Yeast in the blood:

are echinocandins the optimal agents for critically ill or neutropenic patients?

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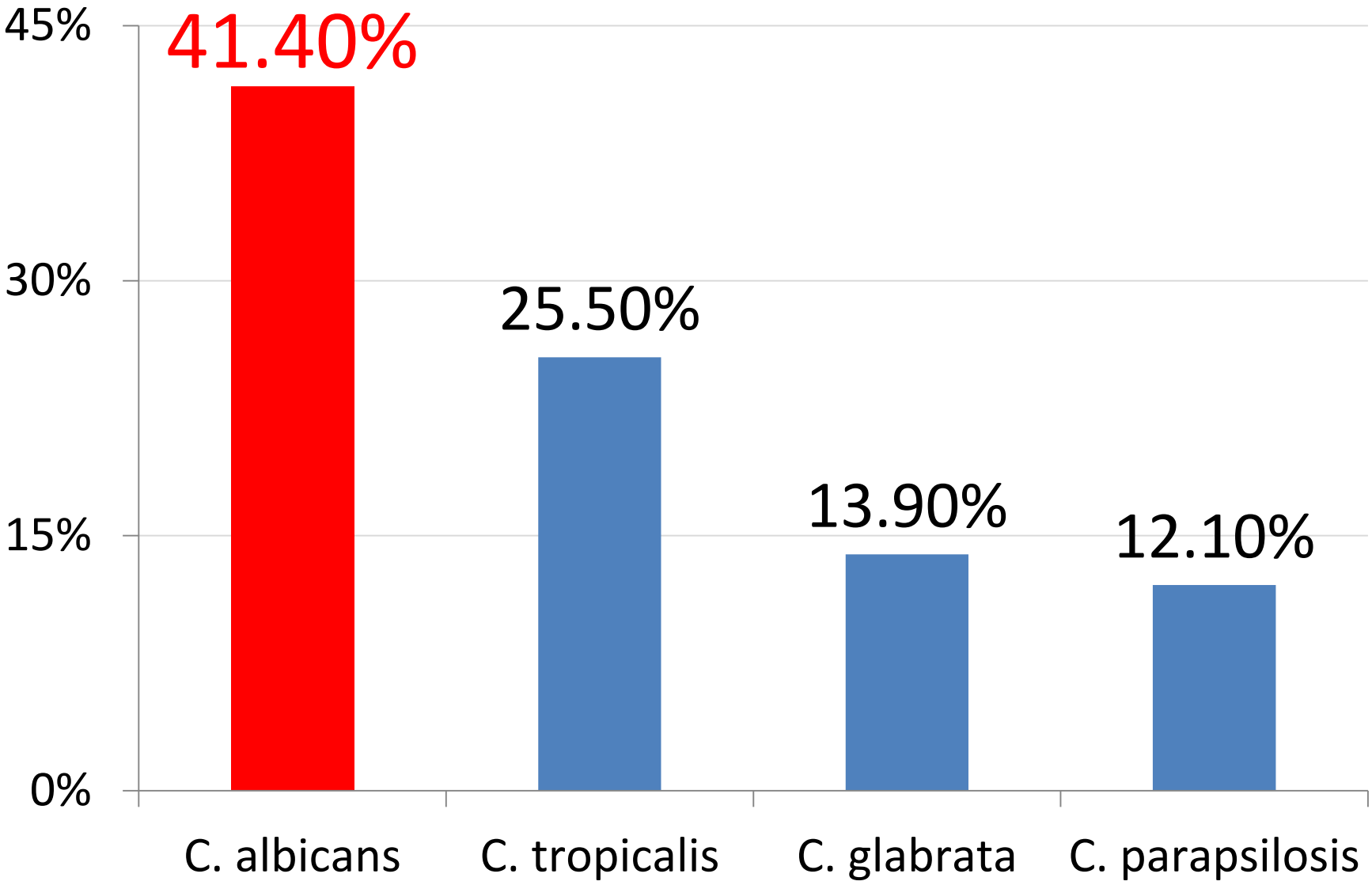
ESCMID 2012 & IDSA 2016 recommendations on initial treatment of IC

WHY echinocandins ?

- Fungicidal
- Broader spectrum
- Rare resistance
- Biofilm activity
- Safety profile
- Fewer drug–drug interactions
- Superior to fluconazole in one RCT

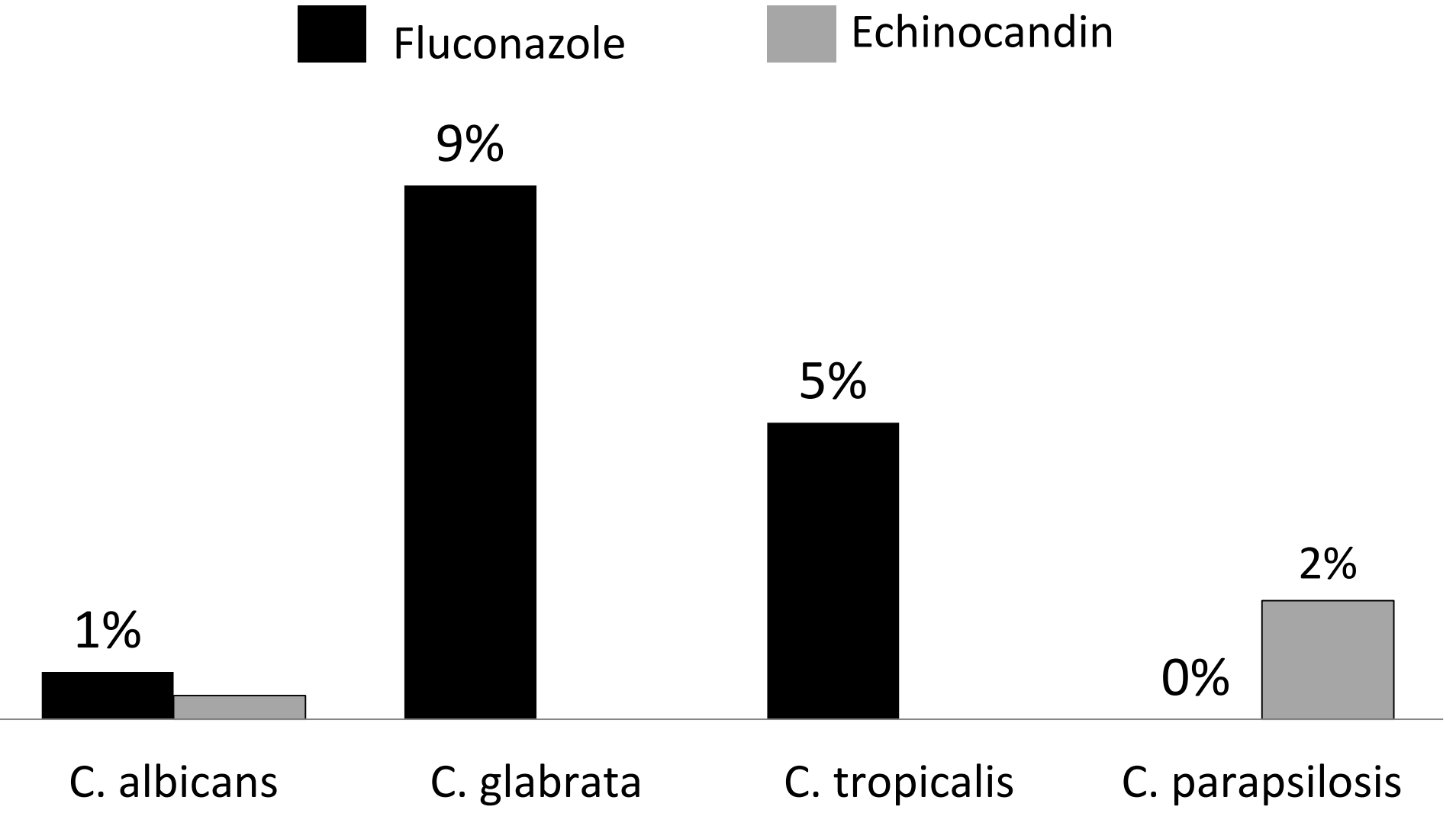
Cornely OA, et al.Clin Microbiol Infect 2012
Peter G. Pappas, Clin Infect Dis. 2016

Distribution of Candida blood isolates



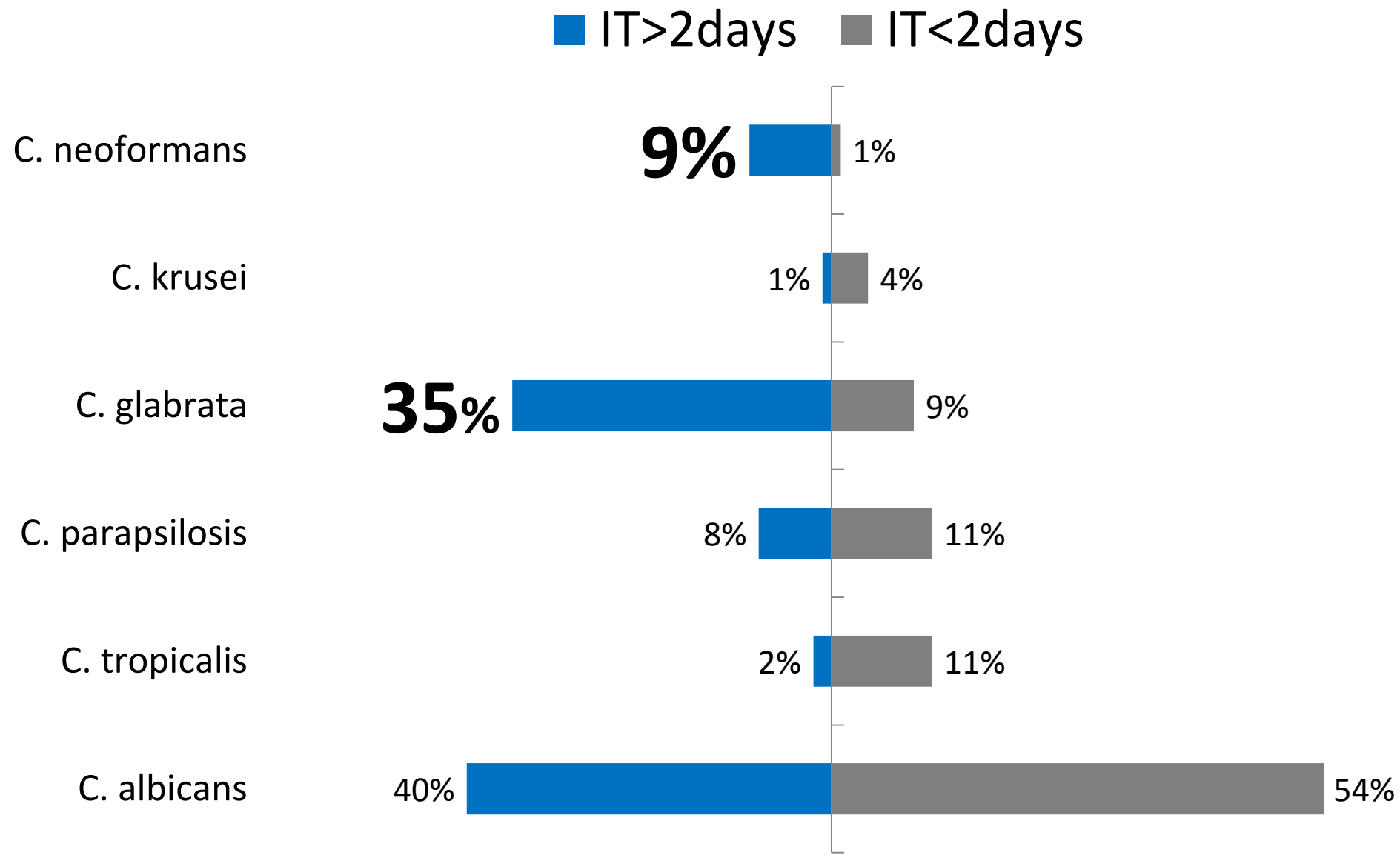
Unpublished data 2015, Chen YC

Patterns of Resistant strains in Taiwan



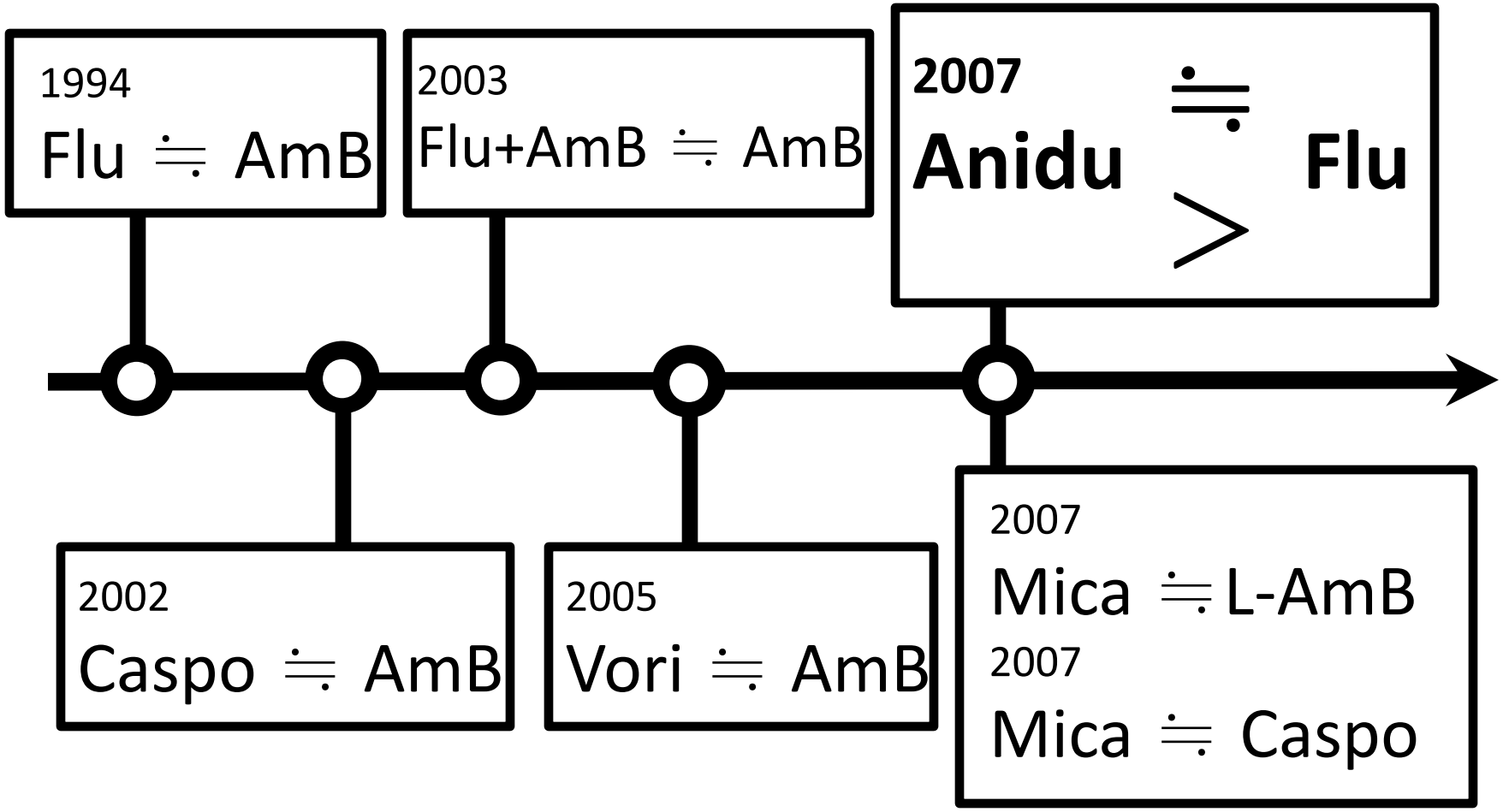
YT Huang, Antimicrobial Agents and Chemotherapy 2014

Clues: Time to positive culture

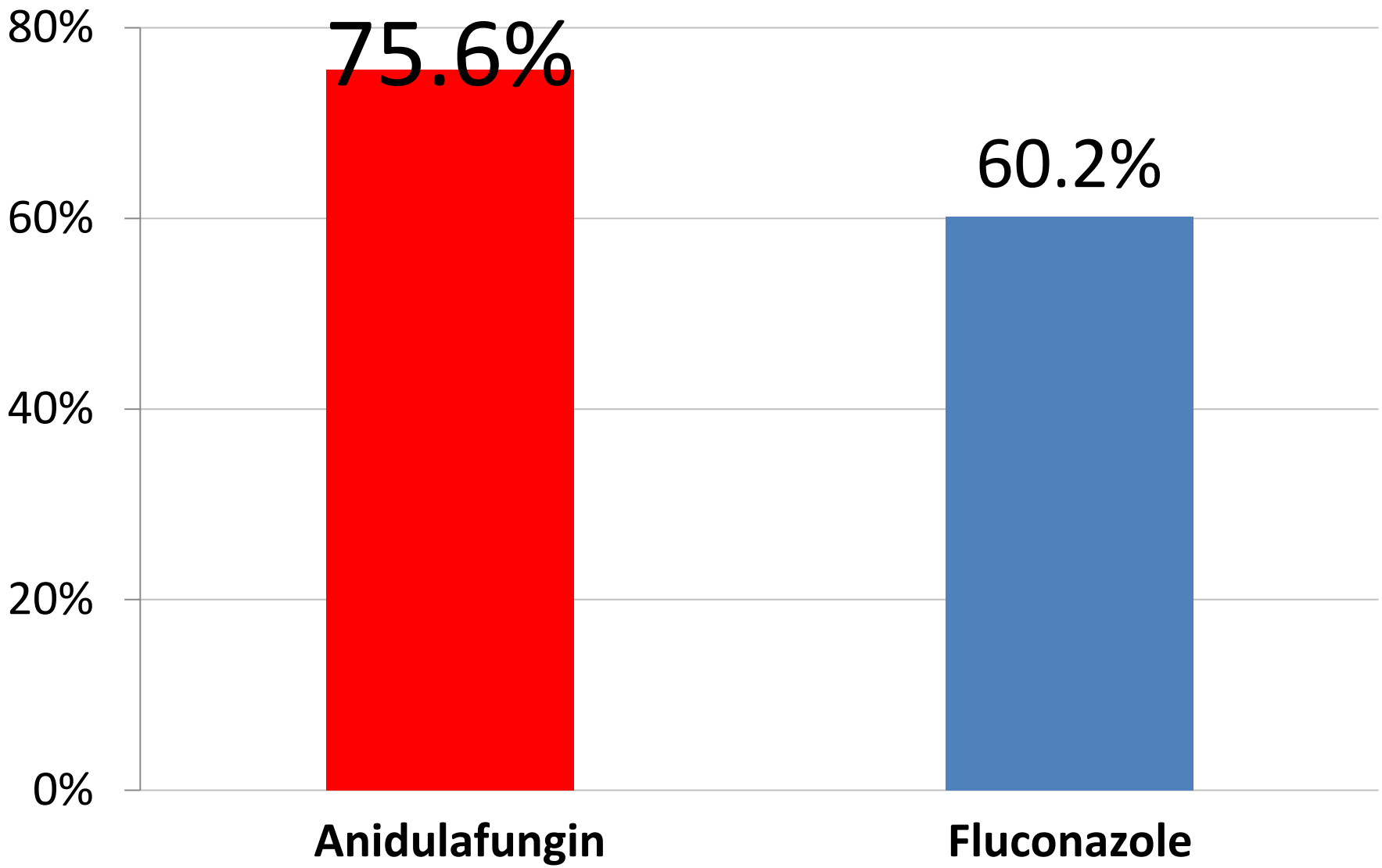


Paugam A,Diagn Microbiol Infect Dis. 2014

Timeline of RCTs for invasive candidiasis

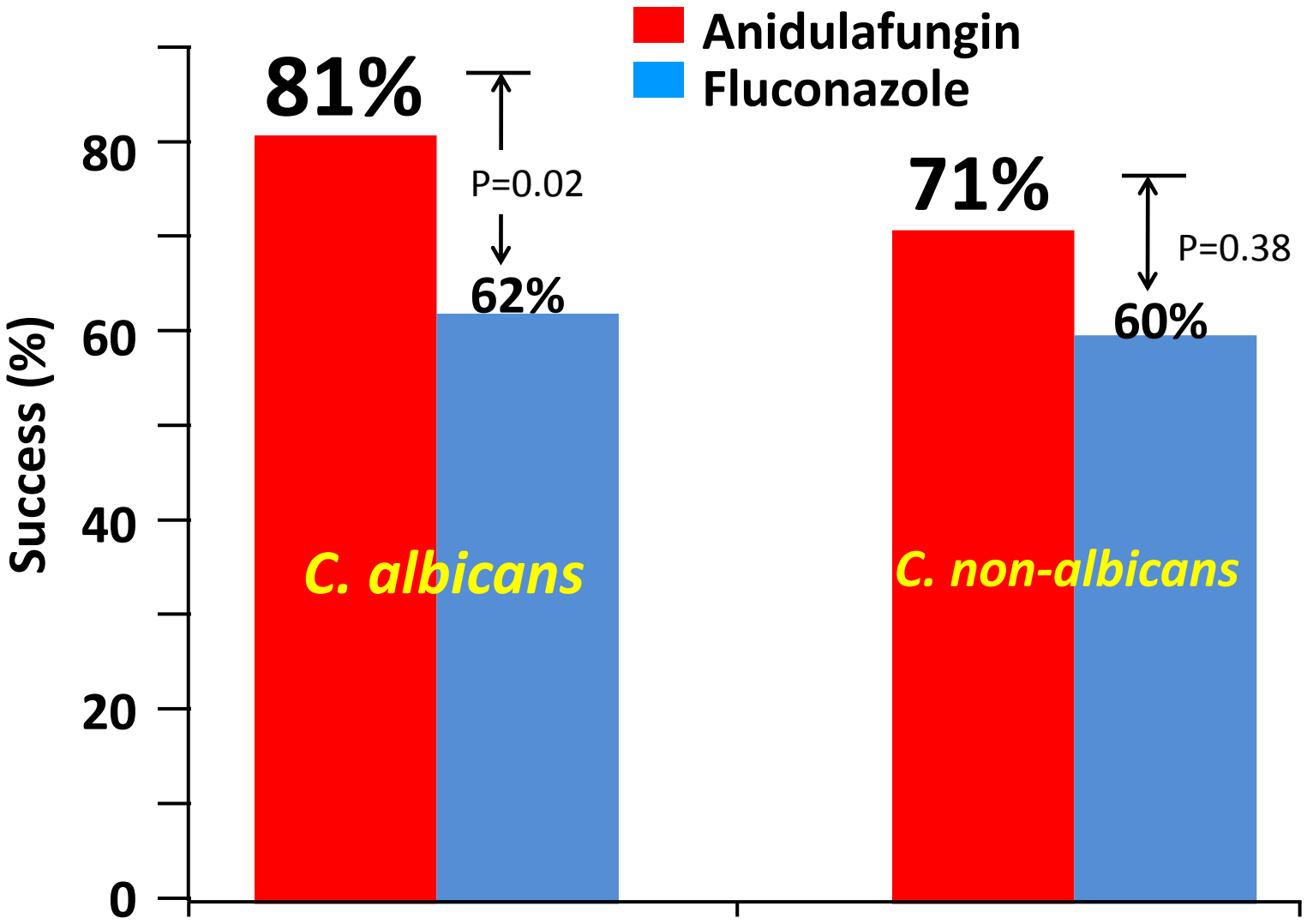


Anidulafungin versus Fluconazole



Reboli AC, N Engl J Med. 2007

Anidulafungin greater efficacy fluconazole



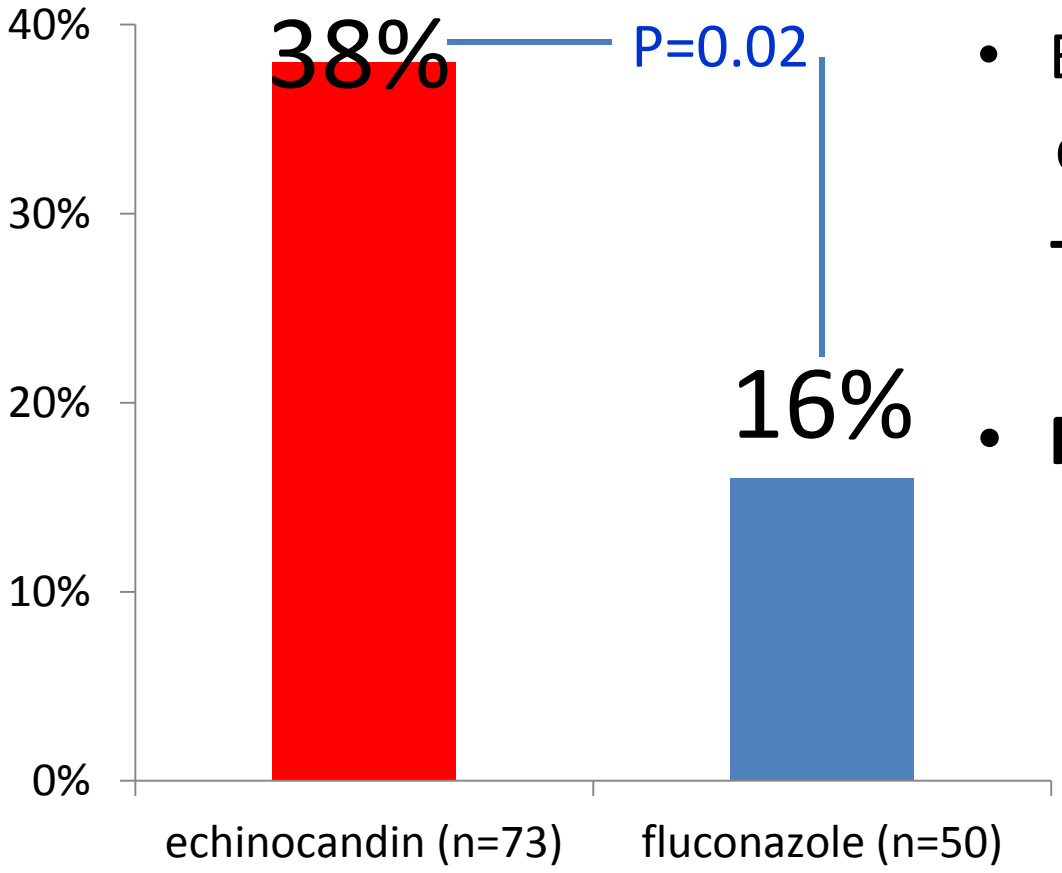
Reboli AC. N Engl J Med. 2007

Controversial points

- **Design:**
  - Superiority in a noninferiority trial?
  - Excluding the highest-enrolling center, global response rates of 73.2% and 61.1%, respectively (95%CI = −1.1 to 25.3)
- **Outcome:**
  - Mortality was not significantly different. (anidu 23% vs flu 31%, respectively; P = 0.13).
  - Anidulafungin did not show the benefit for treating non-albicans C. species infection.

Reboli AC. N Engl J Med. 2007
Scott K. Aberegg,N Engl J Med. 2007

30-day mortality rate



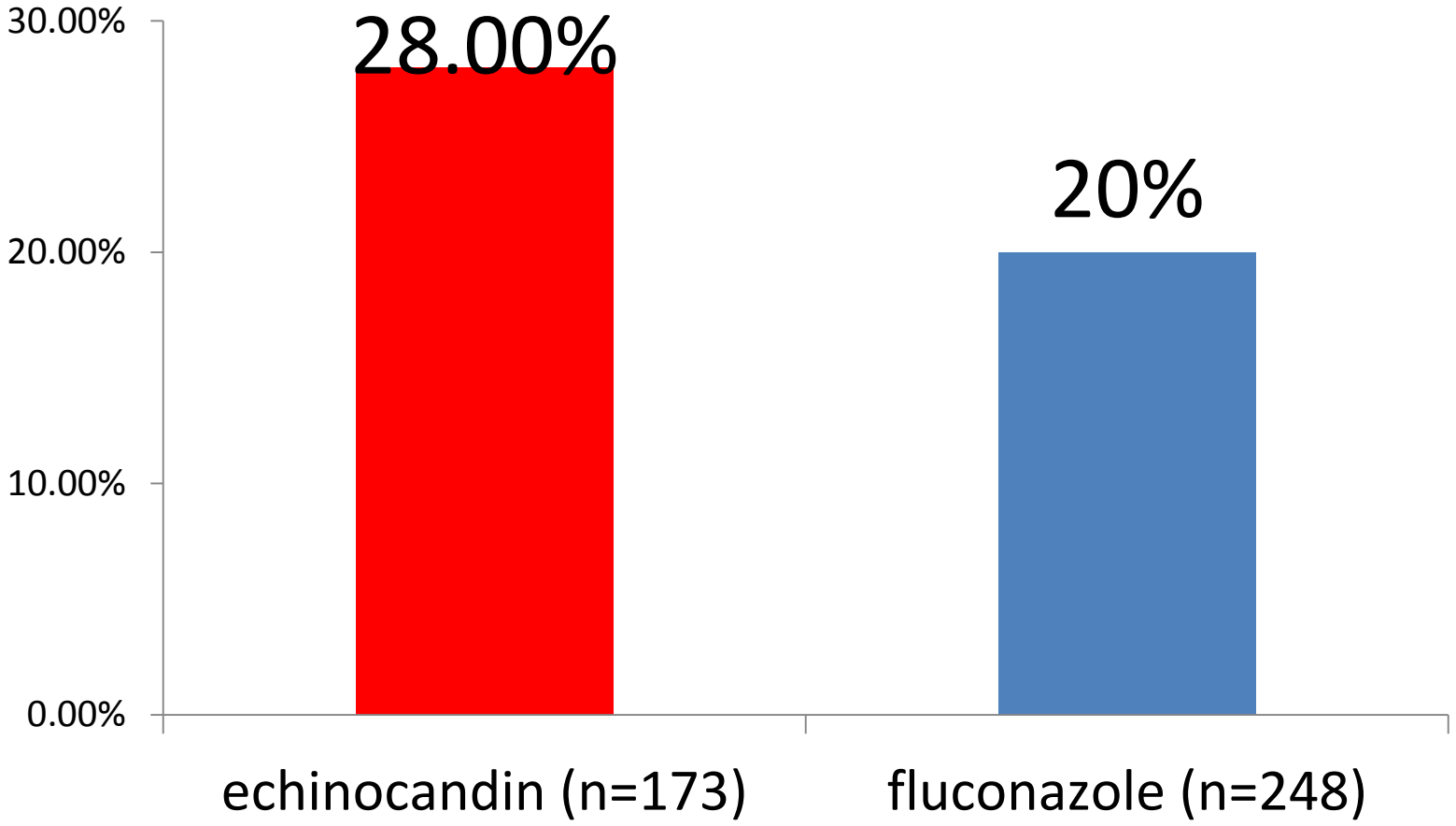
- Epidemiological and clinical parameters
  - **No differences**
- **Multivariate model**
  - **Clinical presentation** is the only factor

R. Murri, Eur J Clin Microbiol Infect Dis, 2016

30-day mortality rate

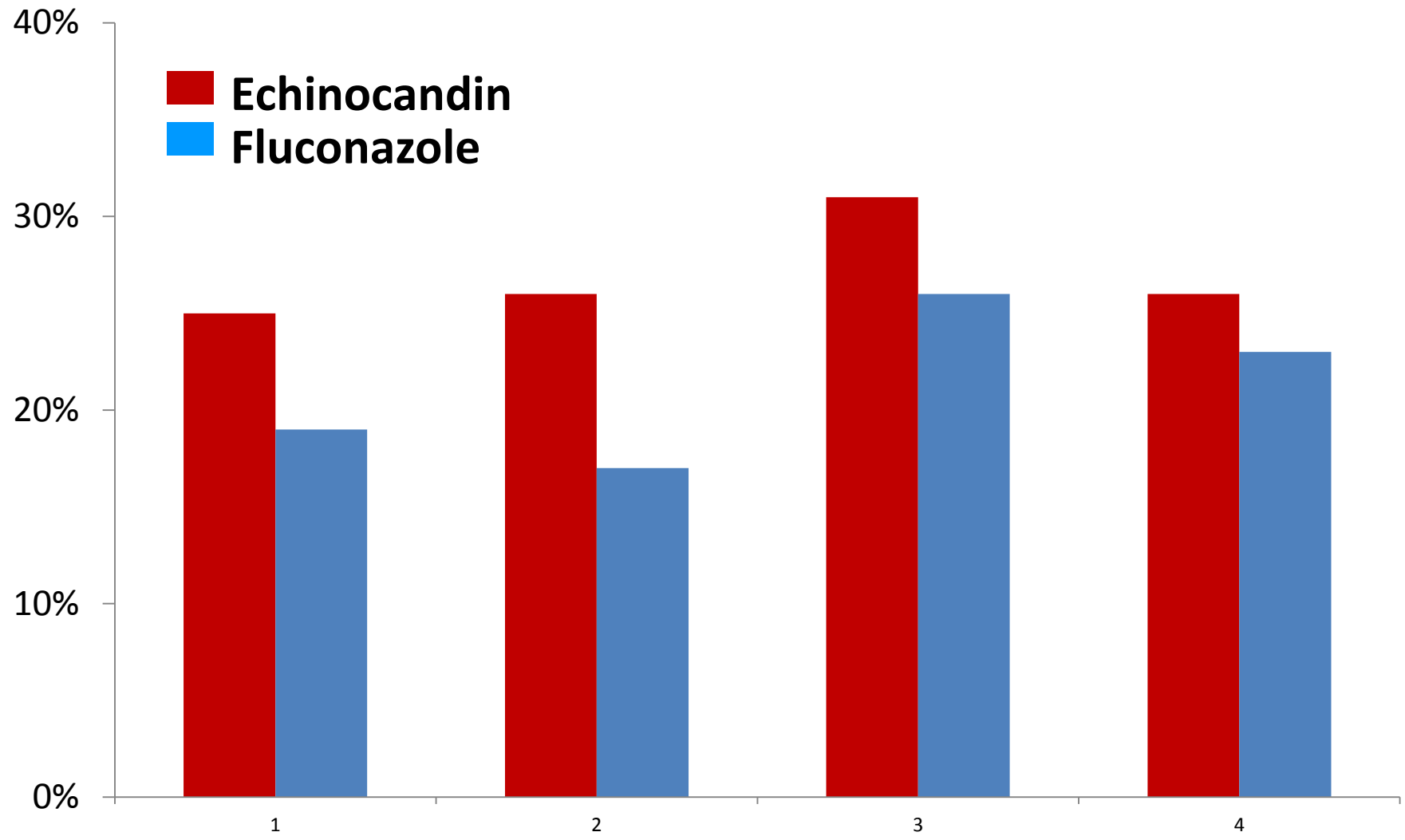
- CANDIPOP study

No differences in multivariate analysis



López-Cortés LE, Clin Microbiol Infect 2016

30-day mortality stratified according to propensity score quartile



López-Cortés LE, Clin Microbiol Infect 2016

Intrinsic higher MICs, thus possibly reflecting reduced efficacy ?

A study of patient-level quantitative review of RCTs (7 trials)

C. glabrata infection

- 206/1915 (10.7%)
- **30-day mortality:**
  - CVC removed
- **Treatment success:**
  - APACHE II score, Echinocandin

C. parapsilosis infection

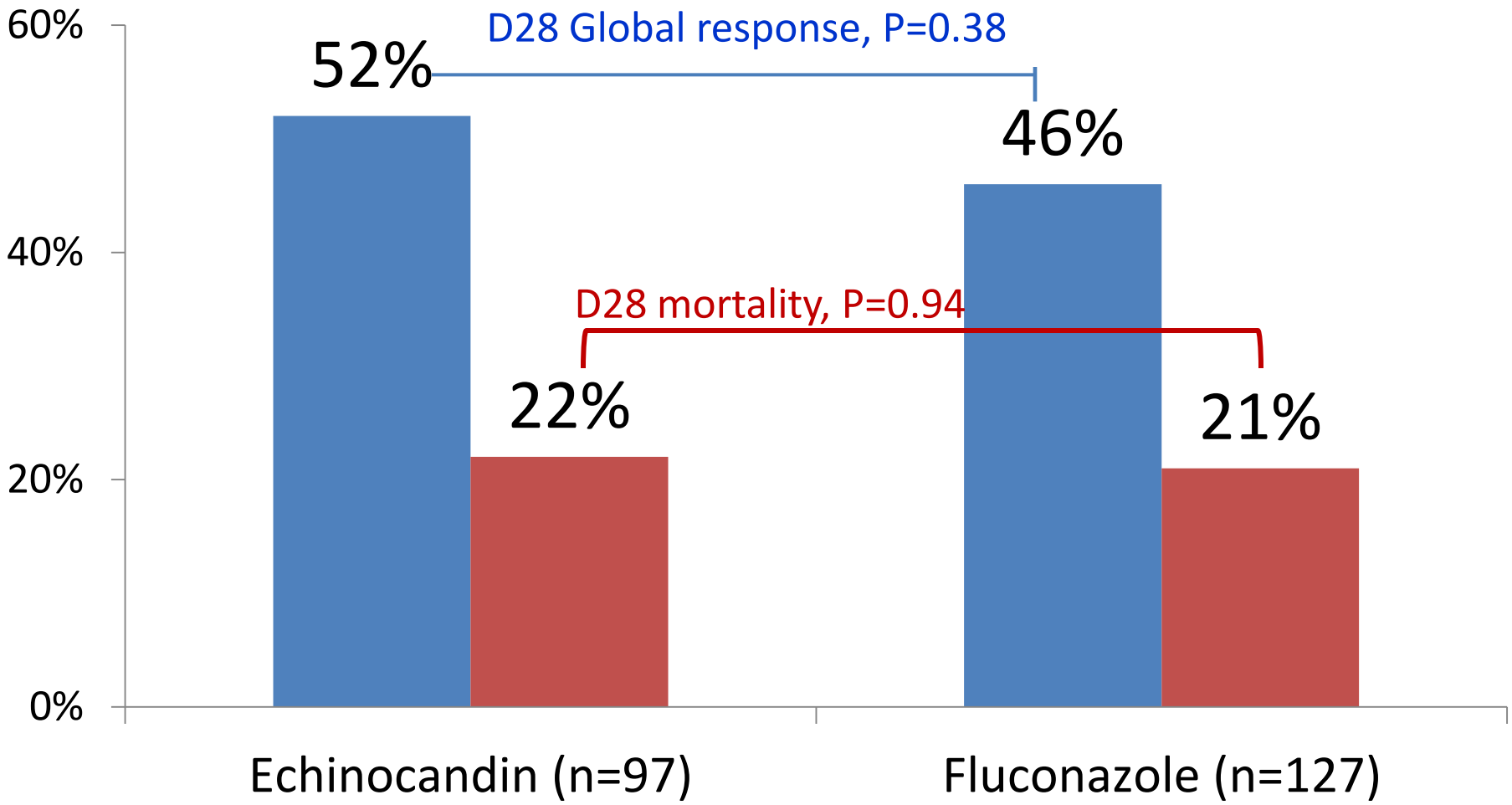
- 299/1915 (15.6%)
- **30-day mortality:**
  - APACHE II score, ICU
- **Treatment success:**
  - APACHE II score

David R. Andes, Clinical Infectious Diseases 2012

Candida glabrata infection

USA, multicentre retrospective study

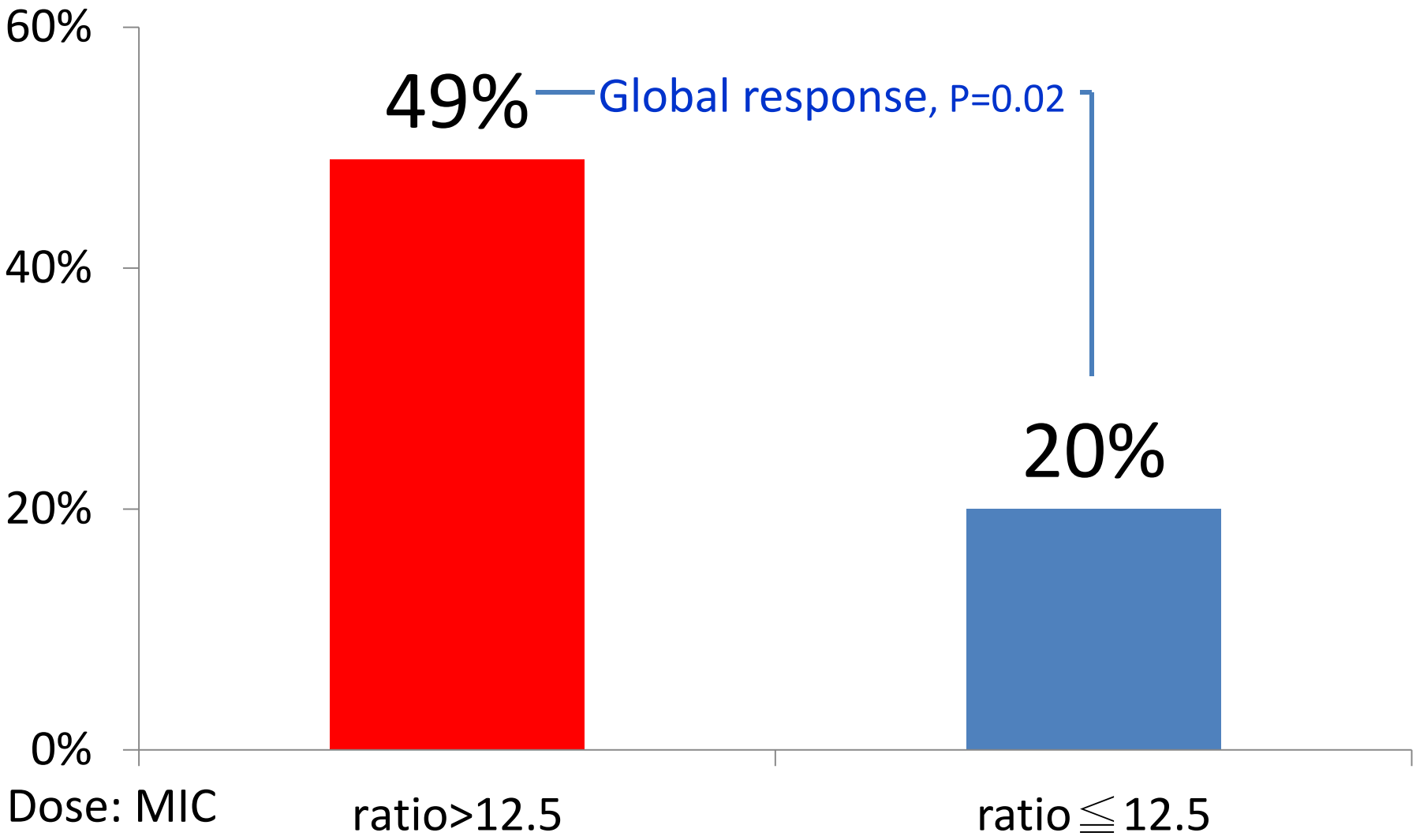
Multivariate: Echi is associated with GR, not mortality



Eschenauer GA, J Antimicrob Chemother. 2013

Candida glabrata infection

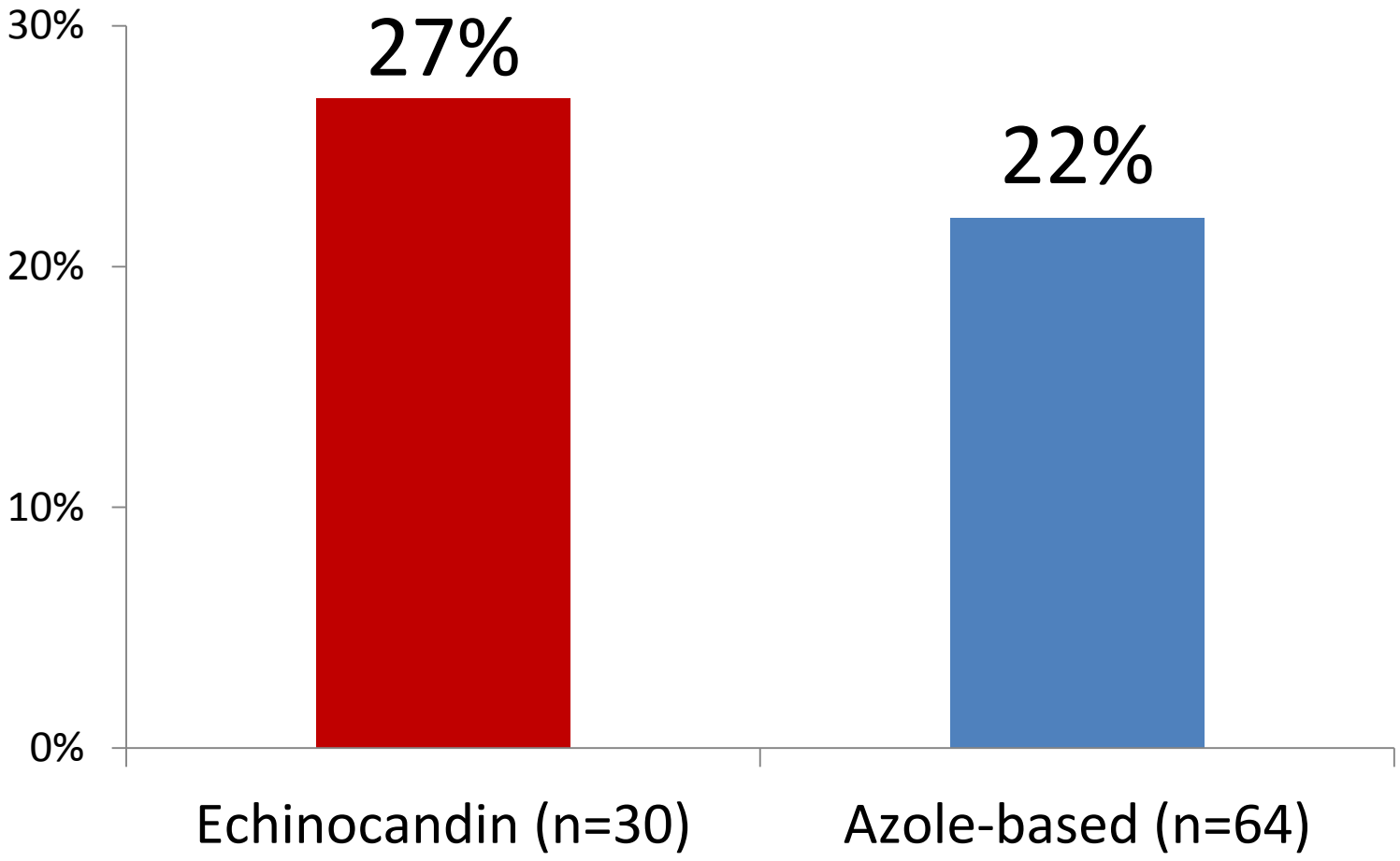
Fluconazole Dose: MIC >12.5 with a better response



Eschenauer GA, J Antimicrob Chemother. 2013

30-d mortality in *C. parapsilosis* Infection

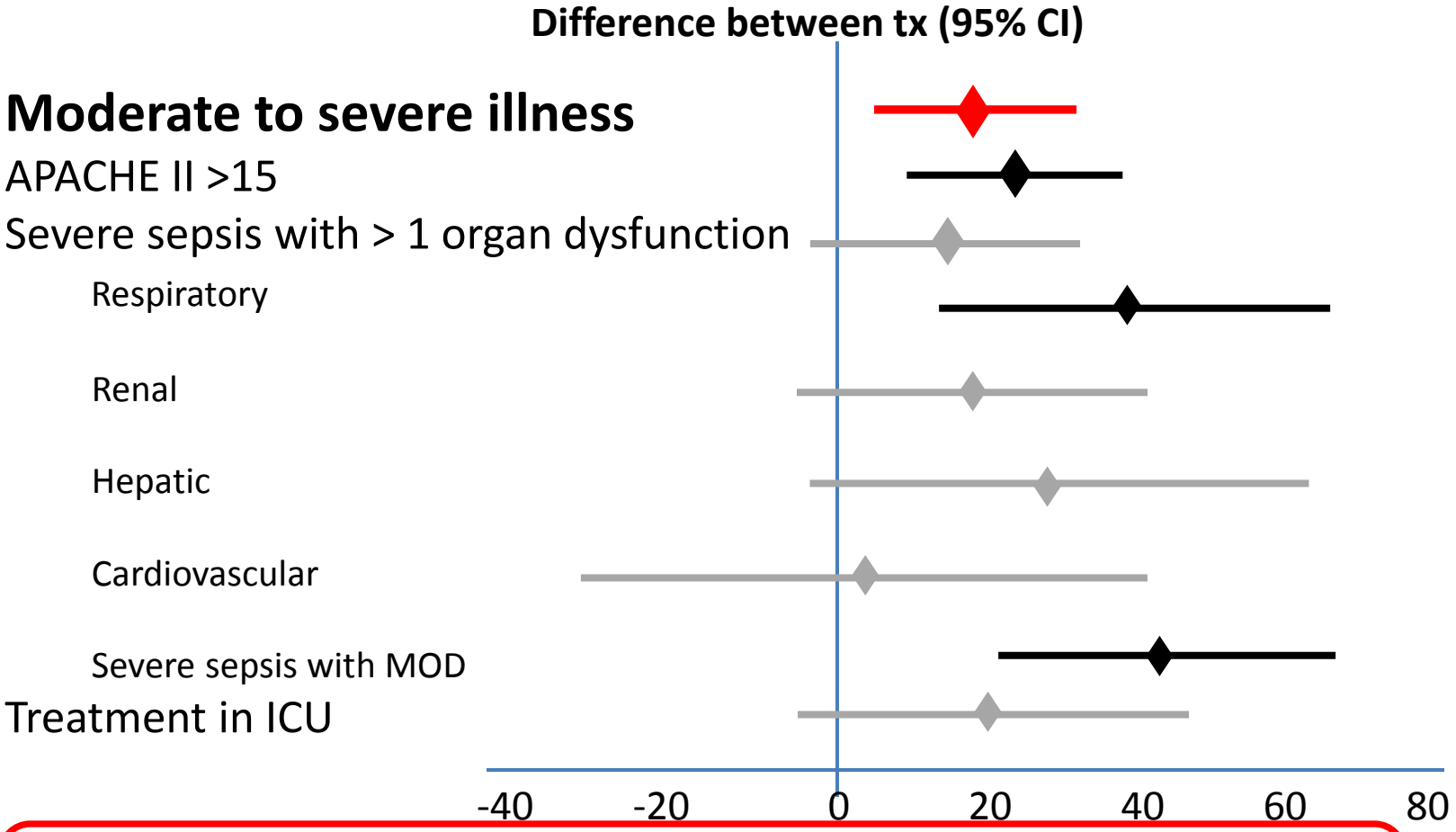
- CANDIPOP study **No differences in both arms**



M Fernández-Ruiz, Clin Infect Dis. 2014

Critically Ill Patients

post hoc analysis of the RCTs



28 days-mortality **24.3%** **vs** **20.2%** (P=0.57)

Kett et al. Critical Care 2011

Critically Ill Patients

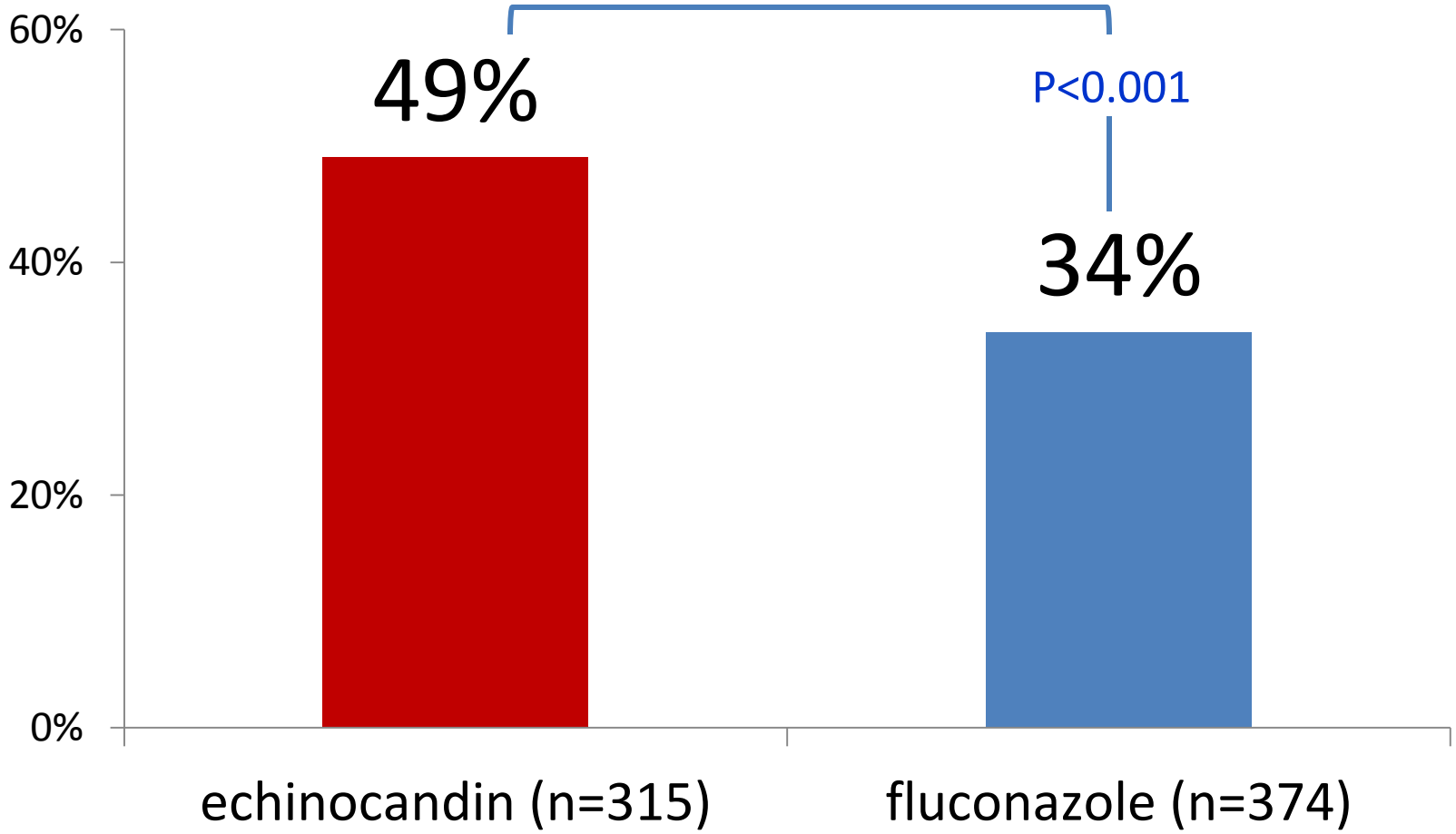
Factors associated with 30-day mortality among ICU patients

	OR	95%CI
Receipt of corticosteroids	4.00	(1.9 – 8.1)
2003 – 2007 Period	2.49	(1.2 – 5.1)
APACHE II score	1.05	(1.0 – 1.1)
Age	1.03	(1.0 – 1.1)
Echinocandin tx	**0.2**	(0.1 – 0.6)

Colombo AL, Intensive Care Med. 2014

28-d mortality in MV patients

- PATH database **Favored fluconazole**



Ferrada MA,BMC Anesthesiol. 2013

Critically Ill Patients

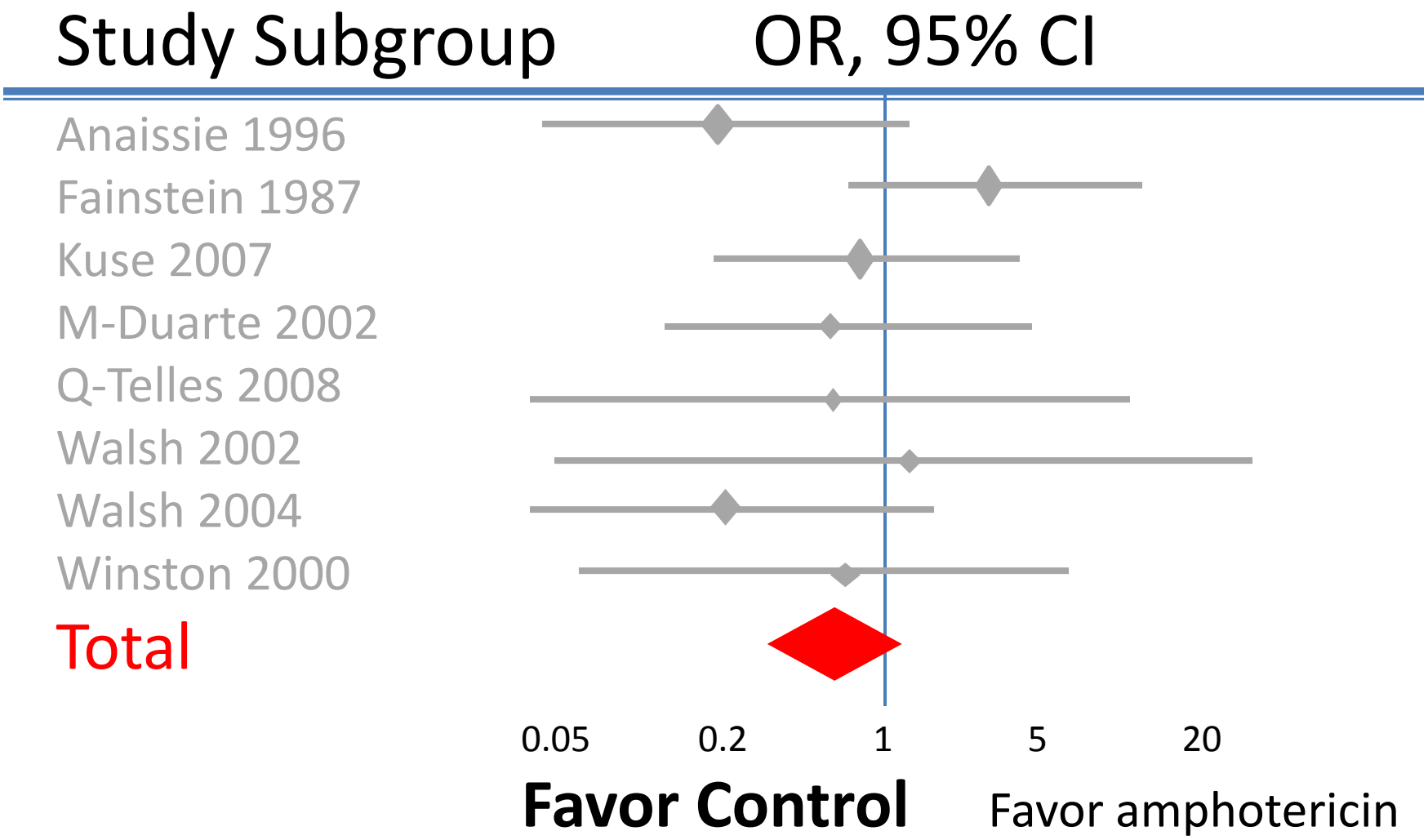
Septic shock due to candidemia

- 216 patients, in Italy and Spain
- echinocandin (41.7 %) vs fluconazole (40 %)
  30-day mortality: **No difference**

Factors for survival	OR	P value
APACHE II score	0.93	<0.01
Adequate therapy	5.99	0.048
Source control	2.99	0.001

Bassetti M, Intensive Care Med 2014

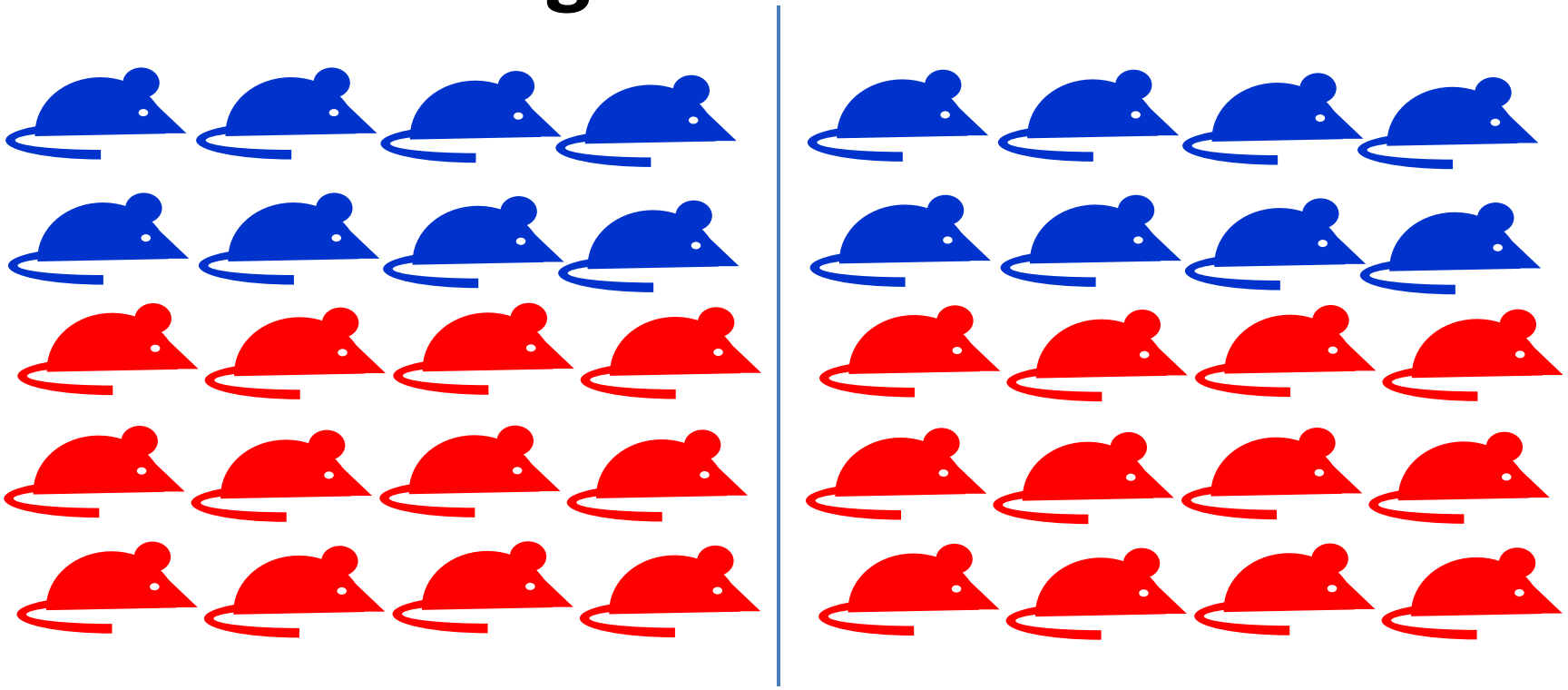
Neutropenic population



Kanji JN, Leuk Lymphoma 2013

Antifungal in vivo activity in **neutropenic** Mice models

Anidulafungin D21 Fluconazole

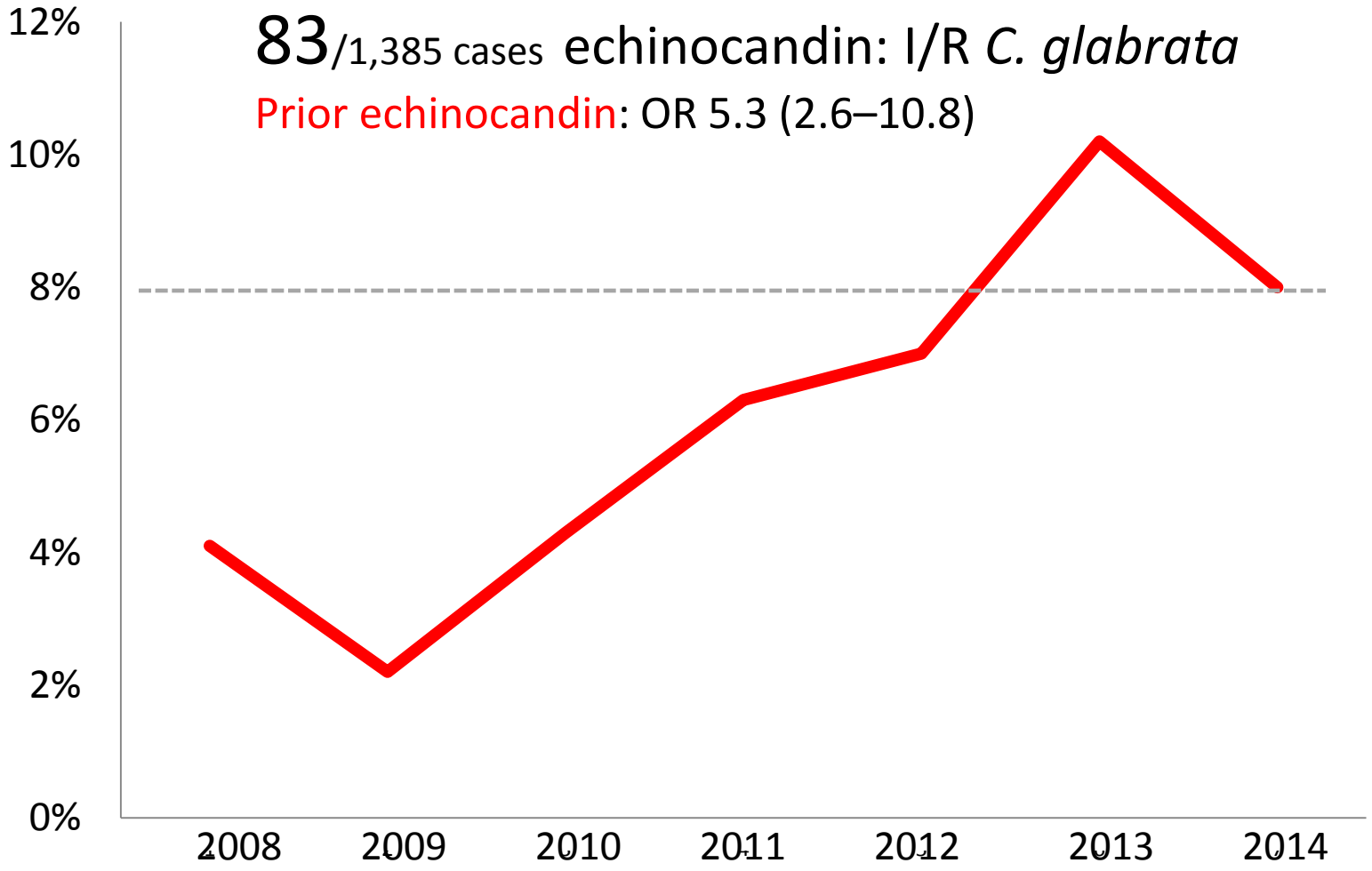


Anidulafungin in vivo efficacy may be dependent on host immune status.

N. P. Wiederhold, Clin Microbiol Infect 2012

Echinocandin resistance a remaining issue

- NS isolates in CDC candidaemia surveillance programme



Vallabhaneni S, et al. Open Forum Infect Dis 2015

Take home messages

- The echinocandins have not been shown to be clearly superior to fluconazole for treatment of candidemia.
  - Comparative, observational studies just were not capable of detecting differences in efficiency.
- Fluconazole could remain a valid first-line treatment option for treating candidemia
  - no difference in mortality was observed
  - wider use of echinocandin could be related to the spread of echinocandin resistance