Antifungals in Medical ICU

Choosing the appropriate initial agent/drug class

DM Seminar
Dr K T Prasad

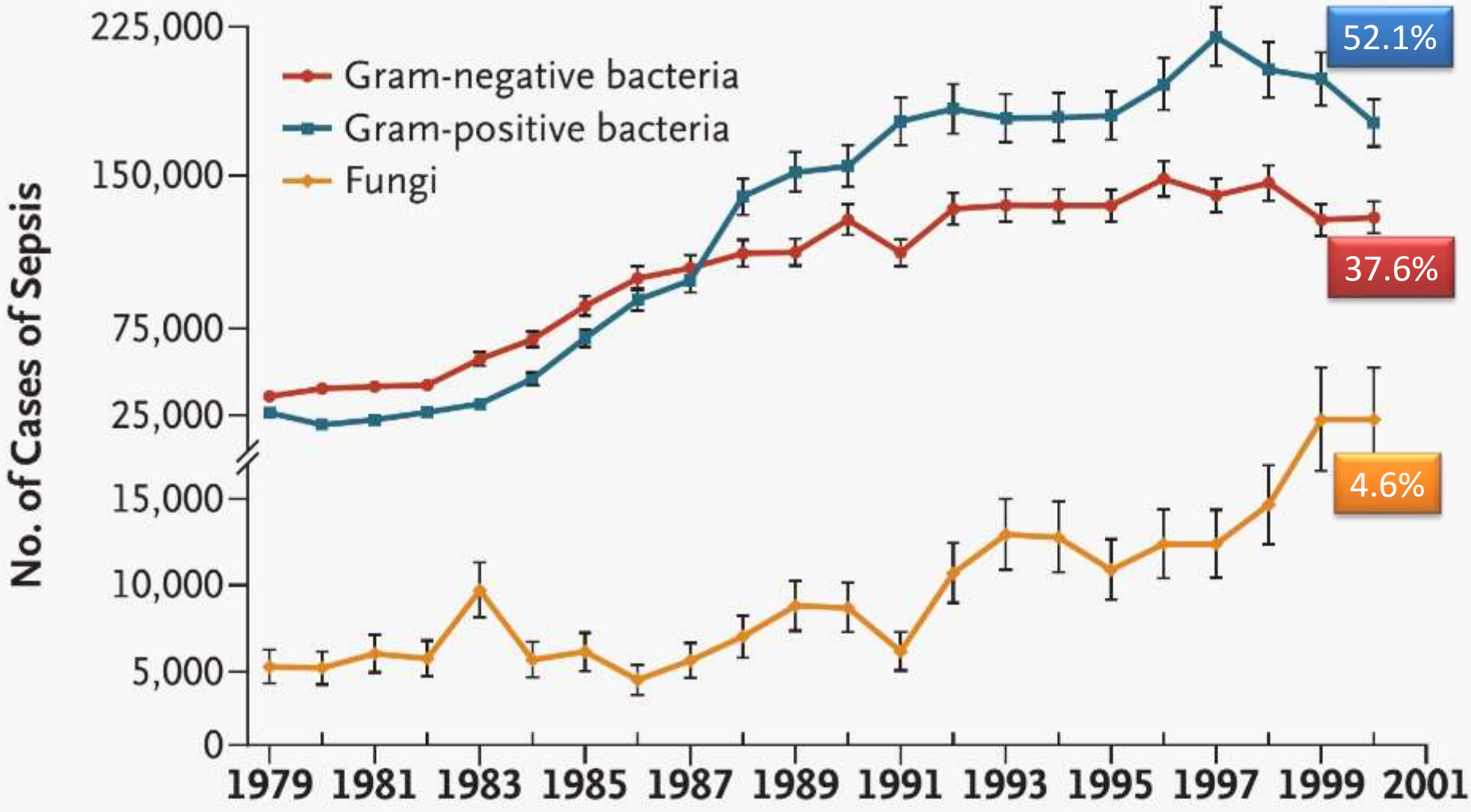
Seminar outline

- Epidemiology of fungal infections in ICU
- Antifungal pharmacology and their spectrum
- Rx of Candidemia/Invasive candidiasis
- Rx of Invasive aspergillosis
- Empirical antifungal Rx

Epidemiology

1. How frequent are fungal infections in the ICU?
2. What are the common fungi encountered?
3. What is the health/economical impact of fungal infections?
4. What is the epidemiology of invasive candidiasis/aspergillosis worldwide?
5. How is the epidemiology different in India?

Review of discharge data on approximately 750 million hospitalizations in the US over a 22-year period (1979-2000) identified 10,319,418 cases of sepsis



Rate of sepsis due to fungal organisms increased by **207 %**

Martin GS. N Engl J Med 2003; 348:1546-1554

International Study of the Prevalence and Outcomes of Infection in Intensive Care Units

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Context Infection is a major cause of morbidity and mortality in intensive care units (ICUs) worldwide. However, relatively little information is available about the global epidemiology of such infections.

Objective To provide an up-to-date, international picture of the extent and patterns of infection in ICUs.

Design, Setting, and Patients The Extended Prevalence of Infection in Intensive Care (EPIC II) study, a 1-day, prospective, point prevalence study with follow-up conducted on May 8, 2007. Demographic, physiological, bacteriological, therapeutic, and outcome data were collected for 14 414 patients in 1265 participating ICUs from 75 countries on the study day. Analyses focused on the data from the 13 796 adult (>18 years) patients.

On the day of the study, 7087 of 13,796 patients (51%) were considered infected

EPIC II study. Vincent JL et al. JAMA. 2009 Dec 2;302(21):2323-9

	No. (%)[a]							
	All	Western Europe	Eastern Europe	Central/ South America	North America	Oceania	Africa	Asia
	7087 (51.4)	3683 (49)	426 (56.4)	1290 (60.3)	607 (48.4)	285 (48.2)	89 (46.1)	707 (52.6)
Gram-positive	2315 (46.8)	1311 (49.0)	185 (51.8)	273 (38.0)[b]	252 (55.1)	104 (51.0)	27 (50.0)	163 (34.1)[b]
Staphylococcus aureus	1012 (20.5)	525 (19.6)	77 (21.6)	138 (19.2)	123 (26.9)[b]	56 (27.5)[b]	16 (29.6)	77 (16.1)
MRSA	507 (10.2)	233 (8.7)	37 (10.4)	79 (11.0)	80 (17.5)[b]	19 (9.3)	11 (20.4)[b]	48 (10.0)
S epidermidis	535 (10.8)	301 (11.2)	43 (12)	67 (9.3)	56 (12.3)	17 (8.3)	8 (14.8)	43 (9.0)
Streptococcus pneumoniae	203 (4.1)	127 (4.7)	16 (4.5)	24 (3.3)	20 (4.4)	5 (2.5)	3 (5.6)	8 (1.7)[b]
VSE	352 (7.1)	250 (9.3)	35 (9.8)	17 (2.4)[b]	24 (5.3)[b]	9 (4.4)	0[b]	17 (3.6)[b]
VRE	186 (3.8)	113 (4.2)	16 (4.5)	15 (2.1)[b]	22 (4.8)	10 (4.9)	0	10 (2.1)
Other	319 (6.4)	184 (6.9)	15 (4.2)	29 (4.0)[b]	48 (10.5)	19 (9.3)	4 (7.4)	20 (4.2)
Gram-negative	3077 (62.2)	1573 (58.7)	258 (72.3)[b]	510 (70.9)[b]	228 (49.9)[b]	122 (59.8)	31 (57.4)	355 (74.3)[b]
Escherichia coli	792 (16.0)	458 (17.1)	53 (14.8)	103 (14.3)	65 (14.2)	27 (13.2)	6 (11.1)	80 (16.7)
Enterobacter	345 (7.0)	184 (6.9)	29 (8.1)	62 (8.6)	37 (8.1)	7 (3.4)	4 (7.4)	22 (4.6)
Klebsiella species	627 (12.7)	261 (9.7)	76 (21.3)[b]	116 (16.1)[b]	41 (9)	24 (11.8)	10 (18.5)	99 (20.7)[b]
Pseudomonas species	984 (19.9)	458 (17.1)	103 (28.9)[b]	189 (26.3)[b]	59 (12.9)	30 (14.7)	8 (14.8)	137 (28.7)[b]
Acinetobacter species	435 (8.8)	149 (5.6)	61 (17.1)[b]	99 (13.8)[b]	17 (3.7)	9 (4.4)	8 (14.8)[b]	92 (19.2)[b]
Other	840 (17.0)	487 (18.2)	54 (15.1)	121 (16.8)	52 (11.4)[b]	42 (20.6)	11 (20.4)	73 (15.3)
ESBL-producing	93 (1.9)	47 (1.8)	7 (2.0)	21 (2.9)	1 (0.2)[b]	0	1 (1.9)	16 (3.3)
Anaerobes	222 (4.5)	142 (5.3)	12 (3.4)	10 (1.4)[b]	36 (7.9)	7 (3.4)	1 (1.9)	14 (2.9)
Other bacteria	76 (1.5)	33 (1.2)	7 (2.0)	14 (1.9)	4 (0.9)	4 (2.0)	3 (5.6)	11 (2.3)
Fungi								
Candida	843 (17)	495 (18.5)	66 (18.5)	92 (12.8)[b]	83 (18.2)	26 (12.7)	6 (11.1)	75 (15.7)
Aspergillus	70 (1.4)	44 (1.6)	1 (0.3)	5 (0.7)	12 (2.6)	3 (1.5)	0	5 (1)
Other	50 (1)	22 (0.8)	5 (1.4)	7 (1)	10 (2.2)	2 (1)	0	4 (0.8)
Parasites	34 (0.7)	18 (0.7)	2 (0.6)	6 (0.8)	3 (0.7)	2 (1)	0	3 (0.6)
Other organisms	192 (3.9)	122 (4.6)	9 (2.5)	15 (2.1)[b]	22 (4.8)	8 (3.9)	2 (3.7)	14 (2.9)

EPIC II study. Vincent JL et al. JAMA. 2009 Dec 2;302(21):2323-9

AJIC major article

The economic costs to United States hospitals of invasive fungal infections in transplant patients

Joseph Menzin,[a] Juliana L. Meyers,[a] Mark Friedman,[a] Jonathan R. Korn,[a] John R. Perfect,[b] Amelia A. Langston,[c] Robert P. Danna,[d] and George Papadopoulos[e]
Waltham, Massachusetts; Durham, North Carolina; Atlanta, Georgia; and Morristown and Kenilworth, New Jersey

9896 patients underwent SOT, and 4661 underwent HSC/BMT. Of these, 80 (0.8%) SOT and 111 (2.4%) HSC/BMT patients had an IFI.

Compared with patients without an IFI, patients with an IFI had:

- 5-fold increase in mortality
- An additional 19.2 hospital days
- $55,400 in excess costs

Menzin J et al. Am J Infect Control. 2011 May;39(4):e15-20

Epidemiology

Candidemia/Invasive candidiasis

Nosocomial Bloodstream Infections in US Hospitals: Analysis of 24,179 Cases from a Prospective Nationwide Surveillance Study

Hilmar Wisplinghoff,[1,2] Tammy Bischoff,[1] Sandra M. Tallent,[1] Harald Seifert,[2] Richard P. Wenzel,[1] and Michael B. Edmond[1]

[1]Department of Internal Medicine, Medical College of Virginia Campus, Virginia Commonwealth University, Richmond, Virginia; and [2]Institute for Medical Microbiology, Immunology and Hygiene, University of Cologne, Germany

Detected 24,179 cases of nosocomial BSI in 49 US hospitals over a 7-year period from March 1995 through September 2002 (60 cases per 10,000 hospital admissions)

Wisplinghoff H et al. Clin Infect Dis. 2004 Aug 1;39(3):309-17

Pathogen	BSIs per 10,000 admissions	Percentage of BSIs (rank)			Crude mortality, %		
		Total (n = 20,978)	ICU (n = 10,515)	Non-ICU ward (n = 10,442)	Total	ICU	Non-ICU ward
CoNS	15.8	31.3 (1)	35.9 (1)[a]	26.6 (1)	20.7	25.7	13.8
Staphylococcus aureus[b]	10.3	20.2 (2)	16.8 (2)[a]	23.7 (2)	25.4	34.4	18.9
Enterococcus species[c]	4.8	9.4 (3)	9.8 (4)	9.0 (3)	33.9	43.0	24.0
Candida species[c]	4.6	9.0 (4)	10.1 (3)	7.9 (4)	39.2	47.1	29.0
Escherichia coli	2.8	5.6 (5)	3.7 (8)[a]	7.6 (5)	22.4	33.9	16.9
Klebsiella species	2.4	4.8 (6)	4.0 (7)[a]	5.5 (6)	27.6	37.4	20.3
Pseudomonas aeruginosa	2.1	4.3 (7)	4.7 (5)	3.8 (7)	38.7	47.9	27.6
Enterobacter species	1.9	3.9 (8)	4.7 (6)[a]	3.1 (8)	26.7	32.5	18.0
Serratia species	0.9	1.7 (9)	2.1 (9)[a]	1.3 (10)	27.4	33.9	17.1
Acinetobacter baumannii	0.6	1.3 (10)	1.6 (10)[a]	0.9 (11)	34.0	43.4	16.3

NOTE. *Bacteroides* species (n = 150; 1.4% of isolates) ranked ninth in non-ICU wards. CoNS, coagulase-negative staphylococci.

[a] $P < .05$ for patients in ICUs vs. patients in non-ICU wards.

[b] Significantly more frequent in patients without neutropenia.

[c] Significantly more frequent in patients with neutropenia.

Candida spp. ranked as the third most common cause of BSI in ICU patients
Candidemia carries a crude mortality of 47.1% (second only to BSI by Pseudomonas spp.)

Wisplinghoff H et al. Clin Infect Dis. 2004 Aug 1;39(3):309-17

TABLE 1. Species distribution of *Candida* and other yeast isolates by year: ARTEMIS DISK Surveillance Program, 1997 to 2003[a]

Organism	1997–1998		1999		2000		2001		2002		2003	
	n	%	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%
Candida	22,533	95.2	20,998	95.7	11,698	97.0	21,804	96.3	24,680	95.3	33,002	95.5
C. albicans	16,514	69.77	14,667	66.87	7,961	66.02	14,268	62.99	15,147	58.51	20,576	59.56
C. glabrata	2,475	10.46	2,047	9.33	1,112	9.22	2,431	10.73	2,635	10.18	3,974	11.50
C. tropicalis	1,036	4.38	1,117	5.09	843	6.99	1,634	7.21	1,838	7.10	2,487	7.20
C. parapsilosis	955	4.03	1,028	4.68	650	5.39	1,501	6.63	1,632	6.30	2,406	6.96
C. krusei	372	1.57	459	2.09	376	3.12	544	2.40	639	2.47	884	2.56
C. guilliermondii	111	0.47	168	0.77	88	0.73	163	0.72	239	0.92	260	0.75
C. lusitaniae	115	0.49	99	0.45	62	0.51	122	0.54	131	0.51	211	0.61
C. kefyr	34	0.14	84	0.38	64	0.53	86	0.38	87	0.34	171	0.49
C. rugosa	7	0.03	7	0.03	21	0.17	151	0.67	150	0.58	116	0.34
C. famata	19	0.08	51	0.23	53	0.44	54	0.24	110	0.42	89	0.26
C. inconspicua					9	0.07	30	0.13	44	0.17	113	0.33
C. norvegensis	1	0.0	1	0.0	9	0.07	32	0.14	18	0.07	42	0.12
C. dubliniensis					1	0.01	19	0.08	26	0.10	18	0.05
C. lipolytica					7	0.06	14	0.06	14	0.05	25	0.07
C. zeylanoides					4	0.03	19	0.08	5	0.02	13	0.04
C. pelliculosa					1	0.01	14	0.06	12	0.05	12	0.03
Candida spp.	894	3.78	1,260	5.74	437	3.62	722	3.19	1,953	7.54	1,605	4.65

140,767 yeast isolates from 127 sites in 39 countries

Candida albicans was the most common species worldwide

C. parapsilosis has a relatively higher echinocandin MIC

ARTEMIS DISK Global Antifungal Surveillance Study
Pfaller MA et al. J Clin Microbiol. 2005 Dec;43(12):5848-59

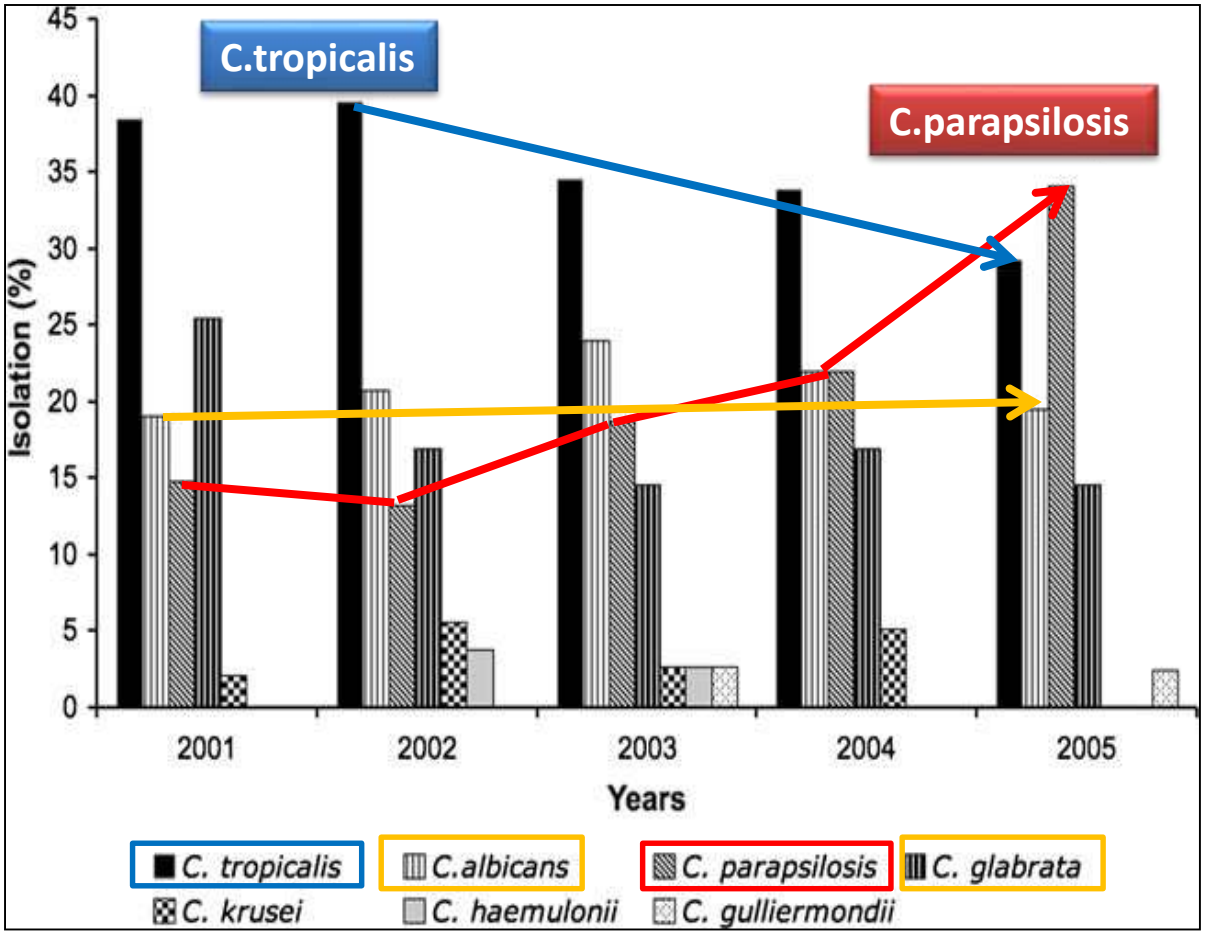
Candidemia: PGI data

- **Late 1980s:** *11-fold increase in candidemia*
- **1991-1995:** *18-fold increase in candidemia*
  - A shift to higher isolation of *non-albicans Candida species* was observed (52.6% in 1992 to 89.5% in 1995)
- **1996-2000:**
  - Higher isolation of *non-C. albicans Candida species (89.8%)* was observed, with *C. tropicalis being the most common* (541, 36.1%)

Candidemia is now the fourth common BSI at PGI

Chakrabarti A et al. Indian J Med Res. 1996 Aug;104:171-6
Chakrabarti A et al. Indian J Med Res. 2002 Jul;116:5-12
Chakrabarti A et al. Nihon Ishinkin Gakkai Zasshi. 2008;49(3):165-72

Candidemia: AIIMS (2001-2005)



C. parapsilosis has a relatively higher echinocandin MIC

Xess I et al. Infection. 2007 Jun;35(4):256-9.

Epidemiology

Invasive aspergillosis

Risk factors for IPA in non-neutropenic critically ill patients in the ICU

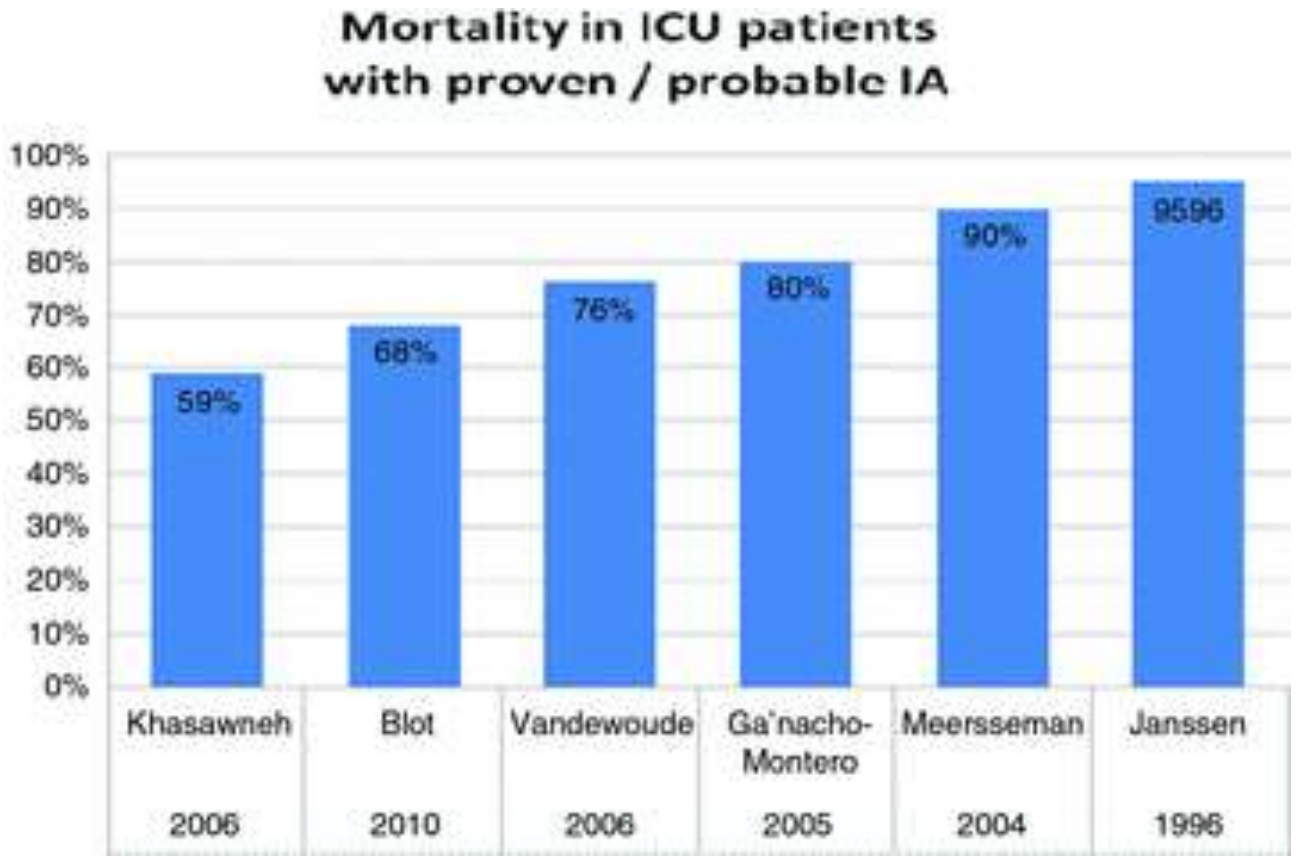
- COPD in combination with prolonged corticosteroid use
- High-dose systemic corticosteroids > 3 weeks (e. g. prednisone equivalent > 20 mg/day)
- Chronic renal failure with RRT
- Liver cirrhosis/acute hepatic failure
- Near-drowning
- Diabetes mellitus

Trof RJ et al. Intensive Care Med. 2007 Oct;33(10):1694-703
Meersseman W et al. Am J Respir Crit Care Med. 2004 Sep 15;170(6):621-5

Table 1. Reported incidence of aspergillosis in the ICU setting

Author	Year	Incidence (%)
Roosen	2000	15
Valles	2002	19
Meersseman	2003	5.8
Dimopoulos	2004	3.7
Garnacho-Montero	2005	1.1
Kumar	2006	0.7
Vandewoude	2006	0.3

Dimopoulos G et al. Ann N Y Acad Sci. 2012 Dec;1272:31-9



Dimopoulos G et al. Ann N Y Acad Sci. 2012 Dec;1272:31-9

Baddley et al. BMC Infectious Diseases 2013, 13:29
http://www.biomedcentral.com/1471-2334/13/29

BMC Infectious Diseases

RESEARCH ARTICLE Open Access

Aspergillosis in Intensive Care Unit (ICU) patients: epidemiology and economic outcomes

John W Baddley[1*], Jennifer M Stephens[2], Xiang Ji[2], Xin Gao[2], Haran T Schlamm[3] and Miriam Tarallo[4]

Methods: Retrospective cohort study using Premier Inc. Perspective™ US administrative hospital database (2005–2008). Adults with ICU stays and aspergillosis (ICD-9 117.3 plus 484.6) who received initial antifungal therapy (AF) in the ICU were included. Patients with traditional risk factors (cancer, transplant, neutropenia, HIV/AIDS) were excluded. The relationship of antifungal therapy and co-morbidities to economic outcomes were examined using Generalized linear models.

Results: From 6,424 aspergillosis patients in the database, 412 (6.4%) ICU patients with IA were identified. Mean age was 63.9 years and 53% were male. Frequent co-morbidities included steroid use (77%), acute respiratory failure (76%) and acute renal failure (41%). In-hospital mortality was 46%. The most frequently used AF was voriconazole (71% received at least once). Mean length of stay (LOS) was 26.9 days and mean total hospital cost was $76,235.

Invasive aspergillosis in India

- Exact prevalence of invasive aspergillosis in India is not known.

- Unlike the western world and temperate countries, where A. fumigatus is the foremost pathogen, A. flavus is the most common etiological agent in India.

Chakrabarti A et al. Nihon Ishinkin Gakkai Zasshi. 2008;49(3):165-72

Invasive aspergillosis in India (Unpublished PGI data)

- Systemic fungal infection was detected in **2.4% of all autopsies** performed (15,040 deaths autopsied over 26 years) and IA was detected in **49% of those fungal positive cases (1.2% of all autopsy cases)**

- Between 1994 and 2008, systemic fungal infection was demonstrated in **34 (9%) of 374 autopsies having liver failure** (224 cirrhosis and 150 acute failure), and **59% of those cases had IA**

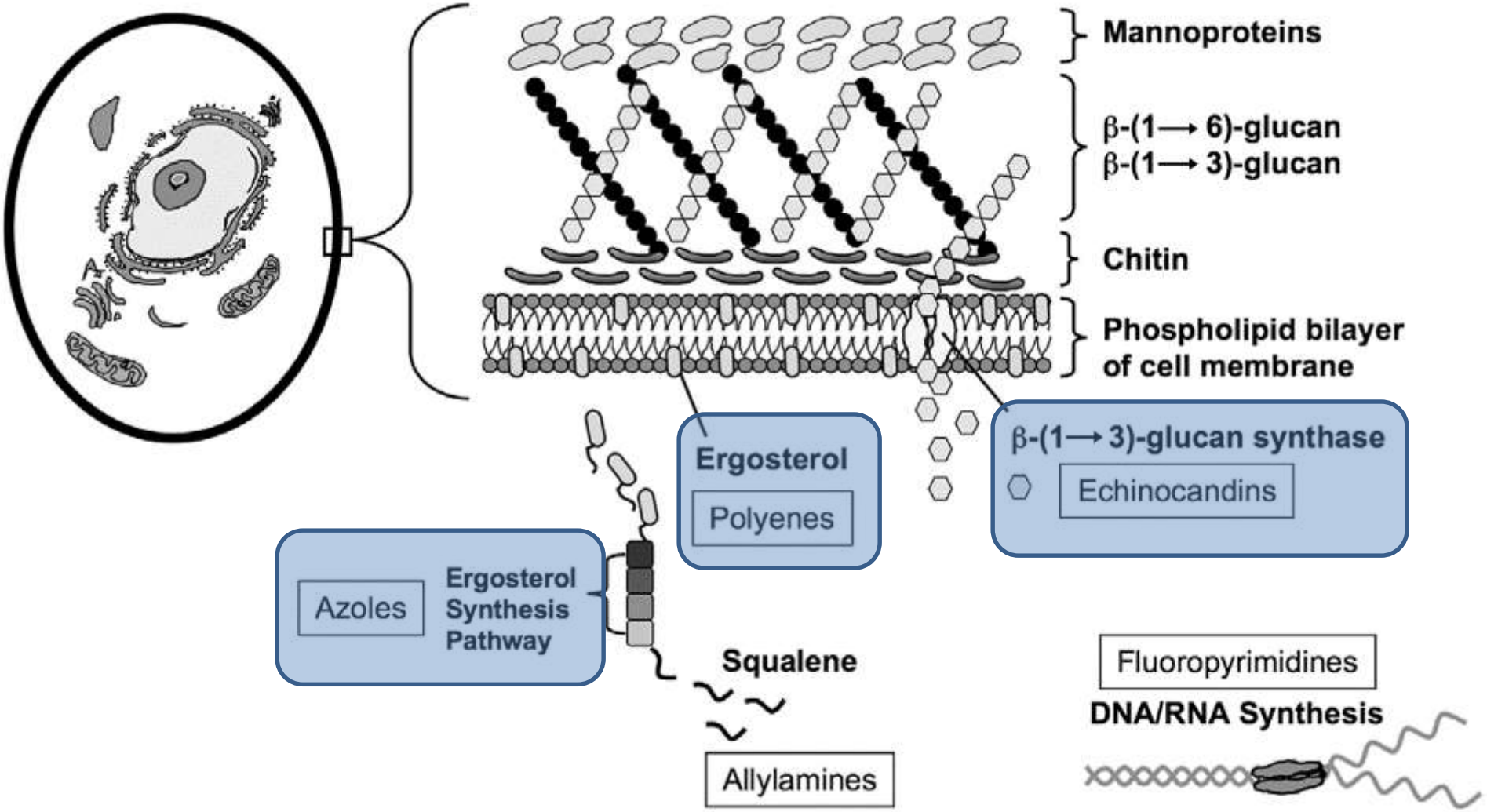
Chakrabarti A et al. Med Mycol. 2011 Apr;49 Suppl 1:S35-47

Antifungal agents

Pharmacology & Antifungal spectrum

Antifungals for invasive fungal infections

- **Polyenes**
  - AmB deoxycholate
  - LAmB
- **Azoles**
  - Fluconazole
  - Itraconazole
  - Voriconazole
  - Posaconazole
- **Echinocandins**
  - Caspofungin
  - Micafungin
  - Anidulafungin



Ashley ESD et al. Clin Infect Dis. (2006) 43 (Supplement 1): S28-S39

Table 6. Comparative toxicities of antifungal agents.

Type of toxicity	Antifungal agent											
	AmB	ABCD	ABLC	LAB	Flu	Itr	Vor	Pos	Anidulafungin	Caspofungin	Micafungin	Flucytosine
Hepatic	++	++	++	++	+	+	+	+	+	+	+	++
Nephrotic	++++	+++	+++	++	–	–	–	–	–	–	–	–
Hematologic	+	+	+	+	NR	NR	NR	NR	NR	+	+	+++
Infusion-related	+++	+++	+++	++	–	–	–	NA	+	+	+	NA
Electrolyte abnormalities[a]	+++	++	++	++	NR	+	+	NR	+	+	NR	+

NOTE. Plus signs indicate degree of toxicity: +, mild; ++, moderate; and +++, severe. ABCD, amphotericin B colloidal dispersion; ABLC, amphotericin B lipid complex; AmB, amphotericin B; Flu, fluconazole; Itr, itraconazole; LAB, liposomal amphotericin B; NA, data not available because of a lack of formulation; NR, not reported; Pos, posaconazole; Vor, voriconazole. Data are derived from [5, 37, 41, 45, 47, 51, 52, 54, 58, 70, 111–118].

[a] Includes hypokalemia and hypomagnesemia.

Ashley ESD et al. Clin Infect Dis. (2006) 43 (Supplement 1): S28-S39.

Organism	Antifungal agent								
	AmB[a]	Flu	Itr	Vor	Pos	Anidulafungin	Caspofungin	Micafungin	Flucytosine
Aspergillus species	+	−	+	+	+	+	+	+	−
A. flavus	±	−	+	+	+	+	+	+	−
A. fumigatus	+	−	+	+	+	+	+	+	−
A. niger	+	−	±	+	+	+	+	+	−
A. terreus	−	−	+	+	+	+	+	+	−
Candida species	+	+	+	+	+	+	+	+	+
C. albicans	+	+	+	+	+	+	+	+	+
C. glabrata	+	±	±	+	+	+	+	+	+
C. krusei	+	−	±	+	+	+	+	+	±
C. lusitaniae	−	+	+	+	+	+	+	+	+
C. parapsilosis	+	+	+	+	+	±	±	±	+
C. tropicalis	+	+	+	+	+	+	+	+	+
Cryptococcus neoformans	+	+	+	+	+	−	−	−	+
Coccidioides species	+	+	+	+	+	±[b]	±[b]	±[b]	−
Blastomyces	+	+	+	+	+	±[b]	±[b]	±[b]	−
Histoplasma species	+	+	+	+	+	±[b]	±[b]	±[b]	−
Fusarium species	±	−	−	+	+	−	−	−	−
Scedosporium apiospermum	±	−	±	+	+	−	−	−	−
Scedosporium prolificans	−	−	−	±	±	−	−	−	−
Zygomycetes	±	−	−	−	+	−	−	−	−

Ashley ESD et al. Clin Infect Dis. (2006) 43 (Supplement 1): S28-S39

TABLE 2. In vitro susceptibilities of *Candida* spp. to fluconazole and voriconazole as determined by CLSI disk diffusion testing: ARTEMIS DISK Surveillance Program, 2001 to 2003[a]

Species	Susceptibility					
	Fluconazole[b]			Voriconazole[b]		
	n	%S	%R	*n*	%S	%R
C. albicans	49,991	97.8	1.3	47,584	98.6	1.0
C. glabrata	9,040	66.7	16.6	8,719	81.7	10.1
C. tropicalis	5,959	89.1	5.0	5,643	87.1	6.7
C. parapsilosis	5,539	93.2	3.6	5,233	96.8	1.8
C. krusei	2,067	9.4	77.2	1,996	83.2	7.5
C. guilliermondii	662	73.3	9.8	633	91.2	4.9
C. lusitaniae	464	93.3	4.1	445	96.4	2.0
C. rugosa	417	39.3	51.8	394	61.4	26.4
C. kefyr	344	95.3	3.5	331	99.1	0.6
C. famata	253	79.8	11.9	238	89.5	5.5
C. inconspicua	187	25.7	49.2	186	89.2	5.4
C. norvegensis	92	50.0	38.0	91	92.3	1.1
C. dubliniensis	63	96.8	3.2	63	100.0	0.0
C. lipolytica	53	54.7	39.6	52	67.3	19.2
C. pelliculosa	38	94.7	0.0	38	100.00	0.0
C. zeylanoides	37	54.1	37.8	35	74.3	11.4
C. sake	12	83.3	8.3	12	100.0	0.0
Candida spp.[c]	4,245	86.6	8.2	4,094	92.7	4.7

Pfaller MA et al. J Clin Microbiol. 2005 Dec;43(12):5848-59

TABLE 5. Geographic variation in the in vitro susceptibilities of *C. albicans* and *C. glabrata* to fluconazole and voriconazole as determined by CLSI disk diffusion testing: ARTEMIS DISK Global Surveillance Program, 2001 to 2003[a,b]

Region/country	Antifungal agent	Susceptibility					
		C. albicans			*C. glabrata*		
		n	%S	%R	*n*	%S	%R
Asia-Pacific							
Australia	Fluconazole	207	96.6	2.4	74	58.1	16.2
	Voriconazole	207	99.0	1.0	74	77.0	9.5
China	Fluconazole	1,071	97.1	1.7	307	74.9	13.4
	Voriconazole	1,055	98.7	0.7	307	83.4	8.5
India	Fluconazole	60	70.0	23.3	6	100.0	0.0
	Voriconazole	60	78.3	20.0	6	100.0	0.0
Malaysia	Fluconazole	4,327	99.1	0.3	623	34.0	24.1
	Voriconazole	3,602	99.5	0.0	518	59.5	0.8
South Africa	Fluconazole	3,324	99.4	0.3	355	49.6	21.1
	Voriconazole	3,286	99.9	0.1	333	73.3	3.0
South Korea	Fluconazole	1,928	99.5	0.2	49	83.7	12.2
	Voriconazole	1,848	99.7	0.3	47	83.0	10.6
Taiwan	Fluconazole	1,395	95.8	2.7	352	75.6	12.2
	Voriconazole	1,389	98.5	1.0	349	84.0	4.9
Thailand	Fluconazole	290	97.6	1.4	93	71.0	5.4
	Voriconazole	289	98.6	1.0	93	92.5	2.2
Europe							
Belgium	Fluconazole	1,761	99.5	0.3	224	39.7	42.0
	Voriconazole	1,683	99.7	0.3	216	53.2	18.5
Czech Republic	Fluconazole	2,633	99.6	0.2	429	44.8	27.5
	Voriconazole	2,402	99.9	0.0	412	65.3	8.7

Note: Table incomplete

India: Uma Banerjee, AIIMS

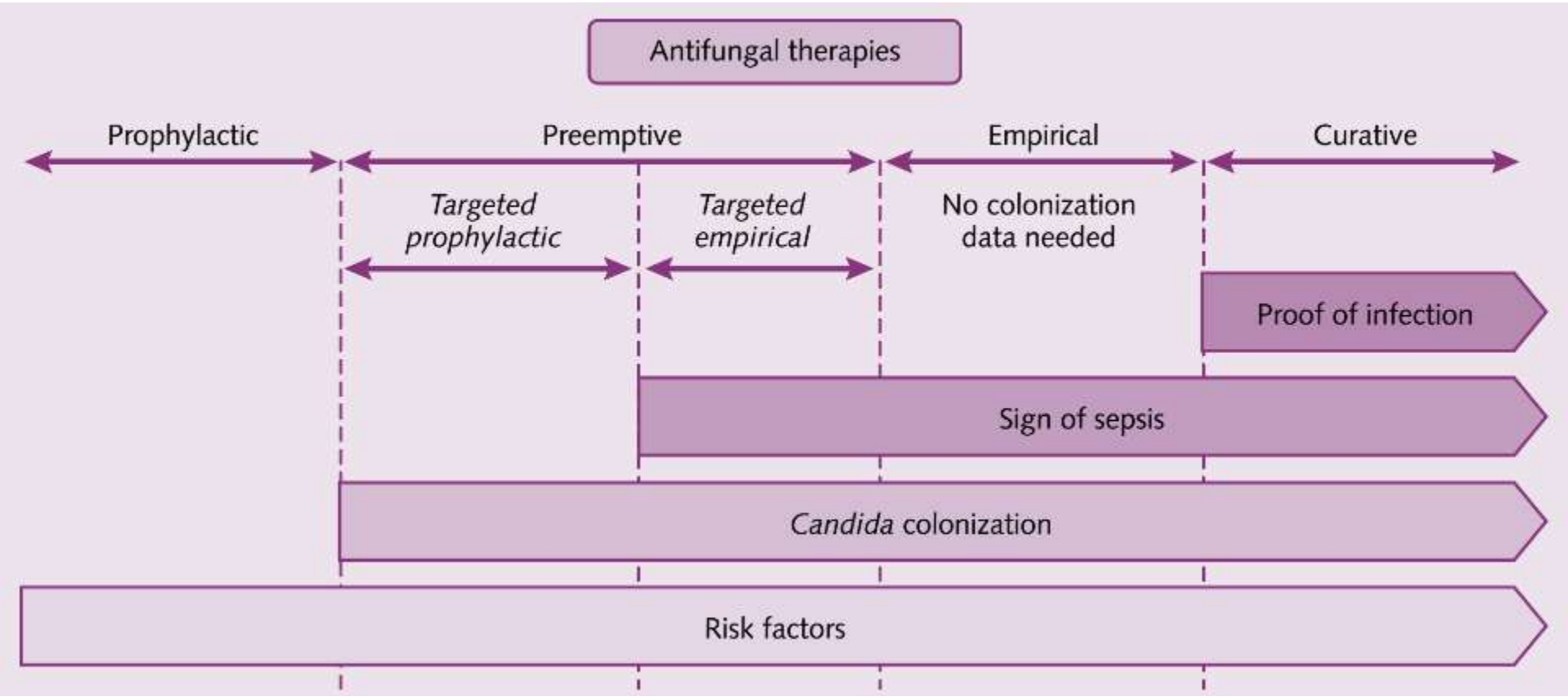
ARTEMIS DISK Global Antifungal Surveillance Study
Pfaller MA et al. J Clin Microbiol. 2005 Dec;43(12):5848-59

Candida resistance: PGI data

- **1991-1995:**
  - Resistance against fluconazole observed in 24.2% of C. krusei, 15.4% C. guilliermondii and 5.7% strains of C. tropicalis. *No resistance was detected against amphotericin B and ketoconazole.*
- **1996-2000:**
  - An *emergence of resistance to amphotericin B* in 15.4% C. albicans, 8.1% C. tropicalis and 33.3% C. krusei strains was observed.

Chakrabarti A et al. Indian J Med Res. 1996 Aug;104:171-6
Chakrabarti A et al. Indian J Med Res. 2002 Jul;116:5-12
Chakrabarti A et al. Nihon Ishinkin Gakkai Zasshi. 2008;49(3):165-72

Treatment of invasive fungal infections



Grenouillet F et al. J Invasive Fungal Infect 2007;1(2):42–9

Table 1. Criteria for proven invasive fungal disease except for endemic mycoses.

Analysis and specimen	Molds[a]
Microscopic analysis: sterile material	Histopathologic, cytopathologic, or direct microscopic examination[b] of a specimen obtained by needle aspiration or biopsy in which hyphae or melanized yeast-like forms are seen accompanied by evidence of associated tissue damage
Culture	
Sterile material	Recovery of a mold or "black yeast" by culture of a specimen obtained by a sterile procedure from a normally sterile and clinically or radiologically abnormal site consistent with an infectious disease process, excluding bronchoalveolar lavage fluid, a cranial sinus cavity specimen, and urine
Blood	Blood culture that yields a mold[d] (e.g., *Fusarium* species) in the context of a compatible infectious disease process
Serological analysis: CSF	Not applicable

[a] If culture is available, append the identification at the genus or species level from the culture results.
[b] Tissue and cells submitted for histopathologic or cytopathologic studies should be stained by Grocott-Gomorri meth
fungal structures. Whenever possible, wet mounts of specimens from foci related to invasive fungal disease should be s
[c] *Candida, Trichosporon,* and yeast-like *Geotrichum* species and *Blastoschizomyces capitatus* may also form pseudohy
[d] Recovery of *Aspergillus* species from blood cultures invariably represents contamination.

(EORTC/MSG) Consensus Group.
De Paw B et al. Clin Infect Dis. 2008 Jun 15;46(12):1813-21

Invasive fungal disease (IFD)

- **Probable IFD**
  - Host factor,
  - Clinical features, **and**
  - Mycological evidence be present
- **Possible IFD**
  - Host factors **and**
  - Clinical evidence consistent with IFD, **but**
  - **No mycological support**

(EORTC/MSG) Consensus Group.
De Paw B et al. Clin Infect Dis. 2008 Jun 15;46(12):1813-21

Treatment

Candidemia/Invasive candidiasis

1. Is fluconazole good enough?
2. Are other azoles better?
3. Are echinocandins better than azoles/AmB?
4. Is any echinocandin better than its peer?

Flconazole vs AmB

MAYO CLINIC
PROCEEDINGS

ORIGINAL ARTICLE

Treatment of Invasive Candidal Infections: Systematic Review and Meta-analysis

ANAT GAFTER-GVILI, MD; LIAT VIDAL, MD; ELAD GOLDBERG, MD; LEONARD LEIBOVICI, MD; AND MICAL PAUL, MD

Meta-analysis of 6 trials which compared fluconazole with AmB was done

Mayo Clin Proc. 2008 Sep;83(9):1011-21

- All randomized controlled trials that compared different types of antifungal agents for the **treatment of confirmed invasive candidiasis (IC)** were included.
- Confirmed IC was defined as 1 or more positive results on blood culture for Candida spp or culture from a normally sterile site during the previous 3 to 4 days, and clinical signs of infection
- 15 trials included
  - 9 compared fluconazole with other drugs (amphotericin B, itraconazole, or a combination of fluconazole and amphotericin B),
  - 4 compared echinocandins with other drugs (fluconazole, amphotericin B, liposomal amphotericin B),
  - 1 compared micafungin and caspofungin, and
  - 1 compared amphotericin B plus fluconazole and voriconazole

Gafter-Gvili A et al. Mayo Clin Proc. 2008 Sep;83(9):1011-21

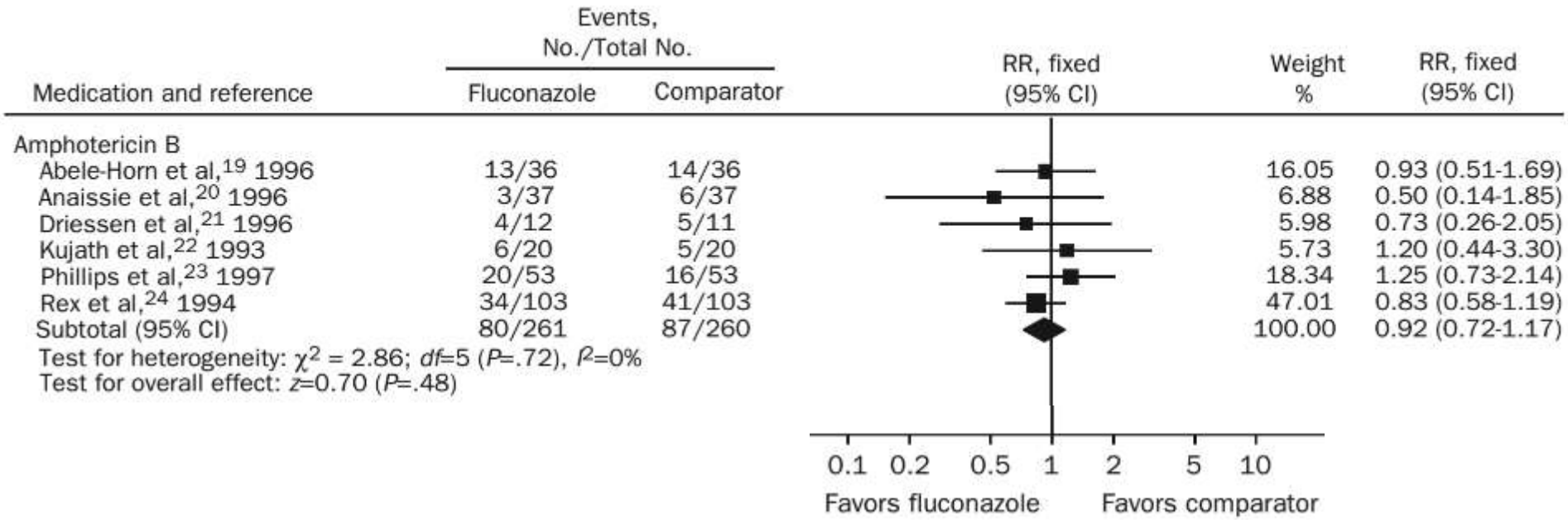
TABLE. **Definitions of Outcomes in Each Trial**[a]

Reference	Time point for assessing mortality[b]	Definition of microbiological failure	Definition of treatment failure
Abele-Horn et al,[19] 1996	End of therapy	No eradication of isolates during treatment; absence of growth at follow-up	Absence of any substantial clinical improvement
Anaissie et al,[20] 1996	48 h, 5 d, end of therapy; analysis at end of therapy	Persistence of infection with *Candida* species at originally infected sites	No change in or worsening of clinical findings of candidiasis; persistence of infection with *Candida* spp at originally infected sites; development of infection at new sites; drug toxicity requiring discontinuation; time assessed: 48 h of therapy, 5 d of therapy, end of therapy
Driessen et al,[21] 1996	30 d	NR	NR
Kujath et al,[22] 1993	End of therapy	No elimination of isolates	NR
Phillips et al,[23] 1997	7 d, 14 d, 28 d, 60 d, 180 d; analysis at 28 d	Persistence of candidemia 7 d after enrollment; no metastatic complications at enrollment, histologic evidence of candidiasis on autopsy	Presence of 1 or more of the following: death within first 7 d, evidence of progressive infection with *Candida* spp, withdrawal from the study with a change to alternative systemic antifungal therapy
Rex et al,[24] 1994	End of follow-up (61-65 d after treatment)	Results on blood cultures remained positive at end of therapy	Unresponsive or progressive infection after more than 5 d of therapy; unacceptable adverse effects; withdrawal before improvement
Mondal et al,[25] 2004	During therapy	No eradication in 2 consecutive blood samples 48 h apart	No resolution of fever or no eradication in 2 blood samples taken 48 h apart
Tuil & Cohen,[26] 2003	No mortality data	NR	NR
Rex et al,[27] 2003	Within 90 d after starting therapy	Persistent fungemia after more than 5 d of therapy	Unresponsive infection after more than 5 d of therapy; unacceptable adverse effects; withdrawal
Reboli et al,[28] 2007	End of therapy	*Candida* spp not eradicated at baseline, as determined at the end of intravenous therapy	No substantial improvement in signs or symptoms, death due to invasive candidiasis, persistent or recurrent candidiasis, or an infection with a new *Candida* spp; any indeterminate response
Mora-Duarte et al,[29] 2002	End of therapy, end of follow-up (6-8 wk after treatment); analysis at end of therapy	Persistently positive findings on cultures at end of therapy	Infection clinically or microbiologically unresponsive; study drug withdrawn; toxic effects
Arrieta et al,[30] 2006	End of follow-up (12 wk after treatment)	NR	NR
Kuse et al,[31] 2007	During therapy, end of follow-up (12 wk after treatment); analysis during therapy	Persistence of *Candida* isolates at end of treatment	No clinical or mycological response at end of therapy
Pappas et al,[17] 2007	End of follow-up (6 wk after treatment)	No eradication in 2 consecutive blood samples taken 48 h apart, at the end of intravenous therapy	Progression of disease or no detectable improvement in patient's condition, independently of culture findings or mycological persistence at the end of intravenous therapy
Kullberg et al,[33] 2005	End of follow-up (14 wk after treatment)	No eradication of isolates at 12-wk follow-up	No mycological eradication, clinical cure, or improvement at 12-wk follow-up

[a] NR = not reported.
[b] For trials that assessed mortality at several time points, the time point we used for the meta-analysis is specified.

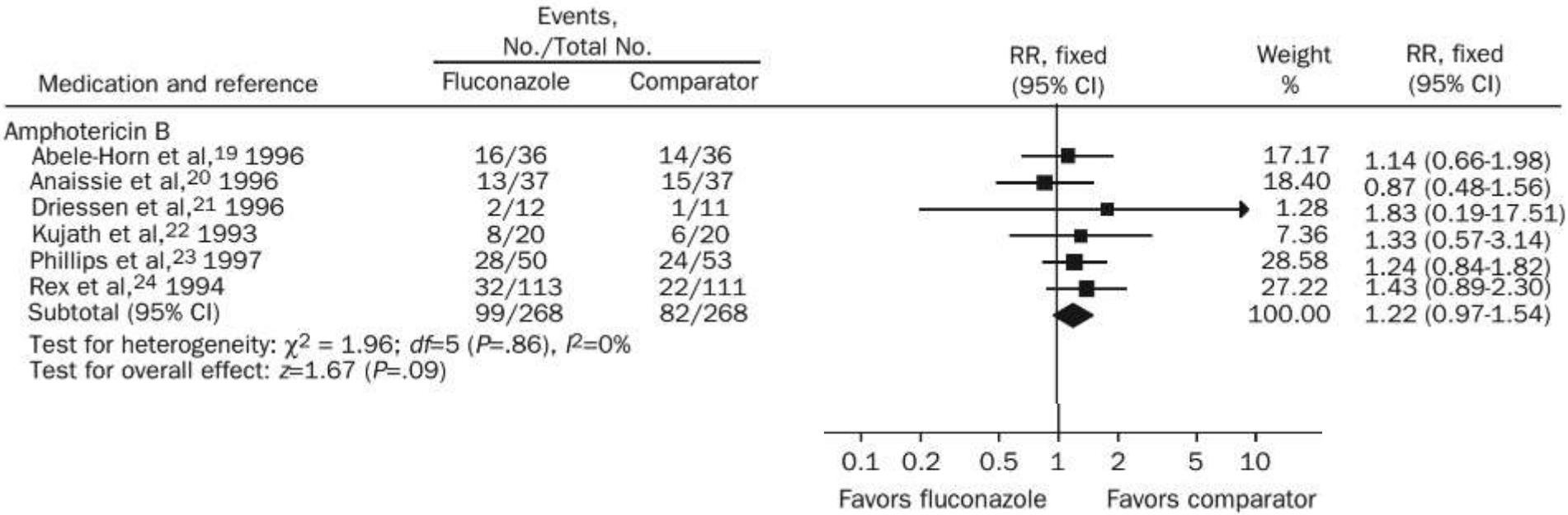
Gafter-Gvili A et al. Mayo Clin Proc. 2008 Sep;83(9):1011-21

All-cause mortality



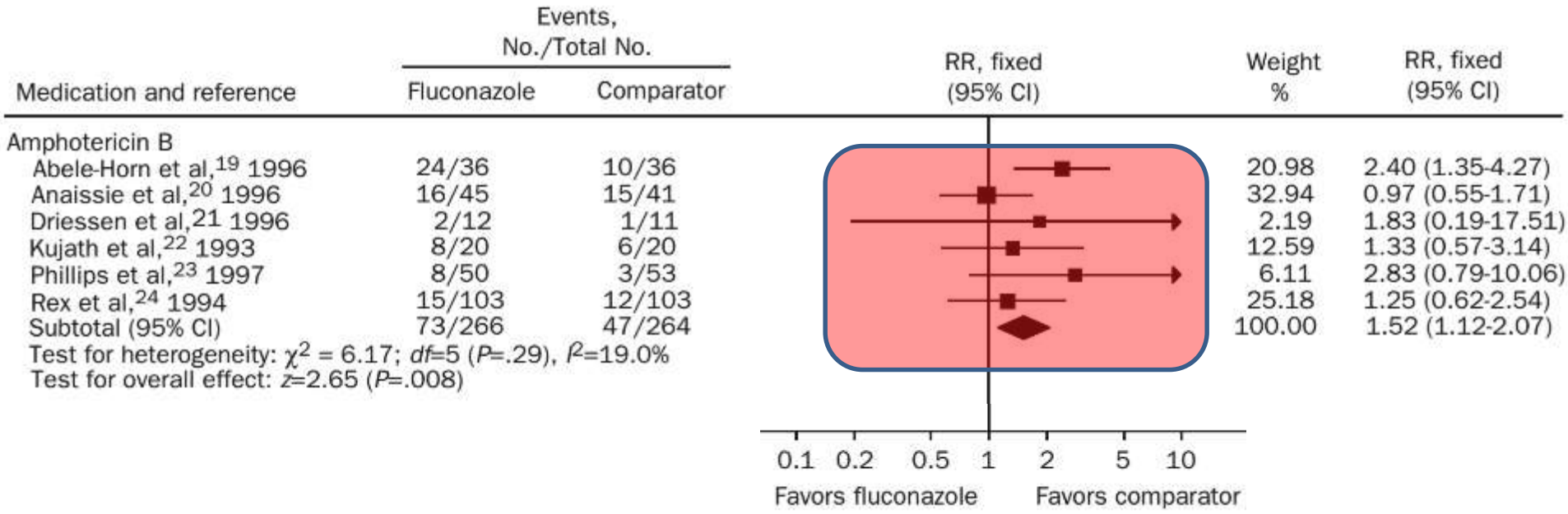
Gafter-Gvili A et al. Mayo Clin Proc. 2008 Sep;83(9):1011-21

Treatment failure



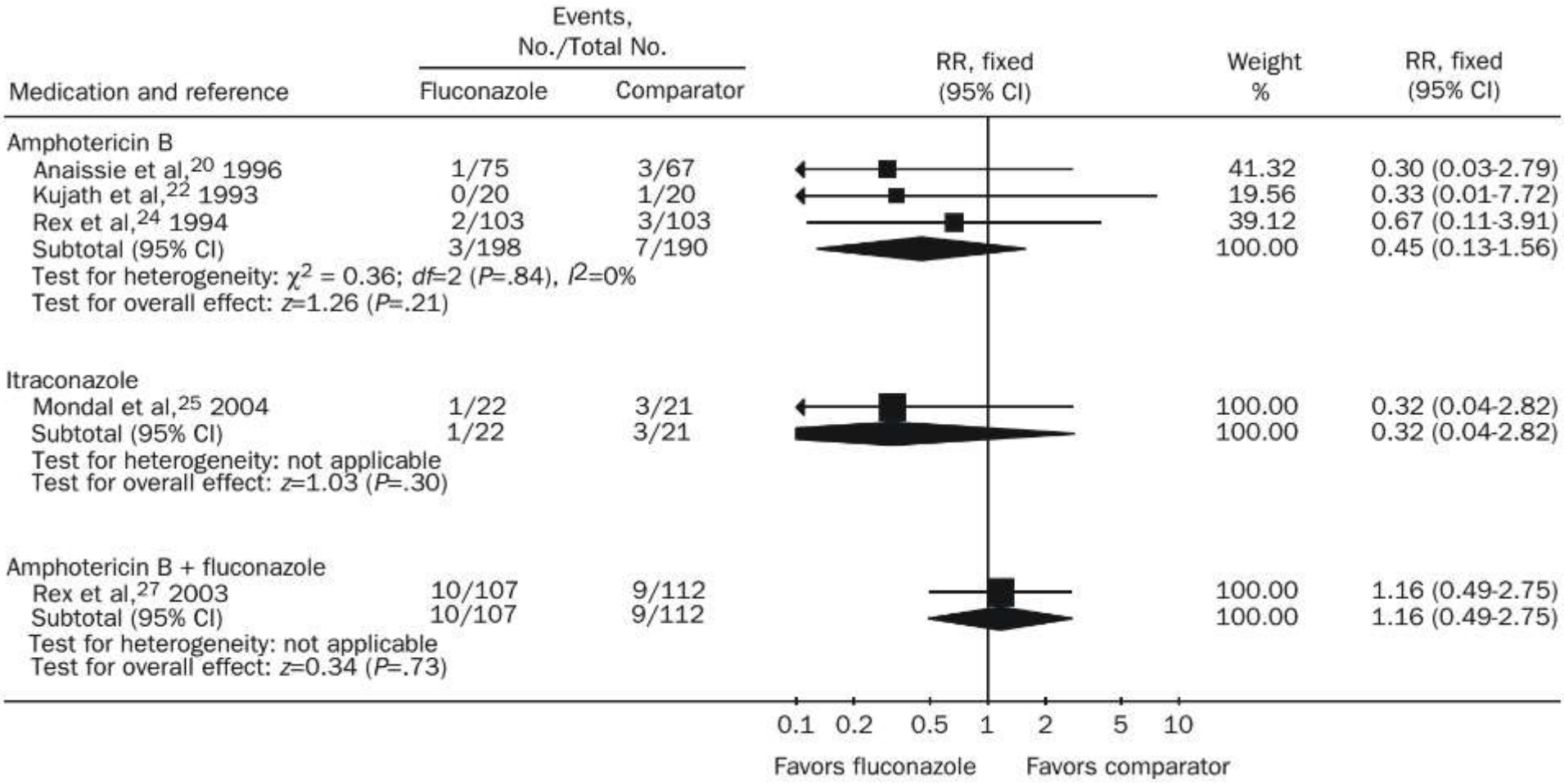
Gafter-Gvili A et al. Mayo Clin Proc. 2008 Sep;83(9):1011-21

Microbiological failure



Gafter-Gvili A et al. Mayo Clin Proc. 2008 Sep;83(9):1011-21

Adverse events requiring discontinuation



Gafter-Gvili A et al. Mayo Clin Proc. 2008 Sep;83(9):1011-21

Is fluconazole good enough?

- **Advantages**:
  - Cheap
  - Minimal adverse effects
- **Drawbacks**:
  - Microbiological failure more common with fluconazole when compared to AmB (27.4% vs 17.8%)
  - High incidence of resistance in C. glabrata, C. krusei
  - Increasing resistance even in C. albicans in certain areas (almost 20% in AIIMS data)

Are other azoles better?

- **Itraconazole**: No RCTs in adult patients with invasive candidiasis

- **Posaconazole**: No RCT for Rx of invasive candidiasis

(Posaconazole has been approved as a prophylactic agent for invasive fungal infections and for Rx of oropharyngeal candidiasis)

- **Voriconazole**: One non-inferiority trial available (Kullberg BJ, Lancet 2005)

Voriconazole versus a regimen of amphotericin B followed by fluconazole for candidaemia in non-neutropenic patients: a randomised non-inferiority trial

B J Kullberg, J D Sobel, M Ruhnke, P G Pappas, C Viscoli, J H Rex, J D Cleary, E Rubinstein, L W P Church, J M Brown, H T Schlamm, I T Oborska, F Hilton, M R Hodges

Lancet 2005; 366: 1435–42
Published online October 12, 2005

Summary

Background Voriconazole has proven efficacy against invasive aspergillosis and oesophageal candidiasis. This multicentre, randomised, non-inferiority study compared voriconazole with a regimen of amphotericin B followed by fluconazole for the treatment of candidaemia in non-neutropenic patients.

	Voriconazole (n=248)	Amphotericin B/ fluconazole (n=122)	p
Primary success rate*	101 (41%)	50 (41%)	0·96
Success by pathogen			
C albicans	46/107 (43%)	30/63 (48%)	
C glabrata	12/36 (33%)	7/21 (33%)	
C parapsilosis	24/45 (53%)	10/19 (53%)	
C tropicalis	17/53 (32%)	1/16 (6%)	0·032
C krusei	1/4 (25%)	0/1	
Secondary success rate†	162 (65%)	87 (71%)	0·25
Success rate at end of treatment‡	173 (70%)	90 (74%)	0·42
Success rate 2 weeks after end of treatment‡	130 (52%)	64 (53%)	0·99
Success rate 6 weeks after end of treatment‡	110 (44%)	56 (46%)	0·78
All-cause 14-week mortality	88 (36%)	51 (42%)	0·23

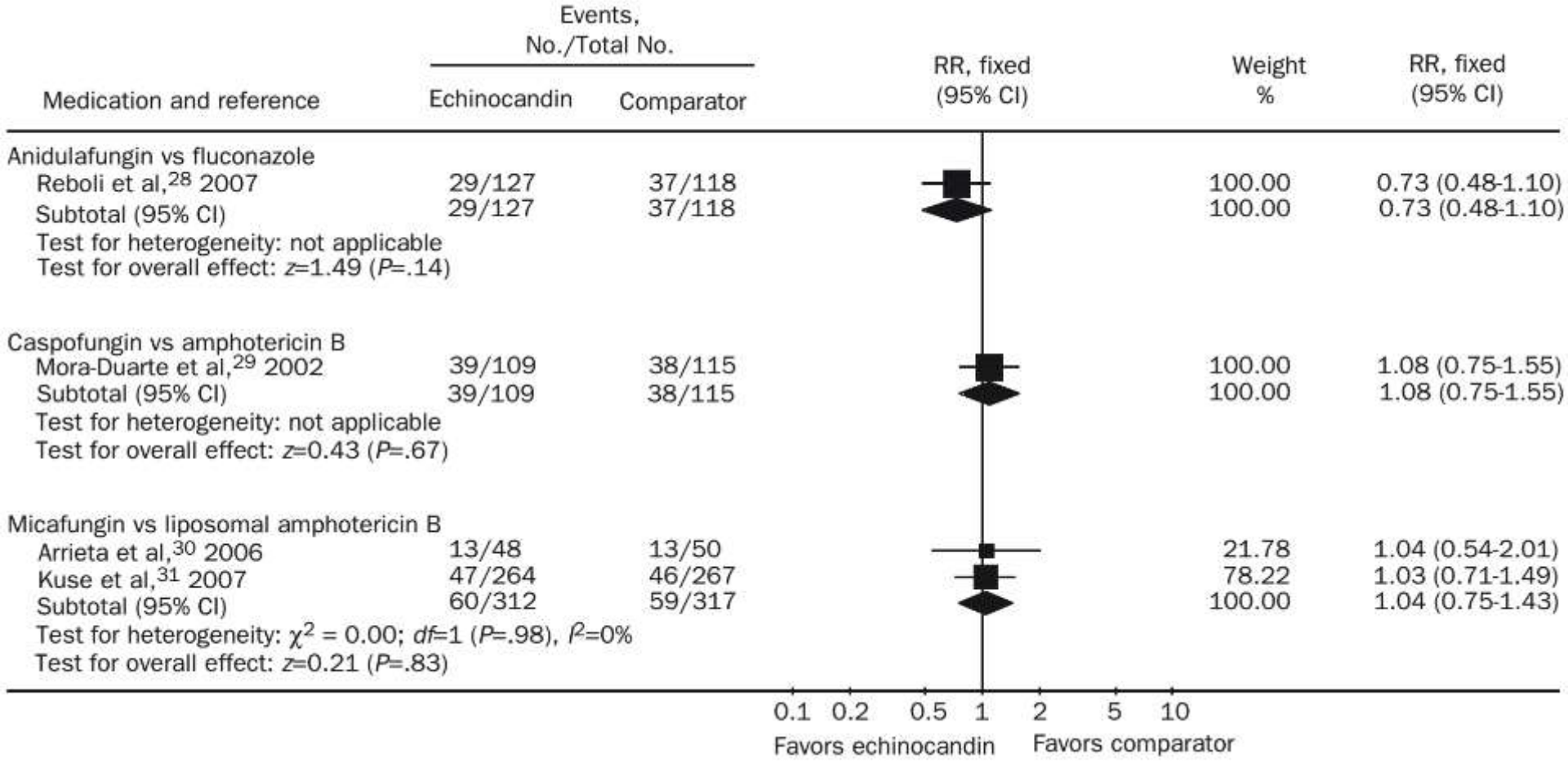
*Sustained successes as assessed by data-review committee at 12-week follow-up visit only. †Successes assessed by data-review committee at latest available study visit (including end of therapy, 2 weeks, or 6 weeks after end of treatment if 12-week assessment after end of treatment was not available). ‡Successes assessed by data-review committee.

	Voriconazole (n=272)	Amphotericin B/ fluconazole (n=131)	p
All-cause adverse events			
Patients with serious adverse events	125 (46%)	74 (57%)	0·048
Hepatic events*	63 (23%)	32 (24%)	0·78
Sepsis	57 (21%)	33 (25%)	0·34
Renal events†	22 (8%)	28 (21%)	0·0002
Fever	41 (15%)	24 (18%)	0·41
Chills	8 (3%)	10 (8%)	0·03
Vomiting	24 (9%)	17 (13%)	0·20
Rash	16 (6%)	7 (5%)	0·83
Visual events	11 (4%)	1 (1%)	0·07

Success rate of voriconazole in candidemia is similar to AmB

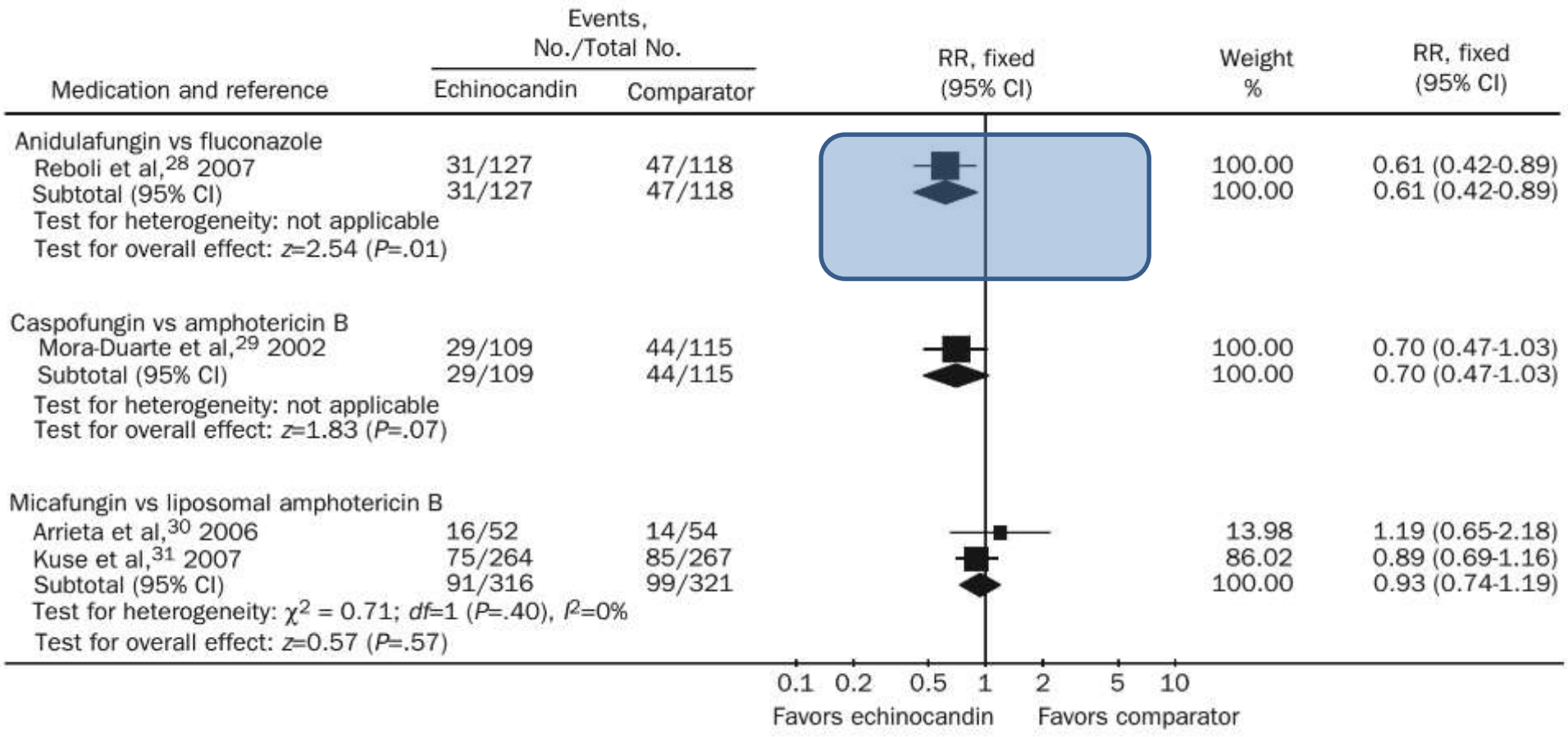
Lancet 2005; 366: 1435–42

All-cause mortality



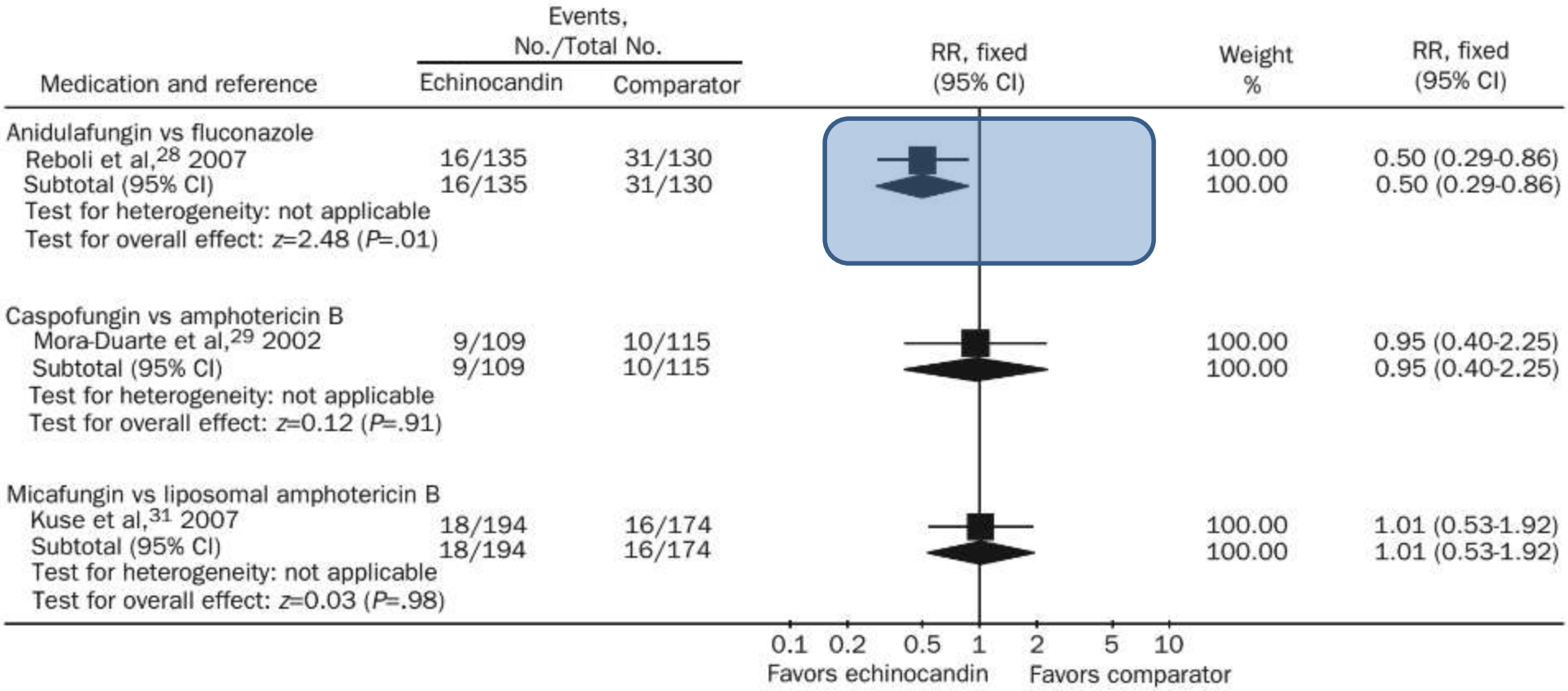
Gafter-Gvili A et al. Mayo Clin Proc. 2008 Sep;83(9):1011-21

Treatment failure



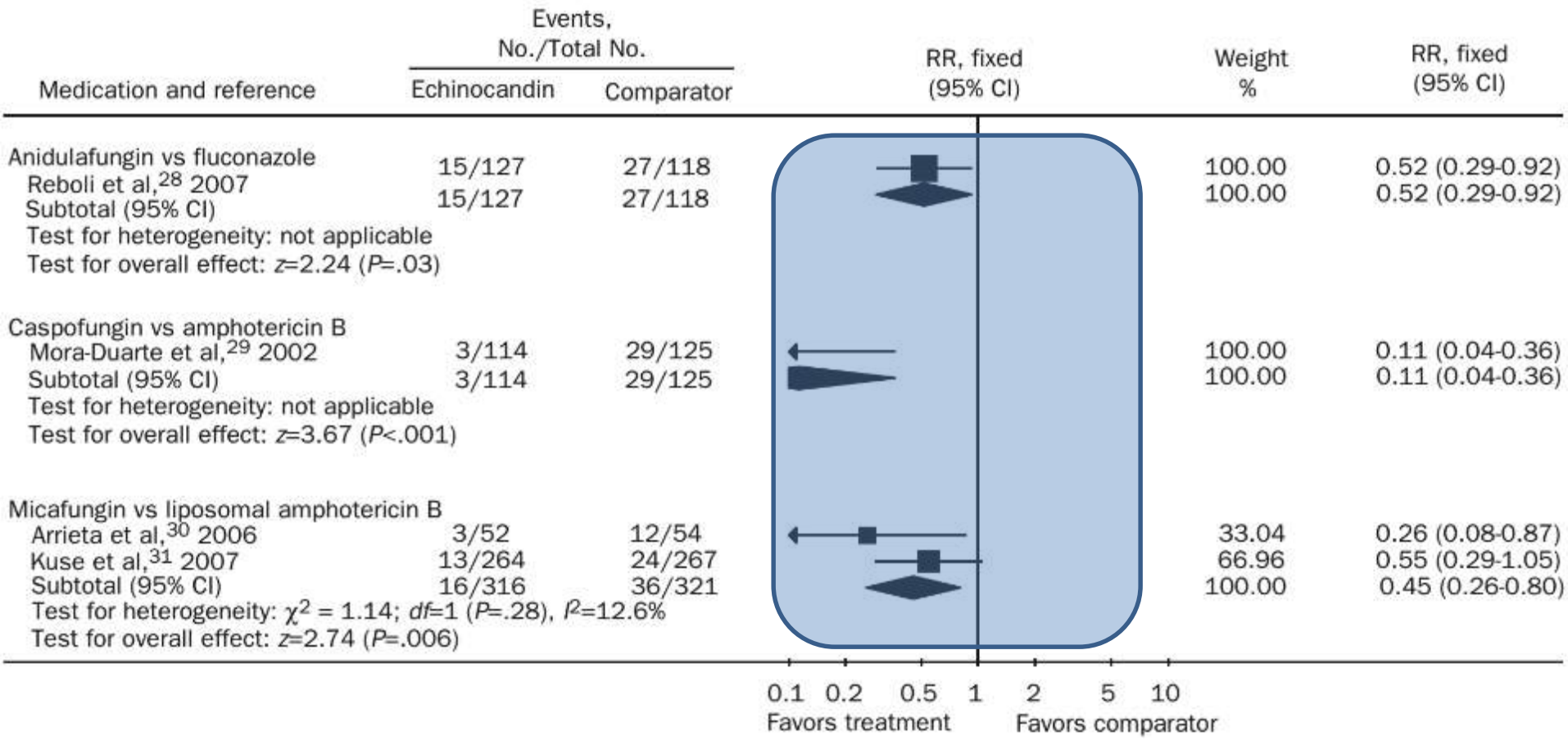
Gafter-Gvili A et al. Mayo Clin Proc. 2008 Sep;83(9):1011-21

Microbiological failure



Gafter-Gvili A et al. Mayo Clin Proc. 2008 Sep;83(9):1011-21

Adverse events requiring discontinuation



Gafter-Gvili A et al. Mayo Clin Proc. 2008 Sep;83(9):1011-21

Are echinocandins better than azoles/AmB?

Author, Year	Drug	n	Treatment success	Mortality	Adverse Events
Mora-Duarte J, 2002	Caspo vs AmB	109 vs 125	73.4% vs 61.7% (P = NS)	34.2% vs 30.4% (P = 0.53)	Infusion-related events (20.2 vs 48.8% P = 0.002) Nephrotoxicity (8.4% vs 24.8% P = 0.02) Hypokalemia (11.4% vs 26.4% P = 0.02) Discontinuation due to AE (2.6% vs 23.2% P = 0.003)
Colombo AL, 2003	Caspo vs AmB	224	74% vs 62%		
Kuse ER et al, 2007	Mica vs LAmB	202 vs 190	89.6% vs 89.5%	40% vs 40%	Infusion-related events (17 vs 28.8% P = 0.001) Nephrotoxicity (1.9% vs 6.4% P = 0.015) Hypokalemia (6.8% vs 12% P = 0.053) Discontinuation due to AE 4.9% vs 9% (P=0.087)
Reboli AC et al, 2007	Anidula vs Flucon	127 vs 118	75.6% vs 60.2% (P <0.02)	22.8% vs 31.4% (P = 0.13)	Nephrotoxicity (3.8% vs 8.8%) Hypokalemia (25.2% vs 19.2) Discontinuation due to AE 11.5% vs 21.6% (P=0.02) Transaminitis 1.5% vs 7.2% (P = 0.03)

Are echinocandins better than azoles/AmB?

- Echinocandins are at least as effective as AmB/LAmB and probably more effective than azoles
- They have a superior adverse effect profile compared to AmB/LAmB/azoles
- Higher cost is a drawback

Is any echinocandin better than its peer?

Micafungin versus Caspofungin for Treatment of Candidemia and Other Forms of Invasive Candidiasis

Peter G. Pappas,[1] Coleman M. F. Rotstein,[9] Robert F. Betts,[2] Marcio Nucci,[10] Deepak Talwar,[11] Jan J. De Waele,[13] Jose A. Vazquez,[3] Bertrand F. Dupont,[14] David L. Horn,[4] Luis Ostrosky-Zeichner,[6] Annette C. Reboli,[7] Byungse Suh,[5] Raghunadharao Digumarti,[12] Chunzhang Wu,[8] Laura L. Kovanda,[8] Leah J. Arnold,[8] and Donald N. Buell[8]

[1]University of Alabama at Birmingham; [2]University of Rochester, Rochester, New York; [3]Henry Ford Health System, Detroit, Michigan; [4]Thomas Jefferson University and [5]Temple University, Philadelphia, Pennsylvania; [6]University of Texas-Houston; [7]Cooper University Hospital, Camden, New Jersey; [8]Astellas Pharma US, Deerfield, Illinois; [9]Hamilton Health Sciences, Hamilton, Canada; [10]Hospital Universitário Clementino Fraga Filho, Rio de Janeiro, Brazil; [11]Metro Hospitals and Heart Institute, Uttar Pradesh, and [12]Nizam Institute of Medical Sciences, Hyderabad, India; [13]Ghent University Hospital, Ghent, Belgium; and [14]Hôpital Necker, Paris, France

Only head-to-head trial comparing echinocandins

Pappas PG et al. Clin Infect Dis. 2007 Oct 1;45(7):883-93

Table 3. Treatment success for the modified intent-to-treat population.

Variable	Micafungin arms		Caspofungin arm (n = 188)
	100 mg arm (n = 191)	150 mg arm (n = 199)	
Duration of therapy, median days (range)[a]	14 (1.0–61.0)	14 (1.0–56.0)	14 (1.0–43.0)
Treatment success[b]			
Investigators	146 (76.4)	142 (71.4)	136 (72.3)
Data review panel	139 (72.8)	139 (69.8)	133 (70.7)
Clinical success			
Overall	167 (87.4)	174 (87.4)	164 (87.2)
Candidemic[c]			
Complete response	128/163 (78.5)	136/168 (81.0)	123/161(76.4)
Partial response	15/163 (9.2)	12/168 (7.1)	21/161 (13.0)
Noncandidemic			
Complete response	14/28 (50.0)	17/30 (56.7)	15/26 (57.7)
Partial response	10/28 (35.7)	9/30 (30.0)	5/26 (19.2)
Mycological success	169 (88.5)	166 (83.4)	158 (84.0)

[a] Number of days from first dose day of blinded study drug to last dose day of either blinded study drug or protocol-defined oral fluconazole, whichever was later.

[b] Concordance between the investigators' assessments and the data review panel's assessment was 92.2%.

[c] Includes patients without candidemia but with *Candida* species recovered from culture of a normally sterile site.

Pappas PG et al. Clin Infect Dis. 2007 Oct 1;45(7):883-93

Table 1. Results in the MITT populations of pivotal trials of echinocandins for therapy of invasive fungal infections [45, 55-57].

	Anidulafungin	**Caspofungin**	**Micafungin**	
Comparator	Fluconazole	Amphotericin B deoxycholate	Liposomal amphotericin B	Caspofungin ****
Patient number (MITT), n	127 / 118	109 / 115	247 / 247	191 / 188
Candidemia, %	91 / 87	82.6 / 79.1	84.2 / 85.8 ***	85.3 / 85.6
Infection with *C. non-albicans*, %	36 / 41 *	64.4 / 45.9 [p = 0.0009]	62.4 / 58.9 ***	54.5 / 60.6
Neutropenia, %	2.4 / 3.4	12.8 / 8.7	11.9 / 7.9 ***	11.5 / 5.9
Switched to oral fluconazole, %	26.0 / 28.0	24.8 / 34.8	Not allowed	20.9 / 21.2
Global success at end of IV therapy, %	75.6 / 60.2 [p = 0.01]	73.4 / 61.7 [p = n.s.]	74.1 / 69.6 [p = n.s.]	76.4 / 72.3 [p = n.s.]
Global success at end of all therapy, %	74.0 / 56.8 [p < 0.02]	72.5 / 61.7 [p = n.s.]	74.1 / 69.6 [p = n.s.]	74.9 / 70.2 [p = n.s.]
Global success at 2 weeks follow up, %	64.6 / 49.2 [p < 0.02]	63.6 / 53.8 [p = n.s.]	Not reported	54.5/ 50.5 [p = n.s.]
Global success at 6 weeks follow up, %	55.9 / 44.1 [p = n.s.]	56.6 /47.5 ** [p = n.s.]	Not reported	46.6 / 42.6 [p = n.s.]
Microbiological success at end of IV therapy, %	88.1 / 76.2	Not reported	Not reported	88.5 / 84.0
Time to negative blood cultures, days	2 / 5 (*C. albicans*)[59]	Not reported	3 / 4 ***	2 / 2
Persistent infection, %	6.3 / 14.4 [p = n.s.]	8.3 / 8.7 [p = n.s.]	8.9 / 8.4 *** [p = n.s.]	5.8 / 9.6 [p = n.s.]
Mortality rate (ITT), %	22.8 / 31.4 [p = n.s.]	34.2 / 30.4 [p = n.s.]	40 / 40 [p = n.s.]	29.0 / 26.4

* Patients with *C. krusei* infection were excluded from the trial.
** Follow-up at 6-8 weeks after end of all therapy.
*** In the per-protocol set.
**** Column excludes results of micafungin 150 mg arm.

Success rate ~75% for all echinocandins

Glockner A. Eur J Med Res. 2011 Apr 28;16(4):167-79

Table 2. Frequencies of drug-related adverse events observed in patients receiving echinocandins

Adverse reaction, % of patients	Anidulafungin	Caspofungin	Micafungin
Phlebitis	< 1	3.5-25	1.6
Fever	< 1	4-40	1-14
Abdominal pain	< 2	3.6	1
Nausea / vomiting	1 / < 1	1-6 / 2-4	2-7 / 1-5
Diarrhea	3.1	3.6	1.6
Headache	1.3	4-15	2-17
Rash / pruritus	1 / <2	1-10 / < 2	1-12 / <1
Leukopenia	< 1	6.2	1.6
Neutropenia	1	1.9	1.2
Thrombocytopenia	< 2	3.1	< 1
Hypokalemia	3-10	2-10	1.2
Liver function test abnormalities	3-5	1-15	1-8

Glockner A. Eur J Med Res. 2011 Apr 28;16(4):167-79

Table 1 Pharmacokinetic parameters of echinocandins in adult subjects (Denning 2003; Deresinski and Stevens 2003; Wiederhold and Lewis 2003; Carver 2004; Murdoch and Plosker 2004; Raasch 2004; Zaas and Alexander 2005)

Variable	Caspofungin	Micafungin	Anidulafungin
C_{max} (mg/L)(50 mg single dose)	7.64	4.95	2.07–3.5
Bioavailability			2%–7%
$t_{1/2}$ (hours)	9-11	11-17	24–26
Vd (L/kg)	0.14 [9.67L]	0.215–0.242	0.5 [30–50L]
AUC (mg•h/L)	87.9–114.8	111.3	44.4–53
Protein binding (%)	96–97	99.8	84
Metabolism	Via slow peptide hydrolysis and N-acetylation. Also spontaneously degrades to inactive product	Via catechol-O-methyltransferase pathway	Not metabolised; undergoes slow chemical degradation to inactive metabolites
Cl_T (mL/min/kg)	0.15	0.185	0.26
f_e	1.4 %	0.7%	<1%
Elimination	35% feces, 41% urine (~1.4% as unchanged drug)	40% feces, <15% urine	Primarily in feces (<10% as intact drug), 1% urine
CSF penetration (% of plasma)	? low	? low	< 0.1 %
Dosage adjustment in renal insufficiency	No significant changes in PK. No dose adjustment needed.	No significant changes in PK. No dose adjustment needed.	No change in PK observed. No dose adjustment needed.
Dosage adjustment in hepatic insufficiency	Child-Pugh 5–6: none Child-Pugh 7–9: Significant increase in AUC. Reduce maintenance dose to 35 mg/day Child-Pugh >9: no data	Moderate dysfunction (Child-Pugh 7–9): C_{max}, Cl not significantly altered, AUC significantly decreased compared with healthy subjects.	No dose adjustment needed

Abbreviations: AUC, area under the plasma concentration-time curve; CI, confidence interval; Cl_T, total clearance; C_{max}, maximum concentration; CSF, cerebrospinal fluid; f_e, fraction of drug excreted unchanged in the urine; PK, pharmacokinetic; $t_{1/2}$, elimination half life; Vd, volume of distribution.

Eschenauer G, Depestel DD, Carver PL. Ther Clin Risk Manag. 2007 Mar;3(1):71-97.

Table 2 Adverse effects of echinocandins (Sable et al 2002; Carver 2004; Raasch 2004; Krause, Reinhardt, et al 2004; Cancidas PI 2005; Groll et al 2005; Mycamine PI 2005; Eraxis PI 2006)

Parameter		Caspofungin	Micafungin	Anidulafungin
Hematologic	Neutropenia		1.2%	1.0%
	Leukopenia		0.9%	0.7%
	Eosinophilia	3%	Rarely related to infusion	
	Thrombocytopenia	<4%		
	Leukopenia	<4%		
	Decreased Hgb, Hct	3%–12%		
Gastrointestinal	Nausea	<3%	2.4%	1.0%
	Diarrhea		2.1%	
	Vomiting	<3%		0.7%
	Dyspepsia			0.3%
Miscellaneous	Hyperbilirubinemia		3.3%	
	Increased GGT			<1%
	Elevated AST/ALT	Do not exceed 5X ULN, transient, reversible. ~14%, <2%, 11%–24%	Rare, and generally insignificant	<1%
	Hypokalemia	11% after 70 mg dose; <4% with 50 mg dose	1.8%	2.4%–3.1%
	Rash			<1%
	Pyrexia	12%–26%, 3.6% (depending on comparator)		0.7%
	Headache	<3%		1.3%
	Flushing	<3%		
	Phlebitis/thrombophlebitis	3.5%, 12%–18%	Rare	1.3%
	Infusion related reactions/ Histamine release	2%	Rare	1 pt "flushing" with infusion

Abbreviations: AST, aspartate aminotransferase; ALT, alanine aminotransferase; GGT, gamma glutaryl transferase; Hct, hematocrit; Hgb, hemoglobin; pt, patient; ULN, upper limit of normal.

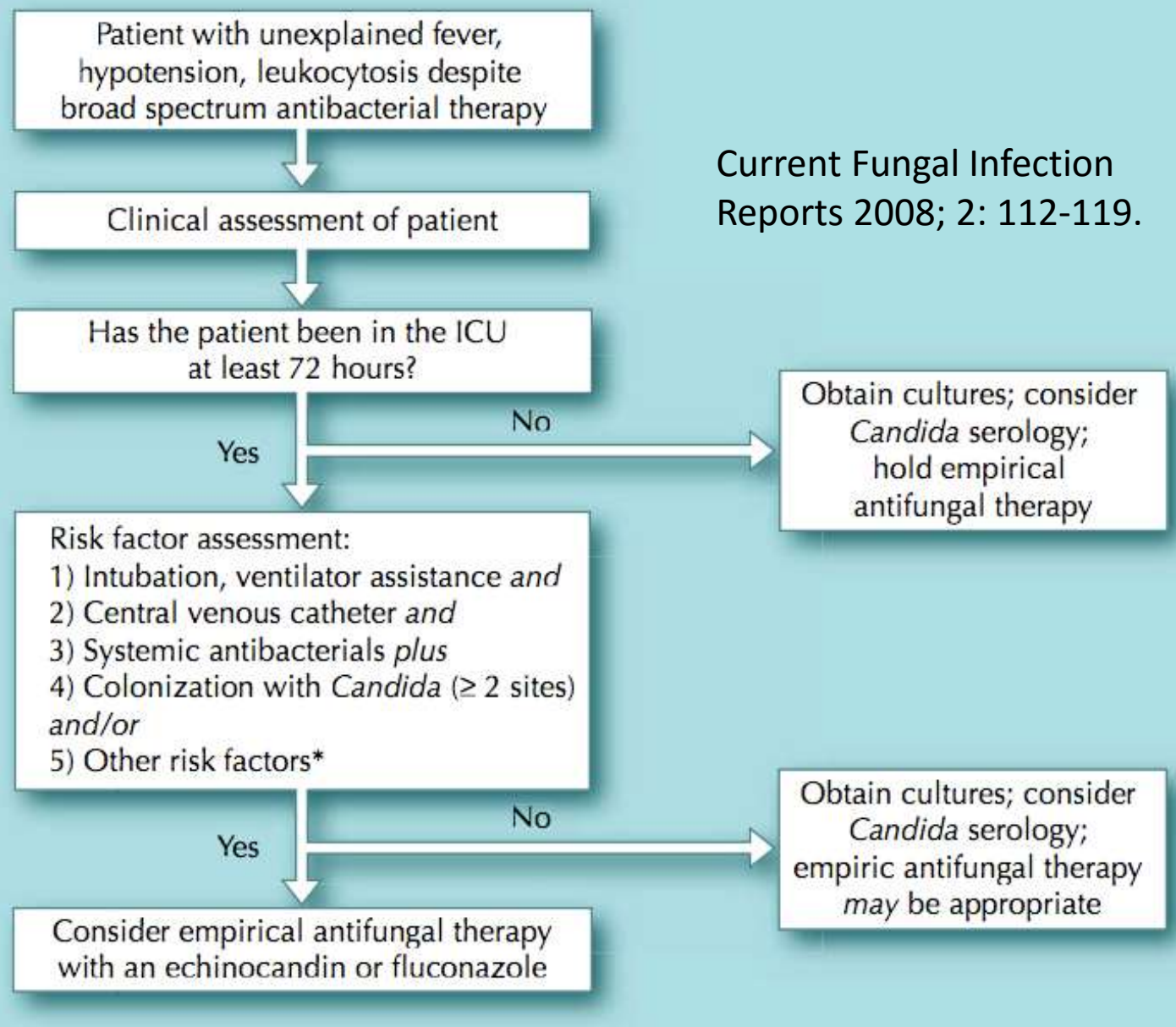
Eschenauer G, Depestel DD, Carver PL. Ther Clin Risk Manag. 2007 Mar;3(1):71-97.

Is any echinocandin better than its peer?

- Overall clinical efficacy appears to be similar between all three echinocandins.
- In vitro studies have shown lower MICs for Anidulafungin against strains of C. parapsilosis with high MICs to caspofungin and micafungin. However, clinical supremacy of anidulafungin over the other two echinocandins is yet to be demonstrated.
- Caspofungin has a slightly higher incidence of adverse events.

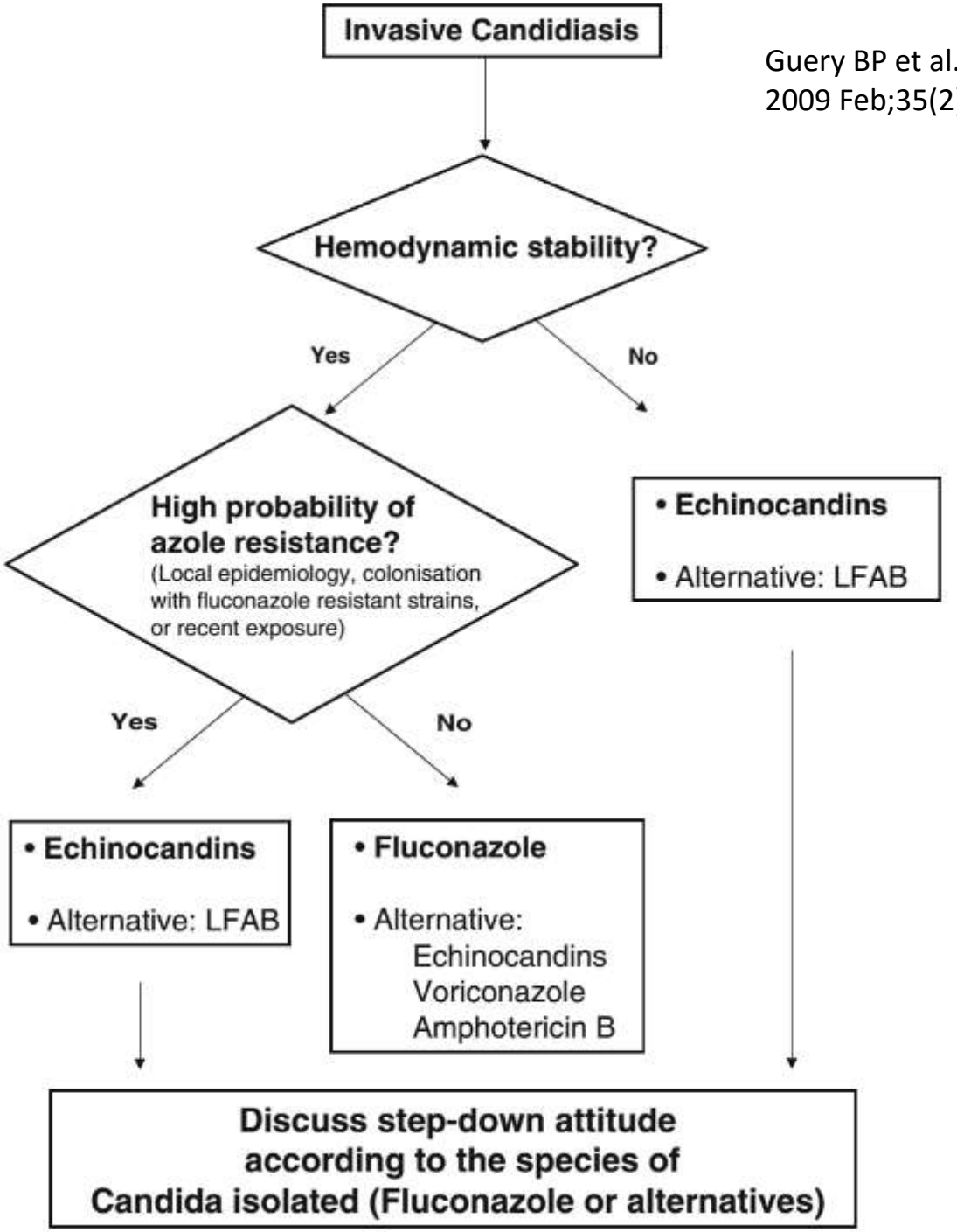
Eschenauer G, Depestel DD, Carver PL. Ther Clin Risk Manag. 2007 Mar;3(1):71-97

Summary:
Rx of candidemia/invasive candidiasis



Current Fungal Infection Reports 2008; 2: 112-119.

*Specific risk factors include, but are not limited to, the following: any hemodialysis, acute pancreatitis, neutropenia, recent surgery, pharmacologic immunosuppression, parenteral nutrition, burns, or trauma.



Guery BP et al. Intensive Care Med. 2009 Feb;35(2):206-14

Treatment

Invasive aspergillosis

1. Which azole?
2. Is voriconazole better than AmB?
3. How good are echinocandins?

How good are azoles for IA?

- Fluconazole: No activity against aspergillus
- Itraconazole: Effective; But no RCT
- Posaconazole: Probably effective; Insufficient data
- Voriconazole: RCT available

Table 5. Summary of the clinical efficacy of itraconazole (ITC) in published phase II clinical trials and compassionate use data

Study /Design	Endpoints of Efficacy	Results
Non-comparative, open-label multicenter study of oral itraconazole (600 mg/day for four days followed by 400 mg/day) for treatment of proven/probable invasive aspergillosis in patients with a variety of underlying conditions [51]	Complete or partial response at end of treatment as defined per protocol	Thirty of 76 (39%) evaluable patients (17% of which were neutropenic at start of therapy) who received itraconazole for 0.3 to 97 weeks (median, 46) had a complete or partial response, and 3 (4%) had stable disease.
Review of compassionate use data of oral itraconazole therapy for proven/probable invasive aspergillosis in patients with a variety of underlying conditions; most patients received from 200 to 400 mg/day [52]	Complete or partial response at end of treatment as defined per protocol	Seventy-nine of 125 (63%) evaluable patients (13% of which were neutropenic at start of therapy) who received itraconazole for 3 to 1675 days (median, 121) had a complete or partial response, and 20 (16%) had stable disease.
Non-comparative, open-label multicenter study investigating intravenous itraconazole (2 days at 400mg/day, 12 days at 200 mg/day), followed by 12 weeks of oral capsules (400mg/day) for treatment of proven/probable invasive aspergillosis; most patients had a hematological malignancy (90%) as underlying condition [53].	Complete or partial response at end of treatment as defined per protocol	15/31 (48%) patients receiving at least one dose had a complete (n = 8) or partial (n = 7) response. The median duration of therapy with IV itraconazole was 14 days (range, 4–28), and that of PO itraconazole was 78.5 days (range, 1–90). Nineteen (61%) of patients were neutropenic at the start of therapy.

The available data support the notion that itraconazole can be a safe and effective therapeutic alternative to amphotericin B in the treatment of invasive aspergillosis. However, since data from a randomized, comparative trial are lacking, induction therapy of invasive aspergillosis with itraconazole is only indicated when standard therapies have failed or cannot be tolerated by the patient.

Phase II trials published in 1994, 1997, 2001

Groll AH. Mycoses. 2002;45 Suppl 3:48-55

NIAID Mycoses Study Group Multicenter Trial of Oral Itraconazole Therapy for Invasive Aspergillosis

David W. Denning, MBBS, *San Jose, California*, Jeanette Y. Lee, PhD, *Birmingham, Alabama*, John S. Hostetler, MD, *San Jose California*, Peter Pappas, MD, *Birmingham, Alabama*, Carol A. Kauffman, MD, *Ann Arbor, Michigan*, Daniel H. Dewsnup, DO, *San Jose, California*, John N. Galgiani, MD, *Tucson, Arizona*, John R. Graybill, MD, *San Antonio, Texas*, Alan M. Sugar, MD, *Boston, Massachusetts*, Antonino Catanzaro, MD, *San Jose, California*, Harry Gallis, MD, John R. Perfect, MD, *Durham, North Carolina*, Bonita Dockery, RN, William E. Dismukes, MD, *Birmingham, Alabama*, David A. Stevens, MD, *San Jose, California*

N = 76

Complete or partial response in only 30 (39%) patients

Denning DW et al. Am J Med. 1994 Aug;97(2):135-44

Treatment of Invasive Aspergillosis with Posaconazole in Patients Who Are Refractory to or Intolerant of Conventional Therapy: An Externally Controlled Trial

Thomas J. Walsh,[1] Issam Raad,[3] Thomas F. Patterson,[4] Pranatharthi Chandrasekar,[5] Gerald R. Donowitz,[6] Richard Graybill,[4] Reginald E. Greene,[7] Ray Hachem,[3] Susan Hadley,[8] Raoul Herbrecht,[16] Amelia Langston,[9] Arnold Louie,[10a] Patricia Ribaud,[17,a] Brahm H. Segal,[11] David A. Stevens,[12] Jo-Anne H. van Burik,[13] Charles S. White,[2] Gavin Corcoran,[14,a] Jagadish Gogate,[14,a] Gopal Krishna,[14] Lisa Pedicone,[14] Catherine Hardalo,[14] and John R. Perfect[15]

[1]National Cancer Institute, Bethesda, and [2]University of Maryland, Baltimore, Maryland; [3]The MD Anderson Cancer Center, Houston, and [4]The University of Texas Health Science Center, San Antonio, Texas; [5]Wayne State University, Detroit, Michigan; [6]University of Virginia, Charlottesville; [7]Massachusetts General Hospital and [8]New England Medical Center, Boston, Massachusetts; [9]Emory University Hospital, Atlanta, Georgia; [10]Albany Medical Center, Albany, and [11]Roswell Park Memorial Cancer Center, Buffalo, New York; [12]Santa Clara Valley Medical Center, San Jose, California; [13]University of Minnesota School of Medicine, Minneapolis; [14]Schering-Plough Research Institute, Kenilworth, New Jersey; [15]Duke University, Durham, North Carolina; and [16]Hôpital de Hautepierre, Strasbourg, and [17]Hospital Saint Louis, Paris, France

Posaconazole monotherapy in patients with invasive aspergillosis and other mycoses (n=107) *who were refractory to or intolerant of conventional antifungal therapy*. Data from 86 external control cases were collected retrospectively to provide a comparative reference group (n=86).

Overall success rate 42% vs 26% (P = 0.006)

Walsh TJ et al. Clin Infect Dis. 2007 Jan 1;44(1):2-12

VORICONAZOLE VERSUS AMPHOTERICIN B FOR PRIMARY THERAPY OF INVASIVE ASPERGILLOSIS

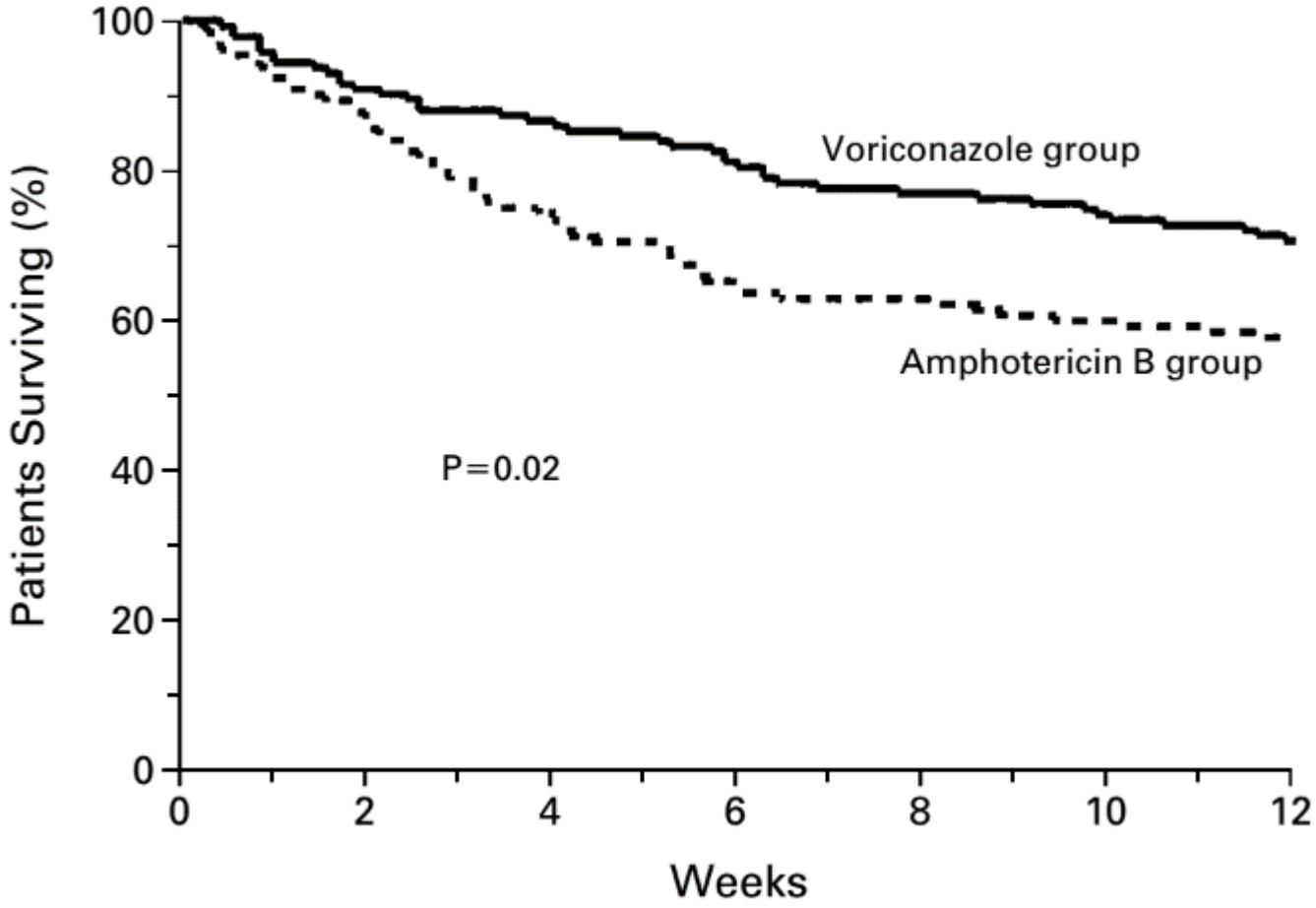
RAOUL HERBRECHT, M.D., DAVID W. DENNING, F.R.C.P., THOMAS F. PATTERSON, M.D., JOHN E. BENNETT, M.D., REGINALD E. GREENE, M.D., JÖRG-W. OESTMANN, M.D., WINFRIED V. KERN, M.D., KIEREN A. MARR, M.D., PATRICIA RIBAUD, M.D., OLIVIER LORTHOLARY, M.D., PH.D., RICHARD SYLVESTER, SC.D., ROBERT H. RUBIN, M.D., JOHN R. WINGARD, M.D., PAUL STARK, M.D., CHRISTINE DURAND, M.D., DENIS CAILLOT, M.D., ECKHARD THIEL, M.D., PRANATHARTHI H. CHANDRASEKAR, M.D., MICHAEL R. HODGES, M.D., HARAN T. SCHLAMM, M.D., PETER F. TROKE, PH.D., AND BEN DE PAUW, M.D., FOR THE INVASIVE FUNGAL INFECTIONS GROUP OF THE EUROPEAN ORGANISATION THE GLOBAL ASPERGILLUS STUDY GROUP*

TABLE 3. RESPONSE RATE AT WEEK 12 IN THE MODIFIED INTENTION-TO-TREAT POPULATION.

RESPONSE	VORICONAZOLE GROUP (N=144)	AMPHOTERICIN B GROUP (N=133)
	no. (%)	
Successful outcome*	76 (52.8)	42 (31.6)
Complete response	30 (20.8)	22 (16.5)
Partial response	46 (31.9)	20 (15.0)
Unsuccessful outcome	68 (47.2)	91 (68.4)
Stable disease	8 (5.6)	8 (6.0)
Failure of therapy	55 (38.2)	78 (58.6)
Indeterminate	5 (3.5)	5 (3.8)

Absolute difference, 21.2% points; 95% CI, 10.4 to 32.9

Herbrecht R et al. N Engl J Med. 2002 Aug 8;347(6):408-15



Herbrecht R et al. N Engl J Med. 2002 Aug 8;347(6):408-15

How good are azoles for IA?

- Fluconazole: Not useful
- Itraconazole: Useful as salvage and maintenance therapy
- Posaconazole: Useful as salvage therapy
- Voriconazole: Azole of choice; Probably better than AmB

How good are echinocandins for IA?

Table 3. First-line Treatment of Invasive Aspergillosis: Prospective Controlled Trials.

Study	N=	Design	Treatment	MDST (range)	Response (CR+PR)	Survival week 12
Herbrecht	277	op, rd	AmB Desoxycholate 1-1.5 mg/kg	10 (1-84)	31.6%	57.9%
2002 NEJM			Vori 2x6mg/kg d1 and 2x4 mg/kg d2+ i.v.*	77 (2-84)	52.8%	70.8%
Cornely	201	db, rd	LAmB 3mg/kg (d1-14) } op 3mg/kg d 15+	14 (1-60)	50%	72%
2007 CID			LAmB 10 mg/kg (d1-14) } op 3mg/kg d 15+	15 (1-57)	46%	59%
Herbrecht 2010 BMT **	24	op, sa	Caspofungin 70mg d1/50 mg d2+	24	33%	50%
Viscoli 2009JAC #	61	op, sa	Caspofungin 70mg d1/50 mg d 2+	15 (3-84)	33%	53%

Abbreviations: op = open, rd = randomized, db = double blind, sa = single arm, MDST = Median duration of study drug treatment in days, * a switch to oral voriconazole was allowed after day 7, **allogeneic cohort of patients, # hematological malignancies and autologous transplantation

Data available only for caspofungin, that too from open-label, single arm trials

Response rates appear poorer compared to that of Vori/LAmB (30% vs 50% approx.)

Karthaus M. Eur J Med Res. 2011 Apr 28;16(4):145-52

Efficacy and Safety of Caspofungin for Treatment of Invasive Aspergillosis in Patients Refractory to or Intolerant of Conventional Antifungal Therapy

Clin Infect Dis. 2004 Dec 1;39(11):1563-71

Johan Maertens,[1] Issam Raad,[2] George Petrikkos,[3] Marc Boogaerts,[1] Dominik Selleslag,[4] Finn B. Petersen,[5] Carole A. Sable,[6] Nicholas A. Kartsonis,[5] Angela Ngai,[6] Arlene Taylor,[6] Thomas F. Patterson,[7] David W. Denning,[8] and Thomas J. Walsh,[9] for the Caspofungin Salvage Aspergillosis Study Group[a]

[1]University Hospital, Gasthuisberg, Leuven, Belgium; [2]The M. D. Anderson Cancer Center, Houston, Texas; [3]Laiko General Hospital, University of Athens, Athens, Greece; [4]AZ St. Jan, Brugge, Belgium; [5]University of Utah Health Sciences Center, Salt Lake City; [6]Merck Research Labs, West Point, Pennsylvania; [7]University of Texas Health Science Center, San Antonio; [8]University of Manchester, Manchester, United Kingdom; and [9]National Cancer Institute, Bethesda, Maryland

Background. Invasive aspergillosis (IA) is an important cause of morbidity and mortality among immunocompromised patients. Echinocandins are novel antifungal molecules with in vitro and in vivo activity against *Aspergillus* species.

Methods. We investigated the efficacy and safety of caspofungin in the treatment of IA. Ninety patients with IA who were refractory to or intolerant of amphotericin B, lipid formulations of amphotericin B, or triazoles were enrolled to receive caspofungin.

Results. Efficacy was assessed for 83 patients who had infection consistent with definitions of IA and who received ⩾1 dose of study drug. Common underlying conditions included hematologic malignancy (48% of patients), allogeneic blood and marrow transplantation (25% of patients), and solid-organ transplantation (11% of patients). Seventy-one patients (86%) were refractory to and 12 patients (14%) were intolerant of previous therapy. A favorable response to caspofungin therapy was observed in 37 (45%) of 83 patients, including 32 (50%) of 64 with pulmonary aspergillosis and 3 (23%) of 13 with disseminated aspergillosis. Two patients discontinued caspofungin therapy because of drug-related adverse events. Drug-related nephrotoxicity and hepatotoxicity occurred infrequently.

Conclusion. Caspofungin demonstrated usefulness in the salvage treatment of IA.

Treatment

Role of combination antifungal therapy

Combination therapy for Candidemia

Role of combination therapy for the treatment of candidemia has not been established clearly

A Randomized and Blinded Multicenter Trial of High-Dose Fluconazole plus Placebo versus Fluconazole plus Amphotericin B as Therapy for Candidemia and Its Consequences in Nonneutropenic Subjects

Rex JH et al. Clin Infect Dis. 2003 May 15;36(10):1221-8

John H. Rex, Peter G. Pappas, Adolf W. Karchmer, Jack Sobel, John E. Edwards, Susan Hadley, Corstiaan Brass, Jose A. Vazquez, Stanley W. Chapman, Harold W. Horowitz, Marcus Zervos, David McKinsey, Jeannette Lee, Timothy Babinchak, Robert W. Bradsher, John D. Cleary, David M. Cohen, Larry Danziger, Mitchell Goldman, Jesse Goodman, Eileen Hilton, Newton E. Hyslop, Daniel H. Kett, Jon Lutz, Robert H. Rubin, W. Michael Scheld, Mindy Schuster, Bryan Simmons, David K. Stein, Ronald G. Washburn, Linda Mautner, Teng-Chiao Chu, Helene Panzer, Rebecca B. Rosenstein, and Jenia Booth, for the National Institute of Allergy and Infectious Diseases Mycoses Study Group[a]

(See the editorial commentary by Odds on pages 1229–31)

A randomized, blinded, multicenter trial was conducted to compare fluconazole (800 mg per day) plus placebo with fluconazole plus amphotericin B (AmB) deoxycholate (0.7 mg/kg per day, with the placebo/AmB component given only for the first 5–6 days) as therapy for candidemia due to species other than *Candida krusei* in adults without neutropenia. A total of 219 patients met criteria for a modified intent-to-treat analysis. The groups were similar except that those who were treated with fluconazole plus placebo had a higher mean (± standard error) Acute Physiology and Chronic Health Evaluation II score (16.8 ± 0.6 vs. 15.0 ± 0.7; $P = .039$). Success rates on study day 30 by Kaplan-Meier time-to-failure analysis were 57% for fluconazole plus placebo and 69% for fluconazole plus AmB ($P = .08$). Overall success rates were 56% (60 of 107 patients) and 69% (77 of 112 patients; $P = .043$), respectively; the bloodstream infection failed to clear in 17% and 6% of subjects, respectively ($P = .02$). In nonneutropenic subjects, the combination of fluconazole plus AmB was not antagonistic compared with fluconazole alone, and the combination trended toward improved success and more-rapid clearance from the bloodstream.

Combination therapy for IA

"In the absence of a well-controlled, prospective clinical trial, routine administration of combination therapy for primary therapy of IPA is not routinely recommended (B-II)"
(IDSA 2008 Treatment of aspergillosis)

Empirical therapy

Delay in start of antifungal Rx

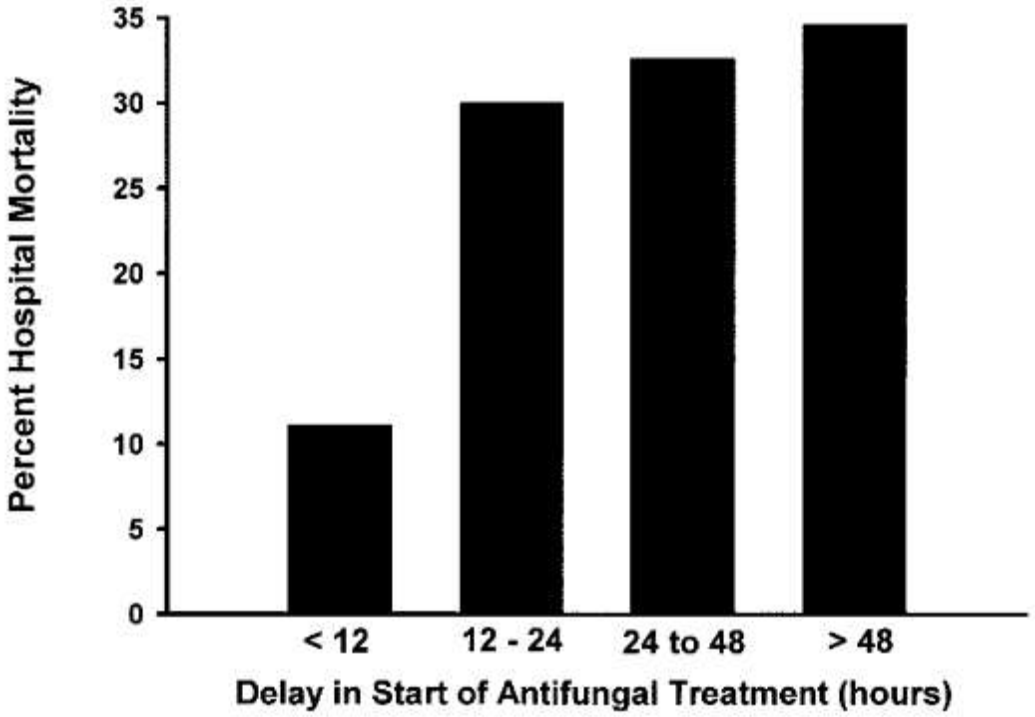


FIG. 1. Relationship between hospital mortality and the timing of antifungal treatment. The timing of antifungal therapy was determined to be from the time when the first blood sample for culture positive for fungi was drawn to the time when antifungal treatment was first administered to the patient.

Morrell M, Fraser VJ, Kollef MH. Antimicrob Agents Chemother. 2005 Sep;49(9):3640-5

Baddley et al. BMC Infectious Diseases 2013, 13:29
http://www.biomedcentral.com/1471-2334/13/29

BMC Infectious Diseases

RESEARCH ARTICLE Open Access

Aspergillosis in Intensive Care Unit (ICU) patients: epidemiology and economic outcomes

John W Baddley[1*], Jennifer M Stephens[2], Xiang Ji[2], Xin Gao[2], Haran T Schlamm[3] and Miriam Tarallo[4]

Methods: Retrospective cohort study using Premier Inc. Perspective™ US administrative hospital database (2005–2008). Adults with ICU stays and aspergillosis (ICD-9 117.3 plus 484.6) who received initial antifungal therapy (AF) in the ICU were included. Patients with traditional risk factors (cancer, transplant, neutropenia, HIV/AIDS) were excluded. The relationship of antifungal therapy and co-morbidities to economic outcomes were examined using Generalized linear models.

Results: From 6,424 aspergillosis patients in the database, 412 (6.4%) ICU patients with IA were identified. Mean age was 63.9 years and 53% were male. Frequent co-morbidities included steroid use (77%), acute respiratory failure (76%) and acute renal failure (41%). In-hospital mortality was 46%. The most frequently used AF was voriconazole (71% received at least once). Mean length of stay (LOS) was 26.9 days and mean total hospital cost was $76,235. Each 1 day lag before initiating AF therapy was associated with 1.28 days longer hospital stay and 3.5% increase in costs ($p < 0.0001$ for both).

EUROPEAN JOURNAL OF CANCER 44 (2008) 2192–2203

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journal homepage: www.ejconline.com

Empirical antifungal therapy for patients with neutropenia and persistent fever: Systematic review and meta-analysis

Elad Goldberg[a,b,*], *Anat Gafter-Gvili*[b,c], *Eyal Robenshtok*[a,b], *Leonard Leibovici*[a,b], *Mical Paul*[b,d]

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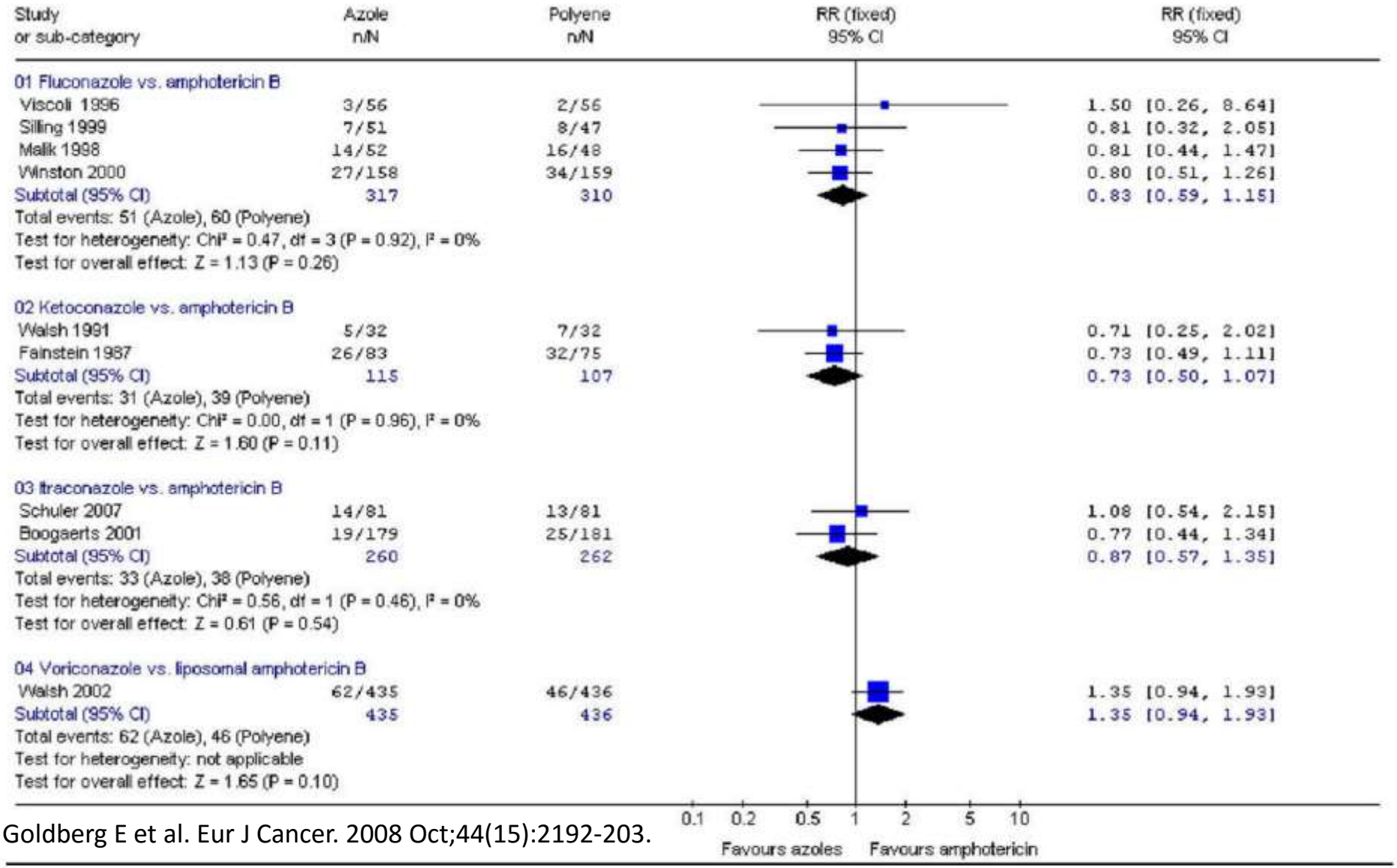
[b]*Sackler School of Medicine, Tel Aviv University, Ramat Aviv, Israel*
[c]*Hematology Department, Rabin Medical Center, Beilinson Campus, Petah-Tiqva, Israel*
[d]*Infectious Disease Unit, Rabin Medical Center, Beilinson Campus, Petah-Tiqva, Israel*



Goldberg E et al. Eur J Cancer. 2008 Oct;44(15):2192-203.

Fig. 4 – All-cause mortality for trials comparing empirical antifungal therapy using azoles versus polyenes (stratified by type of azole and polyene). Relative risks for the subcategories are pooled using the fixed effect model, on a logarithmic scale of 0.1–10. The combined relative risk for all trials comparing azoles versus amphotericin B (non-lipid) is 0.81 [95% CI 0.65–1.01].

Annals of Internal Medicine
Established in 1927 by the American College of Physicians

Intravenous and Oral Itraconazole versus Intravenous Amphotericin B Deoxycholate as Empirical Antifungal Therapy for Persistent Fever in Neutropenic Patients with Cancer Who Are Receiving Broad-Spectrum Antibacterial Therapy: A Randomized, Controlled Trial

Marc Boogaerts, MD, PhD; Drew J. Winston, MD; Eric J. Bow, MD; Gary Garber, MD; Annette C. Reboli, MD; Anthony P. Schwarer, MD, FRACP; Nicolas Novitzky, MD, PhD; Angelika Boehme, MD; Elisabeth Chwetzoff, MD; Karel De Beule, RPh, the Itraconazole Neutropenia Study Group*

[+] Article and Author Information

Ann Intern Med. 2001;135(6):412-422. doi:10.7326/0003-4819-135-6-200109180-00010

Table 2. **Response to Empirical Antifungal Therapy**

Response	Itraconazole Group (n = 179)*	Amphotericin B Group (n = 181)*	Difference (95% CI)†
Overall, *n/n* (%)	84/179 (47)	68/181 (38)	9.0 (−0.8 to 19.5)
By sign/transplantation status, *n/n* (%)‡			
No signs, no transplantation	51/103 (49)	34/105 (32)	17.0 (−4.0 to 30.3)
No signs, transplantation	24/52 (46)	22/48 (46)	0 (−19.2 to 19.9)
Signs, no transplantation	4/14 (29)	6/18 (33)	−4.0 (−36.9 to 27.4)
Signs and transplantation	5/10 (50)	6/10 (60)	−10.0 (−53.4 to 33.4)
Defervescence, *n/n* (%)	131/179 (73)	127/181 (70)	3.0 (−6.3 to 12.3)
Median time to defervescence (range), *d*	7 (1–26)	6 (1–22)	
By previous antifungal prophylaxis, *n/n* (%)			
Yes	63/132 (48)	48/139 (35)	13.0 (1.6 to 24.8)
No	21/47 (45)	20/42 (48)	−3.0 (−23.7 to 17.8)
By duration of fever that did not respond to antibiotic therapy, *n/n* (%)			
<5 d	32/70 (46)	34/70 (49)	−3.0 (−19.4 to 13.7)
≥5 d	52/109 (45)	34/110 (31)	6.0 (4.0 to 29.5)
By duration of neutropenia, *n/n* (%)			
<7 d	27/60 (45)	23/58 (40)	5.0 (−12.5 to 23.1)
≥7 d	56/107 (52)	44/108 (41)	11.0 (−1.6 to 24.8)
Breakthrough fungal infections, *n*	5	5	
Candidemia	2§	2‖	
Filamentous fungal pneumonia	3¶	3**	

* Four patients (3 in the itraconazole group and 1 in the amphotericin B group) had no global evaluation.
† Differences are expressed as percentage points.
‡ Signs or symptoms of invasive fungal infection were cough, dyspnea, chest pain, increased respiratory rate, headaches, or confusion. Transplantation was hematopoietic stem-cell transplantation.
§ *Candida krusei* in 1 patient and *C. guillermondii* in 1 patient.
‖ *Candida albicans*.
¶ *Aspergillus fumigatus* in 1 patient, *A. sydowi* in 1 patient, and *Geotrichum capitatum* in 1 patient.
** *Aspergillus fumigatus*.

Boogaerts M et al. Ann Intern Med. 2001 Sep 18;135(6):412-22

Table 3. **Safety and Toxicity of Empirical Treatment with Itraconazole and Amphotericin B**

Event	Itraconazole Group (n = 192)	Amphotericin B Group (n = 192)
	n (%)	
Drug-related adverse event	9 (5)	103 (54)*
Adverse event leading to treatment withdrawal	36 (19)	73 (38)*
Severe adverse event	37 (19)	65 (34)*
Infusion-related toxicity		
Fever	12 (6)	20 (10)
Chills or rigors	19 (10)†	77 (40)†
Nausea	46 (24)	45 (23)
Vomiting	37 (19)	40 (21)
Dyspnea	17 (9)	21 (11)
Tachycardia	6 (3)	12 (6)
Hypotension	13 (7)	21 (11)
Metabolic toxicity		
Nephrotoxicity‡	10 (5)†	46 (24)†
Hypokalemia	34 (18)§	59 (31)§
Hypomagnesemia	14 (7)	17 (9)
Bilirubinemia	19 (10)†	9 (5)†
Increased serum alanine aminotransferase level	5 (3)	3 (2)
Increased serum aspartate aminotransferase level	4 (2)	1 (1)
Increased γ-glutamyltransferase level	4 (2)	3 (2)
Premedication to support study drug administration		
Analgesics	8 (4)†	82 (43)†
Antihistamines	6 (3)†	69 (36)†
Corticosteroids	1 (0.5)†	50 (26)†

* $P = 0.001$.
† $P < 0.001$.
‡ Defined as a serum creatinine concentration of more than twice the baseline value.
§ $P = 0.004$.

Boogaerts M et al. Ann Intern Med. 2001 Sep 18;135(6):412-22

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VORICONAZOLE COMPARED WITH LIPOSOMAL AMPHOTERICIN B FOR EMPIRICAL ANTIFUNGAL THERAPY IN PATIENTS WITH NEUTROPENIA AND PERSISTENT FEVER

THOMAS J. WALSH, M.D., PETER PAPPAS, M.D., DREW J. WINSTON, M.D., HILLARD M. LAZARUS, M.D., FINN PETERSEN, M.D., JOHN RAFFALLI, M.D., SAUL YANOVICH, M.D., PATRICK STIFF, M.D., RICHARD GREENBERG, M.D., GERALD DONOWITZ, M.D., AND JEANETTE LEE, PH.D., FOR THE NATIONAL INSTITUTE OF ALLERGY AND INFECTIOUS DISEASES MYCOSES STUDY GROUP*

TABLE 2. RESPONSE TO EMPIRICAL THERAPY.

RESPONSE INDICATOR	VORICONAZOLE (N=415)	LIPOSOMAL AMPHOTERICIN B (N=422)	POINT ESTIMATE FOR THE PERCENT DIFFERENCE (95% CONFIDENCE INTERVAL)
Overall response — no. (%)	108 (26.0)	129 (30.6)	−4.5 (−10.6 to 1.6)
No breakthrough fungal infections within 7 days of end of therapy — no. (%)	407 (98.1)	401 (95.0)	+3.1 (0.6 to 5.5)
Survival 7 days after end of therapy — no. (%)*	382 (92.0)	397 (94.1)	−2.0 (−5.5 to 1.4)
No discontinuation due to toxicity or lack of efficacy before recovery from neutropenia — no. (%)	374 (90.1)	394 (93.4)	−3.2 (−7.0 to 0.5)
Resolution of fever during neutropenia — no. (%)	135 (32.5)	154 (36.5)	−4.0 (−10.4 to 2.5)
Complete or partial response of patients with base-line fungal infections by end of treatment — no./total no. (%)	6/13 (46.2)	4/6 (66.7)	−20.5 (−67.0 to 25.9)

There were fewer documented breakthrough fungal infections in patients treated with voriconazole than in those treated with liposomal amphotericin B (1.9% vs. 5.0 %, P=0.02)

Walsh TJ et al. N Engl J Med. 2002 Jan 24;346(4):225-34.

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Caspofungin versus Liposomal Amphotericin B for Empirical Antifungal Therapy in Patients with Persistent Fever and Neutropenia

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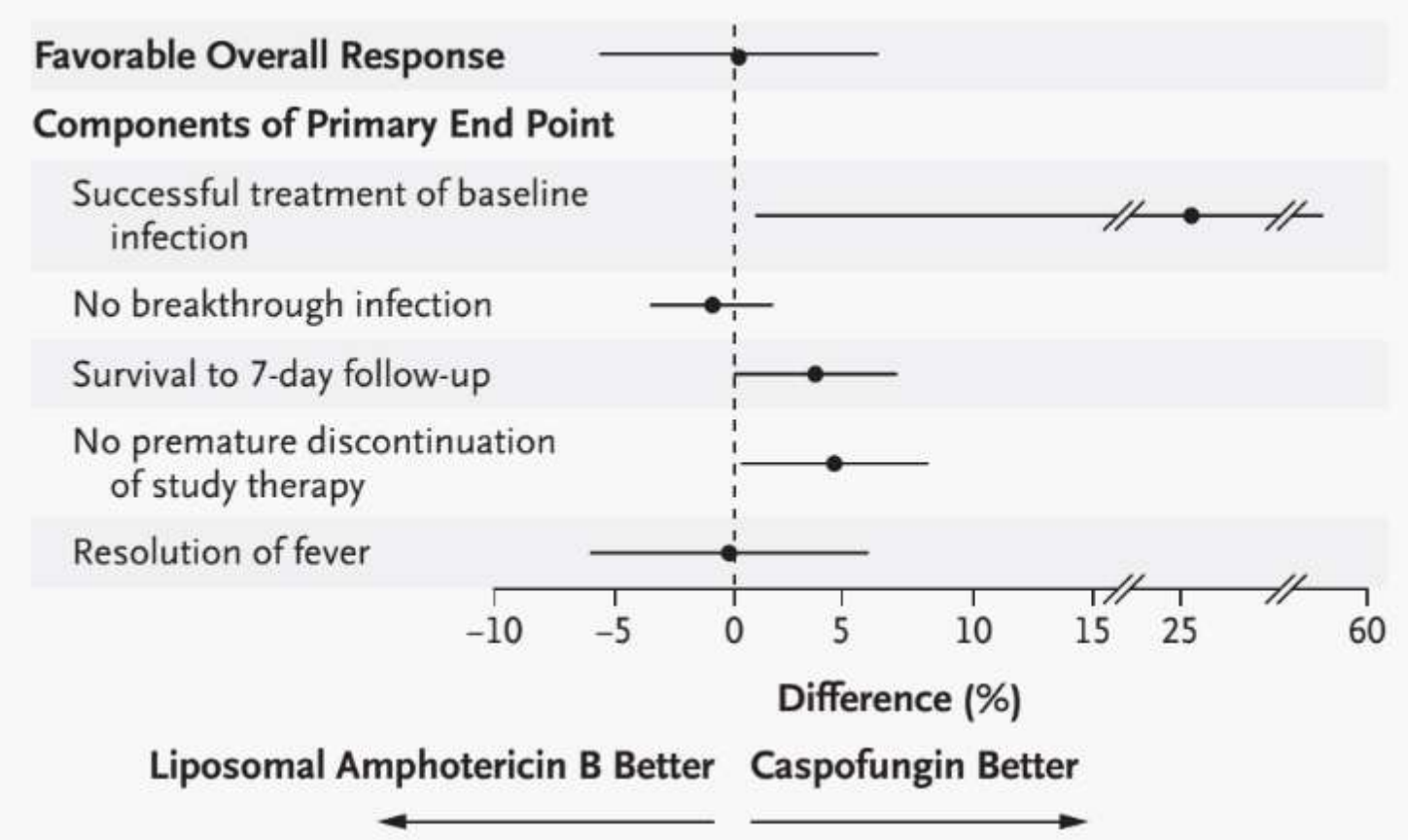

Walsh TJ et al. N Engl J Med. 2004 Sep 30;351(14):1391-402

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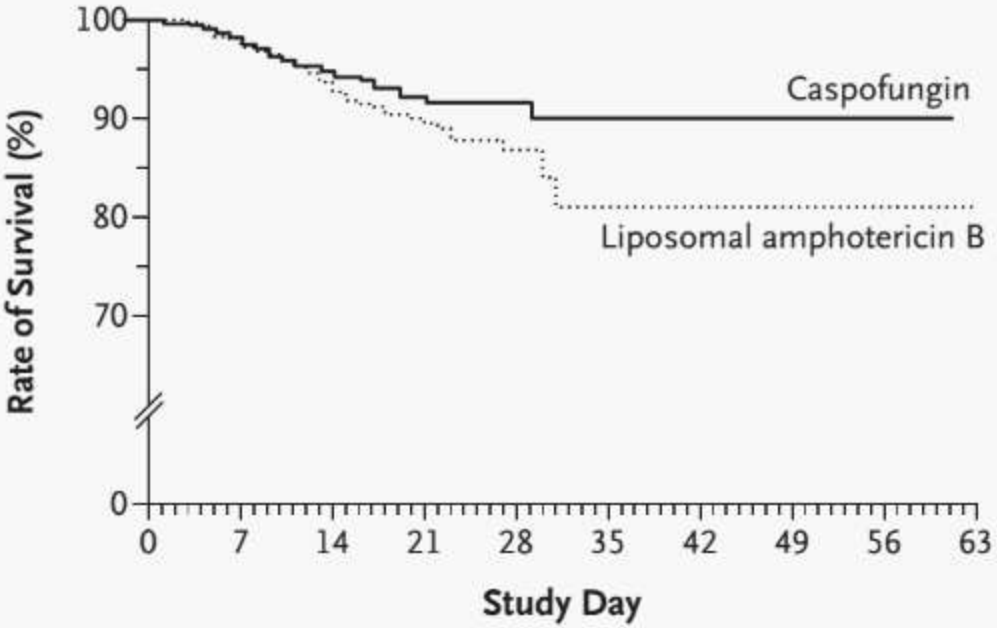
End Point	Caspofungin (N=556)	Liposomal Amphotericin B (N=539)	Difference (CI)†	P Value
			percentage points	
Overall favorable response				
Adjusted for strata — no. of patients (%)	190 (33.9)	181 (33.7)	0.2 (–5.6 to 6.0)	
Not adjusted for strata — no. of patients (%)	190 (34.2)	181 (33.6)	—‡	
Observed, according to risk category — no. of patients/total no. (%)				
High risk	63/146 (43.2)	46/122 (37.7)	5.4 (–6.3 to 17.2)	
Low risk	127/410 (31.0)	135/417 (32.4)	–1.4 (–7.7 to 4.9)	
Antifungal prophylaxis	105/313 (33.5)	100/304 (32.9)		
No antifungal prophylaxis	85/243 (35.0)	81/235 (34.5)		
Observed components of primary end point				
Successful treatment of baseline fungal infection — no. of patients/ no. with infection	14/27 (51.9)	7/27 (25.9)	25.9 (0.9 to 51.0)	0.04
Absence of breakthrough fungal infection — no. of patients/total no.	527 (94.8)	515 (95.5)	–0.8 (–3.3 to 1.8)	0.56
Survival for ≥7 days after completion of study therapy — no. of patients/ total no.§	515 (92.6)	481 (89.2)	3.4 (0.0 to 6.8)	0.05
Resolution of fever in setting of neutropenia — no. of patients/total no.	229 (41.2)	223 (41.4)	–0.2 (–6.0 to 5.6)	0.95
Study therapy discontinued prematurely because of toxicity or lack of efficacy — no. of patients/total no.				
No	499 (89.7)	461 (85.5)	4.2 (0.3 to 8.1)	0.03

Criticism: Successful outcome with L-AmB was seen in only a small proportion (25.9%) of patients with baseline fungal infection in this trial. But the same agent had a very high success rate (66.7%) in a similar trial that compared it with Voriconazole [Walsh, NEJM 2002] and a success rate >80% when compared with conventional AMB [Walsh, NEJM 1999]



No. at Risk

Caspofungin	556	547	412	192	82	37	18	13	8	6
Liposomal amphotericin B	539	523	362	185	80	38	20	10	8	6

Figure 2. Kaplan–Meier Curves Showing the Rate of Survival after Therapy in the Modified Intention-to-Treat Population, According to Treatment Group.

Log-rank chi-square=4.05 and P=0.04 for the difference in survival between patients enrolled in the caspofungin group and those enrolled in the liposomal amphotericin B group.

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Table 2. Summary of trials of empirical antifungal therapy that evaluated alternatives to amphotericin B (AmB).

Reference	*n*	Study drugs		Rate of "success,"[a] % of patients		Rate of invasive fungal infection, % of patients	
		Arm 1	Arm 2	Arm 1	Arm 2	Arm 1	Arm 2
[3]	687	AmB	L-AmB	49	50	8.7	5.0
[8]	384	AmB	Itraconazole	38	47	2.7	2.7
[9]	837	L-AmB	Voriconazole	31	26	5.0	1.9[b]
[10]	1095	L-AmB	Caspofungin	34	34	4.3	5.2

Wingard JR. Clin Infect Dis. 2004 Jul 15;39 Suppl 1:S38-43.

Summary: Empirical antifungals

- LAmB has the broadest antifungal spectrum with an acceptable toxicity profile

- Voriconazole and Caspofungin appear to be as effective as LAmB for this indication with a better toxicity profile

Conclusion

- Fungal infections in ICU are showing a rising trend
- Candida followed by aspergillus are the most common fungi
- Delay in initiation of antifungals produces adverse outcomes
- Drug choice:
  - Candidemia/Invasive candidiasis:
    - Hemodynamically stable, minimal azole resistance: Fluconazole
    - Others: Echinocandins/LAmB
  - Invasive aspergillosis: Voriconazole
  - Empirical Rx: LAmB (Echinocandins, Voriconazole as per clinical situation)