

# **Comparison of treatment appropriateness defined by EUCAST and old and new CLSI and mortality outcome in candidemia**

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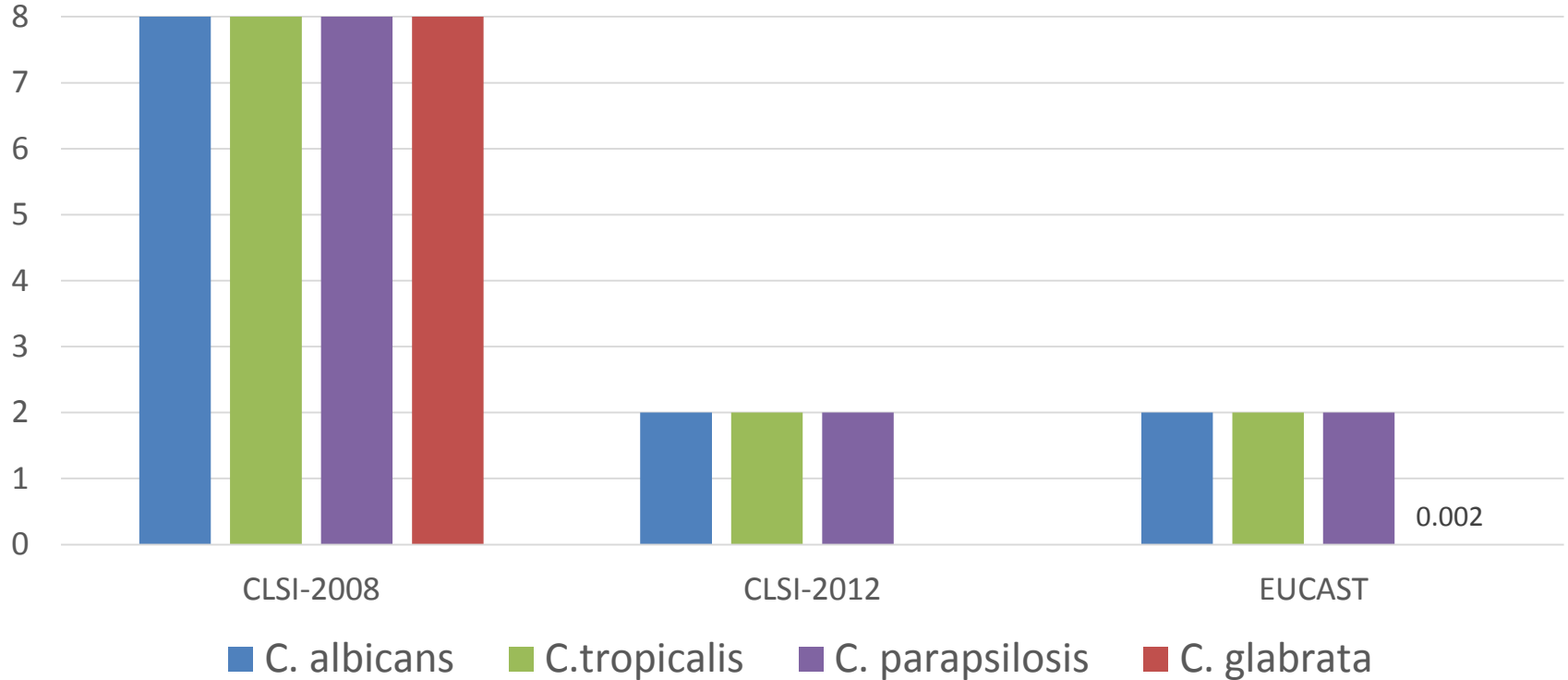
# Conflict of interest

- The authors declare no conflict of interest

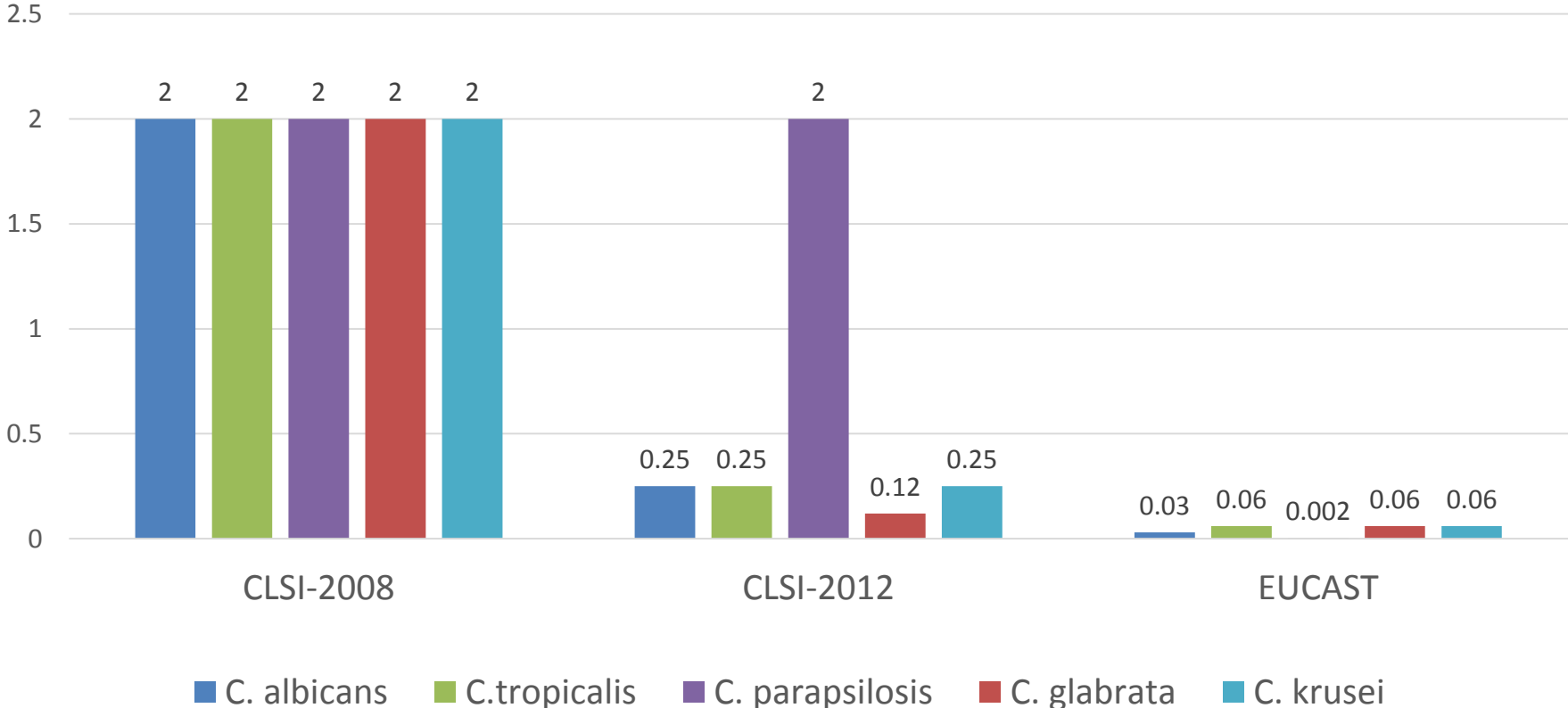
# Introduction

- Mortality of patients with candidemia reaches 40-60%
- Optimal antifungal therapy is necessary to improve the dismal prognosis
- The definition of “appropriate” changes with time and between different regulatory agencies
  - CLSI 2008- M27-S3 (*old* CLSI)
  - CLSI 2012- M27-S4 (*new* CLSI)
  - EUCAST 2014- V7

# Fluconazole: susceptible breakpoint definitions



# Anidulafungin: susceptible breakpoint definitions



# Objectives

- To assess the association of appropriate antifungal treatment and mortality among patients with candidemia, considering the different breakpoint definitions
  - Empiric treatment: first 48-72 hrs. until susceptibility reported
  - Definitive treatment: longest antifungal treatment administered in the first week following the susceptibility report, among patient surviving > 7 days

# Study design, setting and population

- Historical cohort study, between 2009 to 2015
- Rambam Health Care Campus, a primary and tertiary care hospital, 960 beds
- Included all adults with candidemia
- Non-clinically significant episodes excluded
  - Candida growth in blood among patients who survived > 30 days without antifungal treatment

# Study variables

- Exposure variable: Appropriate antifungal therapy
- Outcomes: 30 and 90-day all-cause mortality
- Independent predictors for mortality
  - Demographics and background conditions
  - Predisposing factors for candidemia
  - Sepsis presentation and severity, source of infection and concomitant infections
  - Management of infection, including catheter extraction and invasive procedures



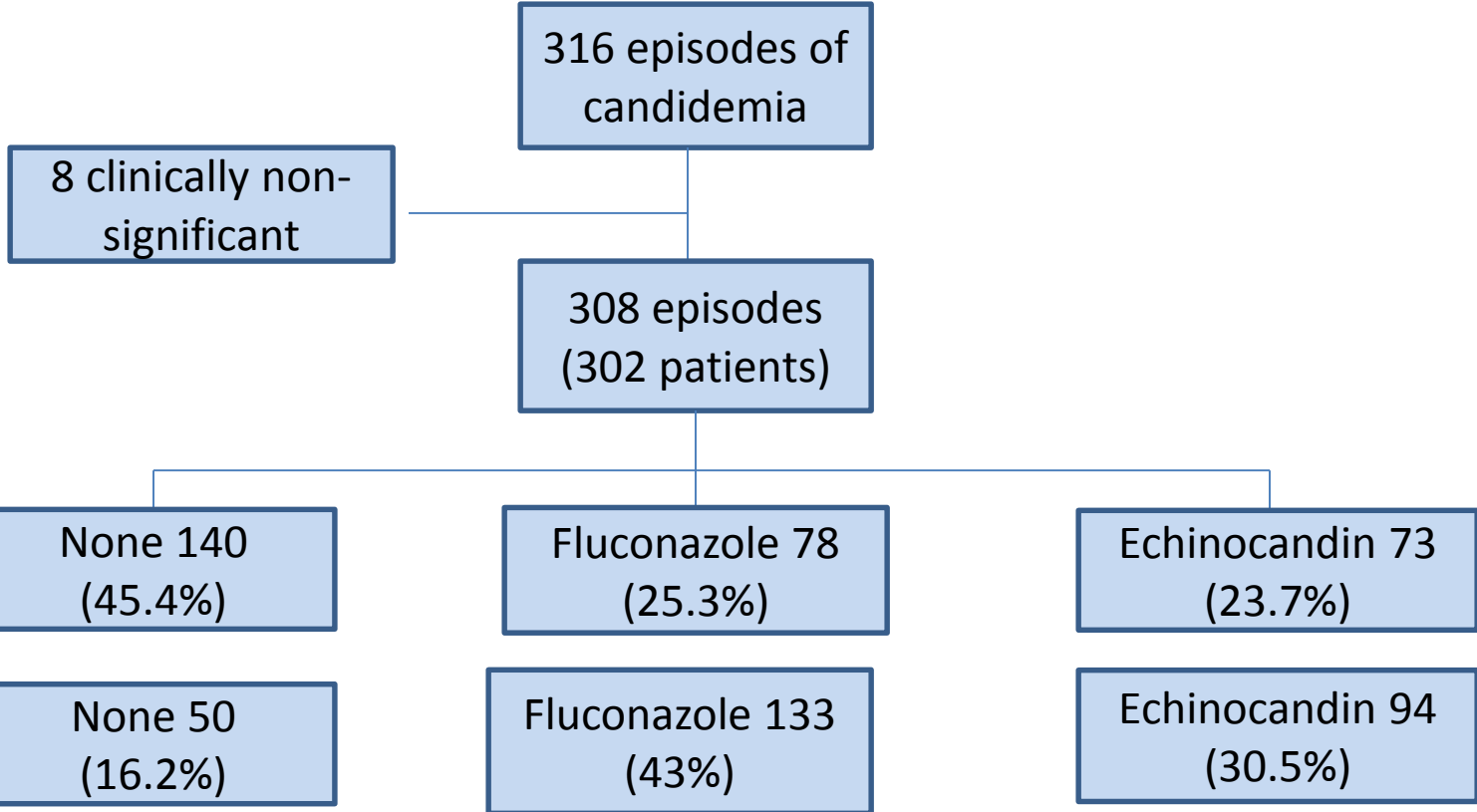
# Microbiological methods

- Antifungal susceptibility testing and MIC determination was performed using E-test (AB Biodisk, Solna, Sweden)
- The echinocandin agent tested changed throughout the study period
  - Anidulafungin was used in 60% of episodes and caspofungin in 38%
  - We classified echinocandin treatment appropriateness based on the anidulafungin, when both were tested

# Appropriateness definitions

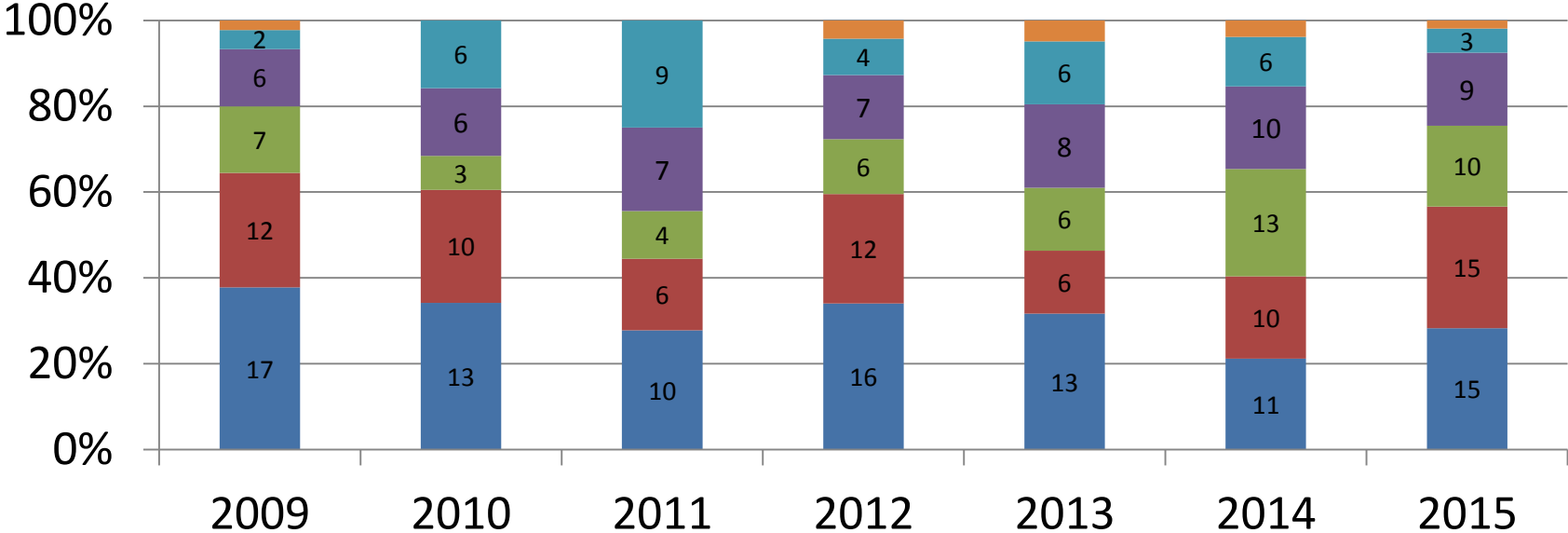
- CLSI: susceptible or susceptible-dose- dependent (SDD)
- EUCAST: susceptible
- For absent clinical breakpoints we referred to epidemiological cut-off points (ECOFFs) and considered susceptible as  $MIC \leq \text{wild type (WT) breakpoint}$  and resistant as  $MIC > \text{WT breakpoint}$

# Results

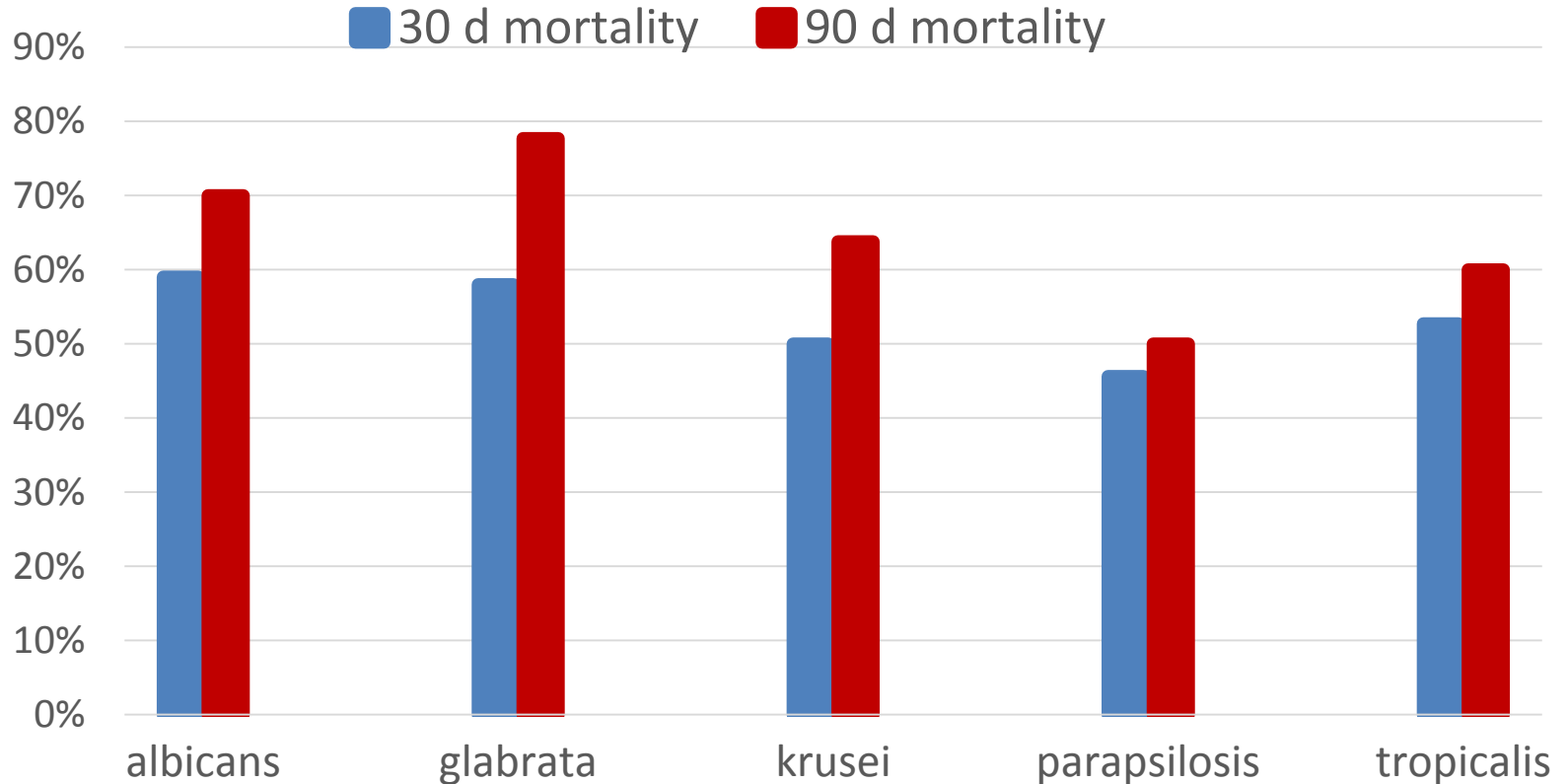


# Candida species 2009 to 2015

■ C.albicans ■ C.glabrata ■ C.parapsilosis ■ C.tropicalis ■ C.krusei ■ Other



# 30-day and 90-day mortality by candida species



# Univariate analysis for mortality

<b>30 day mortality- empiric treatment</b>			
	<b>EUCAST</b>	<b>Old CLSI</b>	<b>New CLSI</b>
<b>Dead-appropriate</b>	45/100 (45%)	73/158 (46.2%)	67/144 (46.5%)
<b>Dead-Inappropriate</b>	123/208 (59.1%)	95/150(63.3%)	101/164 (61.6%)
<b>90 day mortality- definitive treatment</b>			
	<b>EUCAST</b>	<b>Old CLSI</b>	<b>New CLSI</b>
<b>Dead-appropriate</b>	64/136 (47.1%)	106/204 (52%)	89/181 (49.2%)
<b>Dead-Inappropriate</b>	52/82 (63.4%)	10/14 (71.4%)	27/37 (73%)

# Univariate analysis for mortality

<b>30 day mortality –empiric treatment</b>			
	<b>OR</b>	<b>95% CI</b>	<b>P value</b>
<b>EUCAST</b>	0.56	0.35-0.91	<b>0.02</b>
<b>CLSI new</b>	0.54	0.34-0.85	<b>0.008</b>
<b>CLSI old</b>	0.5	0.31-0.78	<b>0.003</b>

<b>90 day mortality – definitive treatment (survivors &gt;7 days)</b>			
	<b>OR</b>	<b>95% CI</b>	<b>P value</b>
<b>EUCAST</b>	0.51	0.29-0.9	<b>0.019</b>
<b>CLSI new</b>	0.36	0.16-0.78	<b>0.008</b>
<b>CLSI old</b>	0.43	0.13-1.42	0.158

Variable	OR	95% CI	p value
Normal functional status	Ref		
Limited	1.02	0.50-2.07	0.94
Bedridden	2.54	1.28-5.02	<b>&lt;0.01</b>
Hypotension	3.30	1.75-6.22	<b>&lt;0.01</b>
Mental status change	2.46	0.92-6.59	0.07
No catheter	Ref		
Exists, not extracted	2.84	1.07-7.52	<b>&lt;0.01</b>
Exists, extracted	0.63	0.35-1.14	<b>0.01</b>
No malignancy	Ref		
Solid, non metastatic	1.02	0.47-2.19	0.95
Solid, metastatic	2.68	0.98-7.52	0.117
Lymphoma	4.27	1.72-10.62	<b>&lt;0.01</b>
Leukemia	1.82	0.82-4.07	0.71
No concomitant bacteremia	Ref		
Inappropriate empiric treatment	3.79	1.69-8.47	<b>&lt;0.01</b>
Appropriate empiric treatment	1.47	0.64-3.39	0.35

## Adjusted 30-day mortality

Approp empiric Tx	OR	95% CI	P
CLSI -new	0.62	0.37-1.04	0.07
CLSI- old	0.56	0.33-0.96	<b>0.03</b>
EUCAST	0.58	0.33-1.00	<b>0.05</b>



Variable	OR	95% CI	p value
Normal functional status	Ref		
Limited	1.12	0.48-2.61	0.78
Bedridden	2.56	1.08-6.08	<b>0.03</b>
Hypotension	2.82	1.19-6.65	<b>0.01</b>
Mental status change	2.25	0.61-8.34	0.22
No catheter	Ref		
Exists, not extracted	9.44	2.31-38.51	<b>&gt;0.01</b>
Exists, extracted	2.36	1.18-4.72	<b>0.01</b>
No malignancy	Ref		
Solid, non metastatic	1.05	0.42-2.63	0.92
Solid, metastatic	2.74	0.78-9.67	0.11
Lymphoma	4.64	1.54-13.96	<b>&gt;0.01</b>
Leukemia	0.84	0.32-2.19	0.71
No concomitant bacteremia	Ref		
Inappropriate empiric treatment	2.52	1.005-6.3	<b>0.04</b>
Appropriate empiric treatment	0.85	0.30-2.35	0.75

## Adjusted 90-day mortality

Approp definitive Tx	OR	95% CI	P
CLSI -new	0.35	0.14-0.86	<b>0.02</b>
CLSI- old	0.54	0.14-2.1	0.37
EUCAST	0.44	0.22-0.87	<b>0.01</b>

# Conclusions

- Breakpoints have changed dramatically throughout the years, disqualifying the use of fluconazole and echinocandins for many patients
- We could not show differences in mortality with the different breakpoint definitions
- With all definitions, whether statistically significant or not, appropriate empirical antifungal therapy was associated with survival

# Limitations

- Retrospective data collection
- Single center study
- MICs by E test (not broth microdilution as recommended)
- Alternating echinocandin agent tested (for ~ 40% caspofungin – known for inaccuracy)

**Thank you**