The evolving fungal landscape

New developments, challenges and approaches

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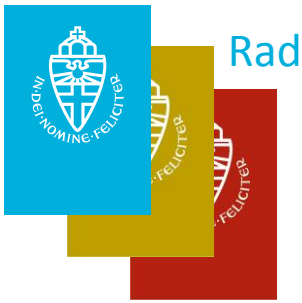

Radboud Center for Infectious Diseases

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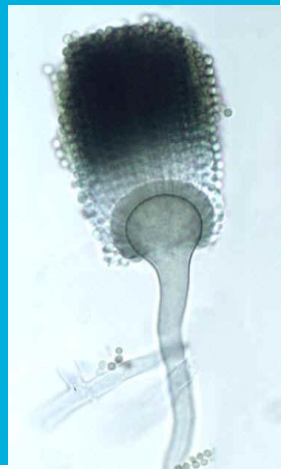
Aspergillus infections in the ICU

Changing epidemiology –
Aspergillosis in ICU patients



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Increasing incidence of invasive Aspergillosis in the ICU: Risk Stratification

- High Risk
  - Neutropenia
  - Hematological malignancy
  - Stem cell transplant
- Intermediate Risk – ICU patients

Meersseman et al. Clin Infect Dis 2007

Increasing incidence of invasive Aspergillosis in the ICU: Risk Stratification

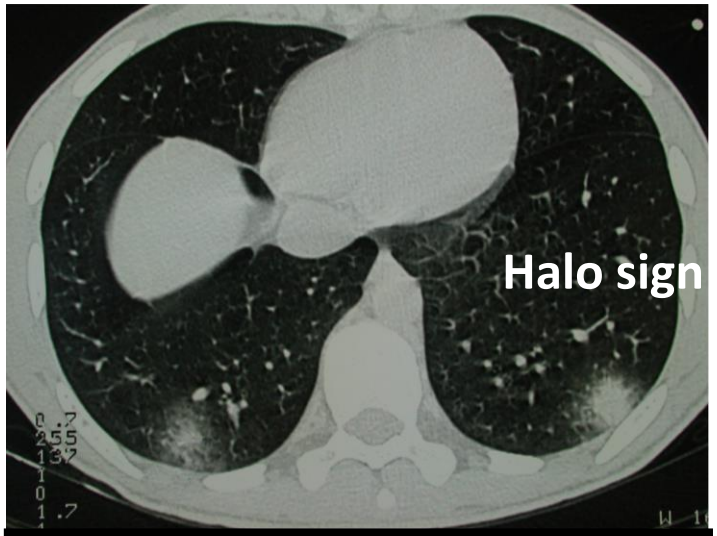
- High Risk
  - Neutropenia
  - Hematological malignancy
  - Stem cell transplant
- Intermediate Risk
  - Corticosteroids !
  - Severe influenza (H1N1) in the ICU !
  - COPD
  - Immunosuppressants for systemic disease
  - Liver cirrhosis
  - Solid organ cancer
  - HIV
  - Lung transplant
- Low Risk
  - Heart/kidney/liver transplant
  - Malnutrition
  - Prolonged ICU stay

Meersseman et al. Clin Infect Dis 2007

Invasive aspergillosis

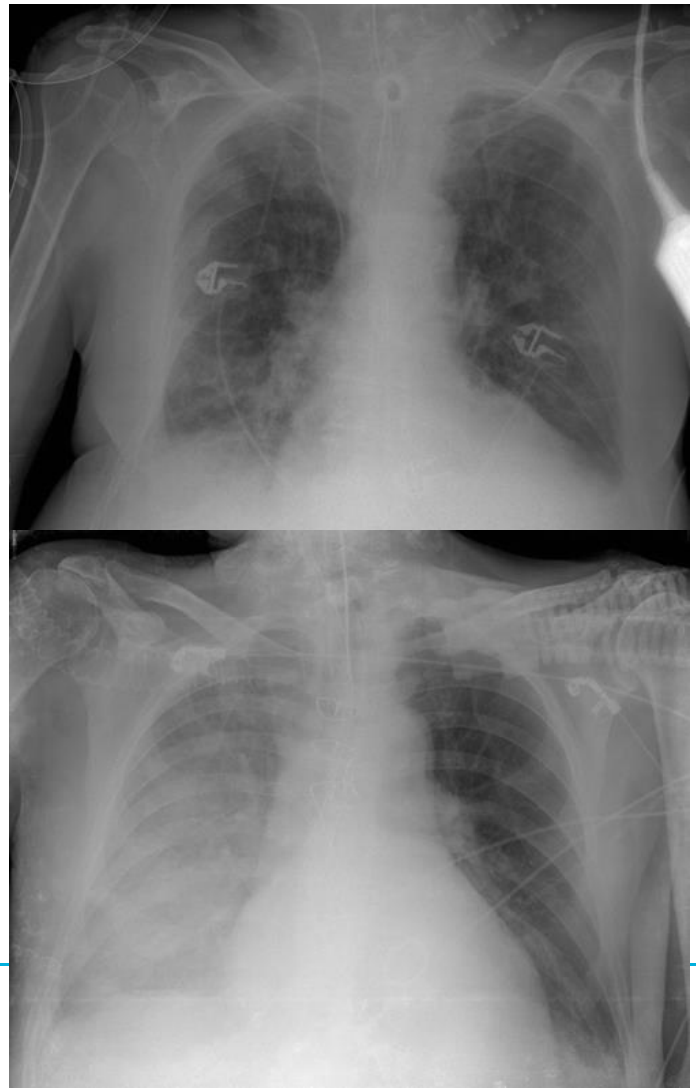
Hemato-oncology

Typical signs



ICU patients

Nonspecific



Greene et al.
Clin Infect Dis 2007

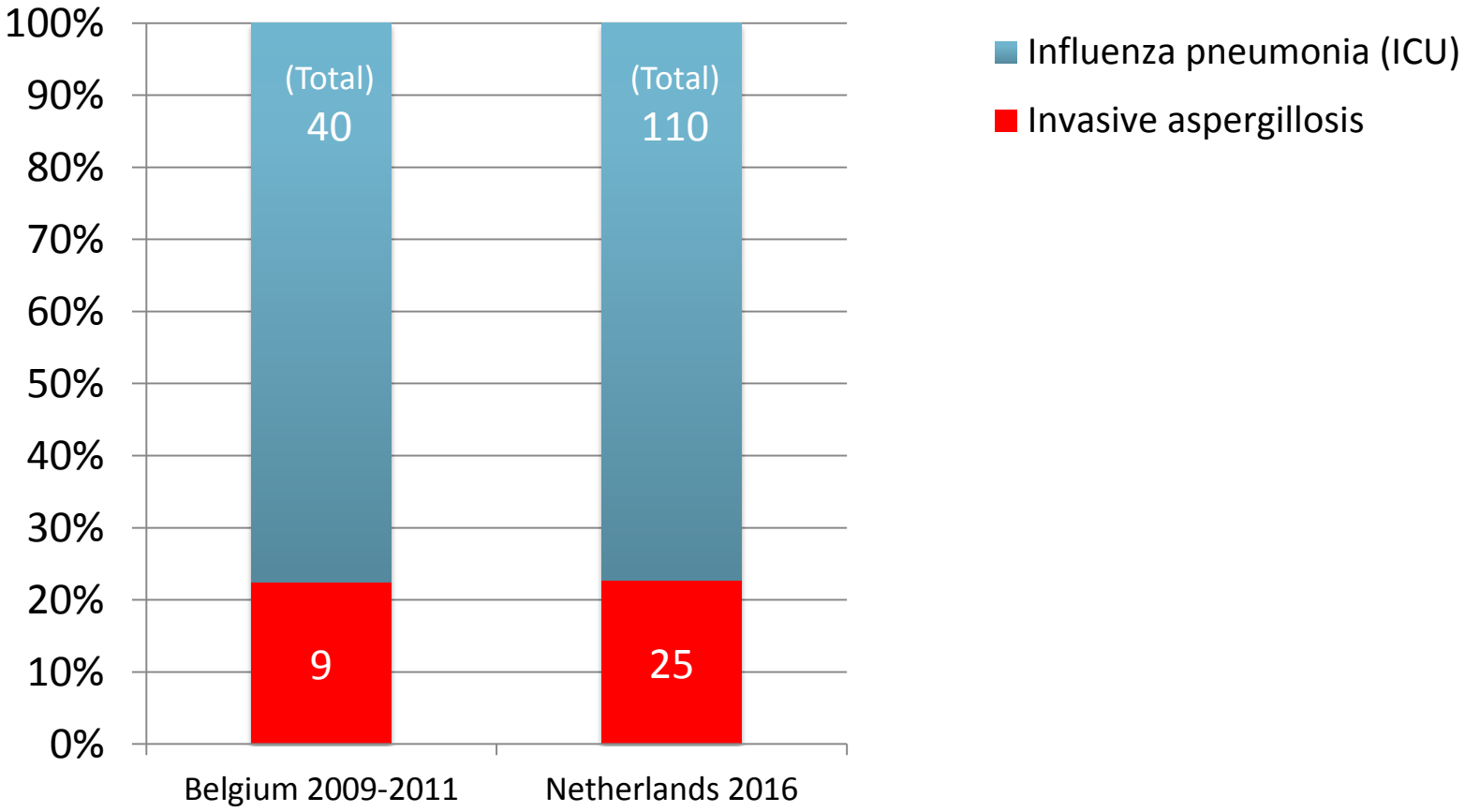
Aspergillosis in ICU patients: BAL Galactomannan

	Proven Invasive Aspergillosis	No Aspergillosis	
N	26	46	
BAL culture/stain positive	15 (58%)	14 (30%)	Specificity 70%
Serum Galactomannan positive	11 (42%)	3 (7%)	
BAL Galactomannan positive	23 (88%)	6 (13%)	Sensitivity 88% Specificity 87%

GM cutoff: 0.5

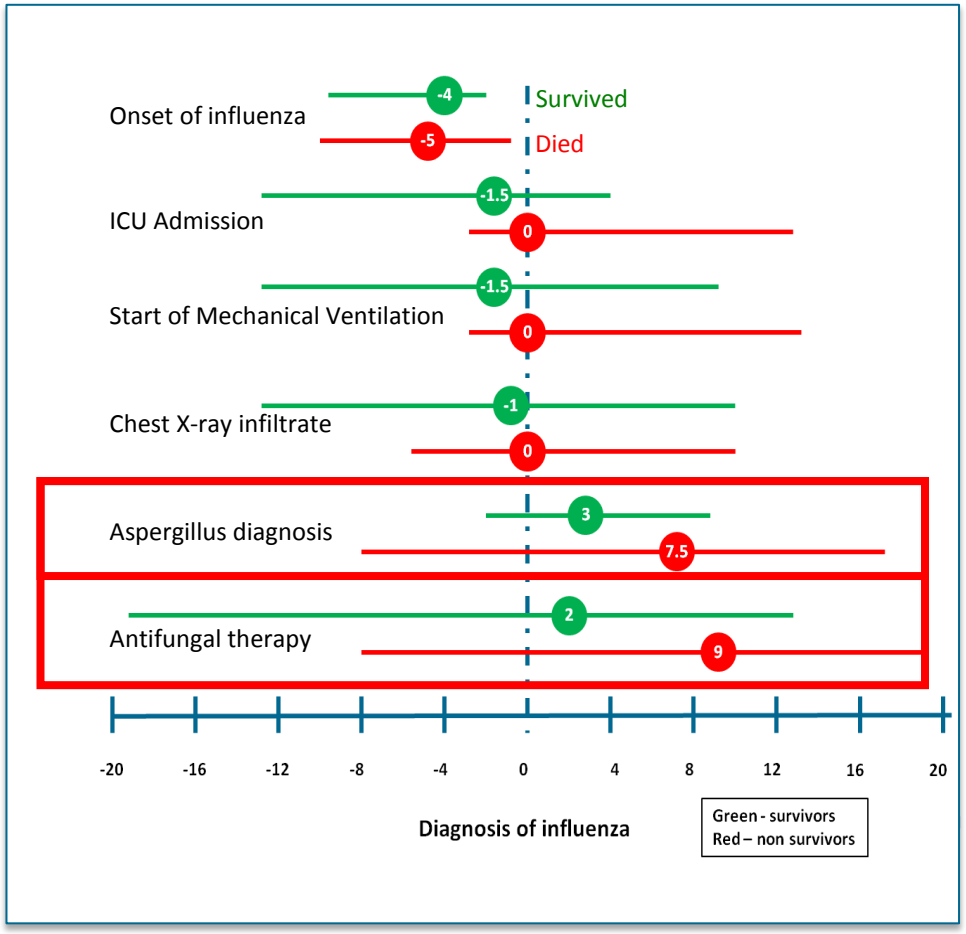
Meersseman et al. AJRCCM 2008

H1N1 Influenza and Invasive Aspergillosis in the ICU



Wauters et al, Intens Care Med 2012
Van de Veerdonk et al, 2016 *submitted*

H1N1 Influenza and Invasive Aspergillosis in the ICU



Netherlands, 2016 flu season

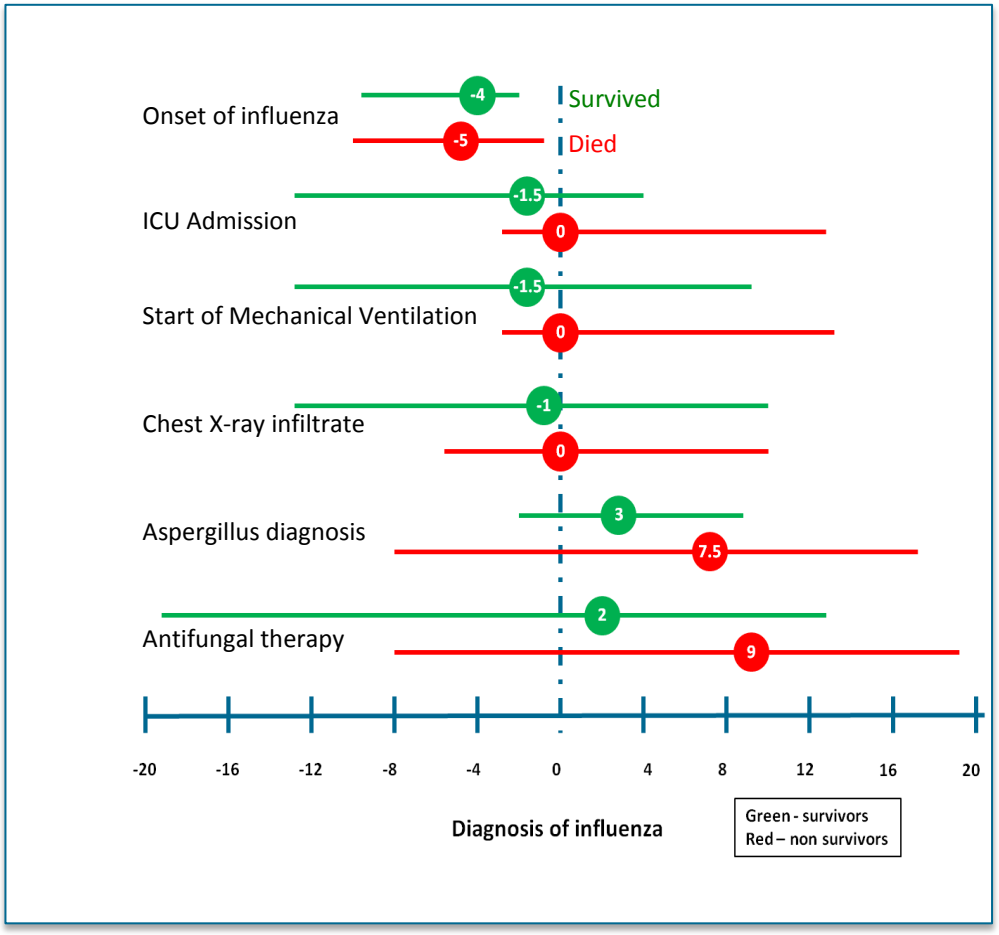
- 8 University Medical Centers
- 110 confirmed influenza pneumonias in ICU
- 25 proven/probable invasive aspergillosis (EORTC-MSG criteria)

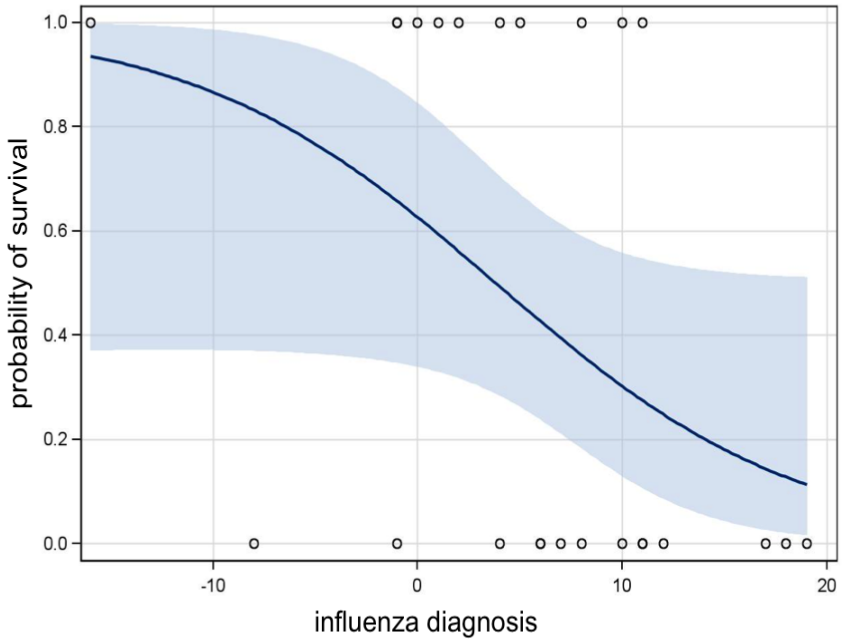
- Corticosteroid use, 80%
- Sensitivity:
  - ✓ BAL culture 84%
  - ✓ BAL Galactomannan 89%
  - ✓ Serum Galactomannan 67%

- Mortality 56%
- Azole resistance, 31%

Wauters et al, Intens Care Med 2012
Van de Veerdonk et al, 2016 *submitted*

H1N1 Influenza and Invasive Aspergillosis in the ICU





time (days) between influenza diagnosis and antifungal therapy

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Van de Veerdonk et al, 2016 *submitted*

Diagnosis of invasive aspergillosis in the ICU: BAL Galactomannan and risk factors

Positive culture
+
Risk factor (COPD, steroids, influenza)
+
Any sign (e.g., infiltrate)

=

Obtain BAL Galactomannan
+
Treat

Positive BAL Galactomannan
+
Risk factor (COPD, steroids, influenza)

=
Treat

Isavuconazole equivalent to voriconazole for invasive aspergillosis

Isavuconazole versus voriconazole for primary treatment of invasive mould disease caused by *Aspergillus* and other filamentous fungi (SECURE): a phase 3, randomised-controlled, non-inferiority trial

Johan A Maertens, Issam I Raad, Kieren A Marr, Thomas F Patterson, Dimitrios P Kontoyiannis, Oliver A Cornely, Eric J Bow, Galia Rahav, Dionysios Neofytos, Mickael Aoun, John W Baddley, Michael Giladi, Werner J Heinz, Raoul Herbrecht, William Hope, Meinolf Karthaus, Dong-Gun Lee, Olivier Lortholary, Vicki A Morrison, Ilana Oren, Dominik Selleslag, Shmuel Shoham, George R Thompson III, Misun Lee, Rochelle M Maher, Anne-Hortense Schmitt-Hoffmann, Bernhardt Zeiher, Andrew J Ullmann

Voriconazole 6mg/kg bid→4mg/kg bid or 200 po bid vs. Isavuconazole 200mg tid x2d→200mg qd iv or po

	Isavuconazole	Voriconazole	Δ (95%CI)
ITT population (proven/prob/possible IA)	258	258	
Mortality (6wk; primary outcome)	19%	20%	-1.6% (-7.8, 5.7) *P*>0.05
mITT population (proven/prob IA)	143	129	
Mortality (6wk)	20%	23%	-2.6% (-12.2, 6.9)
Overall Response (EOT)	35%	36%	1.6% (-9.3, 12.6)
Drug-related adverse events	42%	60%	*P* < 0.001
• Hepatobiliary • Eye • Skin/SCT	9% 15% 33%	16% 27% 42%	*P* = 0.016 *P* = 0.002 *P* = 0.037

Maertens et al, Lancet 2016; 387: 760-9

Combination therapy for invasive aspergillosis

Annals of Internal Medicine

Combination Antifungal Therapy for Invasive Aspergillosis

A Randomized Trial

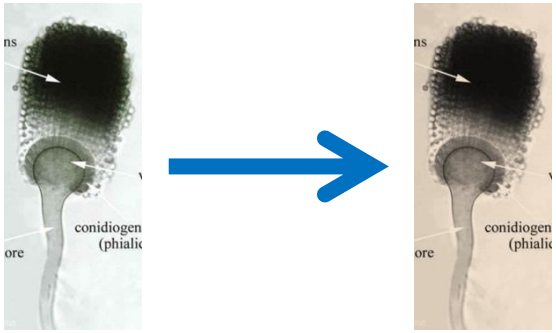
MITT analysis	Voriconazole + anidulafungin	Voriconazole	Δ (95%CI)
n	135	142	
Mortality (6wk; primary outcome)	19.5%	27.8%	-8.3% (-19, 1.5) *P*=0.087
Mortality (12wk)	29.3%	39.4%	-10.1% (-21.4,1.1) *P*=0.077
Post-hoc analysis Galacomannan-positive pts	**Voriconazole + anidulafungin**	**Voriconazole**	**Δ (95%CI)**
n	108	110	
Mortality (6wk)	15.7%	27.3%	-11.6% (-22.7, -0.4) *P*=0.037
Multivariate analysis			HR 2.71 (1.32, 5.56) *P*=0.007

Marr et al, Ann Intern Med 2015; 162: 81-89

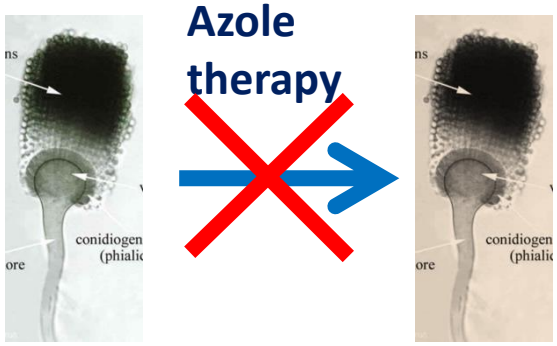
Azole-Resistant *Aspergillus* strains

Environmental Route

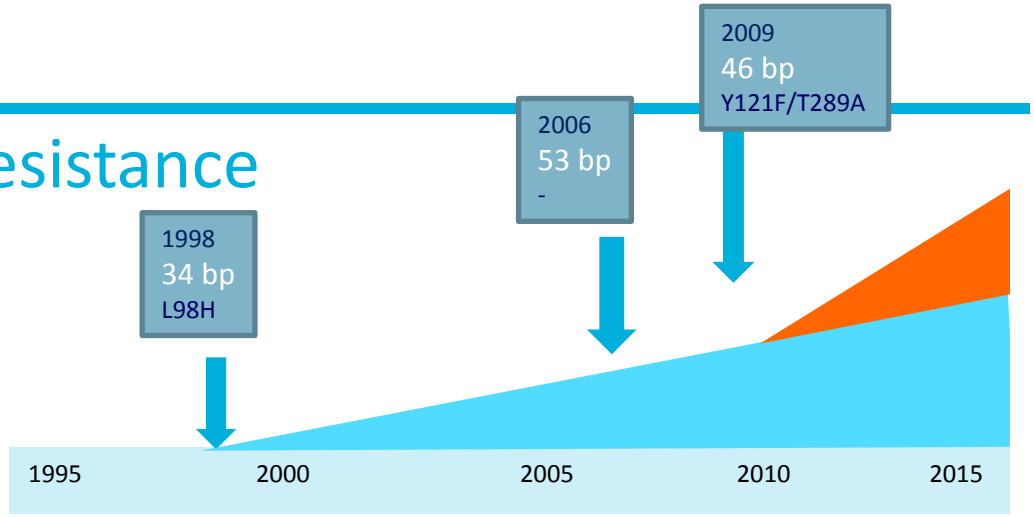
Hospital Route

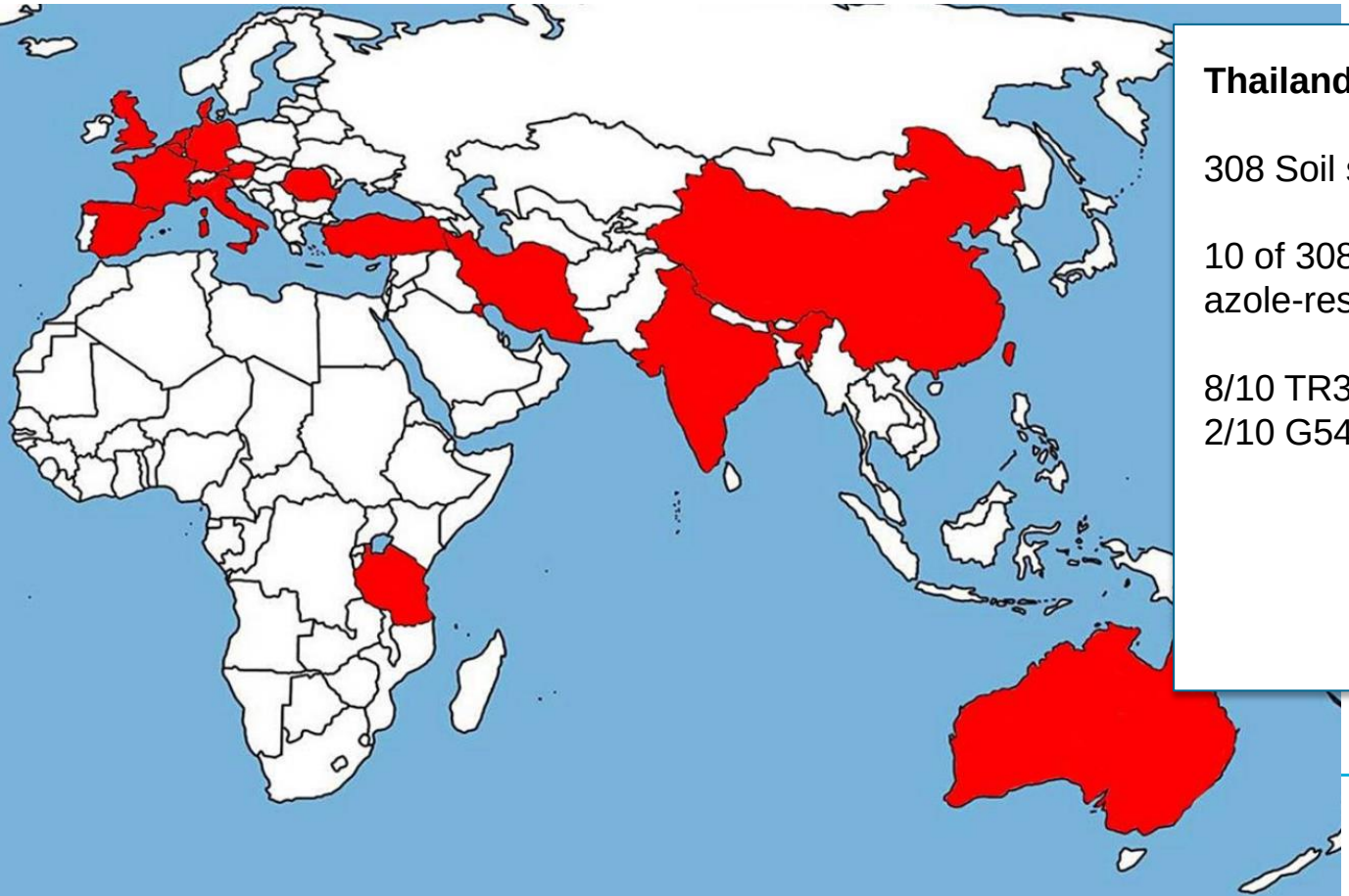


TR_{34}/L98H
TR_{53}
TR_{46}/Y121F/T289A



Aspergillosis – Azole resistance





Thailand 2016

308 Soil samples collected

10 of 308 (3.25%) *A. fumigatus* azole-resistant

8/10 TR34/L98H
2/10 G54R

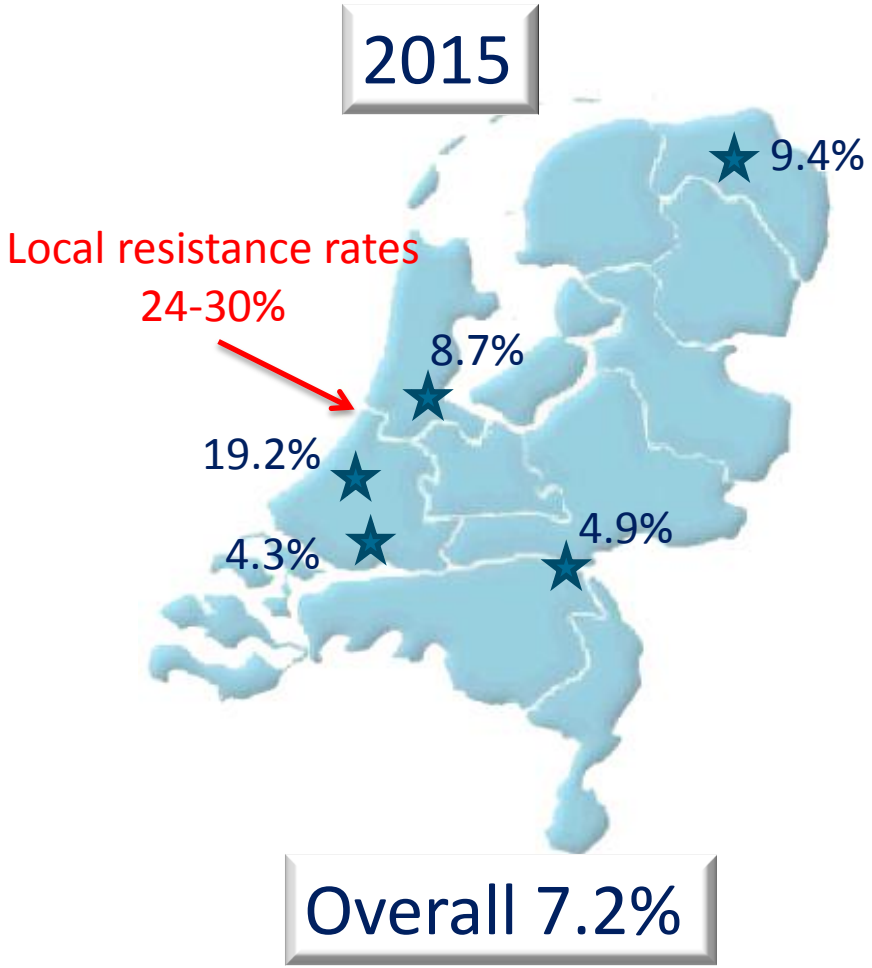
Tangwattanachuleeporn et al.
Med Mycol 2016, in press

Verweij PE, Chowdhary A, et al.
Clin Infect Dis 2016; 62: 362–8

Azole resistant *Aspergillus* spp

NethMap 2015

Consumption of antimicrobial agents and antimicrobial resistance among medically important bacteria in the Netherlands



Environmental sampling – Resistant *Aspergillus* strains

Think Aspergillus

- Invasive aspergillosis in apparently immunocompetent ICU patients
  - COPD, corticosteroids and severe influenza as emerging risk factors
- BAL galactomanan is the preferred diagnostic technique in the ICU
- Voriconazole or isavuconazole are therapy of choice
  - Voriconazole + echinocandin for severe cases
  - L-AmB second line therapy
- Increasing azole resistance rates – Also in SE-Asia

Cryptococcus

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Combination antifungal therapies for HIV-associated cryptococcal meningitis

THE LANCET

Combination antifungal therapies for HIV-associated cryptococcal meningitis: a randomised trial

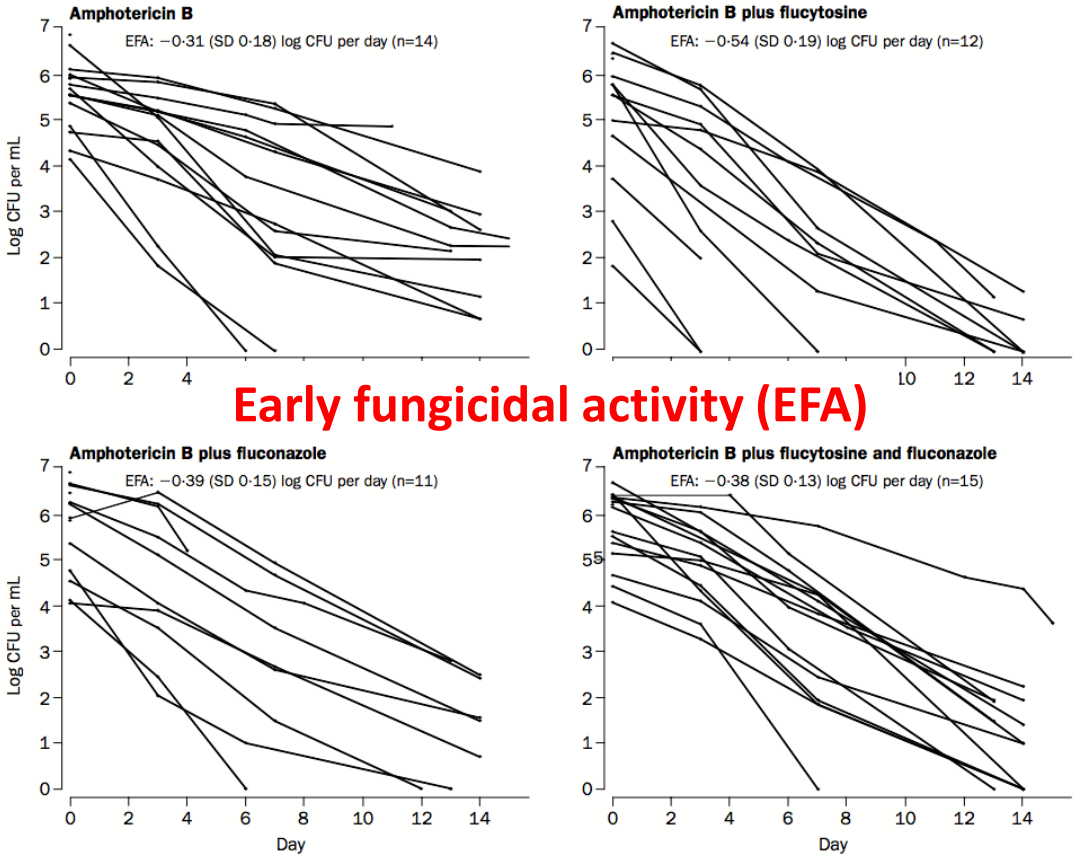
Annemarie E Brou
Thomas S Harrisor

holas J White,

Summary

Background It fre
drug treatments
cerebrospinal fluid
support to the us
flucytosine, and flu
We compared the f
drugs for initial t
meningitis.

non and often fatal
nfected individuals,
northeast Thailand,
to tuberculosis as an
hospital, mortality of
coccal meningitis was
of 14 days, despite
s of amphotericin B.[2]
lain this high acute



Early fungicidal activity (EFA)

Figure 3: **Fall in CSF CFU over time by treatment group**

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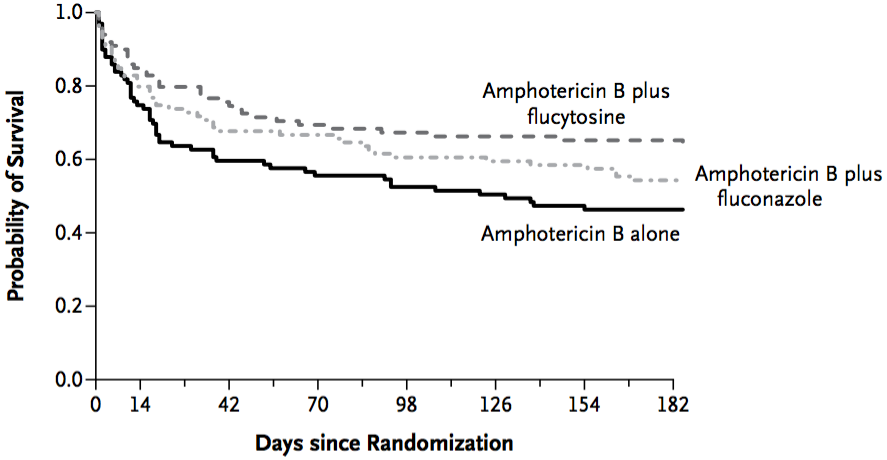
Brouwer AE, et al.
Lancet 2004; 363: 1764-7

Combination antifungal therapies for HIV-associated cryptococcal meningitis



No. at Risk								
Amphotericin B alone	99	74	59	54	51	49	46	30
Amphotericin B plus flucytosine	100	84	73	67	64	63	62	46
Amphotericin B plus fluconazole	99	79	67					

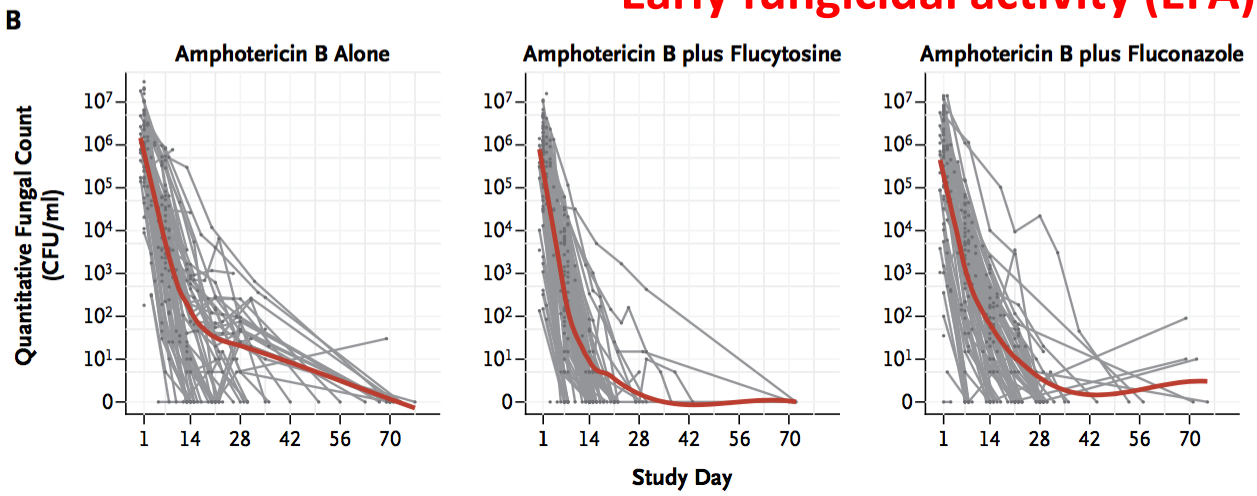
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Combination Antifungal Therapy for Cryptococcal Meningitis

my N. Day, M.D., Ph.D., Tran T.H. Chau, M.D., Ph.D., Marcel Wolbers, Ph.D., Pham P. Mai, M.D., Nguyen T. Dung, M.D., Nguyen H. Mai, M.D., Ph.D., Nguyen H. Phu, M.D., Ph.D., Ho D. Nghia, M.D., Ph.D., Nguyen D. Phong, M.D., Ph.D., Cao Q. Thai, M.D., Le H. Thai, M.D., Ly V. Chuong, M.D., Dinh X. Sinh, M.D., Van A. Duong, B.Sc., hu N. Hoang, M.Sc., Pham T. Diep, B.Sc., James I. Campbell, M.I.B.M.S., n P.M. Sieu, M.D., Stephen G. Baker, Ph.D., Nguyen V.V. Chau, M.D., Ph.D., Tran T. Hien, M.D., Ph.D., David G. Lalloo, M.D., and Jeremy J. Farrar, M.D., D.Phil.

Early fungicidal activity (EFA)



Day J, et al. N Engl J Med 2013; 368: 1291-302

Timing of antiretroviral therapy after diagnosis of cryptococcal meningitis

- Randomized trial in Uganda & South Africa (COAT trial)

  ART initiation within 2 weeks vs. > 5 weeks

  HIV-infected patients with documented cryptococcal meningitis

  R/ Amphotericin B 0.7-1.0 mg/kg/d + fluconazole 800 mg/d

- Planned enrollment n=500

  Terminated early by DSMB after 177

- Primary endpoint: 26 weeks' mortality

Early ART	40/88 (45%)
Deferred ART	27/89 (30%)

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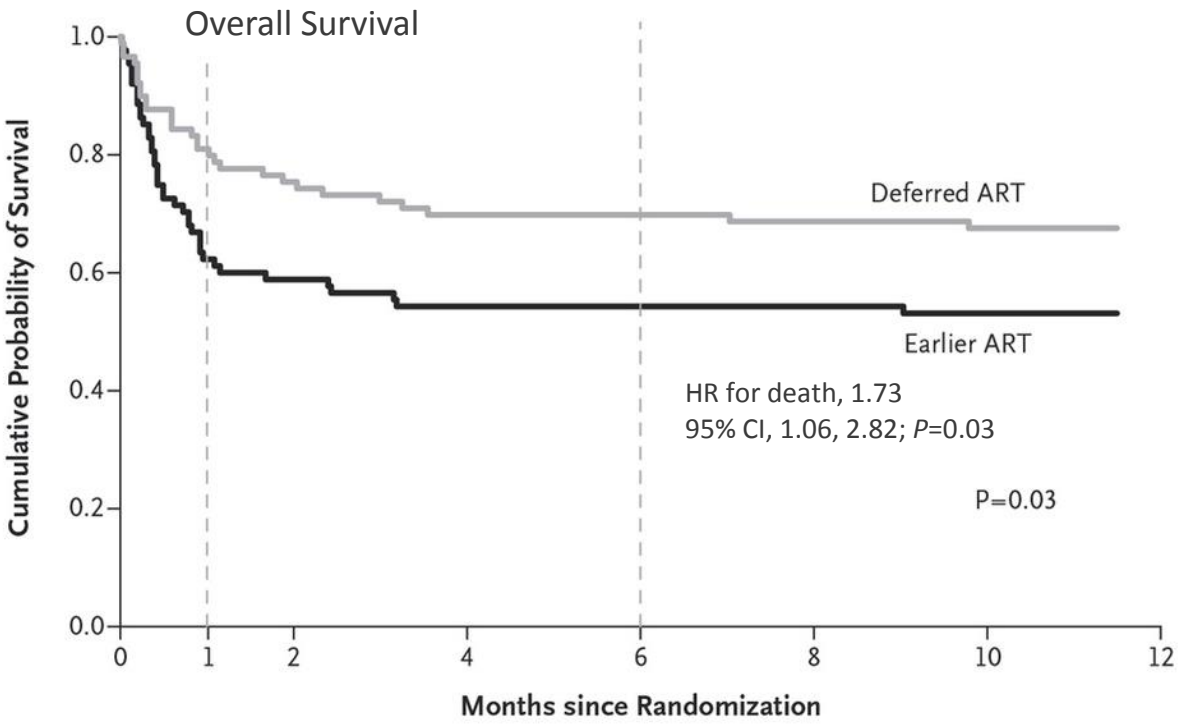
ART, Antiretroviral Therapy
DSMB, Data Safety Monitoring Board

Boulware DR, et al. N Engl J Med 2014;370:2487–98

Timing of antiretroviral therapy after diagnosis of cryptococcal meningitis



- Deferring ART until 5 weeks after start of AmB improves survival
- Highest death risk in patients with low CSF white cell counts and early ART
- Adverse effect of early ART probably related to IRIS

Boulware DR, et al. N Engl J Med 2014;370:2487–98

Adjunctive Dexamethasone in HIV-Associated

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Adjunctive Dexamethasone in HIV-Associated Cryptococcal Meningitis

J. Beardsley, M. Wolbers, F.M. Kibengo, A.-B.M. Ggayi, A. Kamali, N.T.K. Cuc, T.Q. Binh, N.V.V. Chau, J. Farrar, L. Merson, L. Phuong, G. Thwaites, N. Van Kinh, P.T. Thuy, W. Chierakul, S. Siriboon, E. Thiansukhon, S. Onsanit, W. Supphamongkholchaikul, A.K. Chan, R. Heyderman, E. Mwinjiwa, J.J. van Oosterhout, D. Imran, H. Basri, M. Mayxay, D. Dance, P. Phimmasone, S. Rattanavong, D.G. Lalloo, and J.N. Day, for the CryptoDex Investigators*

ABSTRACT

BACKGROUND

Cryptococcal meningitis associated with human immunodeficiency virus (HIV) infection causes more than 600,000 deaths each year worldwide. Treatment has changed little in 20 years, and there are no imminent new anticryptococcal agents. The use of adjuvant glucocorticoids reduces mortality among patients with other forms of meningitis in some populations, but their use is untested in patients with cryptococcal meningitis.

METHODS

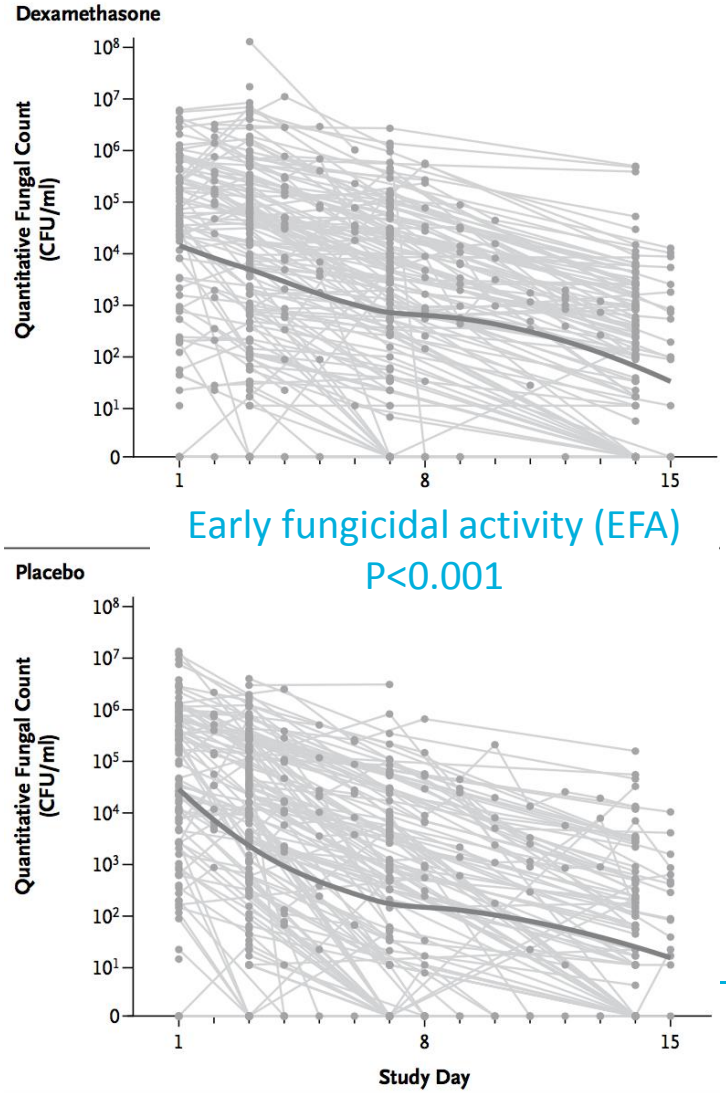
In this double-blind, randomized, placebo-controlled trial, we recruited adult patients with HIV-associated cryptococcal meningitis in Vietnam, Thailand, Indonesia, Laos, Uganda, and Malawi. All the patients received either dexamethasone or placebo for 6 weeks, along with combination antifungal therapy with amphoteri-

- Randomized trial in SE-Asia & Africa (CryptoDex trial)
  Dexamethasone vs. placebo x6 wk
- HIV-infected patients with documented cryptococcal meningitis
  R/ Amphotericin B 1.0 mg/kg + fluconazole 800 mg
- Planned enrollment n=880
  Terminated early by DSMB after 451
- Primary endpoint: 10 weeks' mortality

Dexamethasone	47%
Placebo	41%

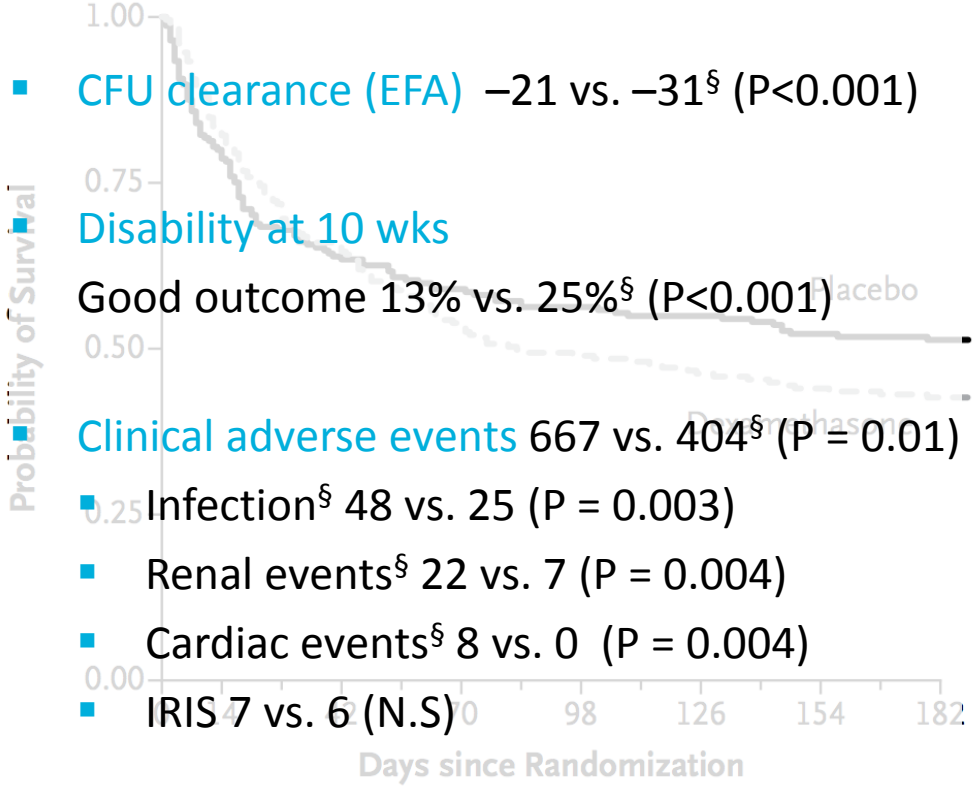
Beardsley J, et al. N Engl J Med 2016;374:542-54

Adjunctive Dexamethasone in HIV-Associated Cryptococcal Meningitis



Early fungicidal activity (EFA)
P<0.001

- Survival at 10 weeks and 6 months
  N.S.



- CFU clearance (EFA) –21 vs. –31§ (P<0.001)
- Disability at 10 wks
  Good outcome 13% vs. 25%§ (P<0.001)
- Clinical adverse events 667 vs. 404§ (P = 0.01)
  - Infection§ 48 vs. 25 (P = 0.003)
  - Renal events§ 22 vs. 7 (P = 0.004)
  - Cardiac events§ 8 vs. 0 (P = 0.004)
  - IRIS 7 vs. 6 (N.S)

§ Dexamethasone vs. Placebo

Beardsley J, et al. N Engl J Med 2016;374:542-54

HIV-associated cryptococcal meningitis

- Early fungicidal activity (EFA) in a marker of treatment efficacy.

- AmB + flucytosine is associated with lower mortality than AmB monotherapy.
- AmB + fluconazole is an acceptable alternative.

- Deferred (>5 wks) inititation of ART is associated with lower mortality.

- Dexamethasone does not improve survival and is associated with slower fungal clearance, and higher adverse events and disablility rates.

Brouwer AE, et al. Lancet 2004; 363: 1764-7; Day J, et al. N Engl J Med 2013; 368: 1291-302; Boulware DR, et al. N Engl J Med 2014; 370: 2487–98; Beardsley J, et al. N Engl J Med 2016;374:542-54

Mucormycosis

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Treatment of Mucormycosis

- Background
  - ✓ Mucormycosis associated with 40% mortality (Haem. malignancy, SOT, DM, trauma)
  - ✓ Amphotericin B, posaconazole, isavuconazole are the only active agents

Lanternier et al. J Antimicrob Chemother 2015; 70: 3116-23

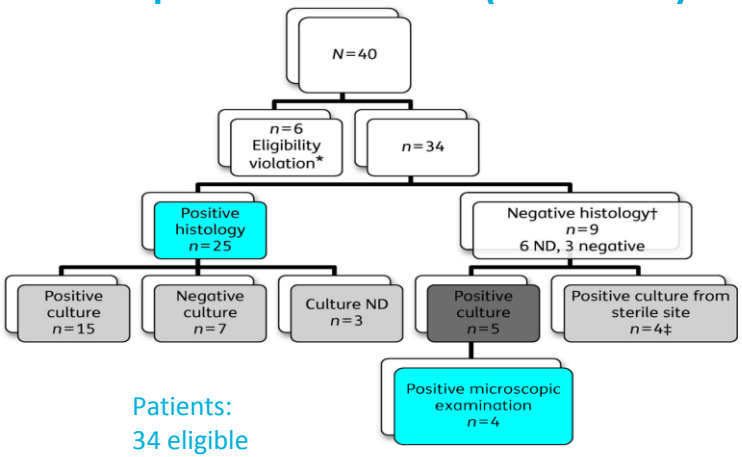
Prospective pilot study of high-dose (10 mg/kg/day) liposomal amphotericin B (L-AMB) for the initial treatment of mucormycosis

- Background
  - ✓ Mucormycosis associated with 40% mortality (Haem. malignancy, SOT, DM, trauma)
  - ✓ Amphotericin B, posaconazole, isavuconazole are the only active agents
  - ✓ High-dose L-AmB suggested in animal model (Lewis 2010), and in Phase I-II (Walsh 2001)

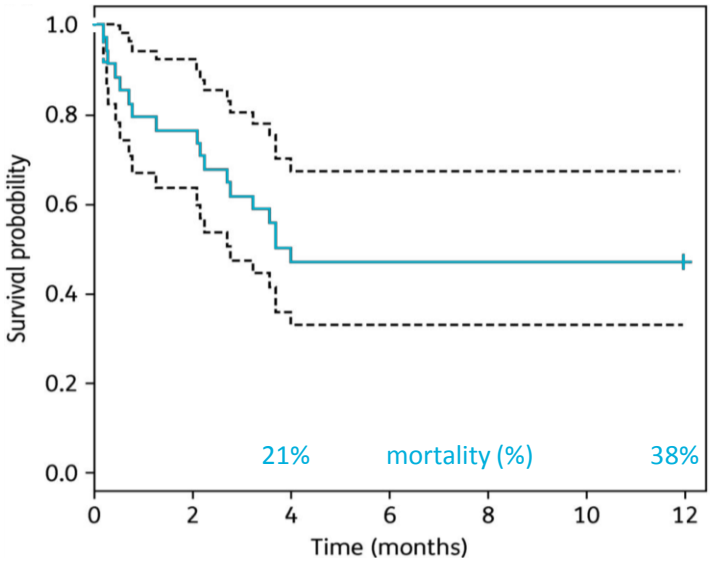
- Methods
  - ✓ Prospective open label study of L-AmB 10 mg/kg/day x 4 weeks in patients with proven/probable Mucormycosis (+/- surgery)
  - ✓ Primary endpoint: Overall response at Week 4
  - ✓ Single arm, open label; powered for a precision of ±15%, N=44

Lanternier et al. J Antimicrob Chemother 2015; 70: 3116-23

Prospective pilot study of high-dose (10 mg/kg/day) liposomal amphotericin B (L-AMB) for the initial treatment of mucormycosis



Patients:
34 eligible
29 proven (85%)
9 probable



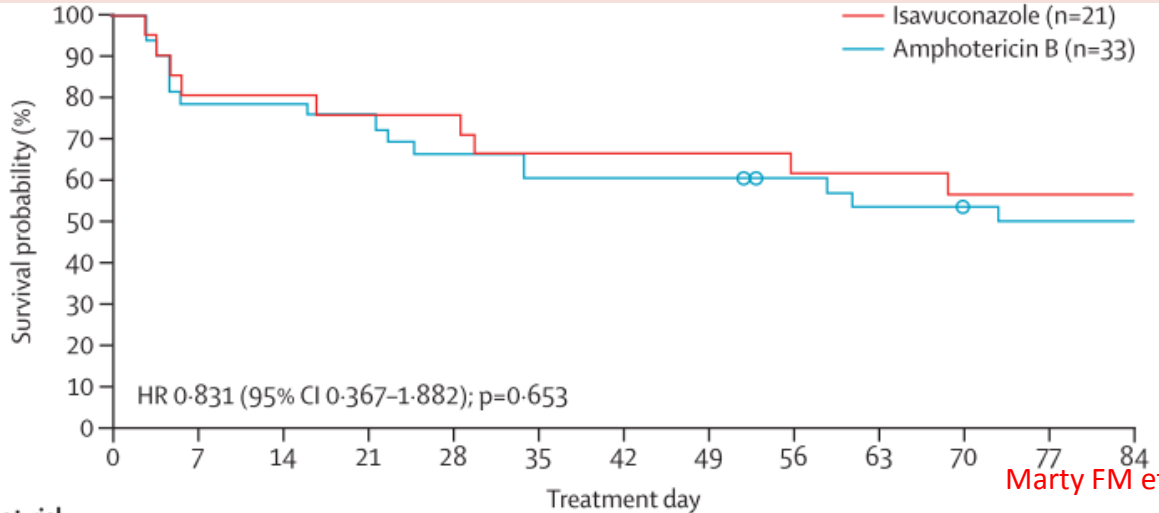
Proven/probable mucor	Week 4	Week 12
Primary endpoint, Response	12/33 (36%)	14/31 (45%)
– complete response	6	10
– partial response	6	4
Mortality	21%	38%
Creatinine doubling	16/40 (40%)	
– Treatment interruption	5	
– Treatment discontinuation	1	

Lanternier et al. J Antimicrob Chemother 2015; 70: 3116-23

An Open-Label Phase 3 Study of Isavuconazole (VITAL):

- Phase 3 open label trial of isavuconazole for rare fungi (EORTC/MSG)
- Primary or salvage therapy – ISA 200mg qd (loading 200mg tid, days 1-2), maximum 180 days
- Of 149 patients enrolled, 37 mucormycosis (32 proven, 5 probable)
- Matched historical controls (AmB)

	Isavuconazole	Amphotericin B	p value
Crude all-cause mortality, n/N (%; 95% CI)*	7/21 (33%; 14·6–57·0)	13/33 (39%; 22·9–57·9)	p=0·775†
Weighted all-cause mortality (%;‡ 95% CI)*	33%; 13·2–53·5	41%; 20·2–62·3	p=0·595§
Crude mortality by matching covariates, n/N (%)			
Haematological malignancy	5/11 (45%)	7/18 (39%)	NA
Severe disease¶	6/12 (50%)	8/13 (62%)	NA
Surgical treatment‖	4/9 (44%)	3/13 (23%)	NA



Marty FM et al. Lancet Infect Dis 2016; 16: 828-37

Candidemia and Invasive Candidiasis

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Invasive candidiasis

- ✓ Prophylaxis or early detection of candidiasis in the ICU

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Candida prophylaxis trials in the ICU

Reference	Patient selection	Invasive candidiasis (prophylaxis/controls)	Mortality (prophylaxis/controls)
Ostrosky-Zeichner 2014	186/16,000 high risk, Selected by prediction rule	10% / 17% *P* = 0.14	17% / 14% *N.S*
Pelz 2001	260/1282 high-risk, >3 days ICU	8.5% / 15% *P* = 0.01	11% / 12% *N.S.*
Garbino 2002	220/5241 highest risk, >3 days ICU, ventilated >2d	4% / 10% *P* = 0.02	39% / 41% *N.S.*
Eggimann 1999	49 extremely high risk, Intestinal suture leak requiring relaparotomy	2% / 9% *P* = 0.06	30% / 50% *N.S*

Ostrosky-Zeichner L, et al. Clin Infect Dis 2014; 58(9):1219–26

Candida prophylaxis trials in the ICU

Reference	Patient selection	Invasive candidiasis (prophylaxis/controls)	Mortality (prophylaxis/controls)
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Garbino 2002	220/5241 highest risk, >3 days ICU, ventilated >2d	4% / 10% *P* = 0.02	39% / 41% *N.S.*
Eggimann 1999	49 extremely high risk, Intestinal suture leak requiring relaparotomy	2% / 9% *P* = 0.06	30% / 50% *N.S*

Ostrosky-Zeichner L, et al. Clin Infect Dis 2014; 58(9):1219–26

Conclusion: No support for antifungal prophylaxis among IC patients other than high-risk groups previously identified in the guidelines

How to select patients for empirical therapy?

Patients admitted to ICU for >7 days (Spain)

Risk factors for developing invasive candidiasis

Develop *Candida score*

Multifocal colonization	1 point
Total Parenteral Nutrition	1 point
Surgery	1 point
Severe sepsis	2 points

- If ≥ 3 points → start treatment
- Sensitivity 60-80%, specificity 74-86%

León et al, Crit Care Med 2006

León et al, Crit Care Med 2009

Predictive models depend on prevalence of candidiasis

- Geographical variability in epidemiology of IC, case-mix & medical practices
- Validation in Australia:

	León model *Candida score*	
	As reported in Spain (prevalence = 5.8%)	Applied to Australian data (prevalence = 0.2 to 2%)
Sensitivity	81%	15-26%
Specificity	74%	98%
Positive predictive value (PPV)	16%	2%
Negative predictive value (NPV)	98%	98%
Comments		Application to patients with ICU LOS ≥7d excludes ⅓-½ cases

Playford et al. Int Care Med 2009

Candida Biomarkers – Not ready for prime time

Single or combined biomarker screening in prospective ICU cohort (candidiasis incidence, 13%)

Patients with (medical or surgical) severe abdominal condition, and expected ICU stay ≥7 days

	Controls			Infected	
	Not colonized	Low-grade colonized	High-grade colonized	Intra-abdominal candidiasis	Candidemia
	N = 48	*N* = 130	*N* = 24	*N* = 20	*N* = 11
BDG ≥ 80 pg/mL, no. (%)	16/46 (34.8)[a]	50/124 (40.3)[a]	17/24 (70.8)[b]	15/20 (75.0)[b]	8/10 (80.0)[b]
CAGTA positive, no. (%)	10/47 (21.3)[a]	44/128 (34.4)[a]	17/24 (70.8)[b]	8/20 (40.0)[a,b]	8/10 (80.0)[b]
Mannan-Ag positive, no. (%)	10/48 (20.8)[a]	40/127 (31.5)[a]	15/24 (62.5)[b]	8/20 (40.0)[a,b]	5/10 (50.0)[a,b]
Mannan-Ab positive, no. (%)	6/48 (12.5)	12/128 (9.4)	4/24 (16.7)	5/20 (25.0)	3/11 (27.3)
C-PCR positive, no. (%)	14/23 (60.9)	37/54 (68.5)	6/8 (75.0)	12/14 (85.7)	9/11(81.8)

- Single assays are highly nonspecific (≈80% of positive results are false)
- Sensitivity is not good enough in high-risk population (≈50% of cases are missed)
- With positive test: chance of candidiasis approx. 1/5 (without testing: 1/7 =13%)

Combining 2 or 3 assays

- "Best" combined assays still is highly nonspecific (81% of positives are false)
- Sensitivity still too low for targeted testing in very high risk (≈30% of cases missed)
- A negative test does not rule out candidiasis in a high-risk patient

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BDG, ß-D-glucan
CAGTA, Candida albicans germ tube antibodies
Mannan Ag, antigen; Ab, antibodies
C-PCR, *Candida* multiplex real time whole blood qPCR

León et al, Crit Care 2016; 20: 149

Empiric echinocandin therapy in ICU patients following surgery for intraabdominal infection (INTENSE)

Randomized, double-blind, multicenter study of micafungin vs. placebo

- Adult patients ≥48h in ICU
- Intraabdominal infection (community- or hospital-acquired)
- Requiring surgery and ICU stay
- Exclusion: e.g., acute pancreatitis, CAPD, organ transplant, *documented* invasive candidiasis

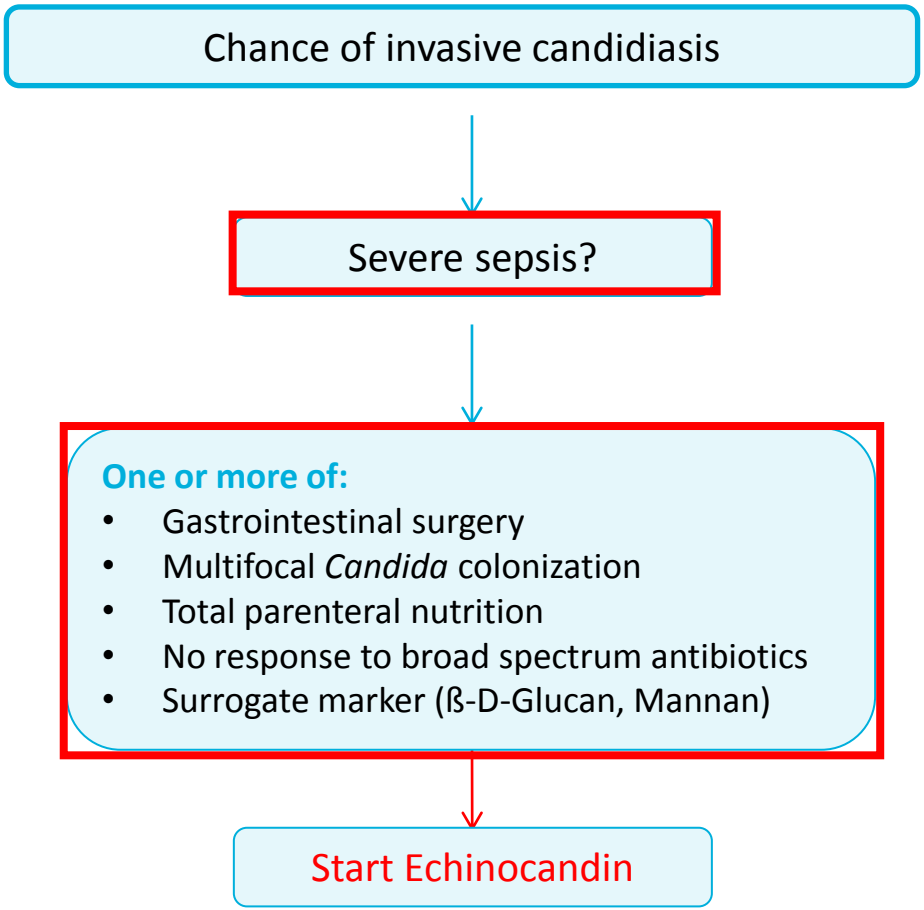
Randomized, N=252	Micafungin	Placebo	Difference (CI)
Baseline invasive candidiasis	5	2	
Full analysis cohort No baseline candidiasis, ≥1 dose	124	117	
Proven invasive candidiasis (IDRB)	11.1%	8.9%	2.24 (-5.52, 10.20)
Mortality	4.3%	0.8%	*P* = NS

Conclusion: No support for post-operative empiric/preemptive treatment

[1] IDRB, independent data review board

Knitsch W et al. Clin Infect Dis 2015; 61: 1671-8

How to select patients for presumptive therapy?
An expert-based view



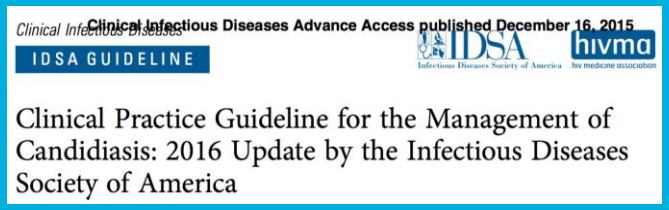
discussed in:
Kullberg & Arendrup New Engl J Med 2015

If prophylaxis/empirical therapy are a delusion, how can we make a change?

Invasive candidiasis

If prophylaxis/empirical therapy are a delusion, how can we make a change?

✓ The evidence is in the treatment guidelines



IDSA Clinical Practice Guideline for Management of Candidiasis 2016

ESCMID Diagnostic & Management Guidelines for *Candida* Diseases 2012

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ESCMID 2012:

Compound	Recommendation	References	Comment
Anidulafungin 200→100 mg	A I	Reboli NEJM 2007 Kett Int J Antimicrob Agents 2008	
Caspofungin 70→50 mg	A I	Mora-Duarte NEJM 2002 Pappas Clin Infect Dis 2007	
Micafungin 100 mg	A I	Kuse Lancet 2007 Pappas Clin Infect Dis 2007	

IDSA 2016:

Compound	Comment	Recommendation	Evidence
Initial therapy			
Anidulafungin 200→100 mg		Strong	High
Caspofungin 70→50 mg		Strong	High
Micafungin 100 mg		Strong	High

Pappas PG et al. Clin Infect Dis 2016;62(4):409–17
Cornely OA,...Kullberg BJ, et al. *Clin Microbiol Infect* 2012; 18(Suppl 7):19–37.

IDSA 2016:
Treatment for candidemia

Compound	Comment	Recommendation	Evidence
Initial therapy			
Anidulafungin 200→100 mg		Strong	High
Caspofungin 70→50 mg		Strong	High
Micafungin 100 mg		Strong	High
Acceptable alternatives			
Fluconazole 800→400 mg	Selected patients – Not critically ill and unlikely to have FLU-resistant *Candida*	Strong	High
Voriconazole 6→3 mg/kg bid*	Little advantage over FLU as initial therapy	Strong	Moderate
L-Amphotericin B 3 mg/kg	Reasonable alternative if intolerance, limited availability, or resistance to other antifungal agents	Strong	High

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*Licensed dose: 6 mg/kg q12h for the first 24 hours, followed by 4 mg/kg BID. Voriconazole is indicated in the treatment of candidaemia in non-neutropenic patients (adults & children ≥2 yrs)

Pappas PG et al. Clin Infect Dis 2016;62(4):409–17

Echinocandin superior to Fluconazole: Anidulafungin invasive candidiasis trial

Randomized, double-blind, multicenter study of Anidulafungin vs. Fluconazole

	Anidulafungin 200→100mg	Fluconazole 400→800mg	Estimated difference % (95%CI; *P*)
Success Rate (MITT; EOivT) N=245	76%	60%	15.4% (3.9, 27.0; *P*<0.02)
Crude Mortality (8 wks)	23%	31%	*P*=0.13

Both arms allowed to switch to oral fluconazole after ≥10 days

MITT. modified intent-to-treat population; EOivT, End of intravenous Treatment

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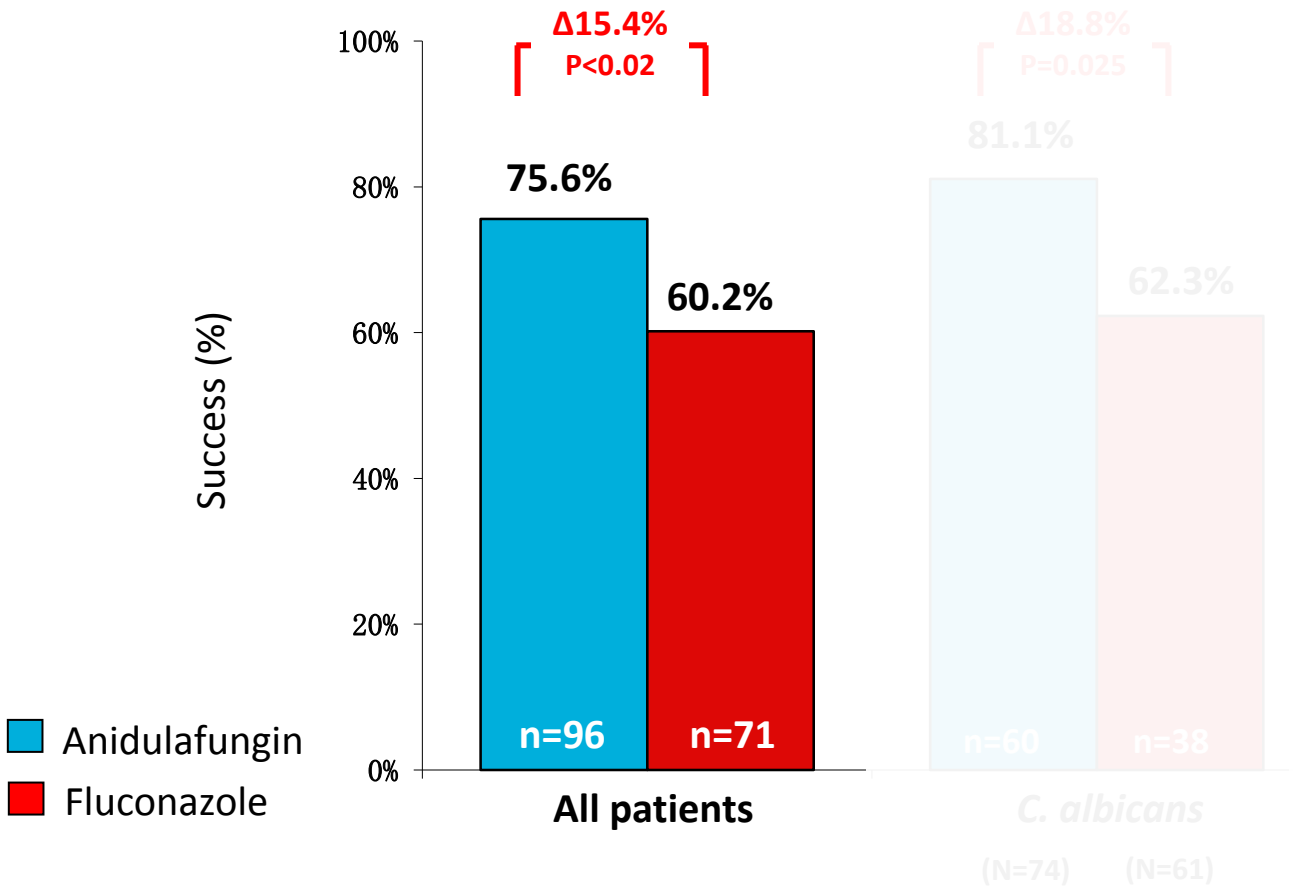
Reboli AC, et al. *N Engl J Med* 2007; 356(24):2472–82.

Anidulafungin candidemia study

*Success difference driven by C. albicans infections**



NS, no significant difference

*Patients with a single baseline pathogen

Reboli AC, et al. *N Engl J Med* 2007; 356(24):2472–82.

New data 2009–2016?

Are echinocandins really superior to fluconazole?

*Reboli AC, et al. *N Engl J Med* 2007; 356(24):2472–82.

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Mycoses Study Group MSG-02 Pooled Analysis

- 1915 patients - Individual patient-level pooled analysis
- Overall mortality 31.4%
- Treatment success (EOT) 67.4%

30-day mortality endpoint:

Increased mortality:	OR	P
Age	1.01	0.02
APACHE II score	1.11	0.0001

Decreased mortality:		
Echinocandin antifungal	0.65	0.02
CVC removal during therapy	0.50	0.0001

1. Treat early
2. Remove catheter
3. Start with echinocandin

Andes, Kullberg et al. Clin Infect Dis 2012; 54:1110

A second azole vs. echinocandin trial

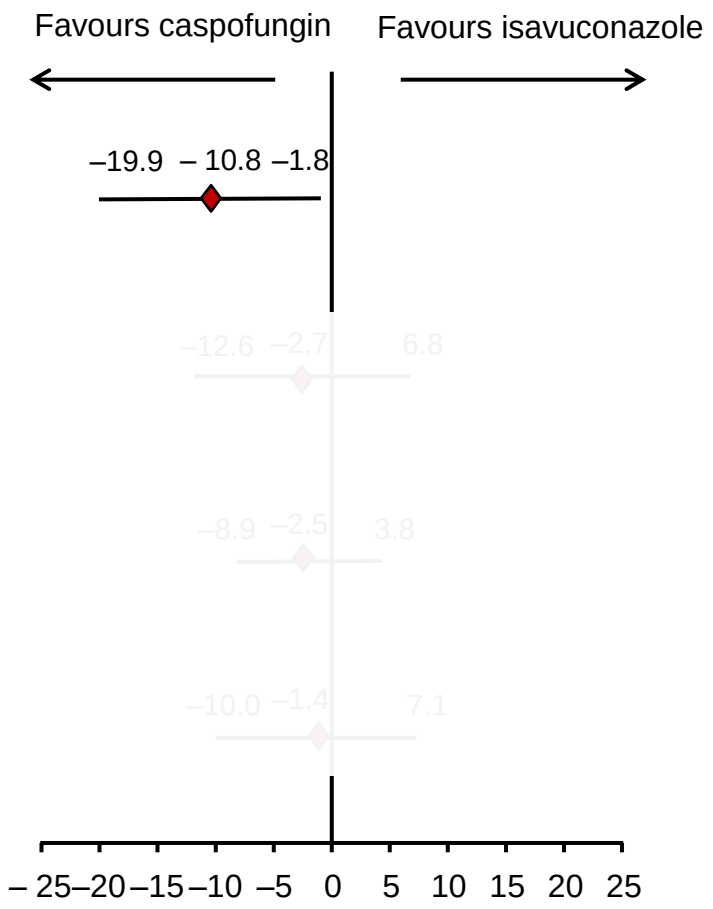
Primary objective	Compare the efficacy of isavuconazole vs caspofungin in patients with candidemia or other invasive *Candida* infections
Study design	Multinational, double-blind, randomized, non-inferiority study Switch to oral treatment >Day 10
Study population	450 adult patients with candidemia/invasive candidiasis
Statistical analysis	>85% power to demonstrate non-inferiority of isavuconazole to caspofungin at a non-inferiority margin of 15%

Kullberg et al. ECCMID 2016, Abstr. 1239; 11 April 2016

Isavuconazole vs. Caspofungin study
Efficacy outcomes

Category, n (%)	Isavuconazole (n = 199)	Caspofungin (n = 201)
Successful overall response at EOivT*	**120 (60.3)**	**143 (71.1)**
Successful overall response at EOT + 2 weeks	109 (54.8)	115 (57.2)
All-cause mortality Day 14	29 (14.6)	25 (12.4)
All-cause mortality Day 56	61 (30.7)	60 (29.9)

*Stratified by geographical region and baseline neutropenia status



Adjusted difference (%; 95% CI) between isavuconazole versus caspofungin

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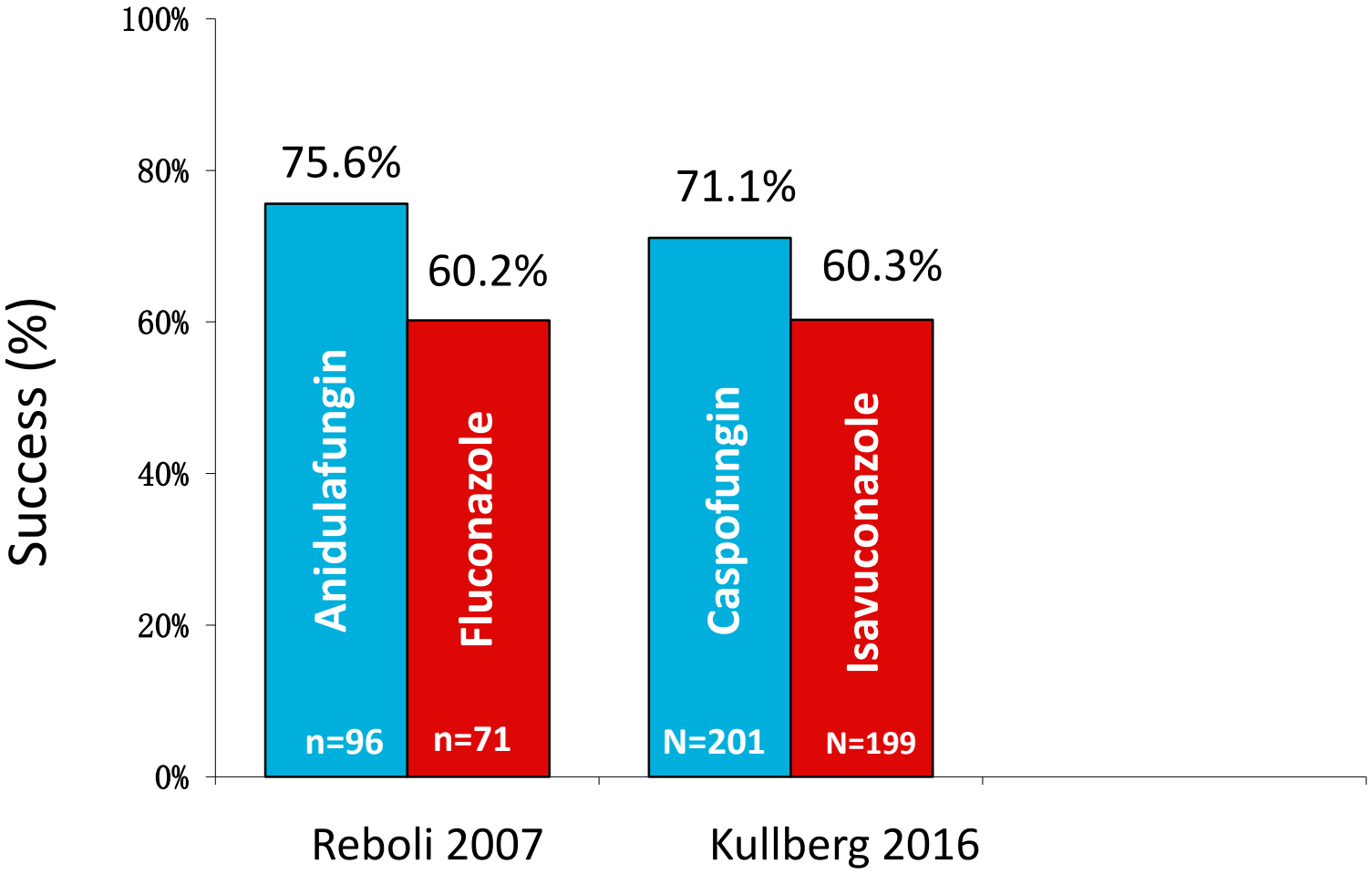
Kullberg et al. ECCMID 2016, Abstr. 1239; 11 April 2016

Second azole vs. echinocandin trial – similar difference



1. Reboli AC, et al. *N Engl J Med* 2007; 356(24):2472–82
2. Kullberg et al. ECCMID 2016,Abstr. 1239; 11 April 2016

Summary thoughts

- Candidemia / invasive candidiasis emerge from intestinal colonization
- Prophylaxis and empirical or biomarker-driven therapy in the ICU are not supported by published trial data
- Supporting data show superiority of echinocandins [1,2,3,4]
- IDSA 2016 and ESCMID 2012 prioritized echinocandins as the first choice for treatment of candidemia/invasive candidiasis [3,5]

1. DiNubile MJ, et al. *J Crit Care* 2007;22(3):237–44; 2. Kett DH, Cubillos GF. *Int J Antimicrob Agents* 2008; 32 (Suppl 2):S99–S102; 3. Cornely OA, et al. *Clin Microbiol Infect* 2012; 18(Suppl 7):19–37; 4. Colombo AL, et al. *Antimicrob Agents Chemother* 2010; 54(5):1864–71; 5. Pappas PG, et al. *Clin Infect Dis* 2016; 62:409-17;.

The evolving fungal landscape

New developments, challenges and approaches

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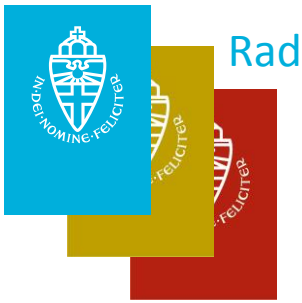

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