

Treatment of invasive candidiasis in non-haematological patients

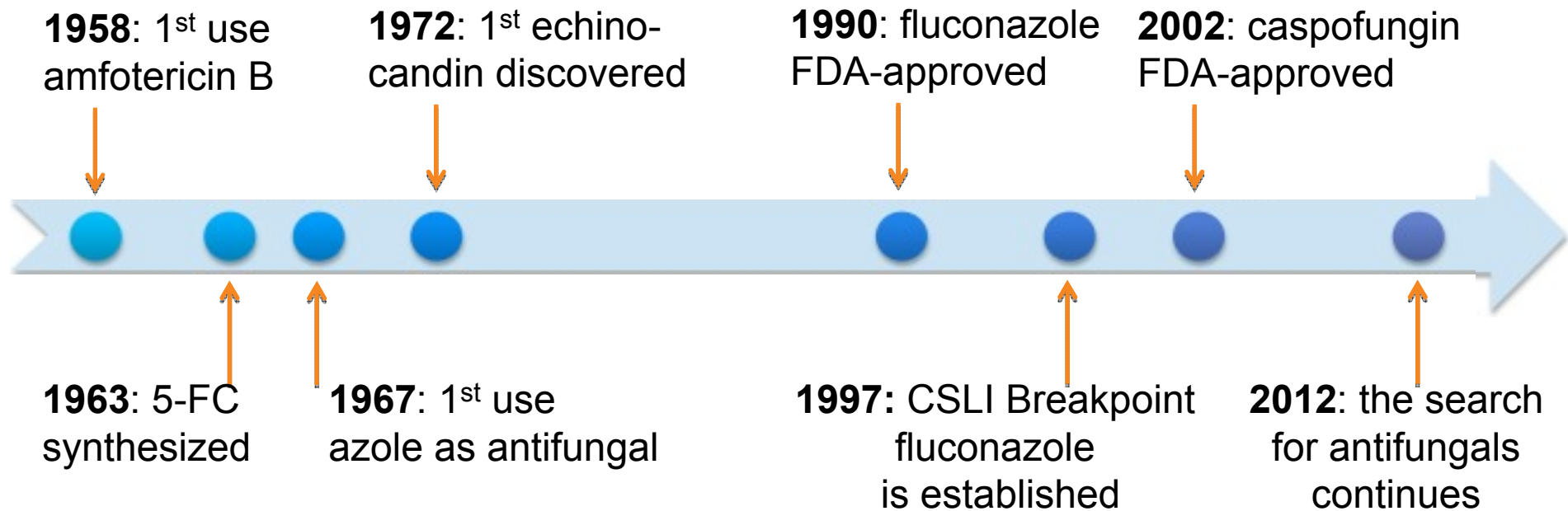
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History of antifungal treatment



Risk factors for candidemia

Presence of intravascular catheters*

Neutropenia

Cancer chemotherapy

Prior colonization with *Candida* spp

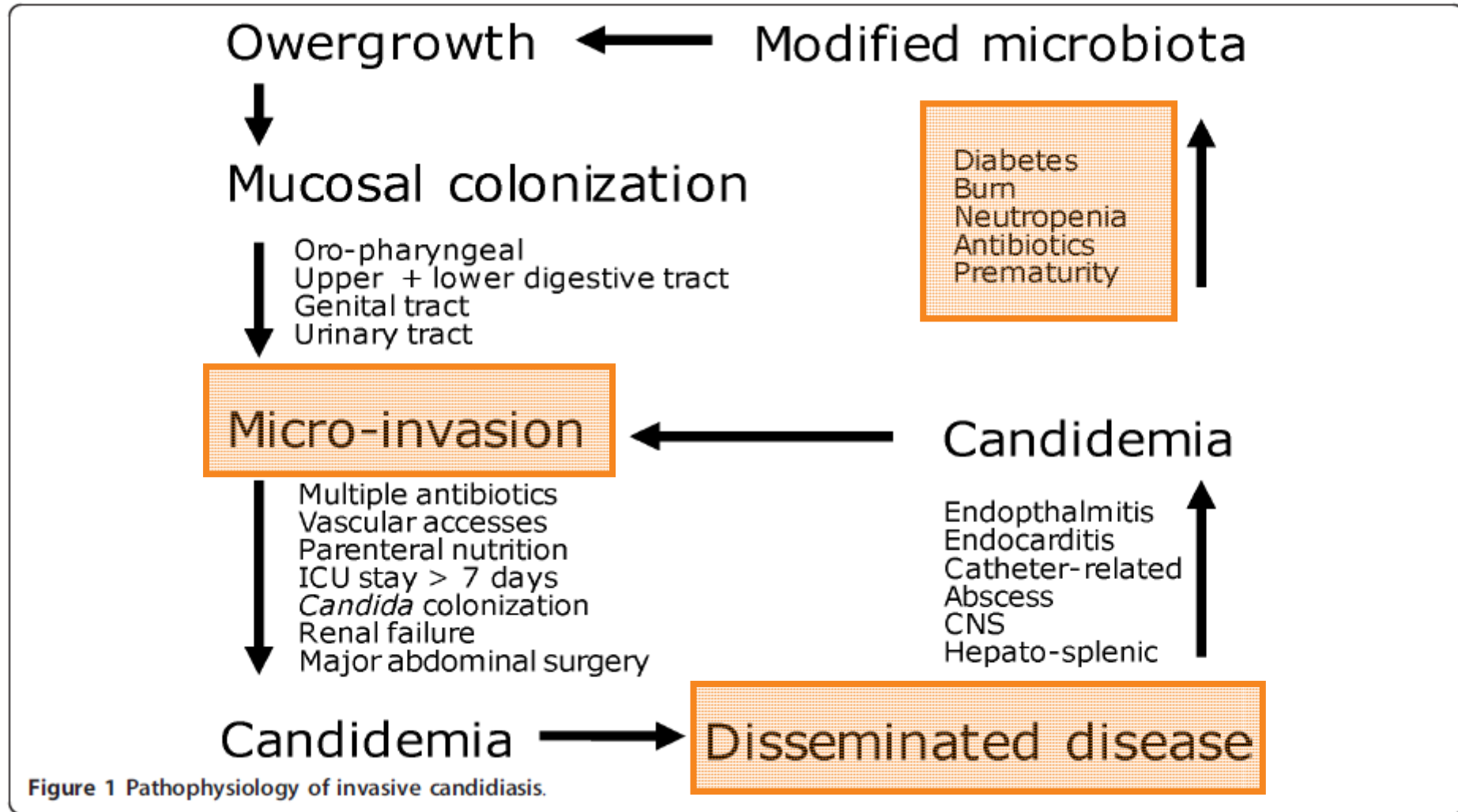
Broad spectrum antibiotics*

Renal failure

Hemodialysis

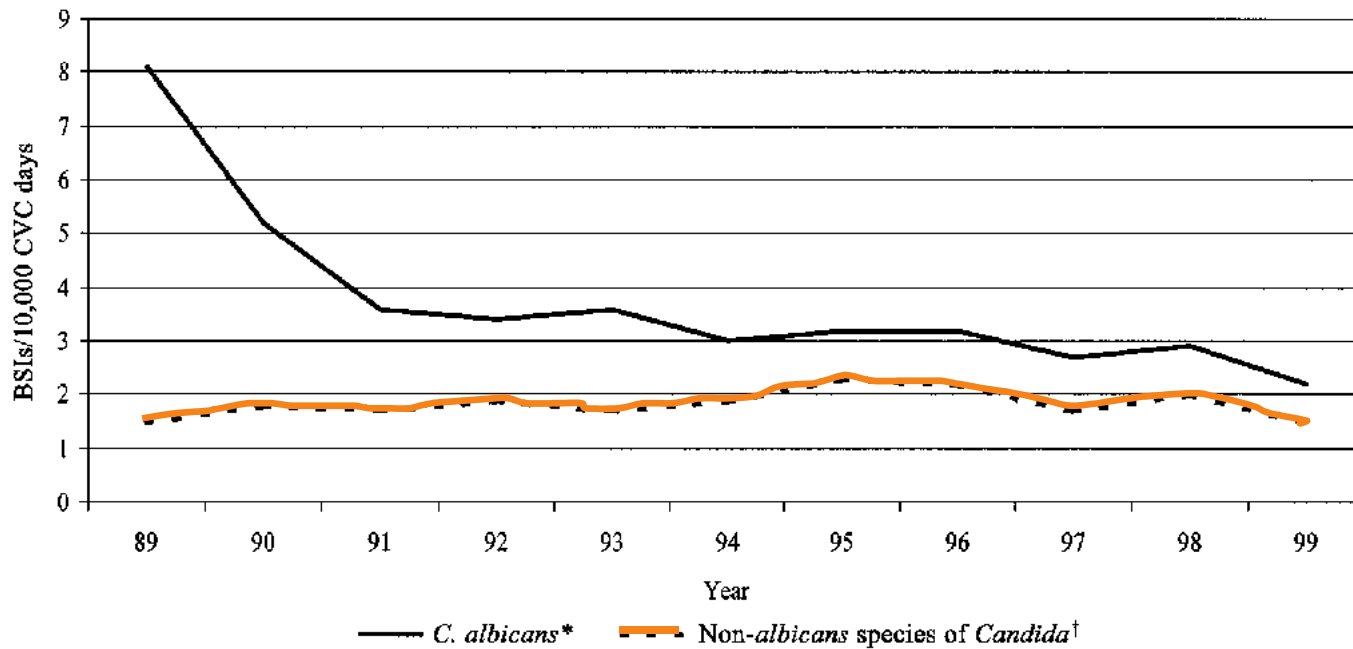


Pathophysiology of invasive candidiasis

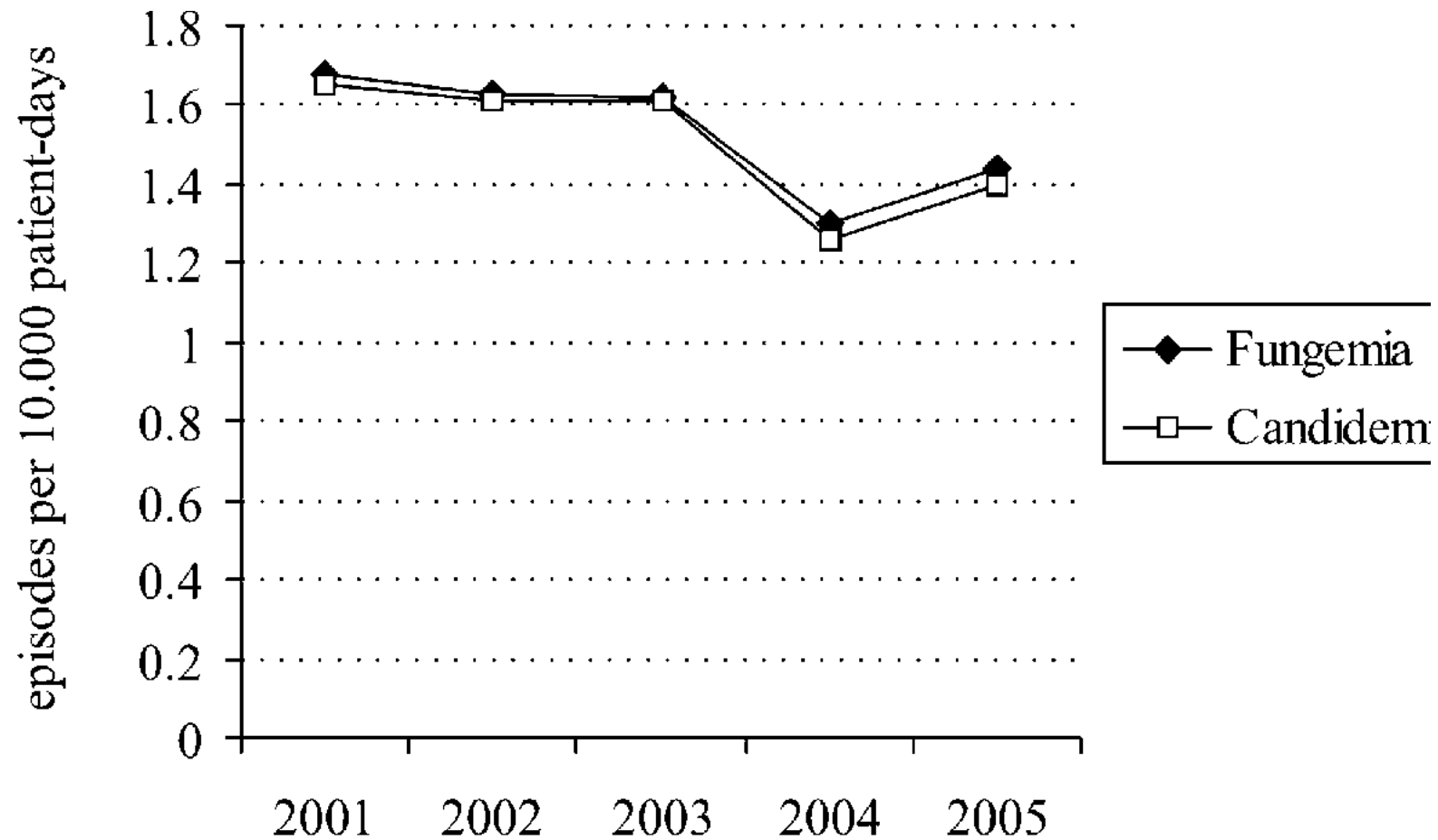


Epidemiology

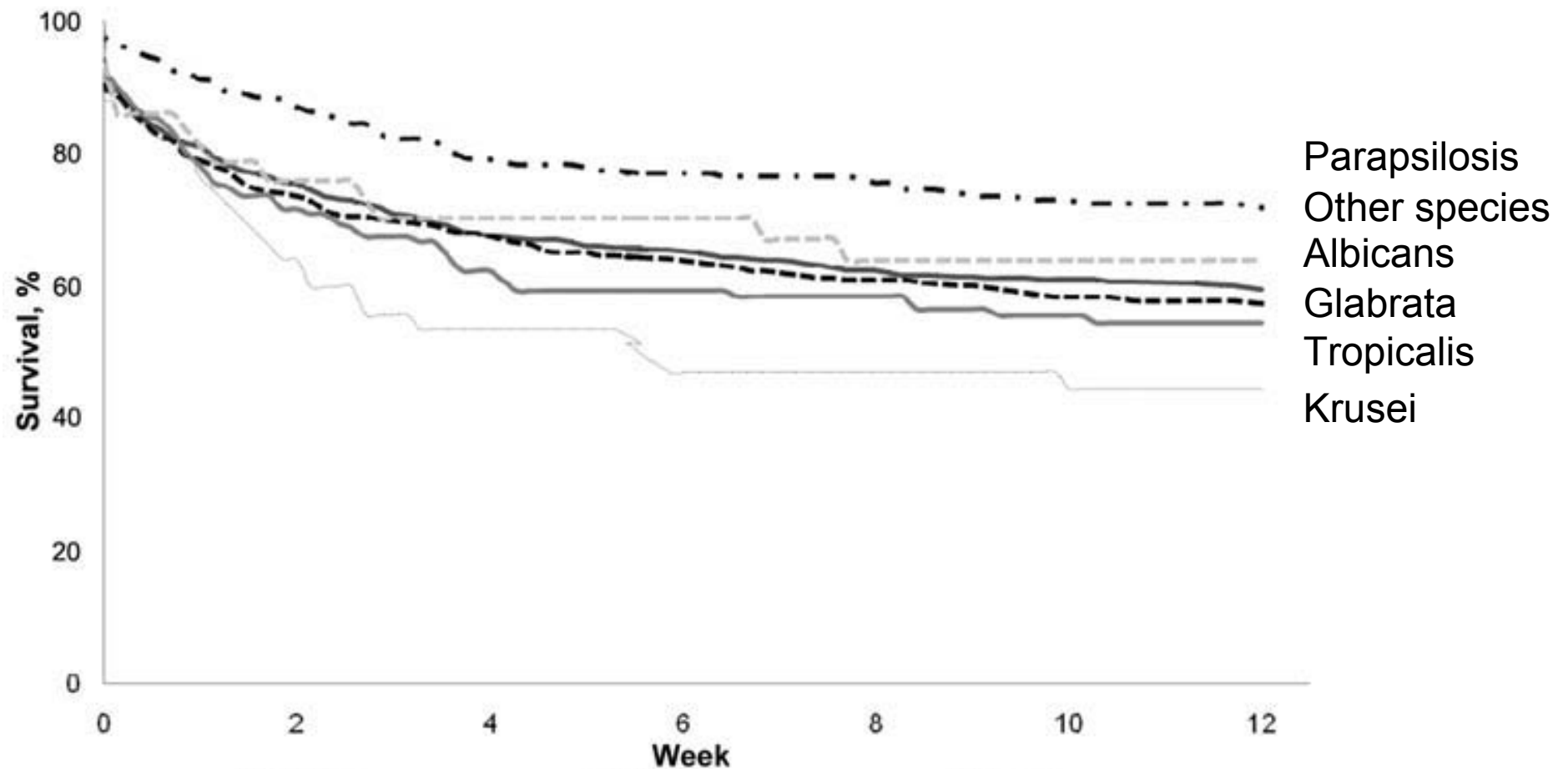
Mainly data from the USA or from individual European countries



Candidemia incidence in Leuven



Survival in candidemia, species related





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Question1 : Which Candida species is most frequently cultured from blood next to *C. albicans* (in Belgium)?

- 1 - *C. glabrata*
- 2 - *C. krusei*
- 3 - *C. parapsilosis*
- 4 - *C. tropicalis*

Question1 : Which Candida species is most frequently cultured from blood next to *C. albicans* (in Belgium)?

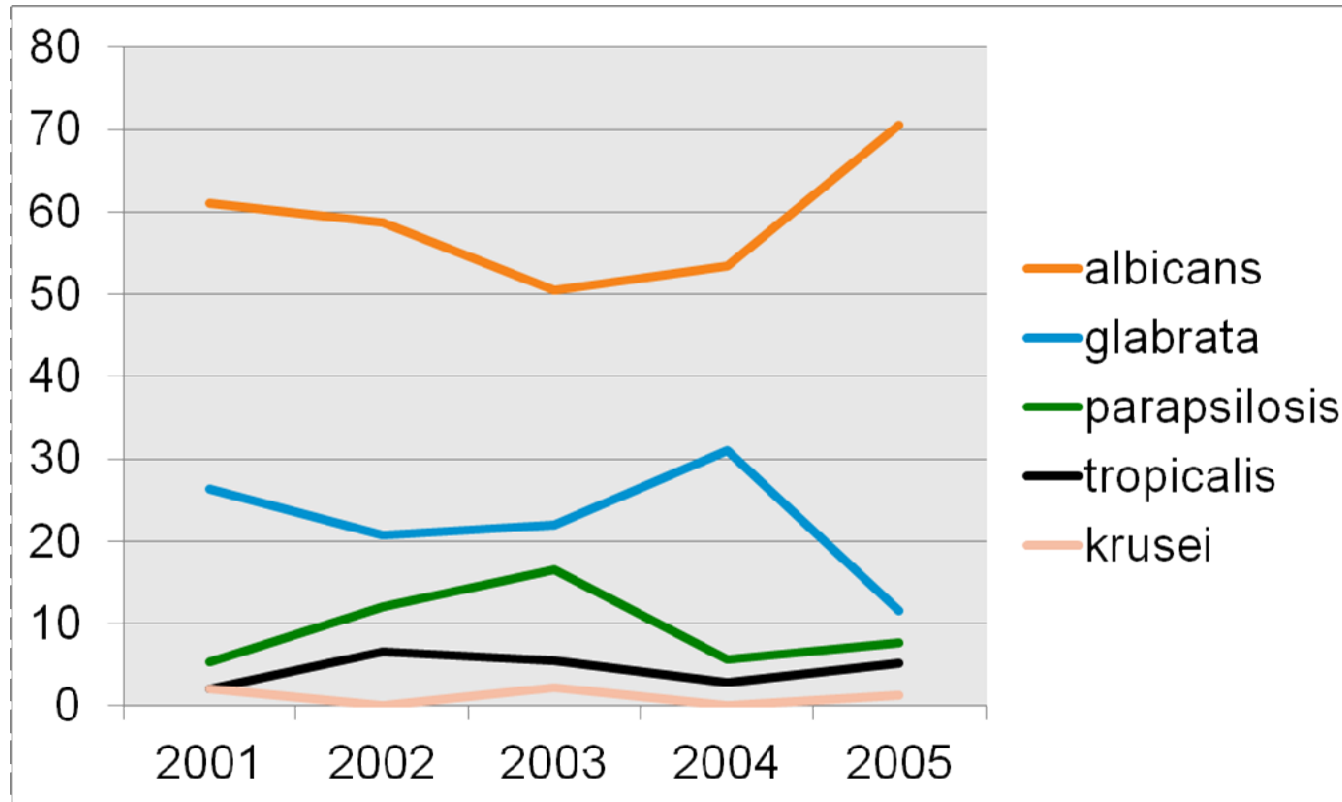
1 - *C. glabrata* | 0%

2 - *C. krusei* | 0%

3 - *C. parapsilosis* | 0%

4 - *C. tropicalis* | 0%

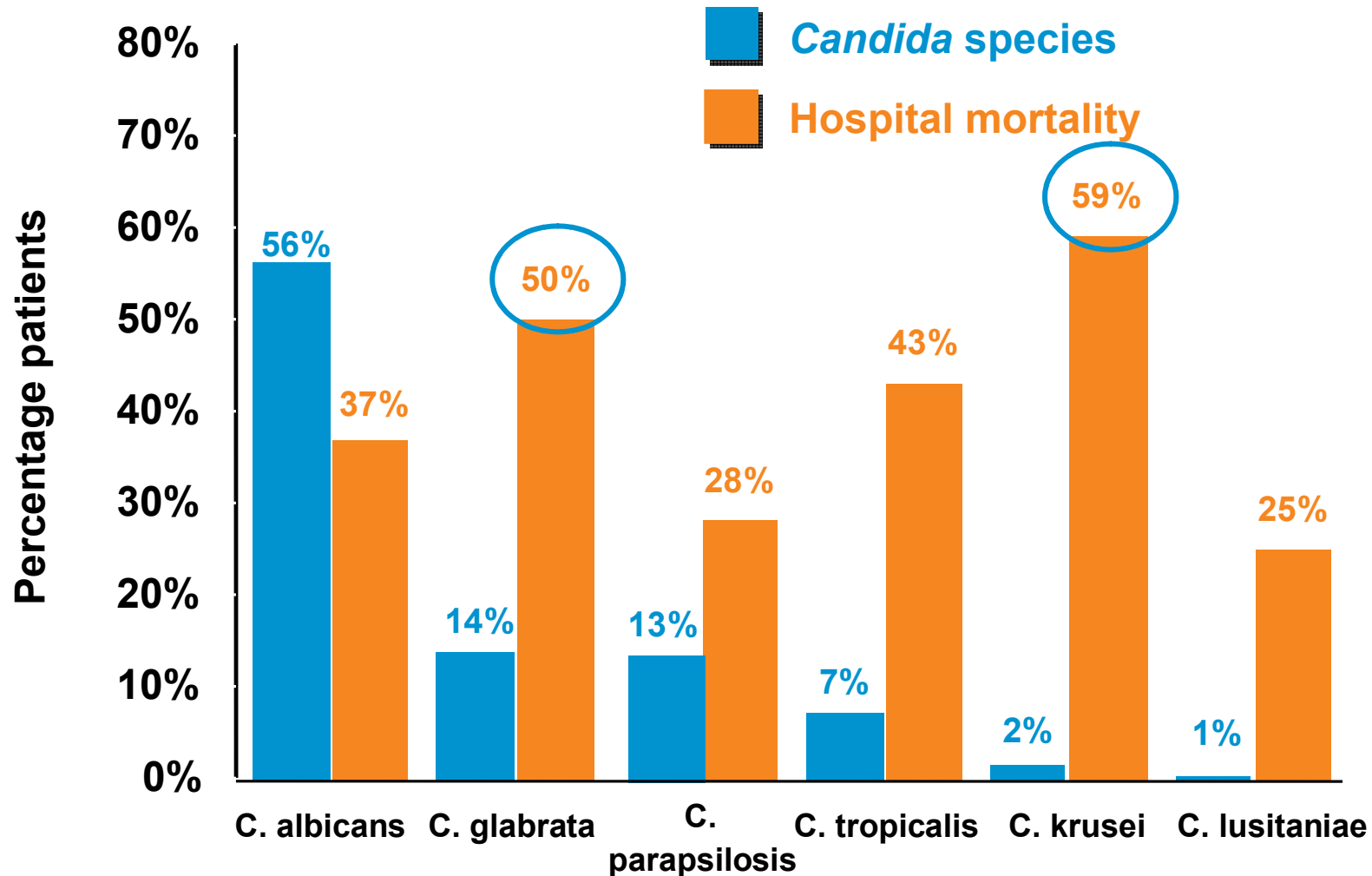
Candida blood stream infections



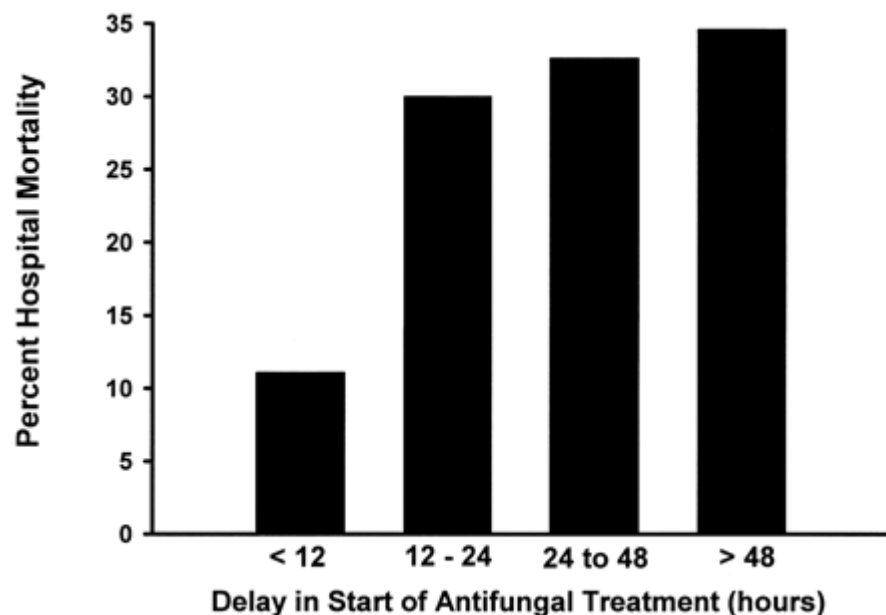
Mean 22% *C. glabrata* candidaemia

What would you start as primary therapy?

Incidence and mortality of *Candida* Species in Europe



Time to start antifungal therapy & hospital mortality

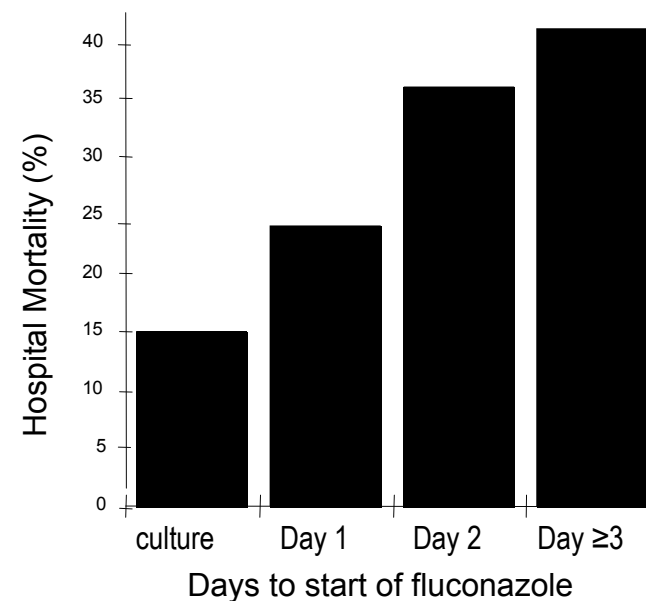


Morrell M, et al. AAC 2005

157 patients – 2001-2004

Independent determinants of mortality:

- APACHE II score (one-point increments) ($p < 0.001$)
- Administration of antifungal therapy >12 hours after the first positive blood culture (AOR, 2.09; $p = 0.018$)



Crude mortality rate is high, the attributable mortality rate varies between 5-71%!

Falagas EJCMID 2006

Garey KW et al, CID 2006

230 patients

Independent determinants of mortality:

- APACHE II score ($\Delta 1$ -pt.; $p < 0.05$)
- Time to fluconazole (AOR, 1.42; $p = 0.0009$)



HOW TO IDENTIFY PATIENTS AT RISK FOR CANDIDEMIA?



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Question 2: Which factor has the greatest independent association with development of invasive candidiasis ?

- 1 - Abdominal surgery at baseline
- 2 - Multifocal colonization
- 3 - Severe sepsis at baseline
- 4 - Total parenteral nutrition

Question 2: Which factor has the greatest independent association with development of invasive candidiasis ?

1 - Abdominal surgery at baseline | 0%

2 - Multifocal colonization | 0%

3 - Severe sepsis at baseline | 0%

4 - Total parenteral nutrition | 0%

Prediction rules

- **Paphitou:** TPN, hemodialysis, diabetes, broad spectrum antibiotics
- **Ostrosky-Zeichner:**
 - CVC +/- broad spectrum antibiotics
and at least 2 of:
 - TPN, hemodialysis, major surgery, pancreatitis, corticosteroids, immunosuppression
- **Candida score:** Multivariate analysis of risk factors that predispose for invasive candidiasis

Identification of patients

“Ostrosky rules”

≥ 4 days on ICU

AND

-Antibiotics (d 1-3)

OR

-CVC (d 1-3)

And at least 2 of these

TPN (d 1-3)

Dialysis (d 1-3)

Major surgery (d -7-0)

Use steroids (d -7-3)

Immunosupp. (d -7-0)

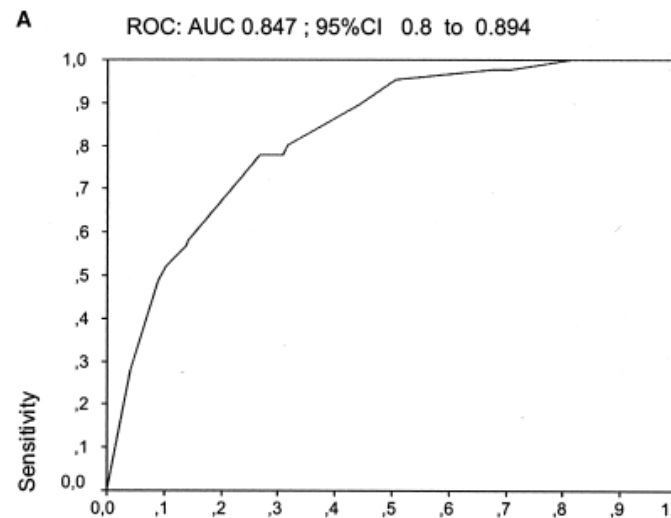
Identify patients for empirical/ pre-emptive therapy

Development of “Candida score”

1699 patients, ≥ 7 days on IC

Multivariate analysis of risk factors for candidemia

	weight	points
o Colonization on multiple locations	1.112	1
o TPN		1
o Surgery at admission		1
o Severe sepsis		2





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Question3: What's the problem with the prediction rules to start empirical treatment?

- 1 - High sensitivity, low specificity
- 2 - Low sensitivity, high specificity
- 3 - Only useful in high incidence areas
- 4 - 1+3
- 5 - 2+3

Question3: What's the problem with the prediction rules to start empirical treatment?

- | | | |
|---|--|----|
| 1 - High sensitivity, low specificity | | 0% |
| 2 - Low sensitivity, high specificity | | 0% |
| 3 - Only useful in high incidence areas | | 0% |
| 4 - 1+3 | | 0% |
| 5 - 2+3 | | 0% |

Identification of patients

“Ostrosky rules”

≥ 4 days on ICU

AND

-Antibiotics (d 1-3)

OR

-CVC (d 1-3)

And at least 2 of these

TPN (d 1-3)

Dialysis (d 1-3)

Major surgery (d -7-0)

Use steroids (d -7-3)

Immunosupp. (d -7-0)

**Sensitivity 34%, specificity 90%,
PPV 1%, NPV 97%**

Prevalence 7% invasive candidiasis

Identify patients for empirical/ pre-emptive therapy

Development of “Candida score”

1699 patients, ≥ 7 days on IC

Multivariate analysis of risk factors for candidemia

	points
o Colonization on multiple locations	1
o TPN	1
o Surgery at admission	1
o Severe sepsis	2

≥ 3 : sensitivity 81%, specificity 74%

PPV 16%, NPV 98%

Prevalence 5.8%

Are the risk predictive models generalizable?

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

Validation in Australia:

	Candida score	
	As reported In Spain (prev = 5,8%)	Applied to Australian data (prev = 0.2% 2.0%)
Sensitivity	81%	15-26%
Specificity	74%	98%
PPV	16%	2%
NPV	98%	98%
Comments		Application to patients with ICU LOS \geq 7d excludes $\frac{1}{3}$ - $\frac{1}{2}$ cases



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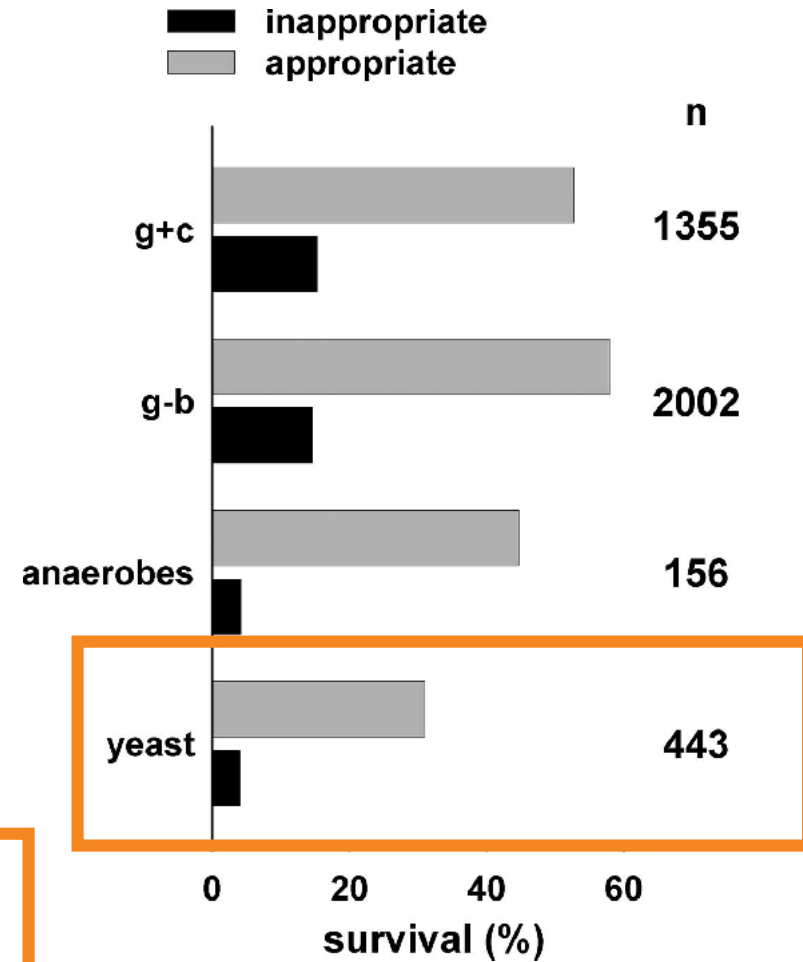
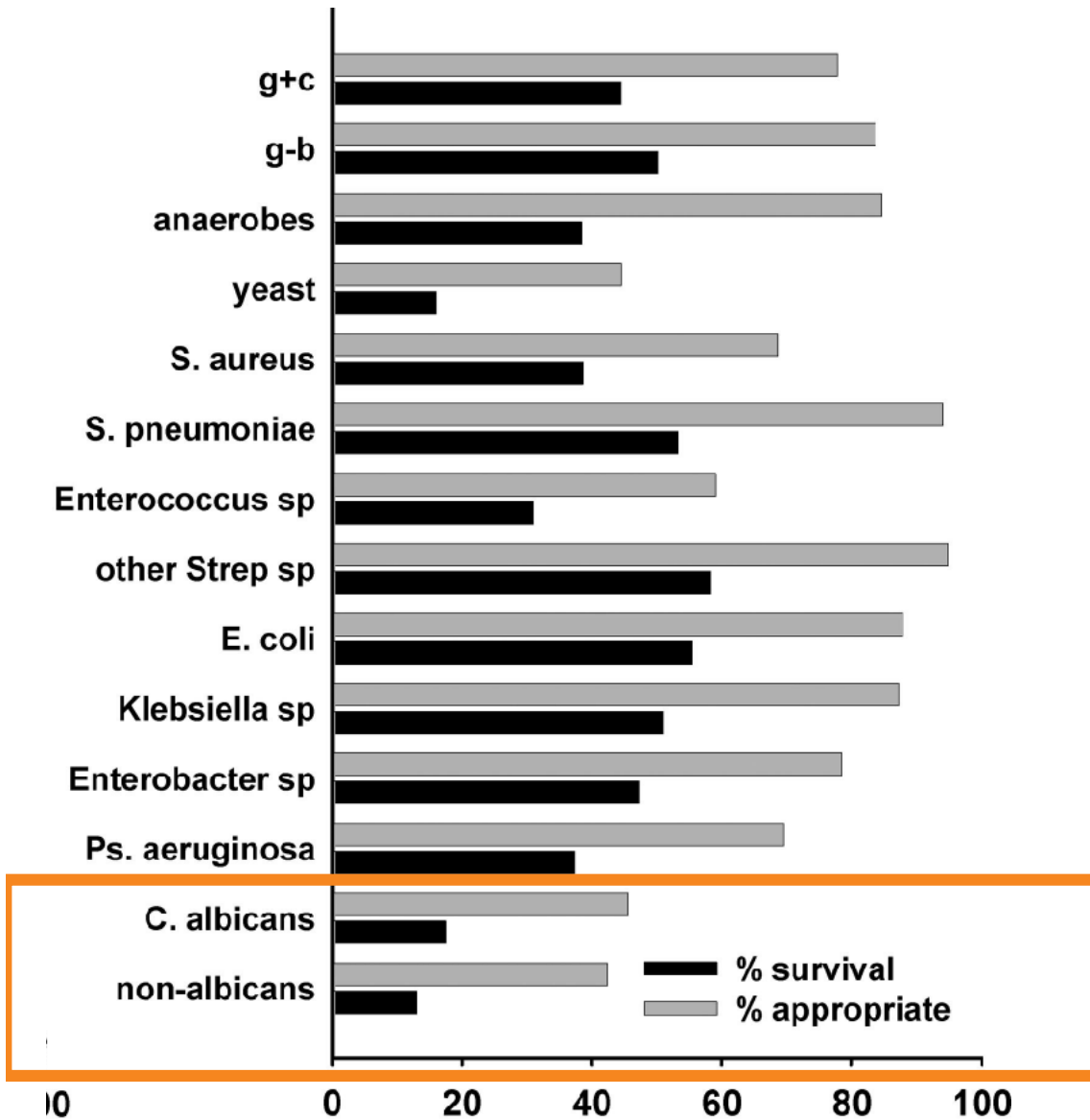
Question 4: Empirical treatment is most often inappropriate in septic ICU patients infected with...

- 1 - Staphylococcus aureus
- 2 - Pseudomonas aeruginosa
- 3 - Klebsiella species
- 4 - Candida albicans

Question 4: Empirical treatment is most often inappropriate in septic ICU patients infected with...

1 - Staphylococcus aureus		0%
2 - Pseudomonas aeruginosa		0%
3 - Klebsiella species		0%
4 - Candida albicans		0%

Appropriate empirical treatment in ICU





HOW TO PREVENT INVASIVE CANDIDIASIS IN THE ICU?

Antifungal prophylaxis in the ICU?

Pro:

-Reduces the incidence of invasive candidiasis!

with app. 50%

-Again: identification of target patients difficult

-High risk patients

-In high incidence area

-Necrotizing pancreatitis

-Recurrent GI leakage

Con:

- Unselected ICUs: 1-2% invasive candidiasis

- In most hospitals;
Ineffective strategy

Empirical antifungal therapy in ICU

RCT Prospective study in ICU patients

Inclusion:

- Unexplained fever > 4 d
- Broad-spectrum antibiotics \geq 4 d
- APACHE-II score \geq 16
- CVC \geq 1 d

(no colonization criteria!)

\Rightarrow 14d Fluconazole (800mg/d) or placebo

Outcome empirical therapy in ICU

Outcome:

- resolution of fever (<38.3, >72h)
- no invasive mycosis
- no discontinuation for toxicity
- no other antifungal drugs

**Total failures:
55% vs 57%**
**No resolution of fever
51% vs 54%**

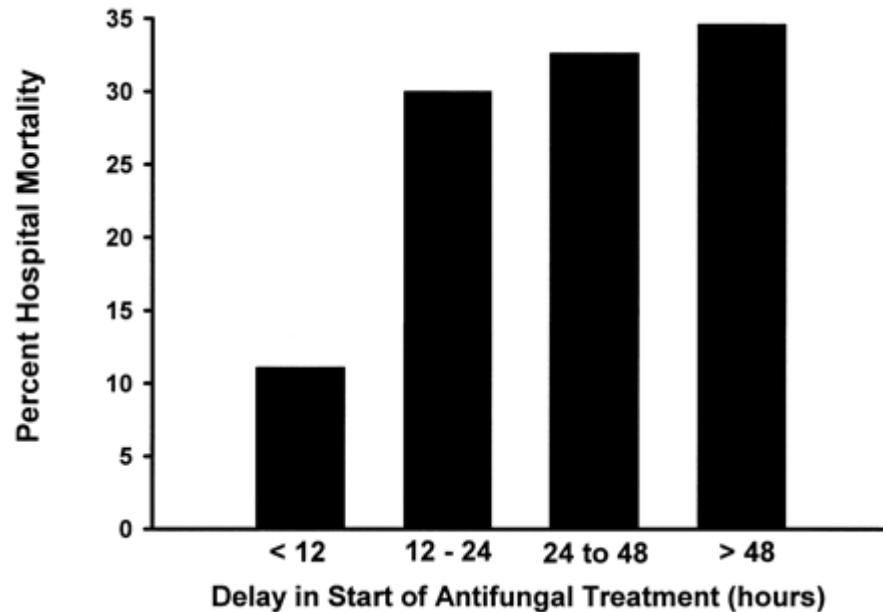
	Fluconazole (122)	Placebo (127)	
Success	34%	38%	(0.69-1.32)
Inv. Mycoses	5%	9%	(0.22-1.49)
Mortality	24%	17%	(0.23-1.67)

No effect of empirical fluconazole! Why?



TREATMENT OF INVASIVE CANDIDIASIS

Time to start antifungal therapy & hospital mortality

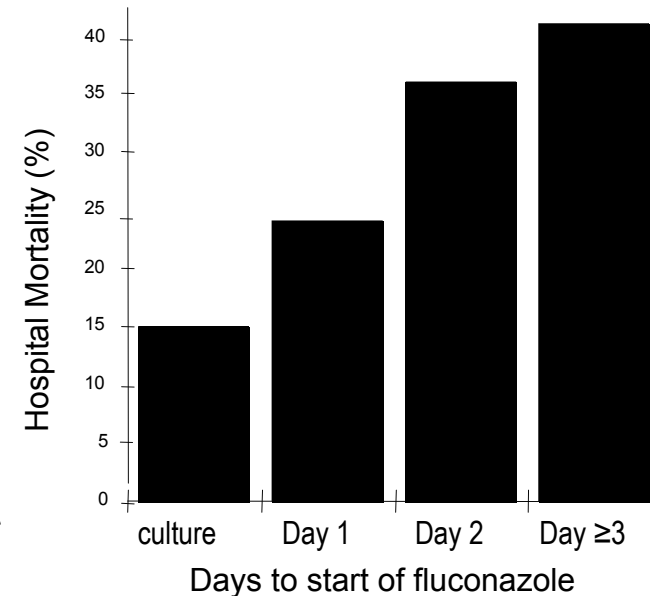


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Why do we choose which antifungal drug?

- Broad spectrum of antifungal activity
- Efficacy
- Patient characteristics
- Safety / interactions

Antifungal agents

Amphotericin B

- deoxycholate AmB
- lipid formulations

Effective, broad spectrum,
but toxic

Lipid: expensive

Azols

- Fluconazole
- voriconazole

Effective, less toxic, less broad
spectrum

Interactions

Echinocandins

- Caspofungin
- Anidulafungin
- Micafungin

Effective, broad spectrum

Little toxicity, few interactions

Expensive

Randomized Non-Inferior Trials

AmB vs fluconazole: **equally effective** (3 trials)

AmB/fluc vs Fluc: **equally effective** Rex, 2003

AmB -> fluc vs Vori: **equally effective** Kullberg, 2005

Caspofungin vs AmB: **equally effective** Mora-Duarte, 2002

Micafungin vs L-AmB: **equally effective** Kuse, 2007

Mica vs Caspo: **equally effective** Pappas, 2007

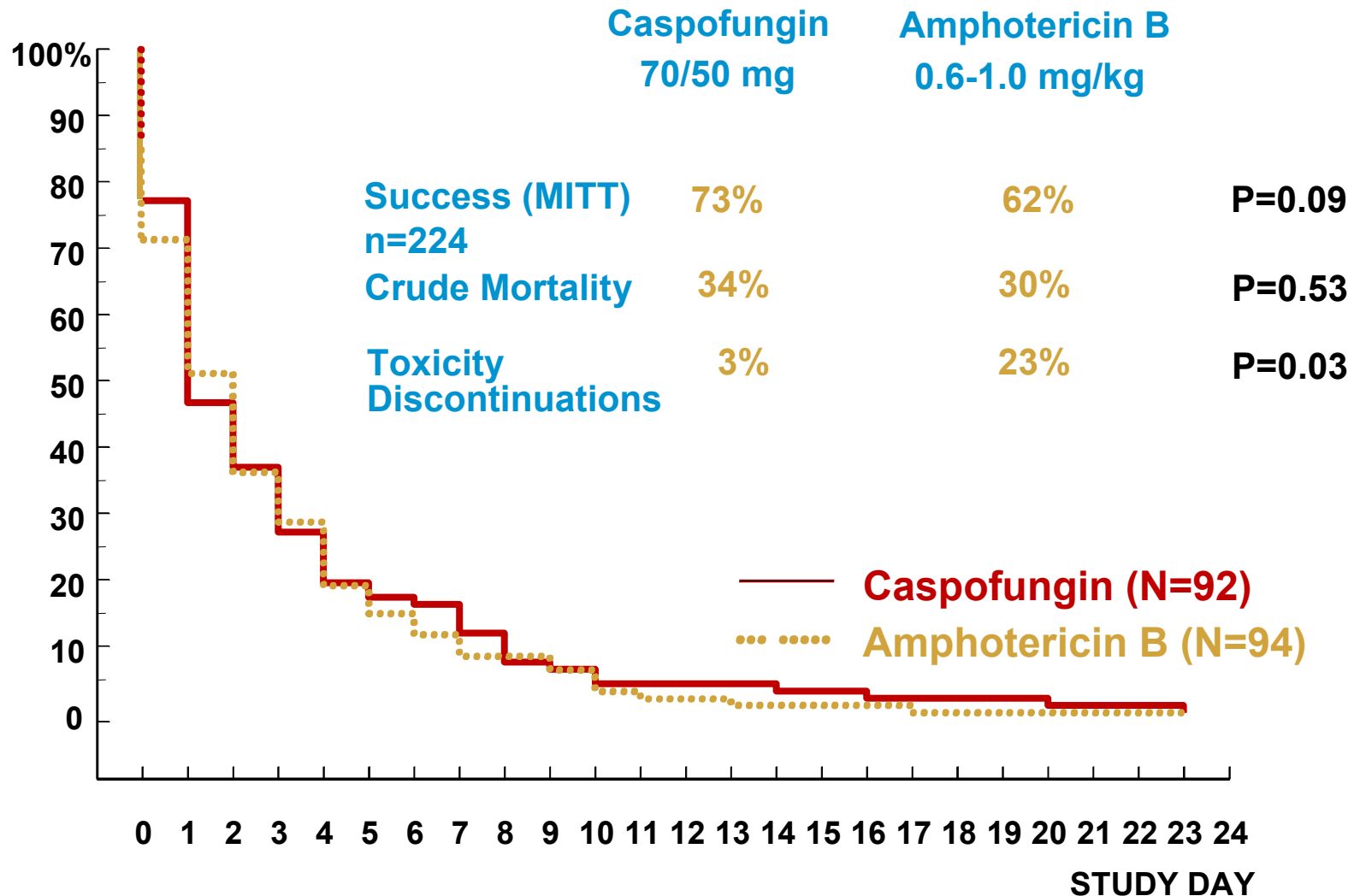
Anidulafungin vs fluc: ***favours Anidula*** Reboli, 2007

Susceptibility

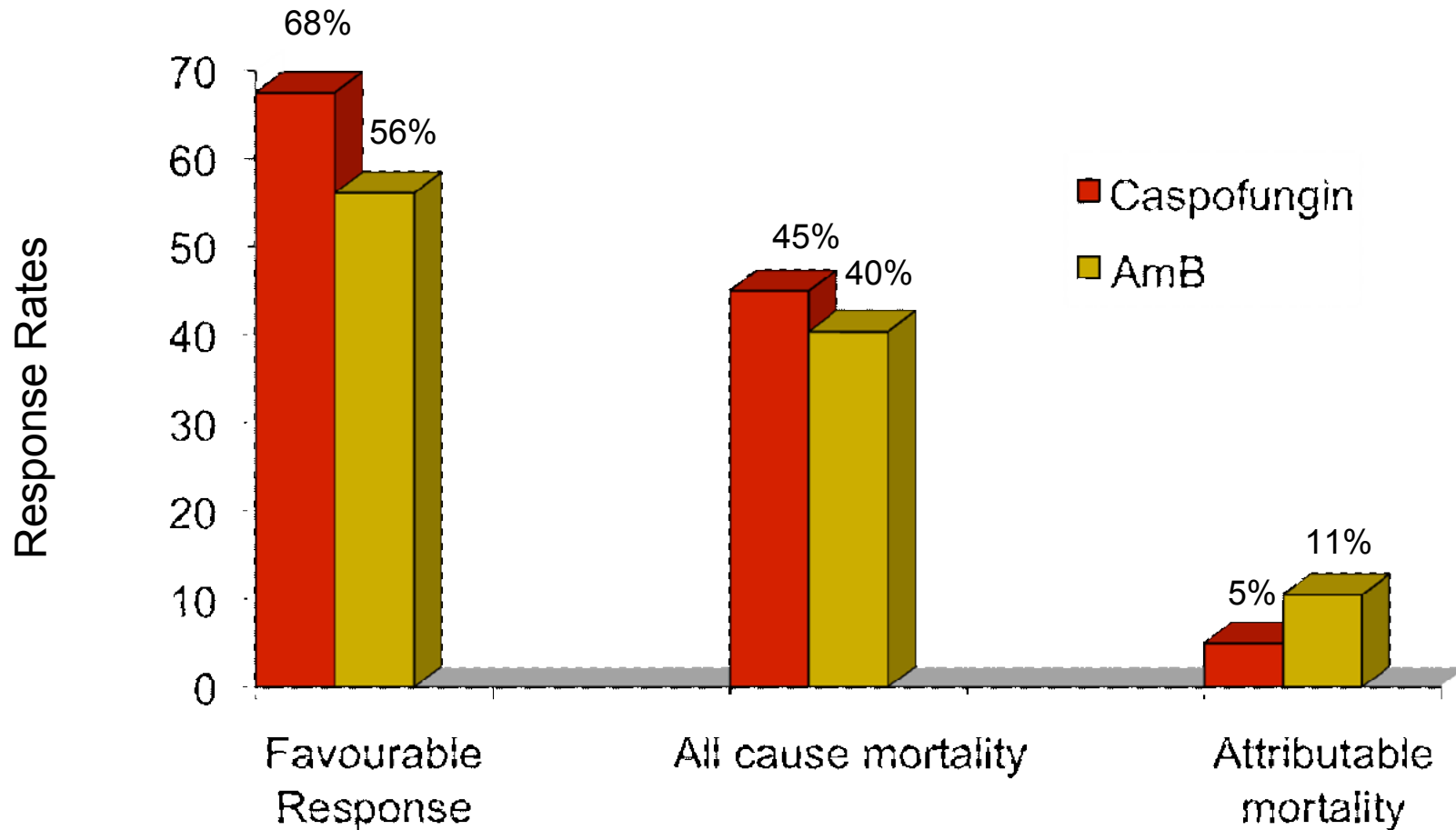
Antifungal	Albicans	Glabrata	Parapsilosis	Tropicali s	Krusei
AmB-d	S	S	S	S	S
L-AmB	S	S	S	S	S
Fluconazole	S	(SDD)-R	S	S	R
voriconazole	S	SDD-R	S	S	S
Anidulafungin	S	S	S/?	S	S
Caspofungin	S	S	S/?	S	S
micafungin	S	S	S/?	S	S

Caspofungin vs. Amphotericin B trial

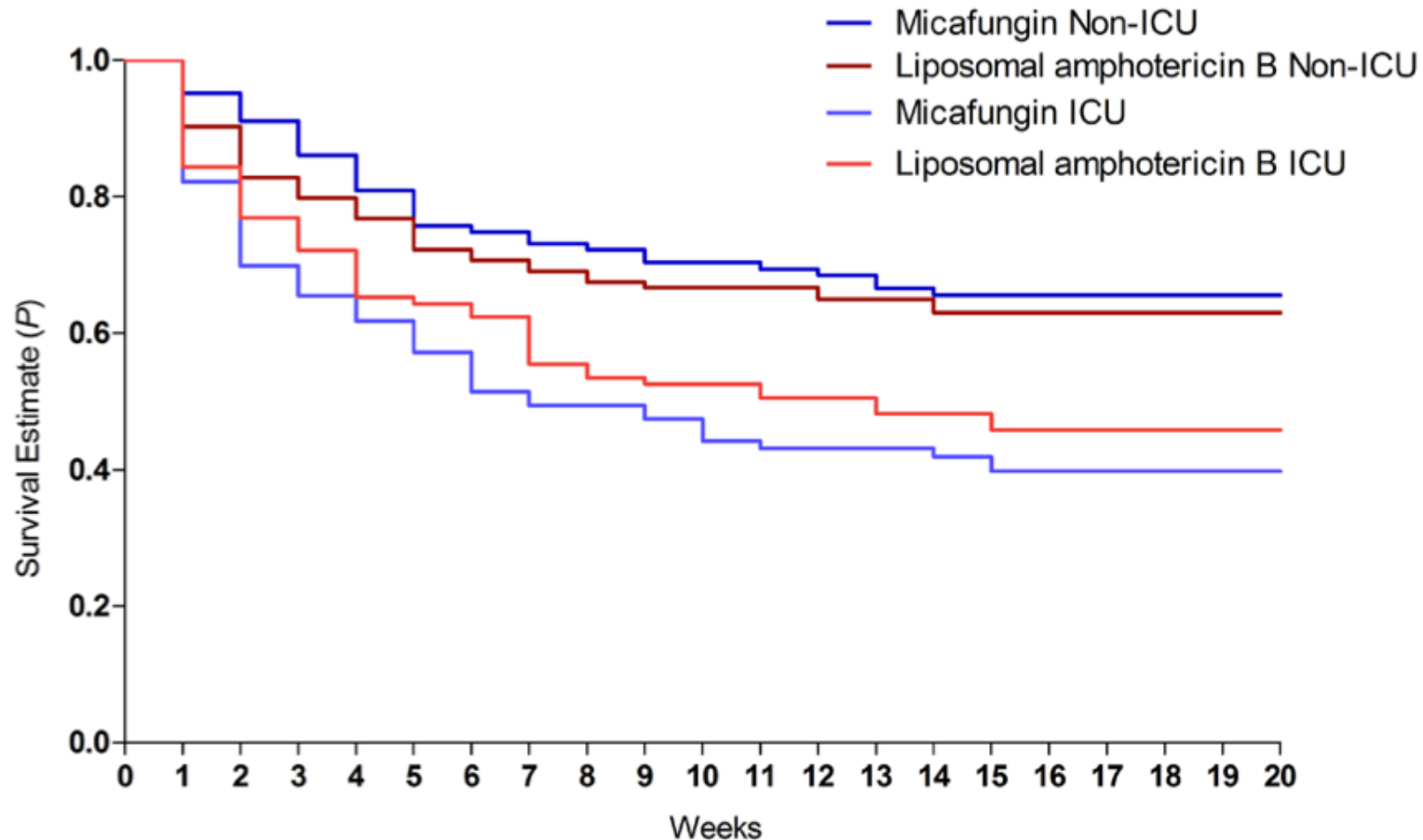
Time to First Negative Blood Culture



Caspofungin vs. AmB in ICU Patients (n=97)



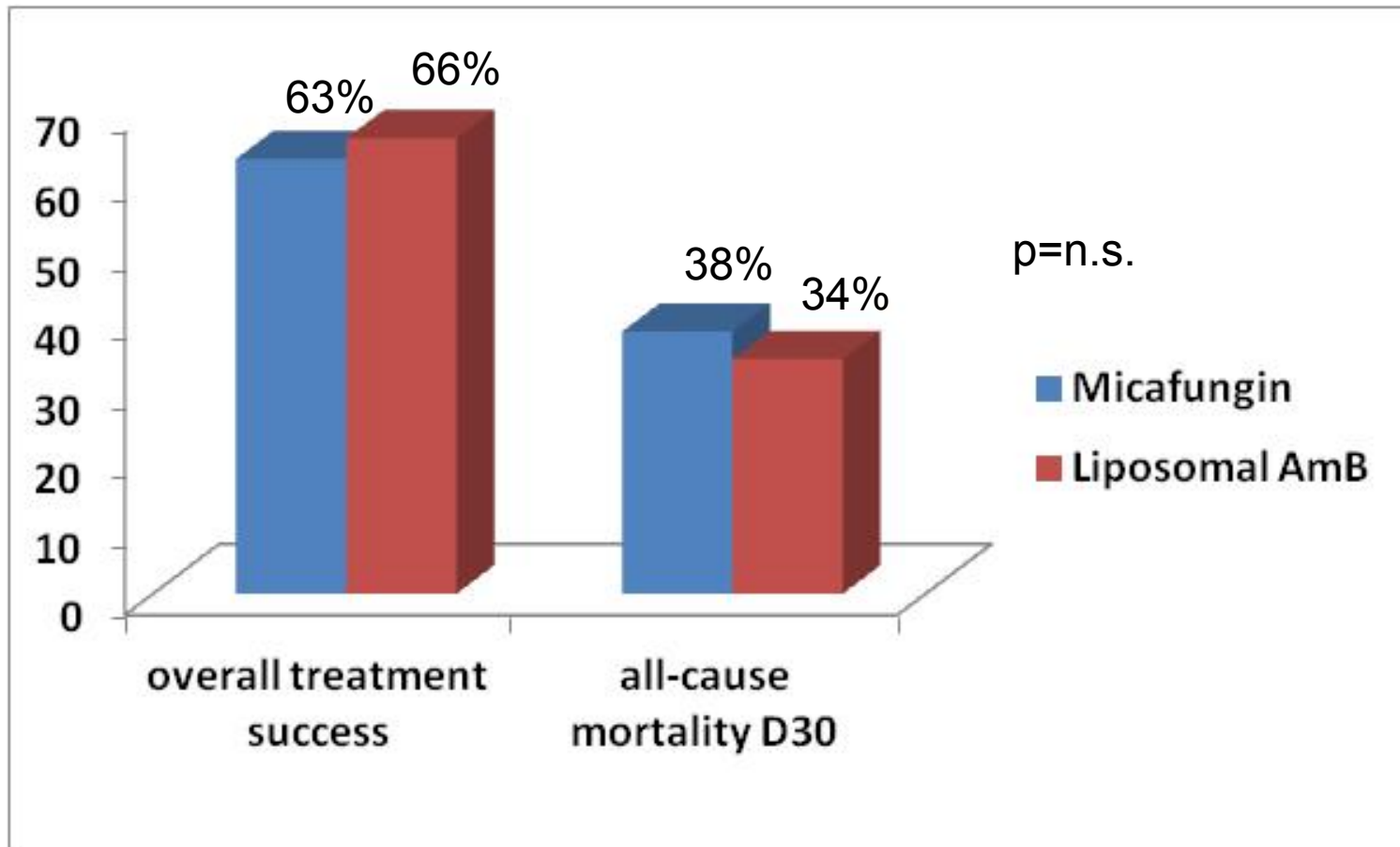
Micafungin vs. L-AmB in ICU Patients (n=230)



Micafungin versus liposomal amphotericin B: log rank test $P=0.6840$

ICU versus non-ICU: log rank test $P<0.0001$

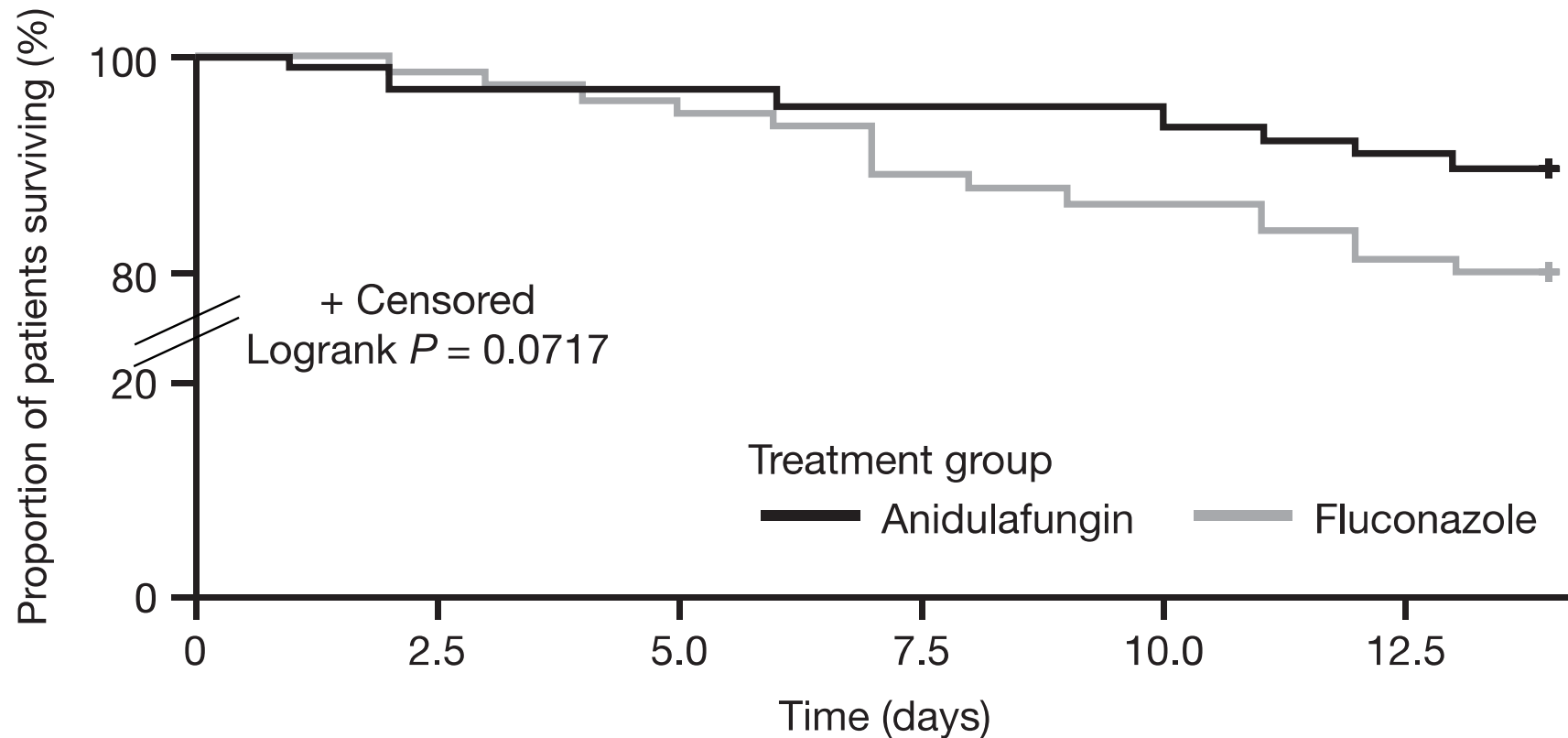
Micafungin vs. L-AmB in ICU Patients (n=230)



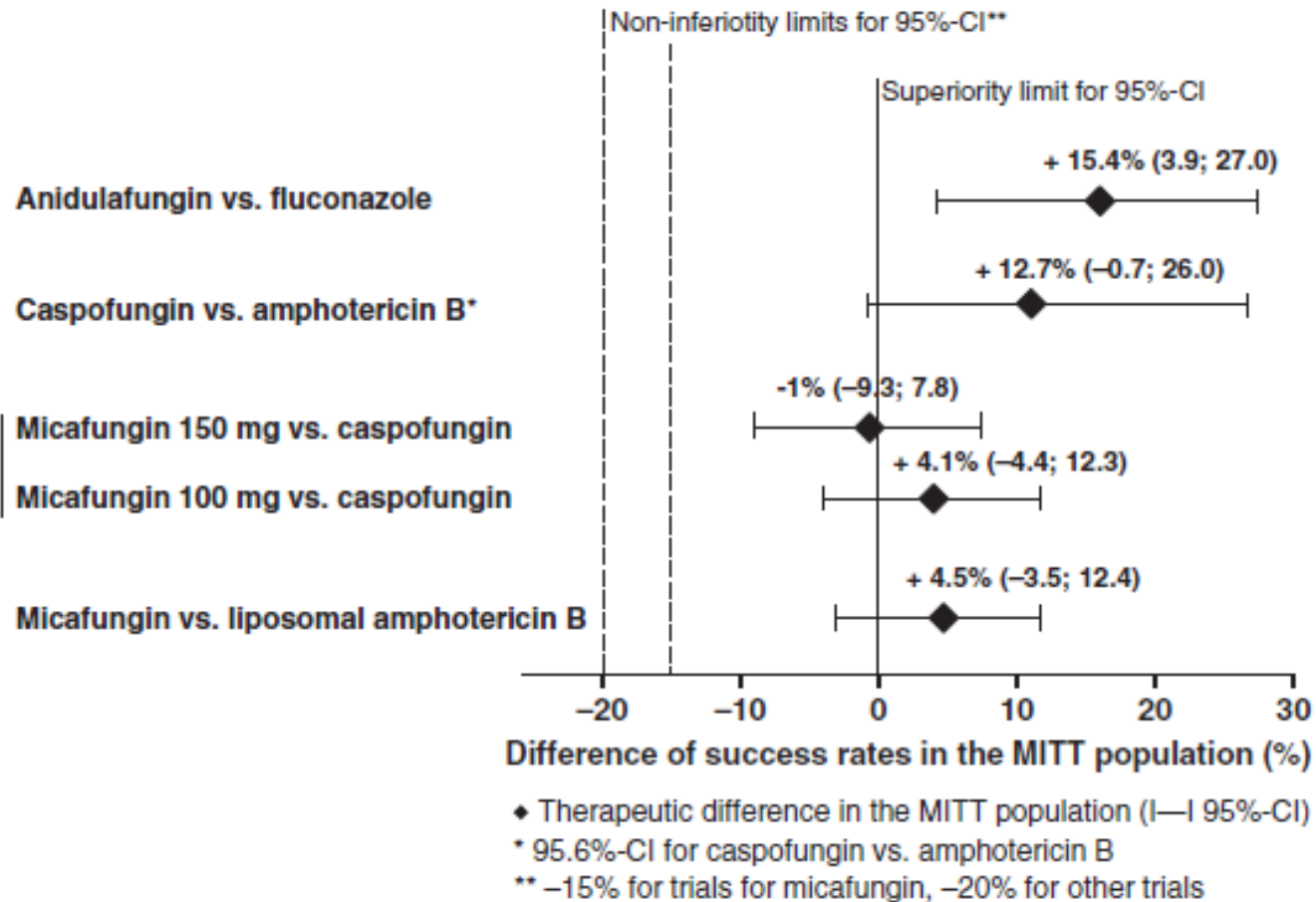
Anidulafungin vs. fluconazole study

MITT population	Anidulafungin N=127 (%)	Fluconazole N=118 (%)	Difference 95% CI
Success EIV	96 (75.6)	71 (60.2)	15.4 (3.9-27.0)(p<0.02)
EOT (all)	94 (74.0)	67 (56.8)	17.2 (5.5-29)(p<0.02)
2 wk follow-up	82 (64.4)	58 (49.2)	15.4 (3.1-27.7)(p<0.02)
Crude Mortality Rate (8wks)	23%	31%	P=0.15

Survival in ICU patients: *anidulafungin vs fluconazole*



Success rates different echinocandins



Source for Tables (modified) and Figure : Glöcker A and Cornely OA; Echinocandine bei Candida - Infektionen [Treatment of Invasive Candidiasis with Echinocandins] Med Klin 2008; 103:397-405; (Copyright Yrban & Vogel. Reproduced with permission.)

Indications per echinocandin

Antifungal agent	Indications	Required daily dose ld/md (minimum treatment duration in days)	Date of approval by US FDA
Caspofungin	Empirical therapy for presumed fungal infections in febrile, neutropenic patients	70/50 (7)	February 2005
	Candidemia, intra-abdominal abscess, peritonitis, pleural space infections	70/50 (14)	July 2003
	Esophageal candidiasis	50 (n.s.)	September 2002
	Invasive aspergillosis if refractory or intolerant to other therapies	70/50 (n.s.)	January 2001
Micafungin	Prophylaxis for <i>Candida</i> infections in hematological stem cell transplantation	50 (n.s.)	March 2005
	Esophageal candidiasis	150 (n.s.)	March 2005
Anidulafungin	Candidemia and intra-abdominal abscess, peritonitis	200/100 (14)	February 2006
	Esophageal candidiasis	100/50 (14)	February 2006

ld/md = Loading dose/daily maintenance dose in milligrams; n.s. = not specified.



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Question 5: Should the intravascular catheters be removed < 24h?

- 1 - Yes, when > 24h mortality is higher
- 2 - No, but < 48h; > 48h mortality is higher
- 3 - No, but it should be removed
- 4 - Removal of the catheter has no effect on mortality

Question 5: Should the intravascular catheters be removed < 24h?

1 - Yes, when > 24h mortality is higher | 0%

2 - No, but < 48h; > 48h mortality is higher | 0%

3 - No, but it should be removed | 0%

4 - Removal of the catheter has no effect on mortality | 0%

Antifungal agents and survival

Candidemia and invasive candidiasis

- 7 randomized controlled trials
- 7 antifungal agents (flu, vori, amB, L-amB, caspo, anidula, mica)
- New analysis of all individual patients
- Primary endpoint: 30 day survival
- Excluding: combination therapy, unknown candida species, multiple species infection
- 1915 patients!

Andes pooled data analysis

1915 patients, two polyenes, two triazoles, three candins

Logistic regression using 30-day mortality as primary outcome

Increased mortality

- Age
- APACHE II
- Immunosuppressive therapy
- *C. tropicalis*

Decreased mortality

- **CVC removal during therapy**
- **Echinocandin antifungal**

"These results support first-line treatment with an echinocandin to the majority of patients"

In conclusion

- Invasive candidiasis still has a high mortality rate
- Antifungal prophylaxis in ICU is effective but inappropriate
- Empirical antifungal therapy in ICU is not proven effective
- Prediction rules to start pre-emptive therapy have a high NPV, and a reasonable specificity. Especially useful in high incidence areas/patients
- Intravascular catheters should be removed/replaced whenever feasible
- Treatment with an echinocandin is preferred, for the higher response rate

Treatment of invasive candidiasis in non-haematological patients

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Treatment of candidemia

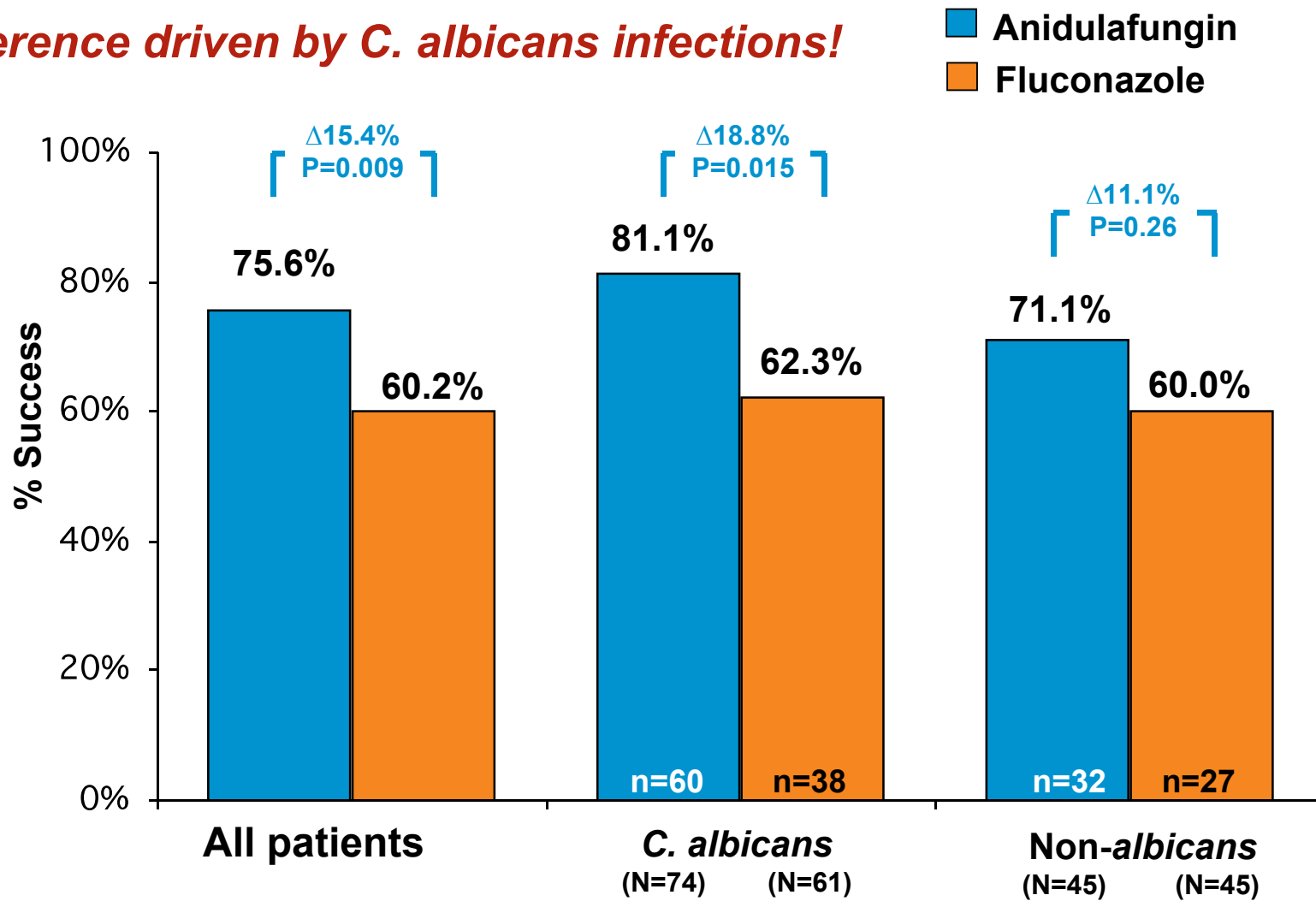
- Candida species and susceptibility
- Localization of infection
 - Candidemia only
 - Disseminated disease
- Mode of administration
- Duration of candidemia
- ...

Empirical treatment is most often inappropriate in septic ICU patients infected with...

1. *Staphylococcus aureus*
2. *Pseudomonas aeruginosa*
3. *Klebsiella species*
4. *Candida albicans*

Success at EIV treatment by pathogen

Difference driven by C. albicans infections!





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Question 6: Should the intravascular catheters be removed < 24h?

- 1 - Yes, when > 24h mortality is higher
- 2 - No, but < 48h; > 48h mortality is higher
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Question 6: Should the intravascular catheters be removed < 24h?

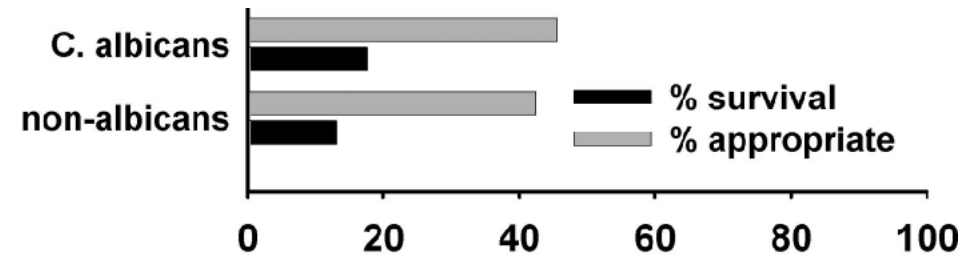
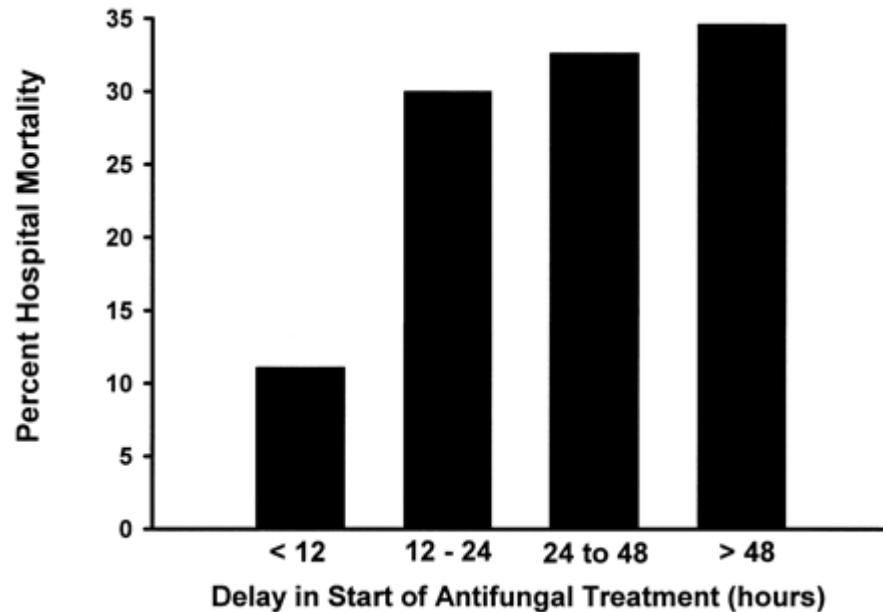
1 - Yes, when > 24h mortality is higher | 0%

2 - No, but < 48h; > 48h mortality is higher | 0%

3 - No, but it should be removed | 0%

4 - Removal of the catheter has no effect on mortality | 0%

Mortality



Crude mortality rate is high, the attributable mortality rate varies between 5-71% depending on the study

Candida Score

in practice

Prospective observational multicenter study

- ≥7 days IC with multifocal colonization (1)
- TPN(1)
- Surgery (1)
- Sepsis(2)

Goal: <5% invasive candidiasis in colonized patients

Treatment of a *Candida* infection was initiated by the local team only!

Results Candida Score *in practice*

1107 patients

892: colonized / infected

- 565: **CS <3** -> 13 (2.3%) invasive Candida infection
- 327: **CS ≥3** -> 45 (13.8%) invasive Candida infection

Table 4. Rates of invasive candidiasis according to the *Candida* score

Cutoff Value	Incidence Rate (%) (95% CI)	Relative Risk (95% CI)
<3	2.3 (1.1–3.5)	1
3	8.5 (4.2–12.7)	3.7 (1.8–7.7)
4	16.8 (9.7–23.9)	7.3 (3.7–14.5)
5	23.6 (12.4–34.9)	10.3 (5.0–21.0)