March 2014

Candida & the anti-fungals; an ICU perspective

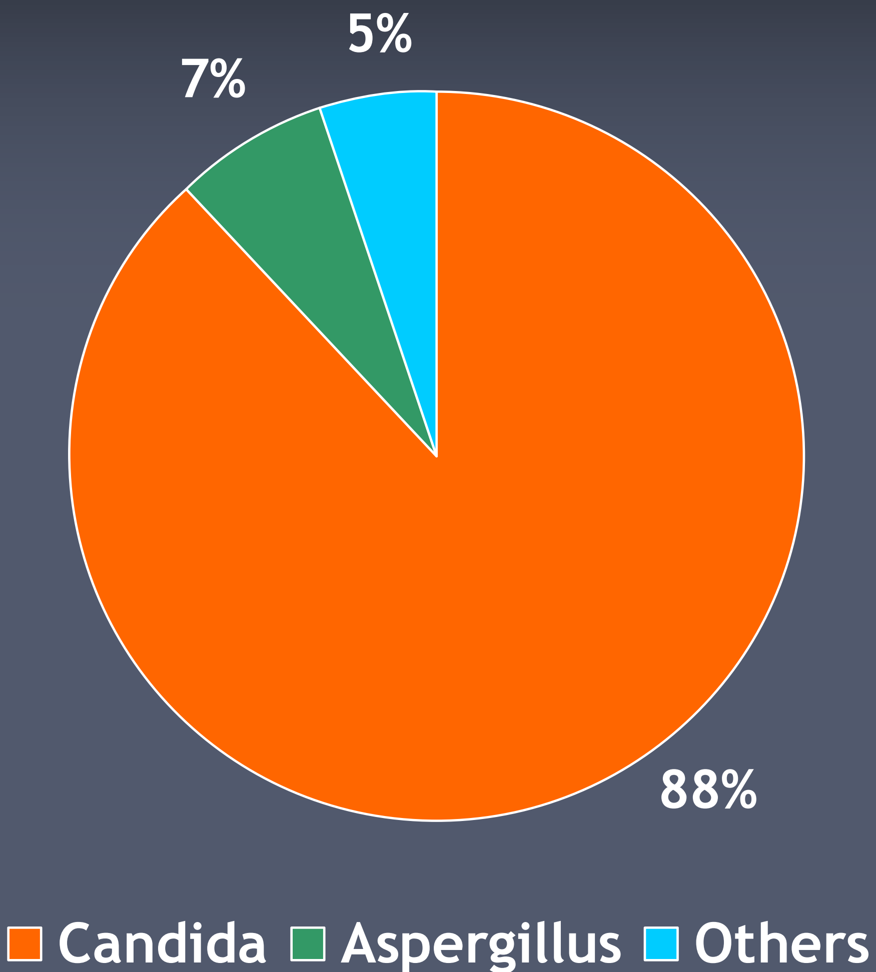
Dr Duncan Wyncoll, Guy's & St Thomas' NHS
Foundation Trust, London, UK

Conflicts of Interest

In the last 5 years I have acted as consultant, or received honoraria/research grants from:

Astellas, AstraZeneca, Bard, Bioproducts, Biovo, ConvaTec, Covidien, Eli Lilly, GSK, Iskus Health, J&J, Kimberly-Clark, Portex, Pfizer, Sage & Venner

Candida is the predominant fungal pathogen in the ICU setting: EPIC II



Global Surveillance Study

- 13,796 adults in 1,265 ICUs in 75 countries
- *Candida* responsible for 88% of 963 fungal infections
- 89% in Europe (n=633) & 85% elsewhere (n=330)

Vincent JL, *et al*. *JAMA* 2009;**302:**2323-9

Candida blood stream infections in the ICU

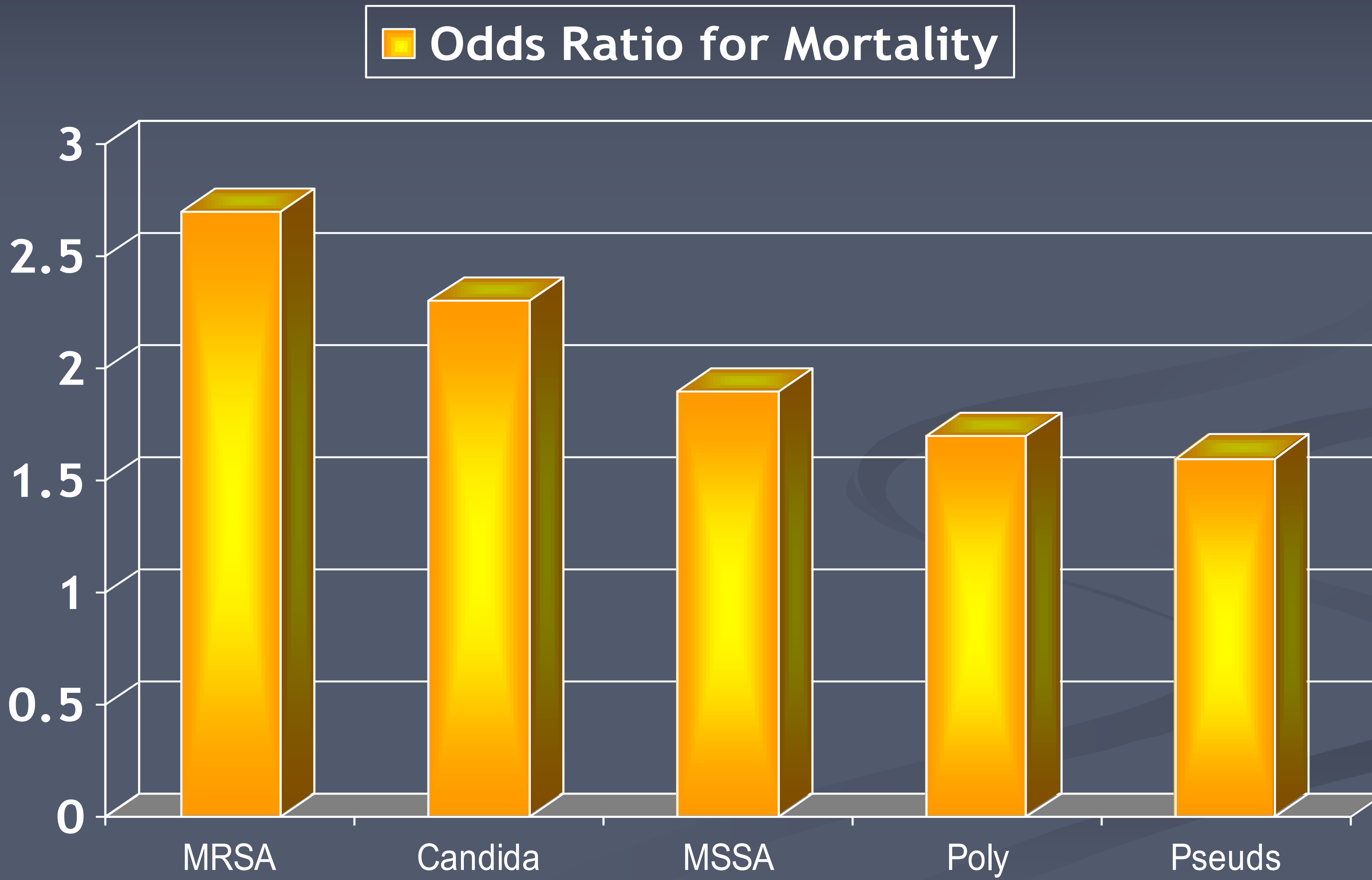
Global Surveillance Study: EPIC II

- 99 patients with Candidaemia
- Prevalence of 6.9/1,000 ICU patients
- 70% *Candida Albicans*
- Mortality of 43% (vs. 25% for gram +ve, & 29% gram –ve BSI)
- Fluconazole was the most frequent therapy given (in 2007)

Kett D, *et al. Crit Care Med* 2011;**39:**665-70

Healthcare-associated BSI: A distinct entity?

Multivariate logistic regression analysis of 6,697 patients

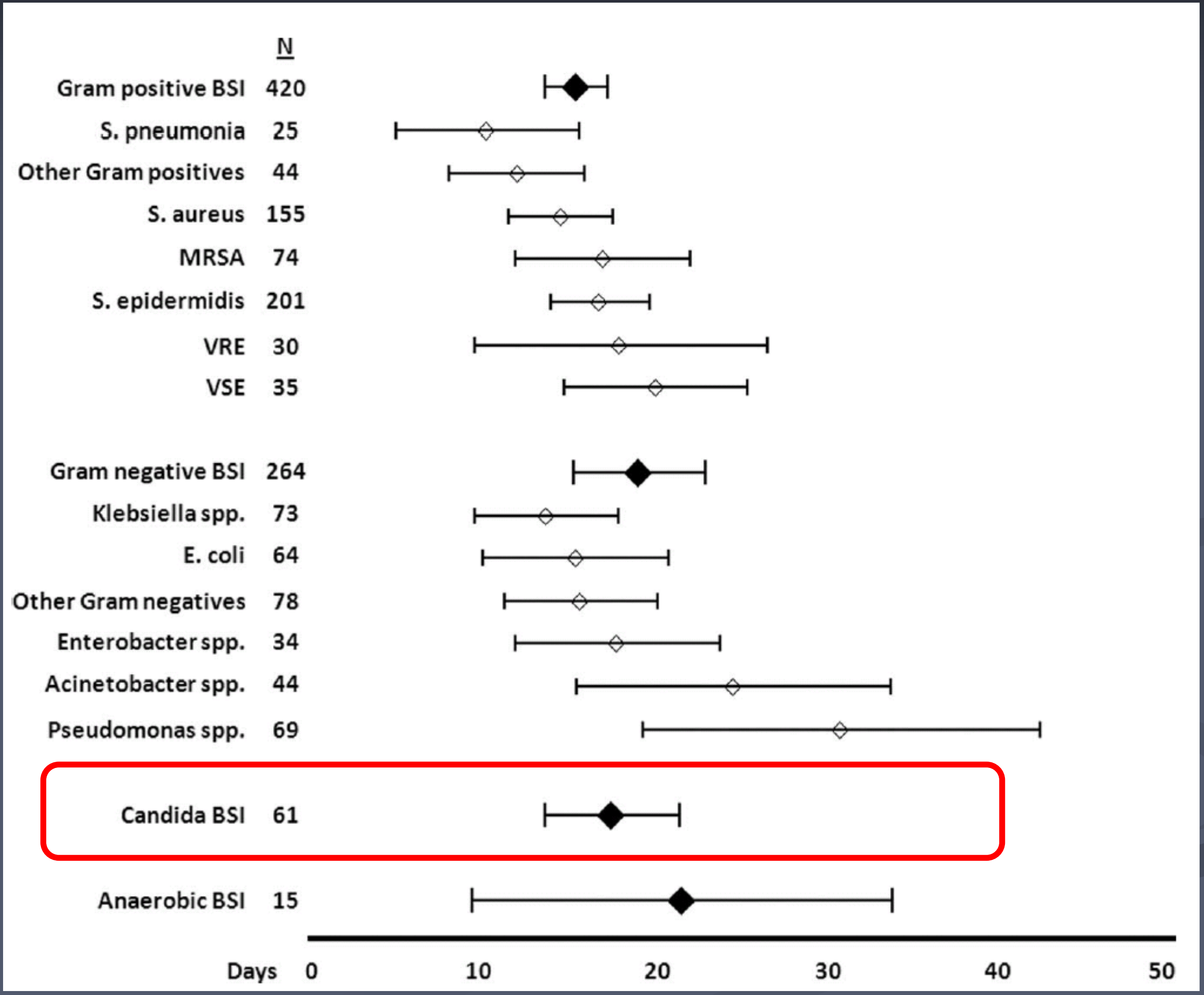


Shorr A et al, *Crit Care Med* 2006;**34:**2588-95

Question 1: In patients who have a Candidaemia BSI, when does it typically occur in relation to 'time from admission'?

1. Early (within the first 7 days of ICU admission)
2. Late (after 14 days or more)
3. Somewhere in the middle (7-14 days)
4. No different to other Blood Stream Infections
5. I don't know…

Candida blood stream infections in the ICU: EPIC II

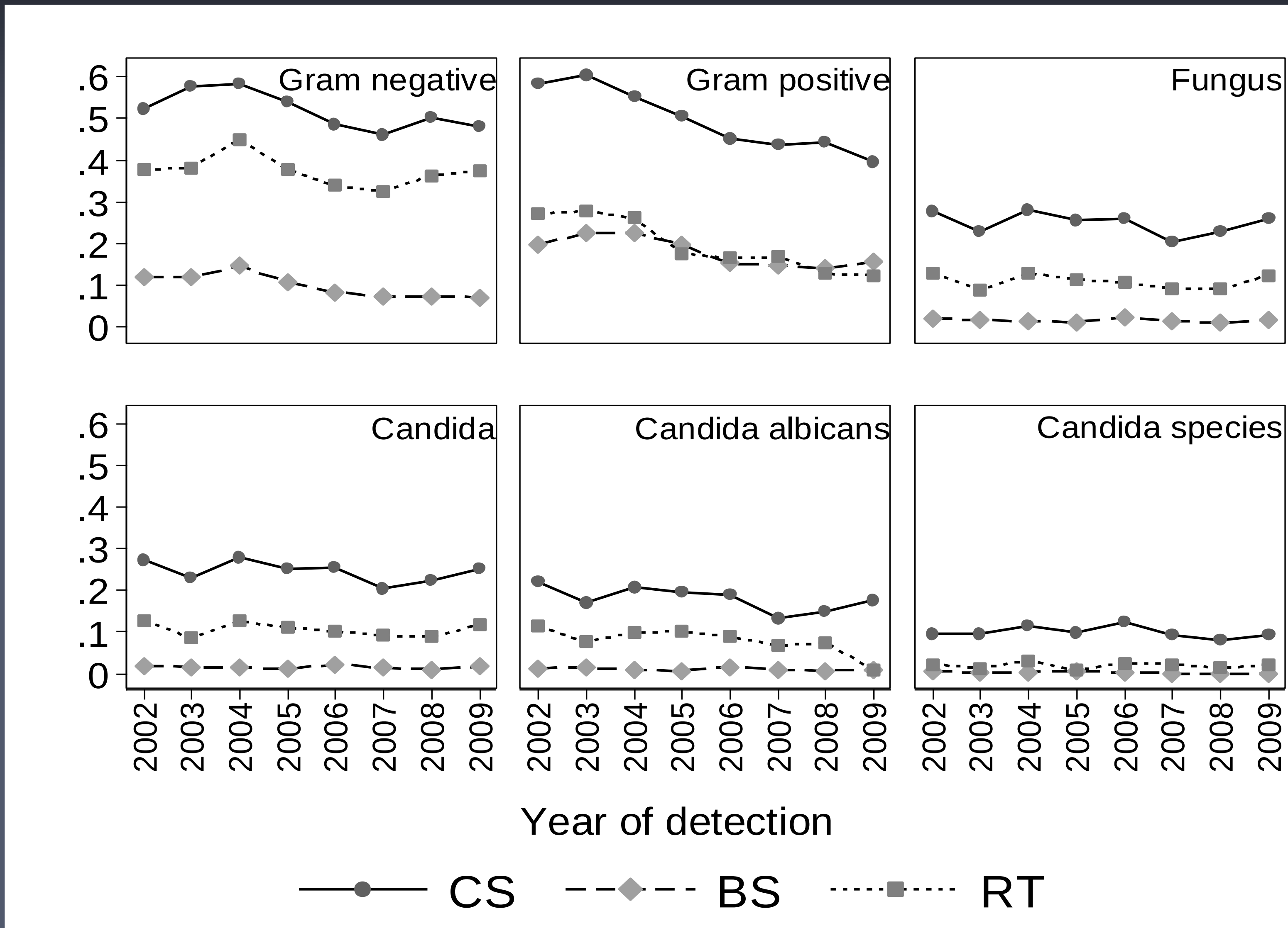


Kett D, *et al*. *Crit Care Med* 2011;**39:**665-70

Question 2: In my ICU, Fungal infections are…

1. Decreasing in frequency
2. Staying about the same
3. Increasing in frequency
4. To be honest, I don't know…

Candida as a proportion of other infections…



St Thomas' Hospital Data: 30-bed ICU over 8 years (Unpublished)

Candida species in epidemiological surveys

Author	**Period of observation**	***Study***	**Region**	**No. of strains**	***Candida albicans***	***Candida tropicalis***	***Candida parapsilosis***	***Candida glabrata***	***Candida krusei***
Pfaller et al. [10]	2008-2009	SENTRY	Worldwide	2'085	48%	11%	17%	18%	2%
			Europe	750	55%	7%	14%	16%	3%
			North America	936	43%	11%	17%	24%	2%
			Latin America	348	44%	17%	26%	5%	1%
			Asia	51	57%	12%	14%	14%	2%
Marra et al. [11]	2007-2010	SCOPE	Brazil	137	34%	15%	24%	10%	2%
Arendrup et al. [9]	2004-2007		Denmark	2901	57%	5%	4%	21%	4%
Horn et al. [12]	2004-2008	PATH	North America	2019	46%	8%	16%	26%	3%
Leroy et al. [7]	2005-2006	AmarCand	France ICU	305	57%	5%	8%	17%	5%
Talarmin et al. [13]	2004		France West	193	55%	5%	13%	19%	4%
Bougnoux et al. [14]	2001-2002		Paris ICU	57	54%	9%	14%	17%	4%
Marchetti et al. [2]	1991-2000	FUNGINOS	Switzerland	1137	64%	9%	1%	15%	2%
Sandven et al. [15]	1991-2003		Norway Nationwide	1393	70%	7%	6%	13%	1%
Pfaller et al. [16]	1997-2005	ARTEMIS	Mondial **	55'229	71%	5%	5%	10%	2%
Tortorano et al. [8]	1997-1999	ECMM	Europe	2089	52%	7%	13%	13%	2%

Eggimann P, *et al. Annals of Intensive Care* 2011;**1**:37

Risk factors for Invasive Candidiasis

- **Colonisation of several body sites**
- **Broad-spectrum antibiotics**
- Neutropaenia
- Burns (>50%)
- **Major abdominal surgery**
- **Surgery of the urinary tract in the presence of candiduria**
- **Parenteral nutrition**
- AKI
- APACHE >20
- **CVC in place**
- Diabetes
- Prolonged ICU stay

Potentially modifiable risk factors in yellow

Eggimann P, *et al. Annals of Intensive Care* 2011;**1**:37

Risk factors for Invasive Disease

Modified microbiota

Diabetes
Burns
Neutropenia
Antibiotics

Overgrowth

Mucosal colonisation

GI tract
Urinary tract
Genital tract

Micro-invasion

Multiple ABXs
Vascular access
Parenteral nutrition
Prolonged ICU stay
Major GI surgery

Candidaemia

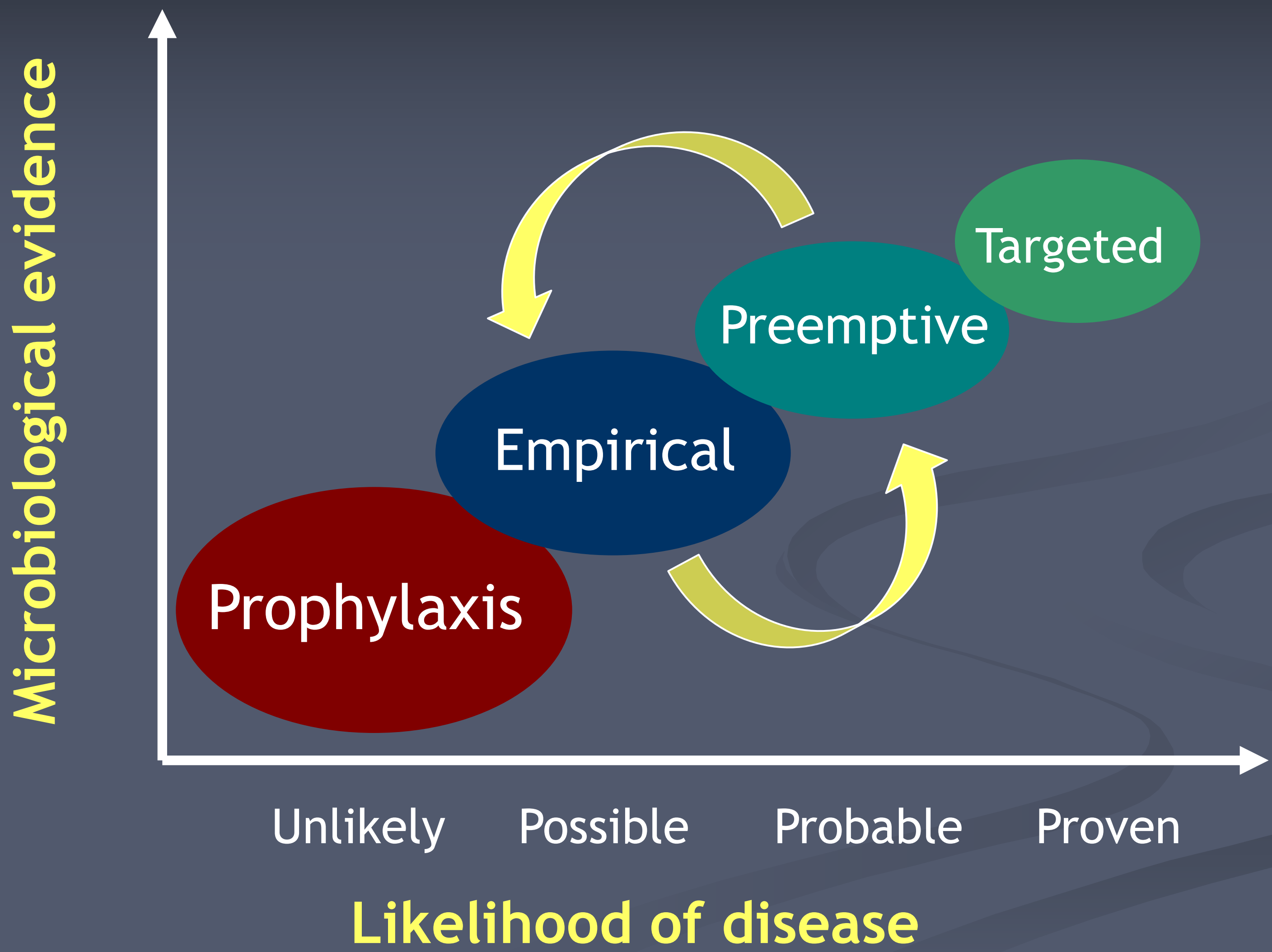
Disseminated disease

Endopthalmitis
Endocarditis
Abscess
CNS
Hepatosplenic

Candidaemia

Eggimann P, *et al. Annals of Intensive Care* 2011;**1**:37

Approaches to antifungal therapy



Eggimann P, *et al. Annals of Intensive Care* 2011;**1**:37

Assessing the risk of Invasive Candidiasis

At-risk patients

Predictive rules	Candida Score	Colonisation Index
• ≥4th day of ICU • Sepsis + CVC + MV + 1 of: • TPN or AKI or Major Surgery or Steroids	• Surgery @ ICU adm • TPN • Severe sepsis • Candida colonisation • >2.5 points	• Number of sites/number screened • 2x weekly • >0.5 or ≥0.4 corrected

Start empirical antifungal treatment

Patients Tx: 10-15% Candidiasis captured: 60-75%	Patients Tx: 15-20% Candidiasis captured: 75-80%	Patients Tx: 10-15% Candidiasis captured: 85-90%

Eggimann P, *et al. Annals of Intensive Care* 2011;**1**:37

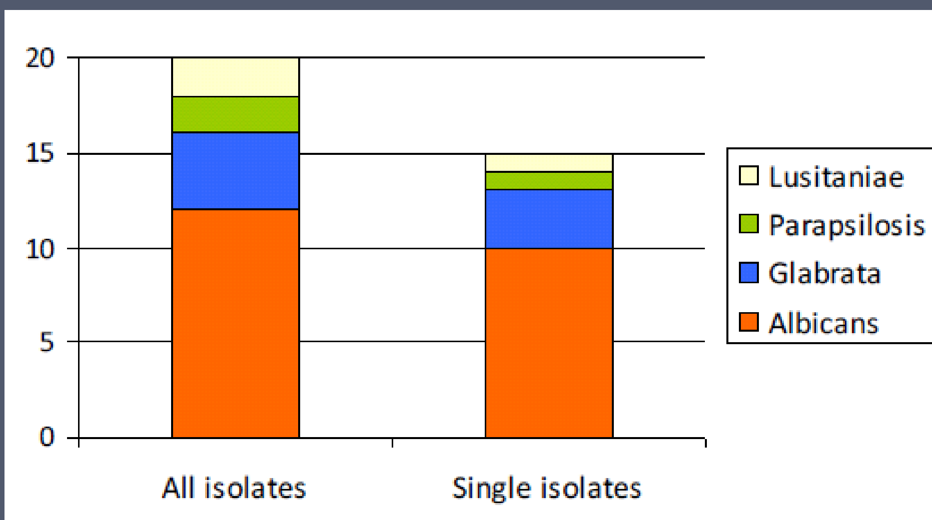
Hall *et al. Critical Care* 2013, **17**:R49
http://ccforum.com/content/17/2/R49

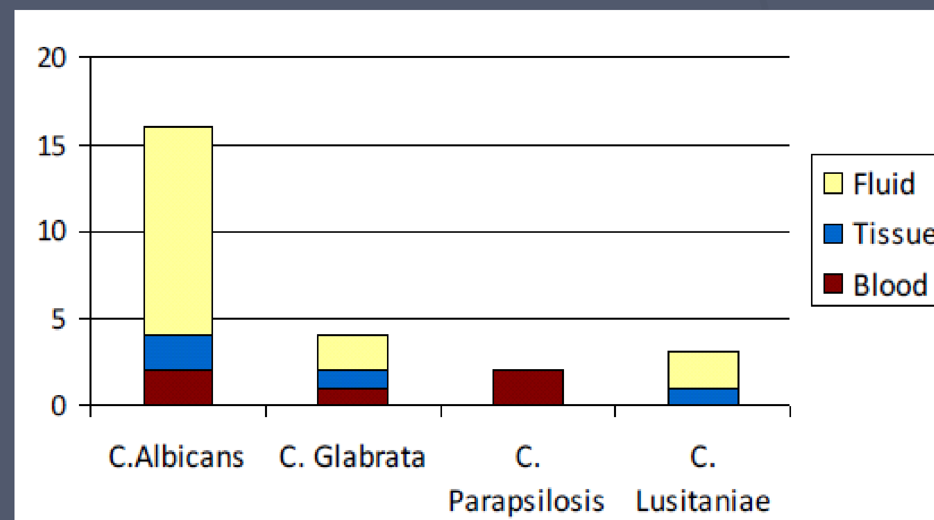
CRITICAL CARE

RESEARCH Open Access

Prediction of invasive candidal infection in critically ill patients with severe acute pancreatitis

Alison M Hall[1], Lee AL Poole[1], Bryan Renton[2], Alexa Wozniak[1], Michael Fisher[3], Timothy Neal[3], Christopher M Halloran[4], Trevor Cox[5] and Peter A Hampshire[1*]





No. of Candida species isolated

Species in infected patients

Hall AM, *et al. Crit Care* 2013;**17:**R49

Comparison of the various scoring systems

	Modified Invasive Candidiasis Score	Candida Score	Candida Colonisation Index
Sensitivity (95% CI)	**0.61 (0.36-0.83)**	**0.23 (0.1-0.42)**	**0.67 (0.41-87)**
Specificity (95% CI)	**0.49 (0.38-0.61)**	**0.85 (0.74-0.92)**	**0.79 (0.68-0.88)**
AUC ROC (95% CI)	**0.59 (0.49-0.69)**	**0.62 (0.52-0.71)**	**0.79 (0.69-0.87)**

Hall AM, *et al. Crit Care* 2013;**17:**R49

Biomarkers vs. Risk Scores

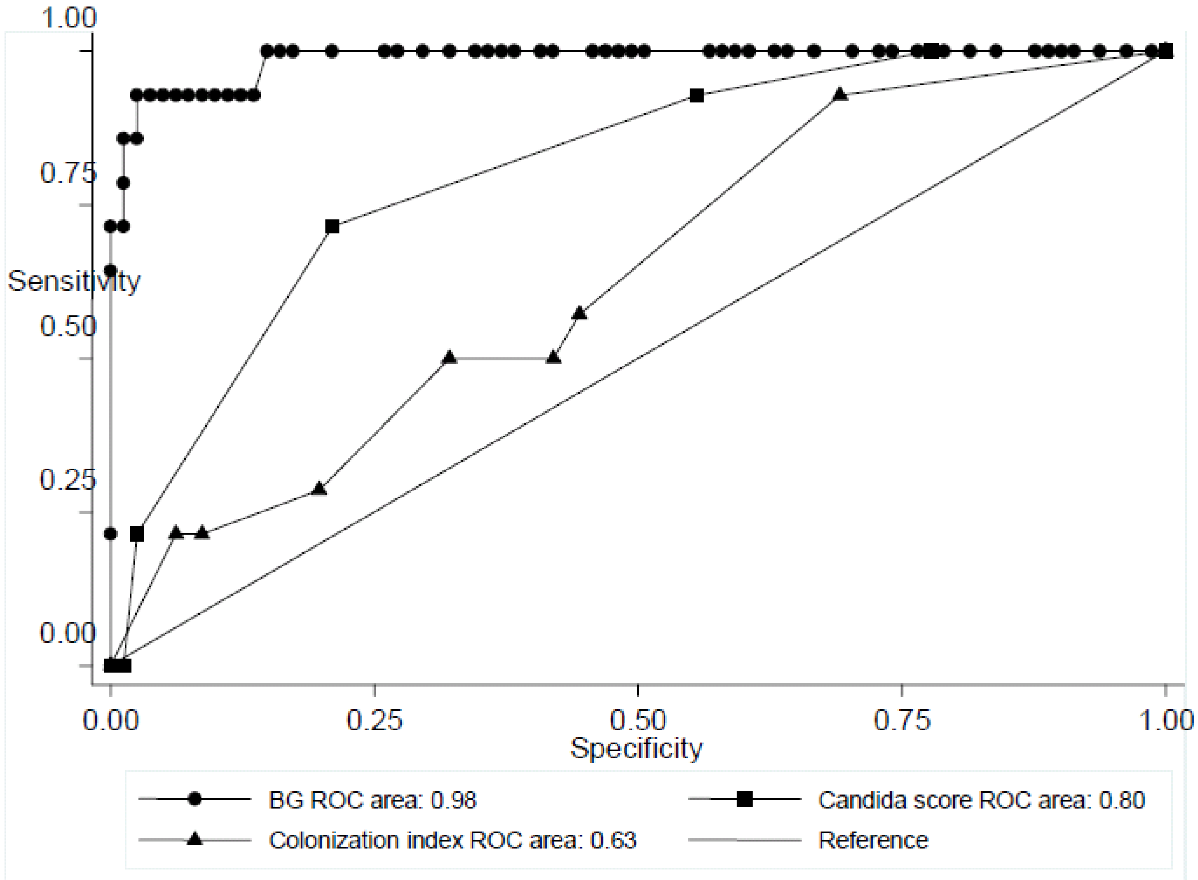


Figure 3 ROC AUC curves of BG, CS, and colonization index for proven IC cases. [The AUC of BG was significantly higher than those of CS (*P* < 0.001) and colonization index (*P* < 0.001), please edit this sentence as a footnote].

Posteraro B, *et al*. *Crit Care* 2011;**15:**R249

Biomarkers vs. Risk Scores

	Assessment	No Candida colonisation (n=61)	Candida colonisation (n=84)	Invasive Candidiasis (n=31)	*P* value
Candida score	Max. 1st	2 2	3 4	4 5	0.001 0.001
$1 \rightarrow 3$-β-D-glucan (pg/ml)	Max. 1st	9 52	45 66	54 268	0.11 0.003
C-reactive Protein (mg/L)	Max. 1st	201 248	207 241	172 283	0.91 0.41
Procalcitonin (ng/ml)	Max. 1st	0.89 1.25	0.58 0.59	1.11 3.33	0.59 0.18

All median values

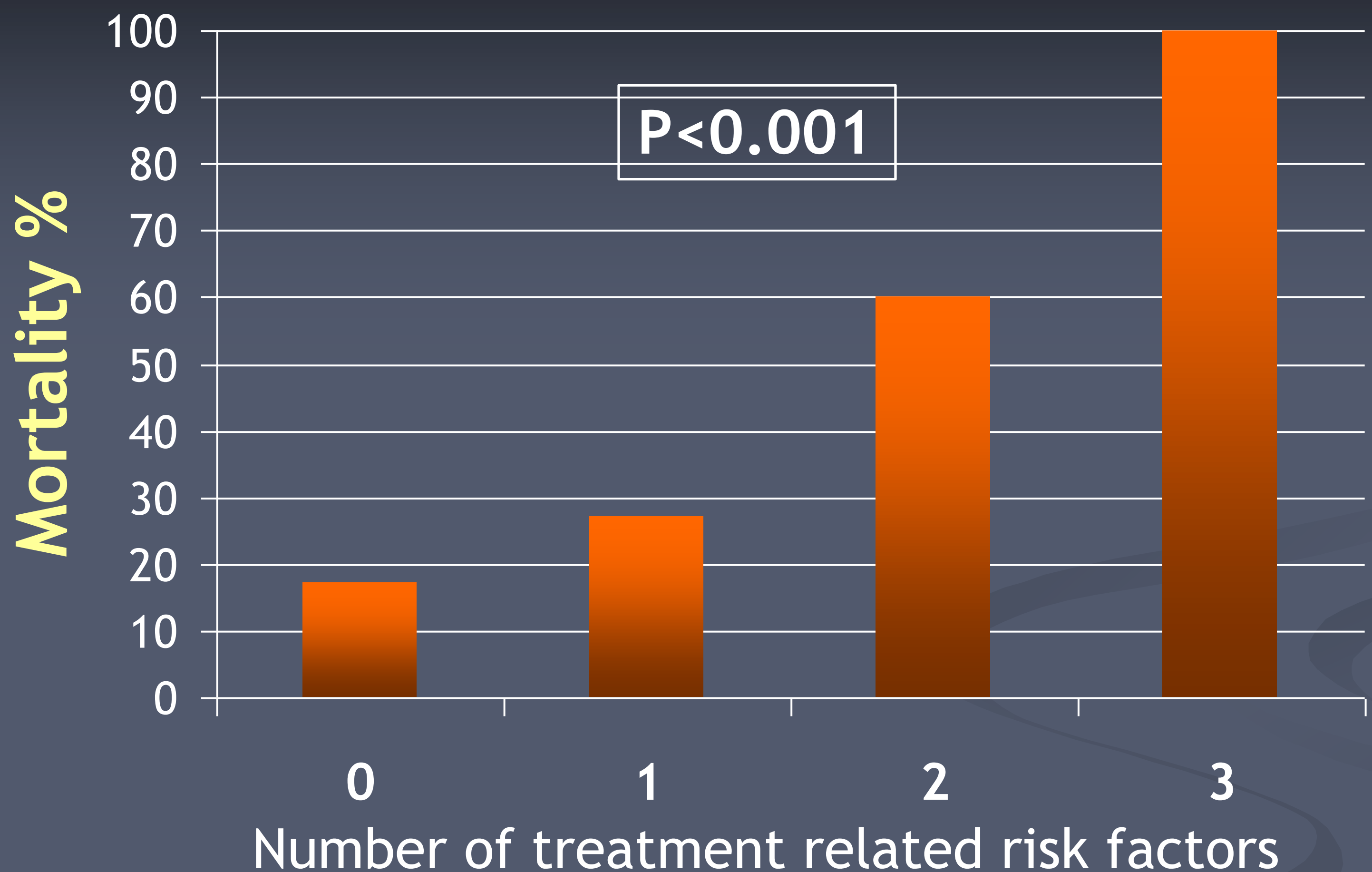
Leon C, *et al. Intensive Care Med* 2012;**38:**1315-25

Treatment related risk factors for Mortality

	All Hospital	
	Lived (n = 173)	Expired (n = 72)
Mechanical ventilation, n (%)		
MV days prior to + culture[a]		
Prior antibiotics, n (%)	151 (87.3)	61 (84.7)
Prior antifungal, n (%)	26 (15.0)	14 (19.4)
Central vein catheter, n (%)	155 (89.6)	62 (86.1)
TPN, n (%)	38 (22.0)	10 (13.9)
Foley catheter, n (%)	97 (56.1)	46 (63.9)
Surgical drain, n (%)	39 (22.5)	10 (13.9)
Corticosteroids, n (%)	42 (24.3)	26 (36.1)
Vasopressor, n[b] (%)	14 (8.1)	26 (36.1)
CVC removed, n (%)	140 (90.3)	36 (58.1)
Treatment within 24 hrs, n (%)	25 (14.5)	12 (16.7)
Treatment within 48 hrs, n (%)	111 (64.2)	34 (47.2)
Inadequate initial fluconazole dosing, n (%)	21 (12.1)	20 (27.8)

Labelle AJ, *et al. Crit Care Med* 2008;**36**:2967-72

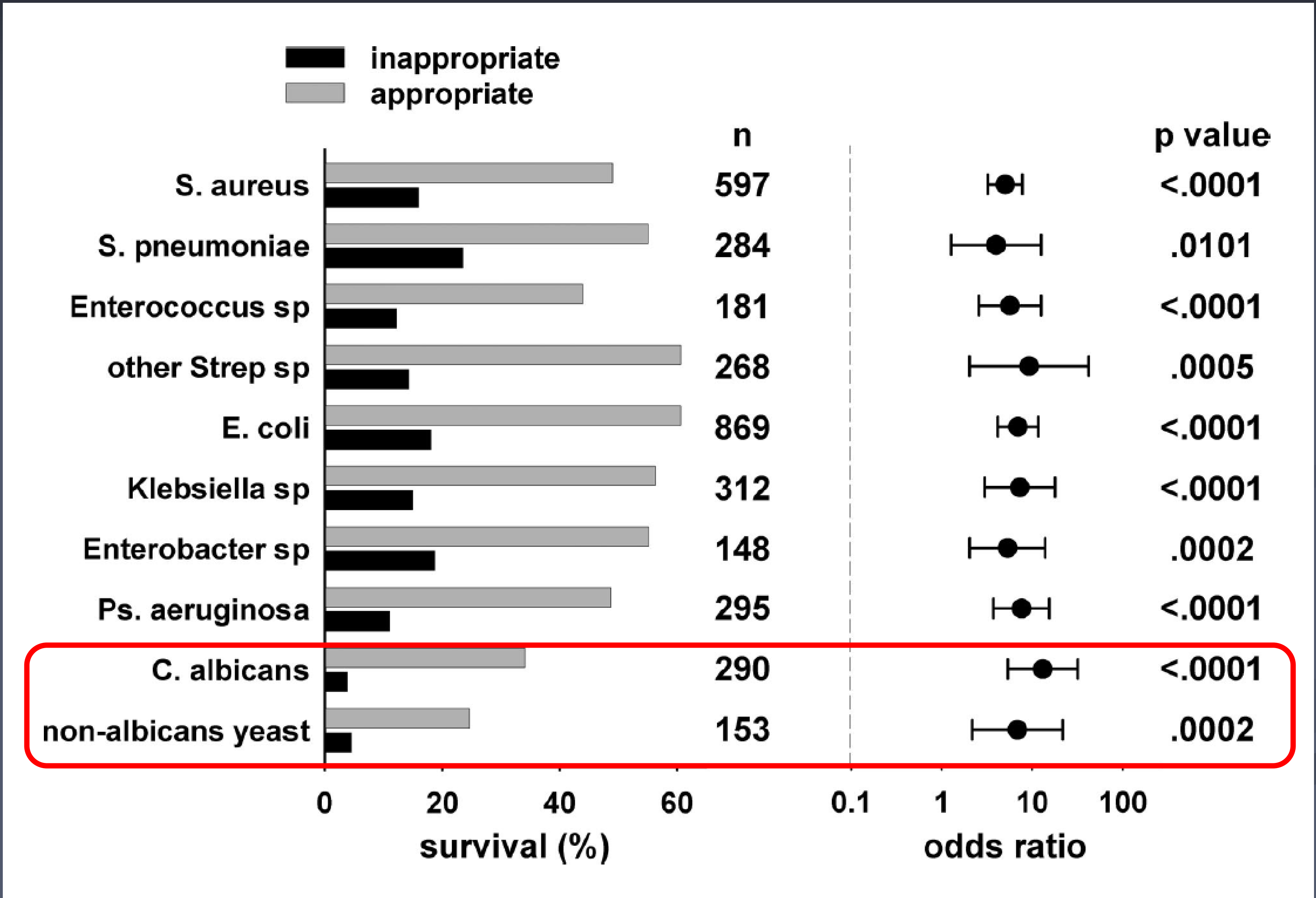
Treatment related risk factors for Mortality



- Retention of CVC
- Inadequate initial fluconazole dosing
- Therapy delayed beyond 48 hours

Labelle AJ, *et al. Crit Care Med* 2008;**36:**2967-72

Treatment related risk factors for Mortality: inappropriate antimicrobial therapy



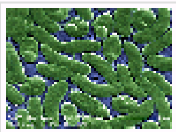
Kumar A, *et al*. *Chest* 2009;136:1237-48

Question 4: Which statement is most accurate about my institution?

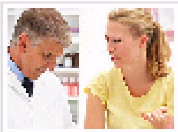
1. We struggle to get 50% of patients with septic shock to receive antimicrobials within 1 hour
2. We are better than 50% but still less than 75%
3. I think/know we are better than 75%
4. We're not too bad with antibacterials, but there can be significant delays with Antifungals for patients with Candidaemia

Medscape NEWS General Surgery

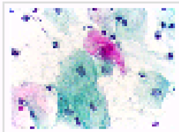
News



CDC Releases Foodborne Illness Report Card



New ASCCP Guidelines: Equal Management for Equal Risk



ASCCP Updated Consensus Guide FAQs

Medscape Medical News

Candida: New Rapid Blood Test Could Cut Mortality

Ricki Lewis, PhD

Apr 25, 2013

Print Email

Editors' Recommendations

Empiric Antifungal Therapy for Candidiasis in Preemies

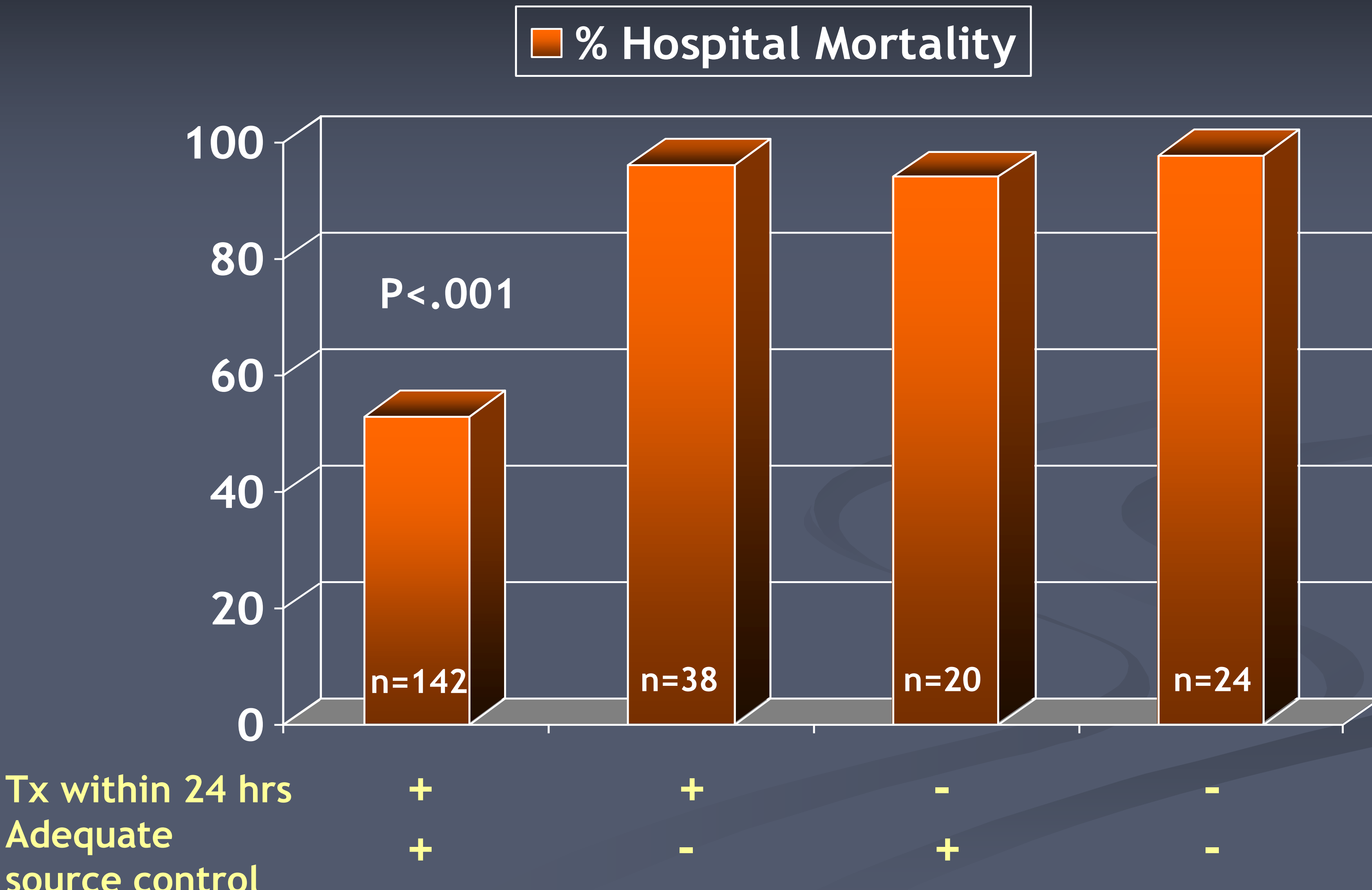
American Thoracic Society Issues Guidelines on Treating Pulmonary Fungal Infections

A new, rapid test for *Candida* infections of the bloodstream may cut mortality from 40% to 11%, according to a report published in the April 24 issue of *Science Translational Medicine*.

Lori A. Neely, PhD, from T2 Biosystems in Lexington, Massachusetts, and colleagues teamed polymerase chain reaction (PCR) and nanotechnology with T2 magnetic resonance (T2MR) technology to create an assay that

'Medscape' 25th April 2013

Delay in initiation of antifungal therapy



Kollef M, *et al. Clin Inf Dis* 2012;**54:**1739-46

Delay in initiation of antifungal therapy

Table 2. Infection and Treatment-Related Characteristics

	Lived (n = 69)	Died (n = 155)	*P* value
Infection source, n (%)			
Vascular catheter–associated	37 (53.6)	86 (55.5)	.796
Respiratory	11 (15.9)	24 (15.5)	.931
Urinary	11 (15.9)	21 (13.5)	.636
Gastrointestinal	8 (11.6)	19 (12.3)	.888
Central nervous system	1 (1.4)	0 (0.0)	.308
or skin structure	7 (10.1)	14 (9.0)	.792
Surgical site	0 (0.0)	2 (1.3)	1.000
Cardiac	0 (0.0)	0 (0.0)	1.000
Other	1 (1.4)	5 (3.2)	.669
Candida species, n (%)[a]			
C. albicans	34 (49.3)	86 (55.5)	.390
C. glabrata	21 (30.4)	34 (21.9)	.172
C. parapsilosis	10 (14.5)	18 (11.6)	.547
C. tropicalis	4 (5.8)	10 (6.5)	1.000
C. krusei	1 (1.4)	5 (3.2)	.669
Other species	2 (2.9)	3 (1.9)	.645

Kollef M, *et al. Clin Inf Dis* 2012;**54:**1739-46

Delay in initiation of antifungal therapy

	Lived (n = 69)	Died (n = 155)	*P* value
Prior antibiotics, n (%):	45 (65.2)	112 (72.3)	.288
Initial antifungal agent, n (%)			
Echinocandin	53 (76.8)	76 (49.0)	<.001
Fluconazole/voriconazole	13 (18.8)	25 (16.1)	…
Amphotericin	3 (4.3)	13 (8.4)	…
None	0 (0.0)	41 (26.5)	…
Treatment within 12 h, n (%)[b]	31 (44.9)	65 (41.9)	.676
Treatment within 24 h, n (%)[b]	68 (98.6)	112 (72.3)	<.001
Drotrecogin alfa (activated), n (%)	1 (1.4)	1 (0.6)	.522
Corticosteroids, n (%):	12 (17.4)	42 (27.1)	.117
GCSF, n (%)	2 (2.9)	19 (12.3)	.026
Source control required, (n (%)[c]	49 (71.0)	97 (62.6)	.221
Inadequate source control, n (%)[d]	1 (1.4)	61 (39.4)	<.001
Mechanical ventilation, n (%)	34 (49.3)	143 (92.3)	<.001
Red blood cell transfusion, n (%)	28 (40.6)	123 (79.4)	<.001
Total crystalloid solution (L)[b]	4.3 ± 1.3	4.9 ± 1.5	.010

Kollef M, *et al*. *Clin Inf Dis* 2012;**54:**1739-46

The cost of delayed therapy

Hospital resource utilization & cost of treatment of candidaemia

- 167 Adults with Candidaemia
- Culture confirmed BSI with *Candida* within 14 days of admission
- Appropriate = according to IDSA Guideline & ‘in-vitro sens’
- Post-culture stay was shorter with appropriate therapy (mean 7 vs. 10 days p = 0.037)
- Costs were also lower: ~$16,000 vs. ~$33,000 (p<0.001)

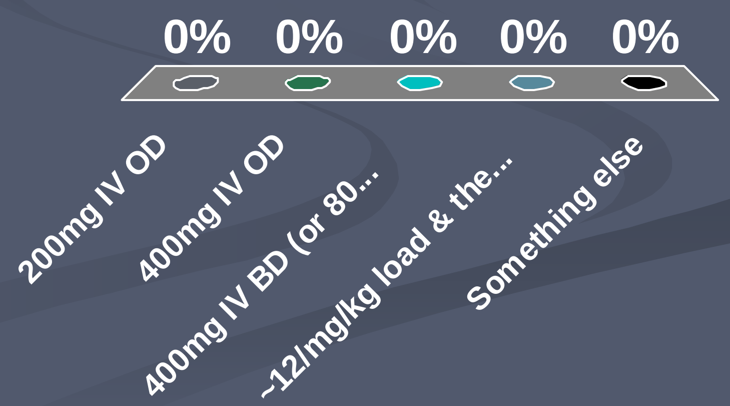
Arnold HM, *et al. Pharmacotherapy* 2010;**30:**361-8

Question 5: The dose of fluconazole I would use in a patient with septic shock & receiving RRT (~25mls/kg/hour CVVHF/DF) is…

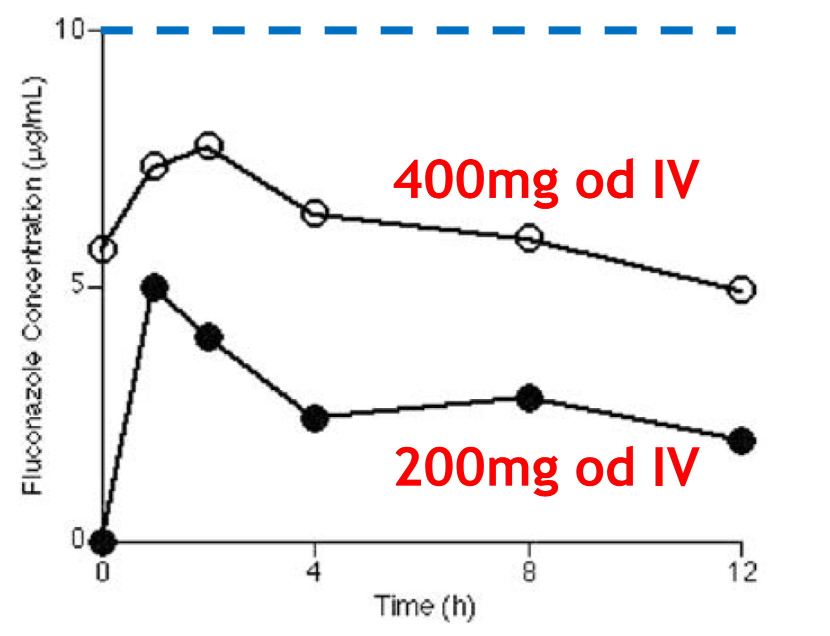
1. 200mg IV OD
2. 400mg IV OD
3. 400mg IV BD (or 800mg OD)
4. ~12/mg/kg load & then ~6mg/kg
5. Something else

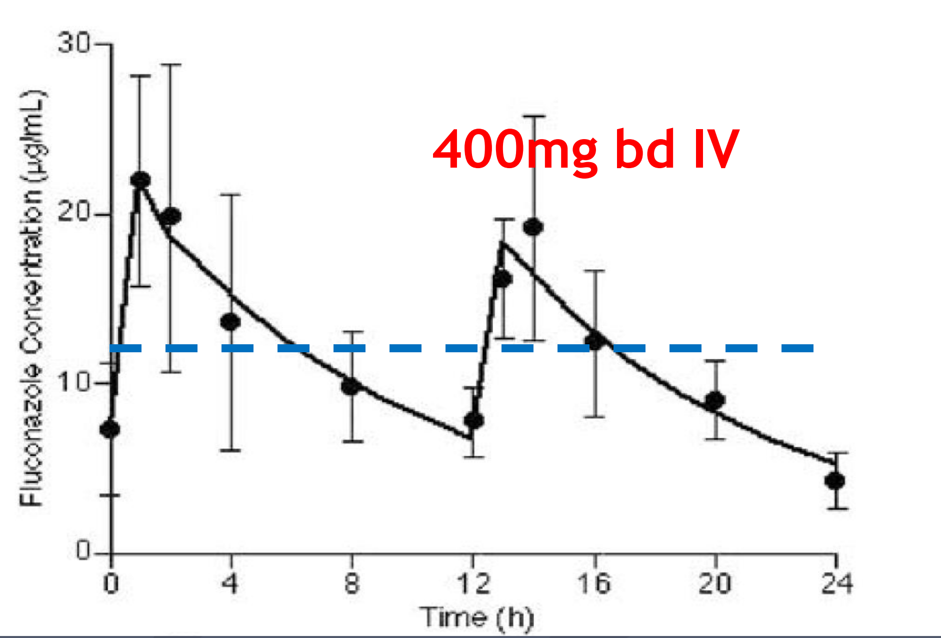
Question 5: The dose of fluconazole I would use in a patient with septic shock & receiving RRT (~25mls/kg/hour CVVHF/DF) is…

1. 200mg IV OD
2. 400mg IV OD
3. 400mg IV BD (or 800mg OD)
4. ~12/mg/kg load & then ~6mg/kg
5. Something else



Fluconazole dosing with RRT

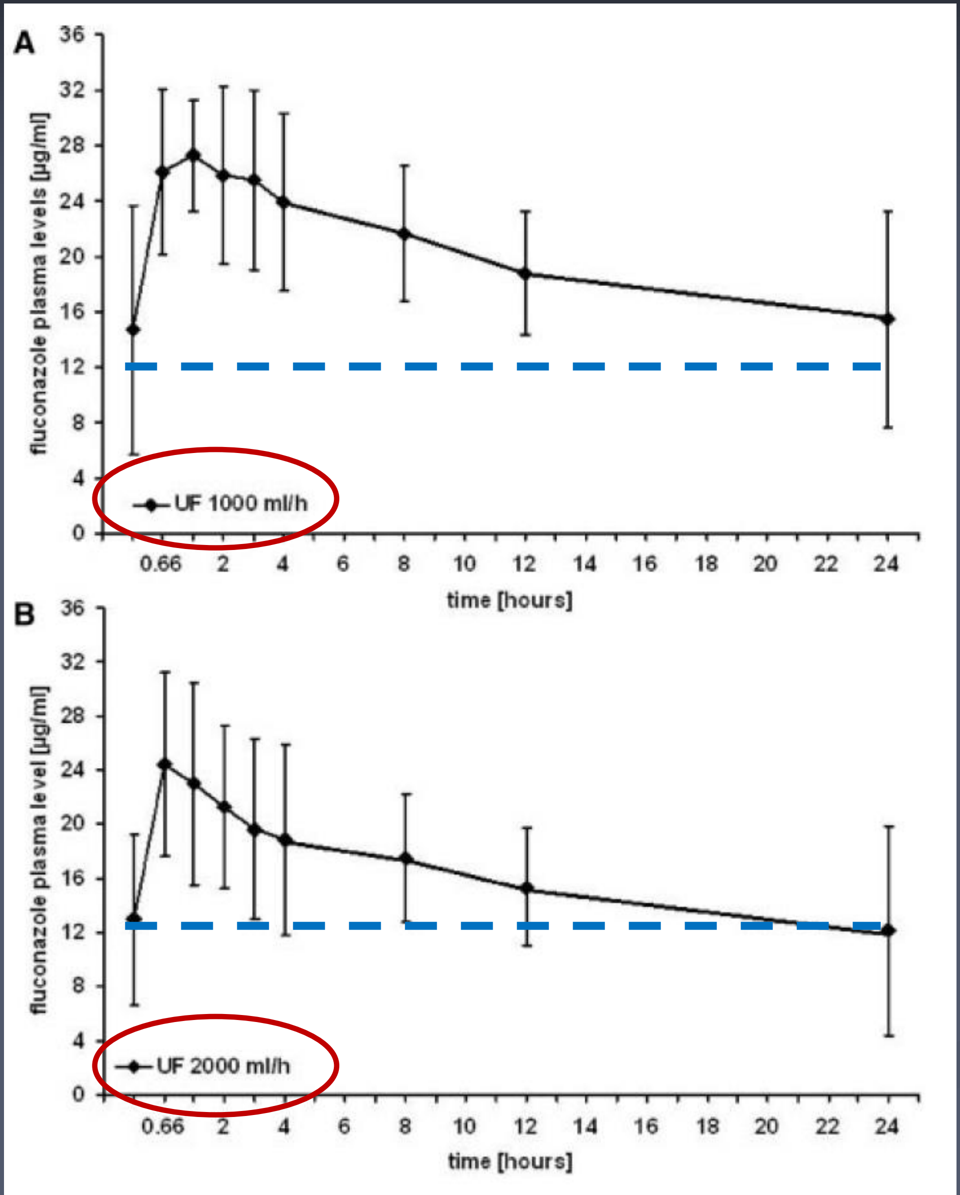




- Variable doses of fluconazole in 4 CVVHDF treated patients
- MIC for fluconazole is considered 6 µmol/ml
- 'Estimated correct dose could be as high as 500-600mg 12 hourly…'

Kagasaki Y, *et al. Intensive Care Medicine* 2003;**29:**1844-8

Fluconazole dosing with RRT



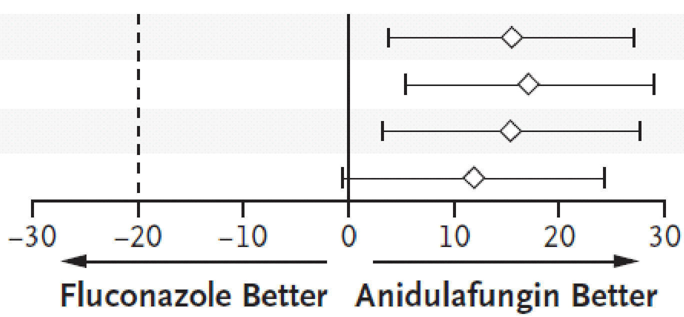
- 9 CVVHF treated patients
- Fluconazole 800mg IV od
- CVVHF at 1L or 2L/hour (1/3rd predilution)

Bergner R, *et al*. *NDT* 2006;**21:**1019-23

Anidulafungin versus Fluconazole for Invasive Candidiasis

Annette C. Reboli, M.D., Coleman Rotstein, M.D., Peter G. Pappas, M.D., Stanley W. Chapman, M.D., Daniel H. Kett, M.D., Deepali Kumar, M.D., Robert Betts, M.D., Michele Wible, M.S., Beth P. Goldstein, Ph.D., Jennifer Schranz, M.D., David S. Krause, M.D., and Thomas J. Walsh, M.D., for the Anidulafungin Study Group

End Point	Global Success: Fluconazole Group (N=118)	Global Success: Anidulafungin Group (N=127)	Absolute Percent Difference between Treatments (95% CI)
	no. (%)		
End of intravenous therapy	71 (60.2)	96 (75.6)	15.4 (3.9 to 27.0)
End of all therapy	67 (56.8)	94 (74.0)	17.2 (5.5 to 29.0)
2-Week follow-up	58 (49.2)	82 (64.6)	15.4 (3.1 to 27.7)
6-Week follow-up	52 (44.1)	71 (55.9)	11.8 (–0.6 to 24.3)



Reboli R, *et al. N Engl J Med* 2007;**346:**2472-82

Response according to different species

Table 3. Microbiologic and Global Responses at the End of Intravenous Therapy in the Modified Intention-to-Treat Population.*

Candida Pathogen	Successful Microbiologic Response			Successful Global Response†		
	Anidulafungin Group	Fluconazole Group	P Value	Anidulafungin Group	Fluconazole Group	P Value
	no. of isolates/total no. (%)			*no. of patients/total no. (%)*		
Candida albicans	77/81 (95)	57/70 (81)	0.01	60/74 (81)	38/61 (62)	0.02
C. glabrata	15/20 (75)	18/30 (60)	0.37	9/16 (56)	11/22 (50)	0.75
C. parapsilosis	9/13 (69)	14/16 (88)	0.36	7/11 (64)	10/12 (83)	0.37
C. tropicalis	13/15 (87)	7/11 (64)	0.35	13/14 (93)	4/8 (50)	0.04
Other candida species	5/6 (83)	3/3 (100)	1.00	3/4 (75)	2/3 (67)	1.00
All candida species	119/135 (88)	99/130 (76)	0.02	92/119 (77)	65/106 (61)	0.01

Reboli R, *et al. N Engl J Med* 2007;**346:**2472-82

Kett *et al. Critical Care* 2011, **15**:R253
http://ccforum.com/content/15/5/R253

CRITICAL CARE

RESEARCH Open Access

Anidulafungin compared with fluconazole in severely ill patients with candidemia and other forms of invasive candidiasis: Support for the 2009 IDSA treatment guidelines for candidiasis

Daniel H Kett[1*], Andrew F Shorr[2], Annette C Reboli[3], Arlene L Reisman[4], Pinaki Biswas[5] and Haran T Schlamm[4]

- Re-analysis of the Reboli (NEJM paper)
- Focus on patients who were critically ill
- 163/245 (66.5%) – severe sepsis or APACHE >15

Kett DH, *et al. Critical Care* 2011;**15:**R253

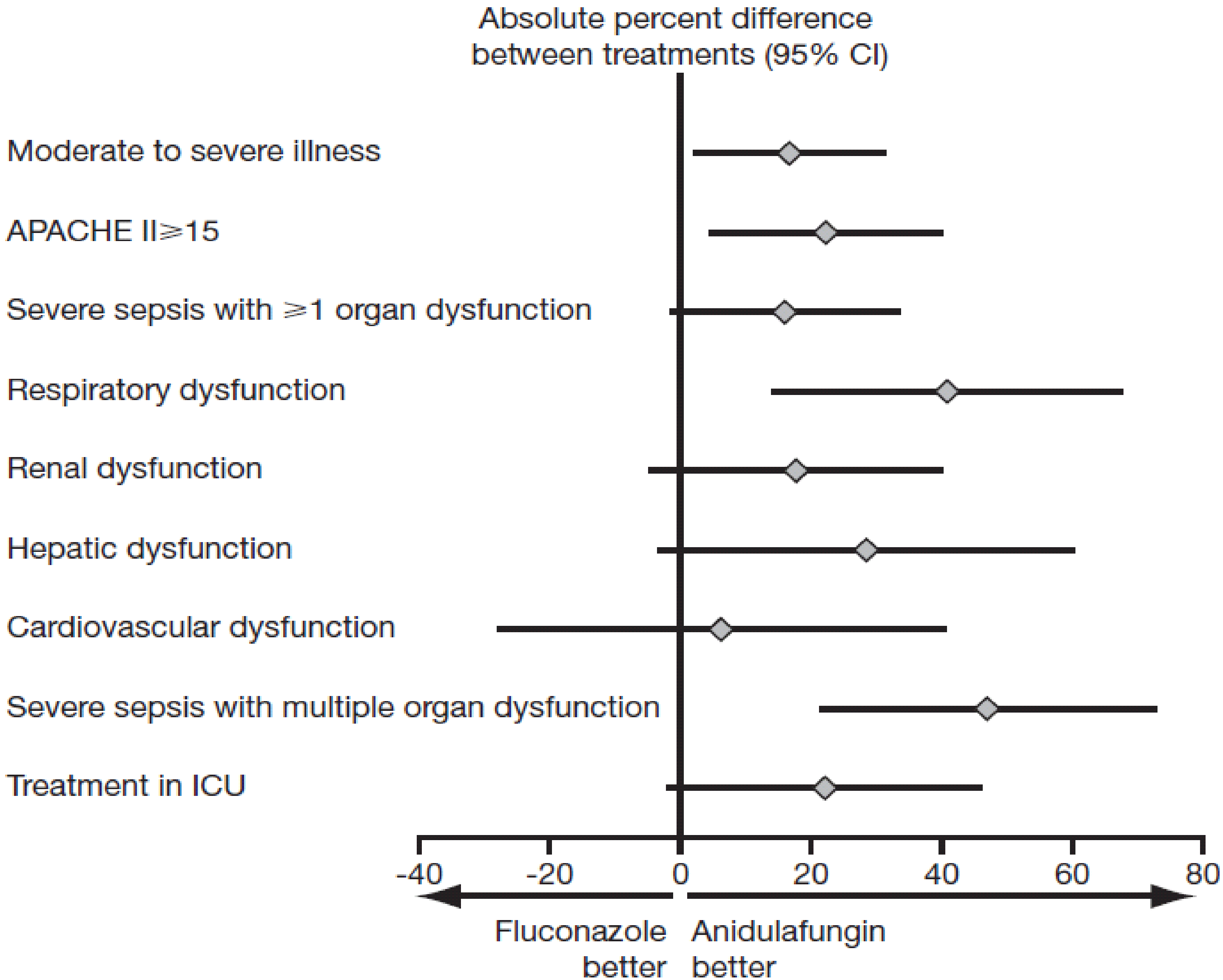
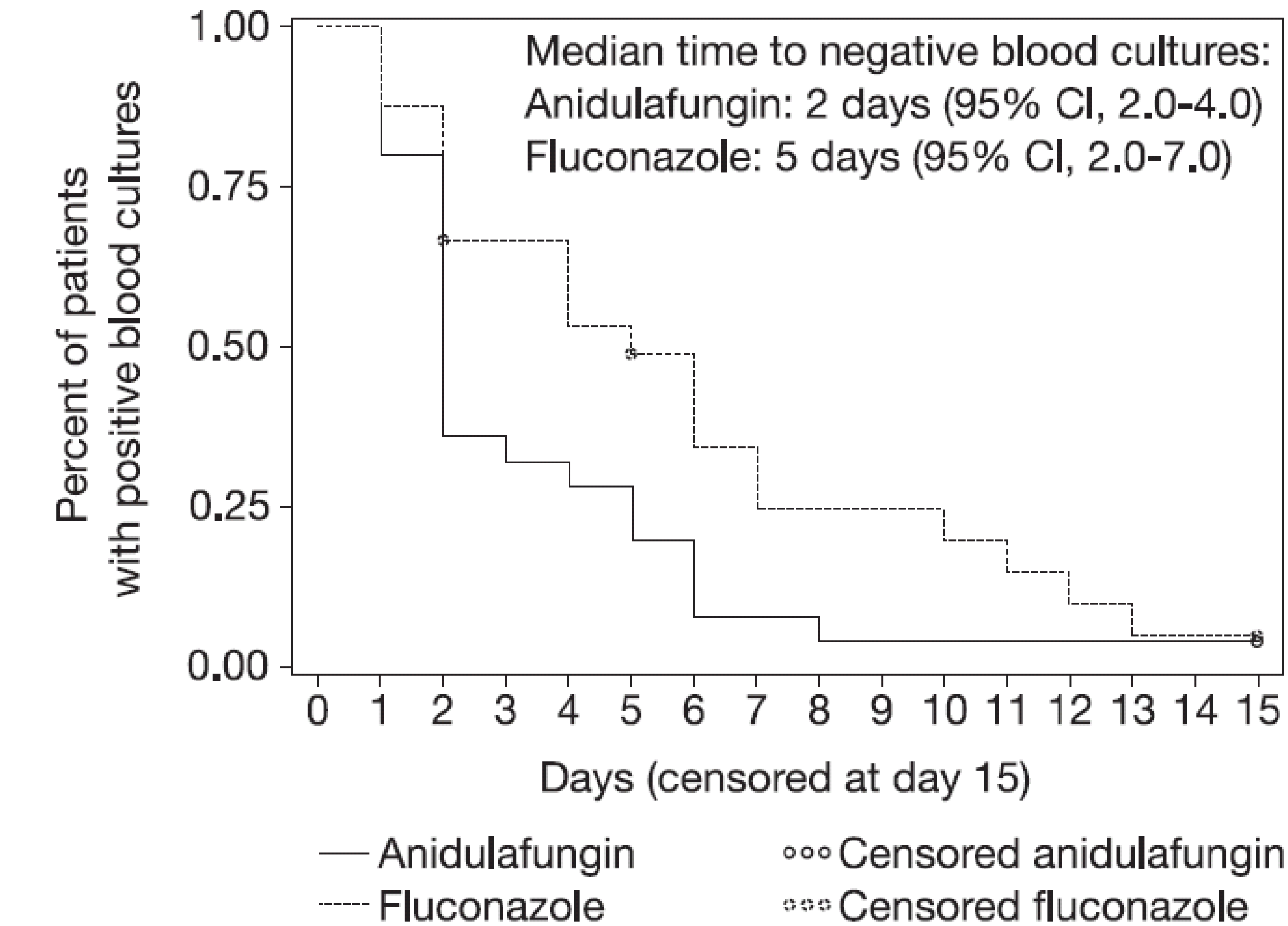


Figure 1 Difference in global response at end of treatment among severely ill patients and the various subpopulations.

Kett DH, *et al*. *Critical Care* 2011;**15:**R253

Time to negative blood cultures: Static vs. Cidal



No. at risk:

Days	0	2	4	6	8	10	12	14
Anidulafungin	25	20	8	5	2	1	1	1
Fluconazole	24	21	15	10	5	5	3	1

Reboli AC, *et al*. *BMC Infectious Diseases* 2011;**11**:261

2012 ESCMID Recommendations on fever- & diagnosis-driven therapy of candidaemia & invasive candidiasis

Population & Intention	Intervention	SoR & QoE
ICU patients with fever despite ABXs & APACHE >16; to resolve fever	Flucon 800mg od	D-1
ICU patients with persistent fever but with no micro evidence; to reduce mortality	Fluconazole or echinocandin	C-2
ICU patients with *Candida* from respiratory secretions	Any antifungal	D-2
Any patient with *Candida* isolated from a blood culture	**Antifungal treatment**	**A-2**

A-D: Strength of the Recommendation
1-3: Quality of the Evidence

Cornely O, *et al. Clin Microbiol Infect* 2012;**18:**19-37

2012 ESCMID Guidelines for *Candida* diseases in non-neutropaenic adults

Confirmed infection:
Candida from blood culture

Strongly recommended:
Echinocandins (A-1)
- Anidulafungin
- Micafungin
- Caspofungin

Moderately recommended:
Liposomal ampho (B-1)
Voriconazole (B-1)

Marginally recommended:
Fluconazole (C-1)
Ampho B (C-2)

NOT recommended:
Itraconazole
Posaconazole

A-D: Strength of the Recommendation
1-3: Quality of the Evidence

Cornely O, *et al. Clin Microbiol Infect* 2012;**18:**19-37

2012 ESCMID Recommendations on antifungal prophylaxis in ICU patients

Population & Intention	Intervention	SoR & QoE	Note
Recent Abdo surgery AND with perforation; to prevent intra-abdominal candida infection	Flucon 400mg od	B-1	n=43
	Caspo 70/50mg od	C-2	n=19
ICU Surgical patients with LOS >3 days; to prevent invasive candidiasis/candidaemia	Flucon 400mg od	C-1	n=260
	Flucon 100mg od	C-1	n=204
Ventilated, LOS >3 days, CVC +/- TPN or RRT or pancreatitis or steroids; to prevent invasive candidiasis/candidaemia	Caspo 50mg od	C-2	n=186
Surgical ICU patients	Ketocon 200mg od	D-1	n=57
ICU patients with risk factors; to prevent invasive candidiasis/candidaemia	Itracon 400mg od	D-1	n=147

Cornely O, *et al. Clin Microbiol Infect* 2012;**18:**19-37

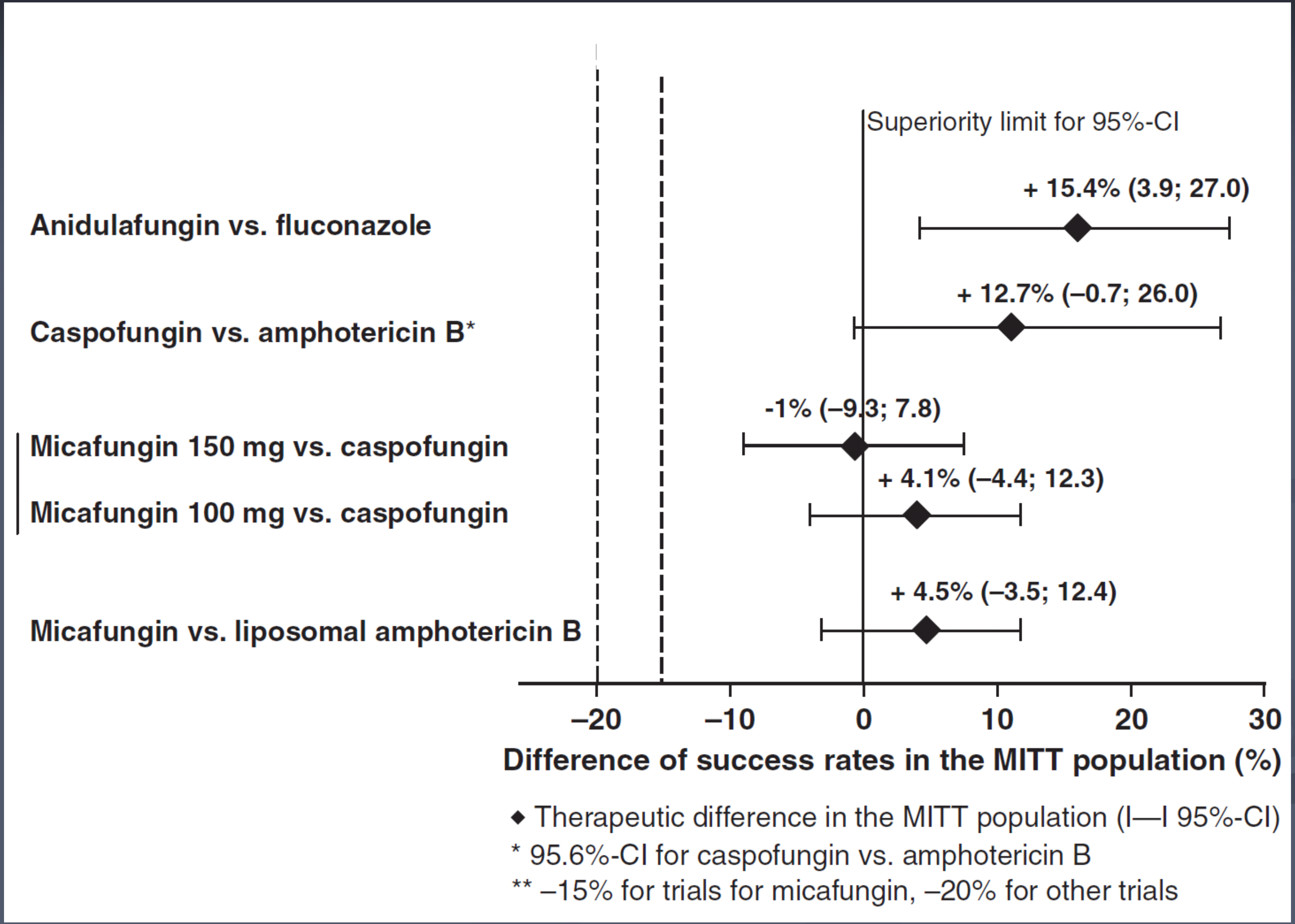

Fluconazole


Caspofungin


Anidulafungin


Micafungin

The Echinocandin trials



Glockner A, *et al*. *Mycoses* 2008;**52:**476-86

The Echinocandins

	Anidulafungin	Caspofungin	Micafungin
Number of papers	>50	>140	>60
Clinical experience	++	+++	++
Interactions	+++	++	+++
Biofilm activity	+++	+++	+++
In vitro activity	+++	+++	+++
Neutropaenic data	ND	+++	+++
Dose in RRT	No change	No change	No change
Disseminated candidiasis	+	+	ND
Dose in liver disease	No change	Reduce	No change
Price (£/$)	Anidula < Mica < Caspo		

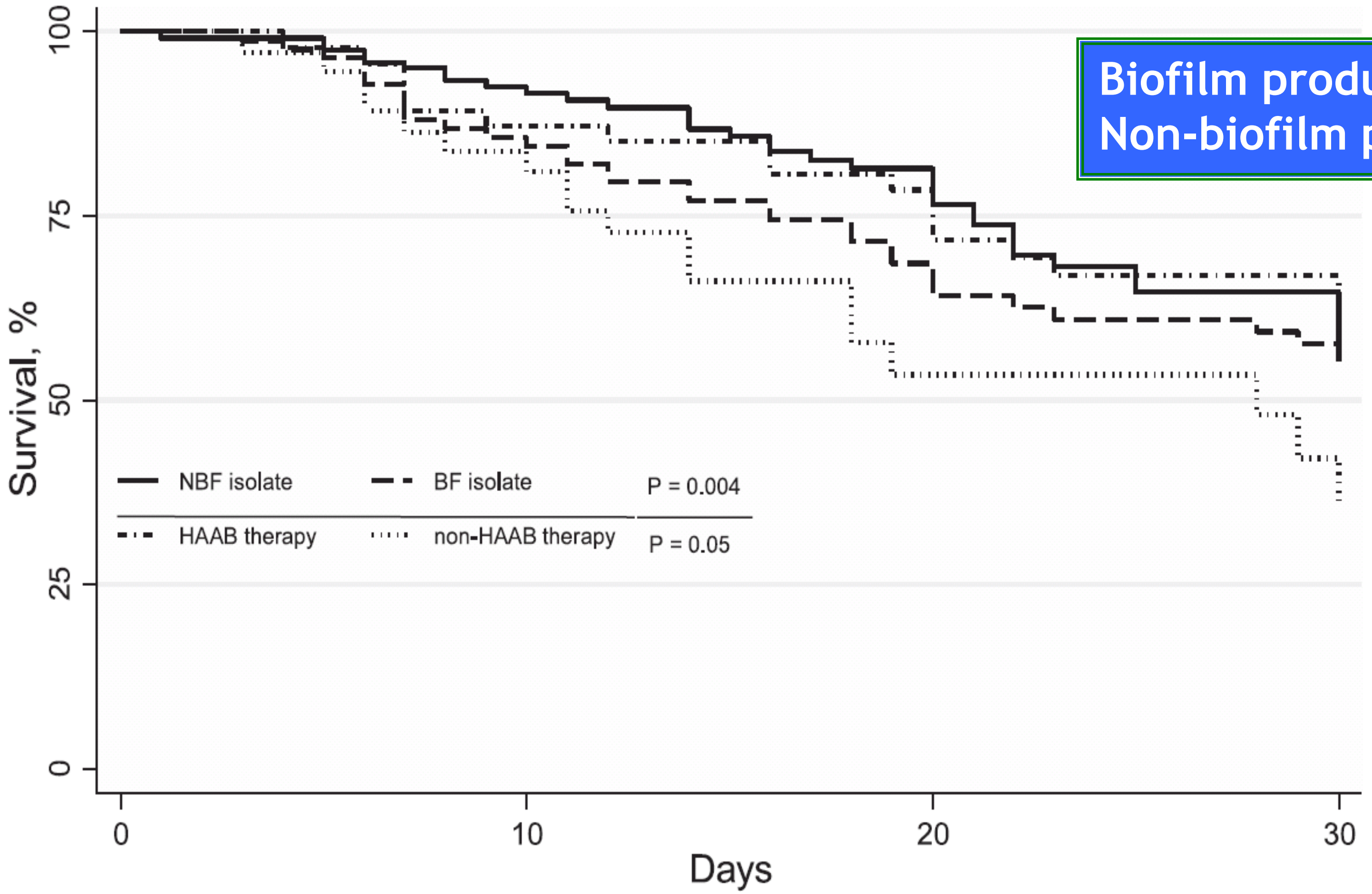
ND = No data

Based on PubMed search, data sheets & BNF

Question 6: A patient with a tunneled Hickman line develops a candidaemia, & has severe sepsis thought secondary to the line. What is the correct line management?

1. It depends whether the Candida species is a biofilm producer
2. The line should **always** be removed; recovery cannot occur if the line is left in place
3. The line only needs to be removed if the patient deteriorates & develops shock
4. The line does not need to be removed if the patient is treated with an Echinocandin

Candidaemia outcomes: biofilm vs. non-biofilm producers



Biofilm producers: n=84
Non-biofilm producers n=123

Figure 1. Survival among patients with *Candida* bloodstream infection (CBSI) at 30 days. Patients were grouped according to the biofilm-forming (BF) or non-biofilm-forming (NBF) *Candida* isolate (for all CBSIs), and according to receiving of highly active anti-biofilm (HAAB) or non-HAAB antifungal therapy (for BF CBSIs only). P-values for statistically significant differences between the groups are shown.
doi:10.1371/journal.pone.0033705.g001

Tumbarello M, *et al*. *PLoS ONE* 2012;7:e33705

The Aggregation Of Marginal Gains

The Learning Cycle

Conclusions

- Mortality from *Candida* infections in the critically ill remains high
- Outcome is likely to be significantly improved with:
  - Earlier recognition with scoring systems & biomarkers
  - Earlier antifungal therapy & source control
  - More appropriate dosing
  - Earlier use of Echinocandins in the more severe patients