uganda



Rolfes MA et al. Clin Infect Dis 2014 Dec;59:1607

# LP in Crypto Meningitis

- Most common cause of adult meningitis in Sub Saharan Africa
- Elevated ICP is associated with mortality
- Guidelines recommend frequent lumbar punctures
- Magnitude and impact of LP on CM related mortality are unknown

# Results

- 248 individuals with HIV-associated CM
- LP for diagnosis then for ICP≥ 250 mm$H_2O$ or new symptoms
- Compared survival till d 11 between those receiving 1 therapeutic LP vs none
- Death occurred in
  - 18% of pts with no LP
  - 7% among those with at least 1 therapeutic LP

  adjusted relative risk of mortality 0.31, 95% CI 0.12-.82

⇒**Therapeutic LPs were associated with a 69% relative improvement in survival, regardless of initial intracranial pressure**

Rolfes MA et al. Clin Infect Dis 2014 Dec;59:1607

# References


- **Marr KA et al. Ann Intern Med 2015 Jan;162:81**
- ***Raad II et al. Int J Antimicrob Agents 2015 Mar;45:283***
- **van Ingen J, et al. J Antimicrob Chemother 2015;70:178**
- ***Hachem R et al. J Antimicrob Chemother 2014 Nov; 69:3148***
- ***Ostrosky-Zeichner L et al. Clin Infect Dis 2014 May;58:1219***
- ***Benjamin DK Jr et al. JAMA 2014 May;311:1742***
- ***Bochennek K et al. J Antimicrob Chemother 2015 May; 70:1527***
- ***Vazquez Jet al. BMC Infect Dis 2014 Feb;14:97***
- ***Lorelle N et al. Clin Microbiol Infect 2014 Nov;20:O952***
- ***Schrenk KG et al. J Cancer Res Clin Oncol 2015 Mar [Epub ahead of print]***
- ***Fernández-Ruiz M et al. Clin Infect Dis 2014 May;58:1413***
- ***Li W et al. Future Microbiol 2015;10:161***
- ***Malani AN et al. Clin Infect Dis 2014 Aug;59:e61***
- ***Falci DR, Leuk Lymphoma 2015 Feb :1-6 [Epub ahead of print]***
- ***Chan TS et al. Ann Hematol 2014 Mar;93:493***
- ***Boulware DR et al. Engl J Med 2014 Jun;370:2487***
- ***Jarvis JN et al. Clin Infect Dis 2014 Mar;58:736***
- ***Rolfes MA et al. Clin Infect Dis 2014 Dec;59:1607***

# Alopecia and Nail Changes with Voriconazole

**Table 2. Alopecia and Nail Findings Associated With Voriconazole Therapy**

| Finding | Number (%)[a] (n = 152) |
|---|---|
| Presence of alopecia | 125 (82) |
| Scalp | 120 (96) |
| Extremities | 52 (42) |
| Eyebrows | 47 (38) |
| Eyelashes | 47 (38) |
| Underarms | 42 (34) |
| Pubic region | 36 (29) |
| Face | 23 (18) |
| Chest[b] | 15 (27) |
| Shaved less while taking voriconazole | 59 (47) |
| Required wig/hat | 19 (15) |
| Changes in nails | 106 (70) |
| Loss of nails | 15 (10) |

[a] Most patients had more than 1 site involved.

[b] Only men were asked about loss of chest hair (n = 56).

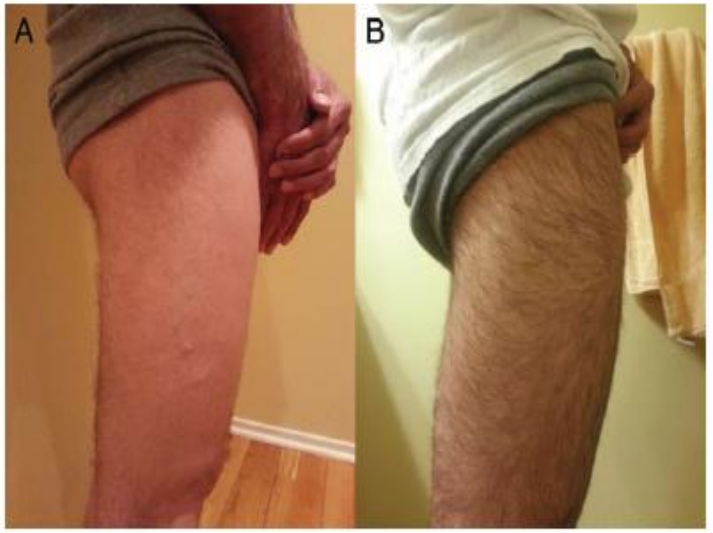



**Figure 1.** *A*, Voriconazole-associated alopecia is shown on the right leg of a 47-year-old man who had an epidural abscess associated with contaminated methylprednisolone injection. *B*, Three months after discontinuation of voriconazole, the alopecia had resolved.

Malani AN et al. Clin Infect Dis 2014 Aug;59:e61

Journal of Cancer Research and Clinical Oncology
March 2015

Date: 24 Mar 2015

# Efficacy of antifungal prophylaxis with oral suspension posaconazole during induction chemotherapy of acute myeloid leukemia

Karin G. Schrenk, Ulf Schnetzke, Katy Stegemann, Marie von Lilienfeld-Toal, Andreas Hochhaus, Sebastian Scholl

- In 70 AML pts with induction chemoRx , assessed:

- Incidence of IFD classified as proven, probable or possible
- Antifungal therapy including empiric treatment in high-risk patients
- Tolerability of posaconazole

- Posaconazole was well tolerated, had to be stopped in 6 pts
- Overall incidence of IFD was 30 %
- 55.7 % (Including pts classified as possible IFD) underwent at least first-line antifungal treatment

**=> frequent necessity of systemic antifungal treatment despite prophylaxis with oral suspension posaconazole**

Schrenk KG et al. J Cancer Res Clin Oncol 2015 Mar [Epub ahead of print]

# Risk Stratification

- Pts were divided into standard-risk and high-risk groups and treated with IV caspofungin for either 1 or 2 weeks, followed by oral voriconazole
- Favorable responses occurred in 75.9% of pts
- no significant differences in response rates between pts receiving 1 or 2 weeks in the standard-risk group

In the high-risk group, response rates were significantly higher in the 2-week than the 1-week treatment group

Li W et al. Future Microbiol 2015;10:161