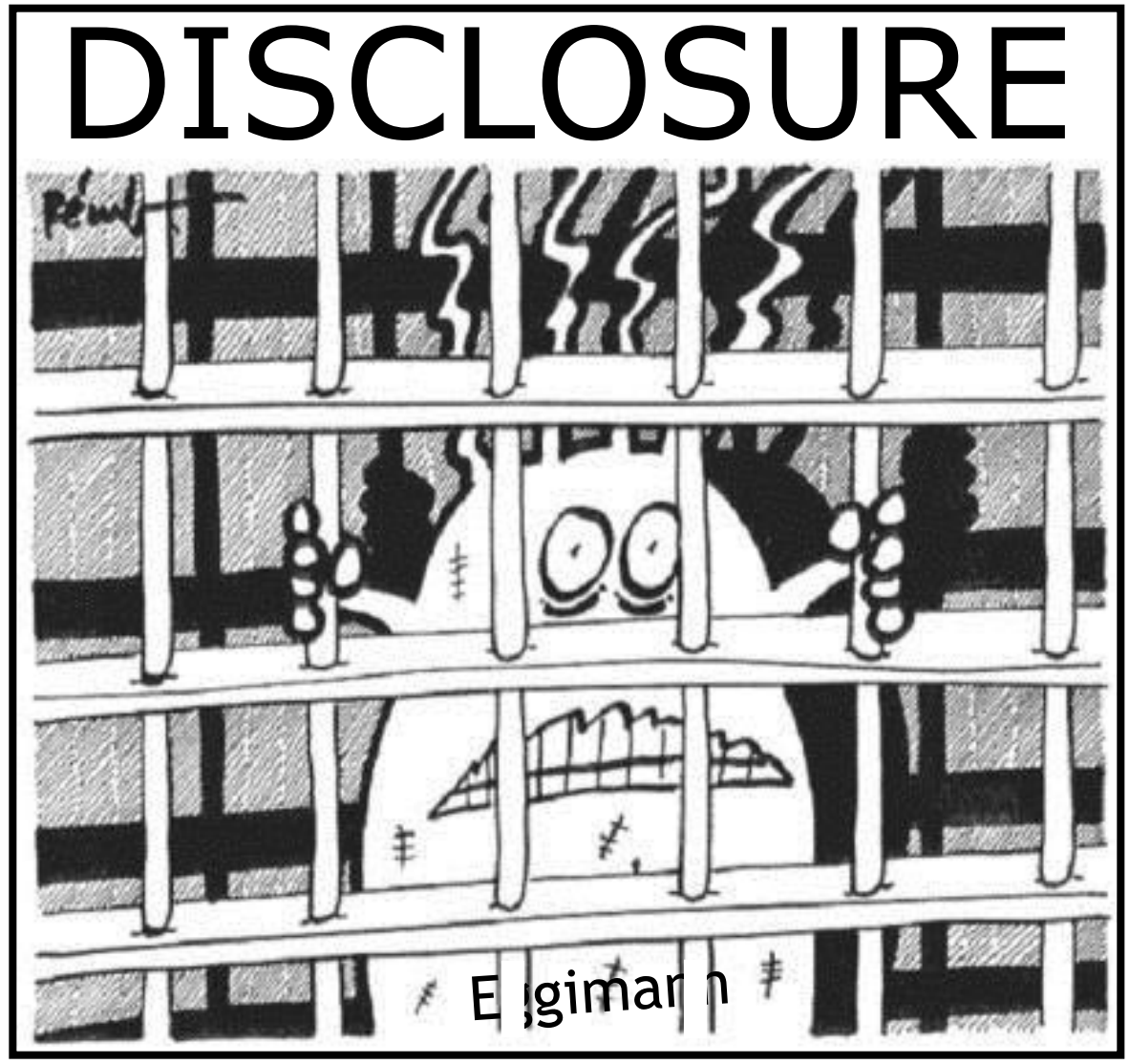
Preventing invasive candida infections – Where could we do better ?

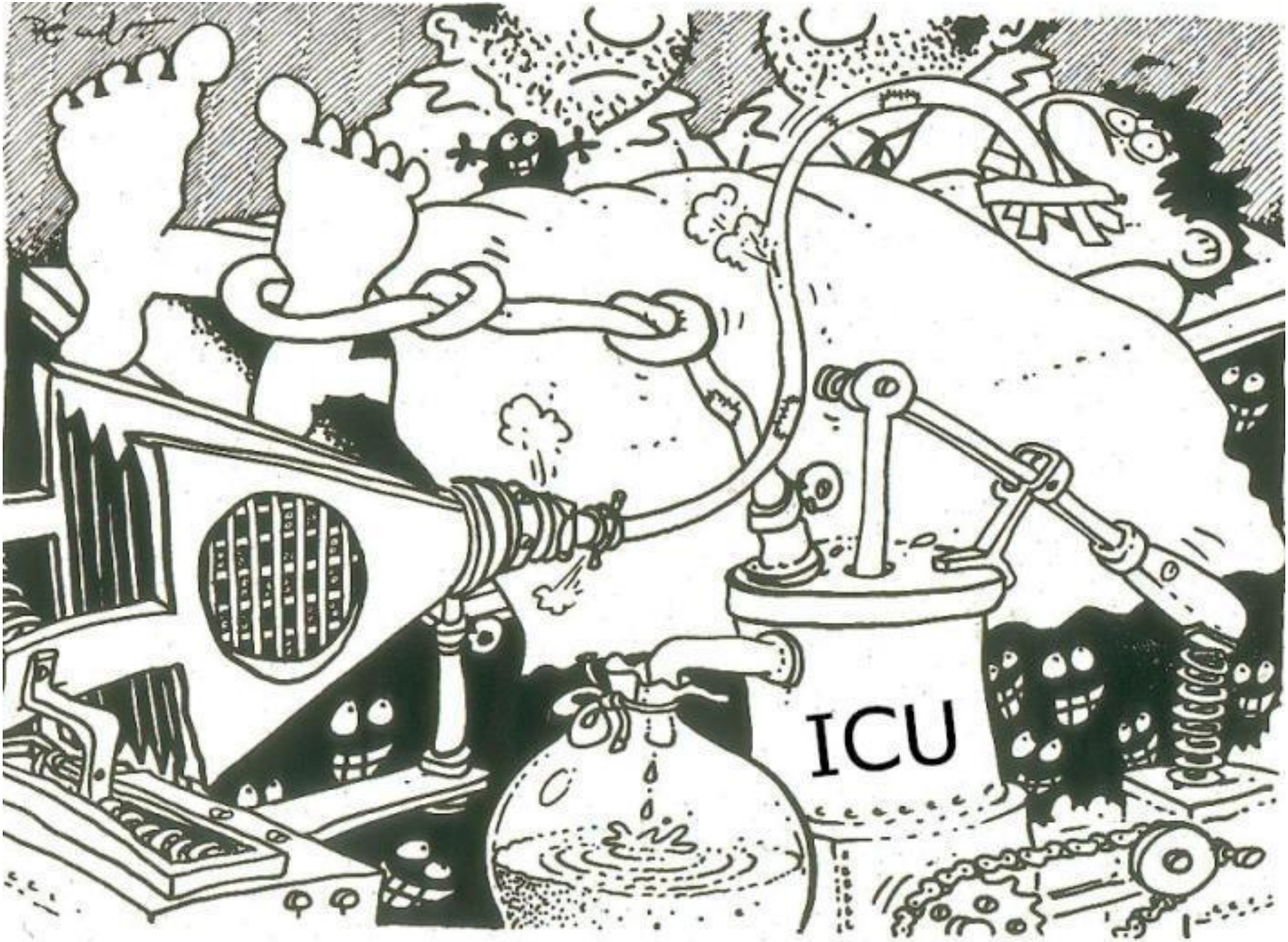
Dr Philippe Eggimann, PD&MER
Service de Médecine Intensive Adulte
www.soins-intensifs.chuv.ch

Anything I say can be highly biased

Dr Eggimann collaborated in several industry-sponsored clinical trials since 1990.



Dr Eggimann served on advisory board for and/or presented sponsored lectures for Pfizer, MSD, Astellas, Roche, Weyth-Lederle, Lilly, Medex Kenta-Biotech


ICU

Talk ID: 308

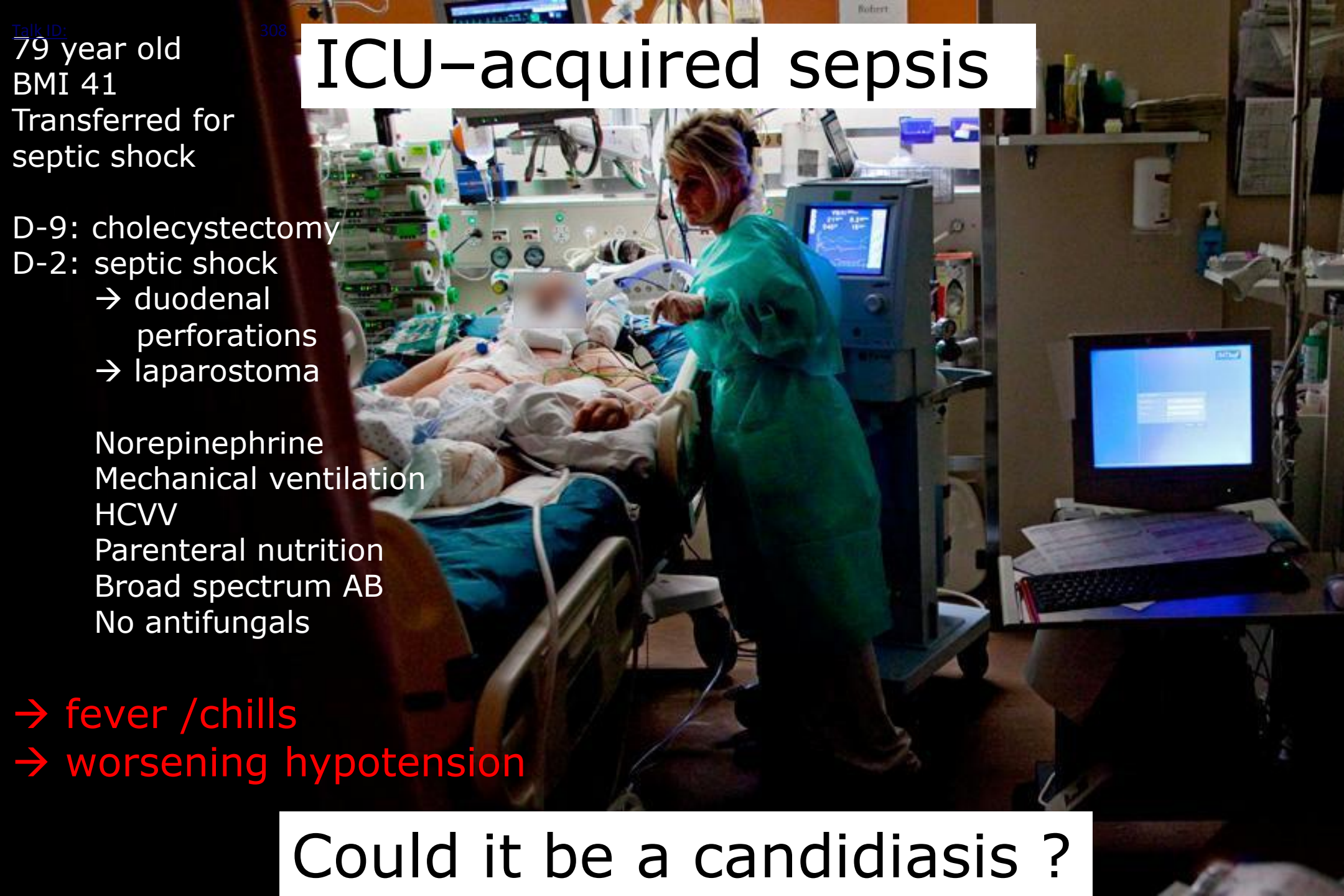
ICU–acquired sepsis

79 year old
BMI 41
Transferred for
septic shock

D-9: cholecystectomy
D-2: septic shock
→ duodenal perforations
→ laparostoma

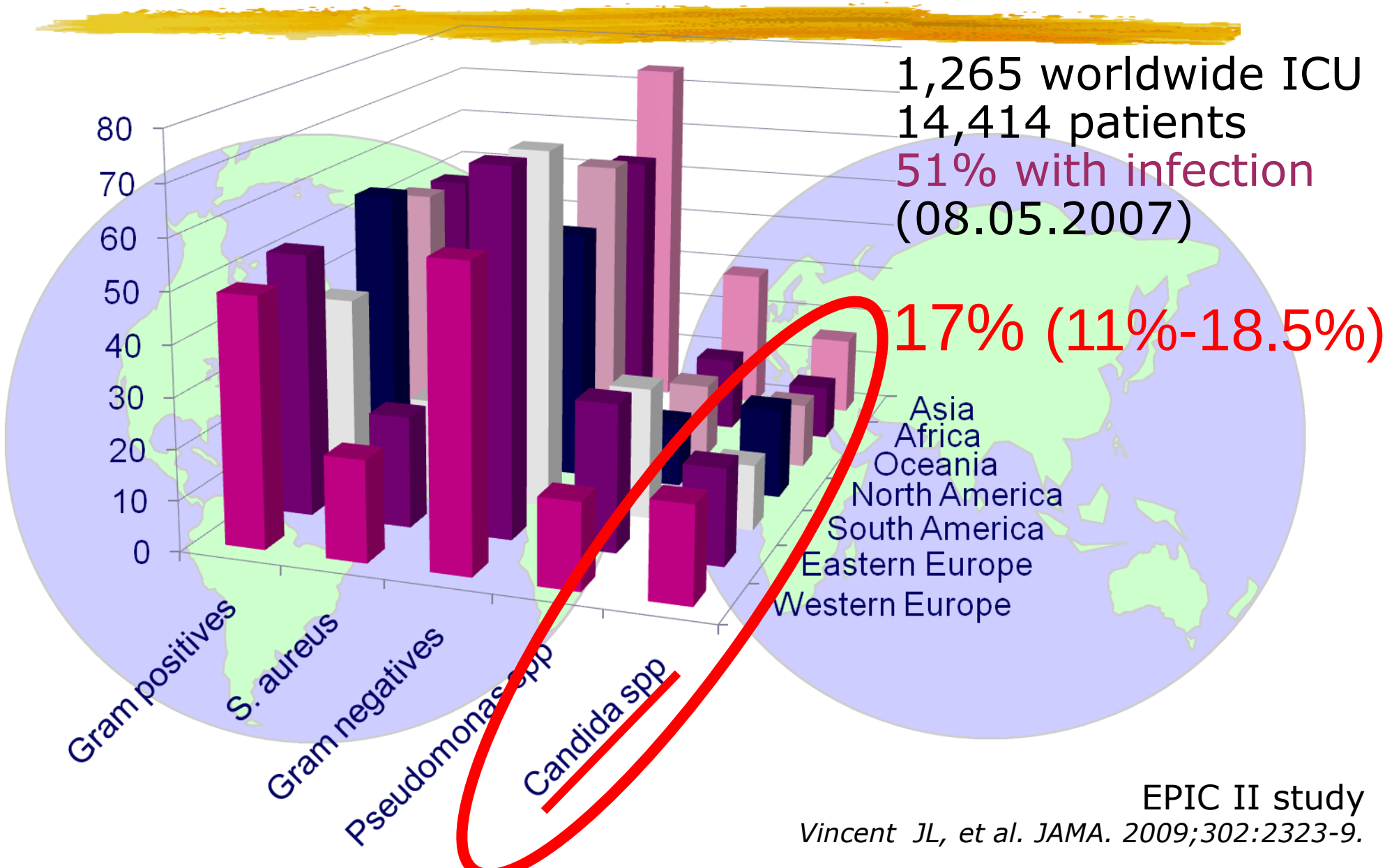
Norepinephrine
Mechanical ventilation
HCVV
Parenteral nutrition
Broad spectrum AB
No antifungals

→ fever /chills
→ worsening hypotension



Could it be a candidiasis ?

ICU: the world of infection



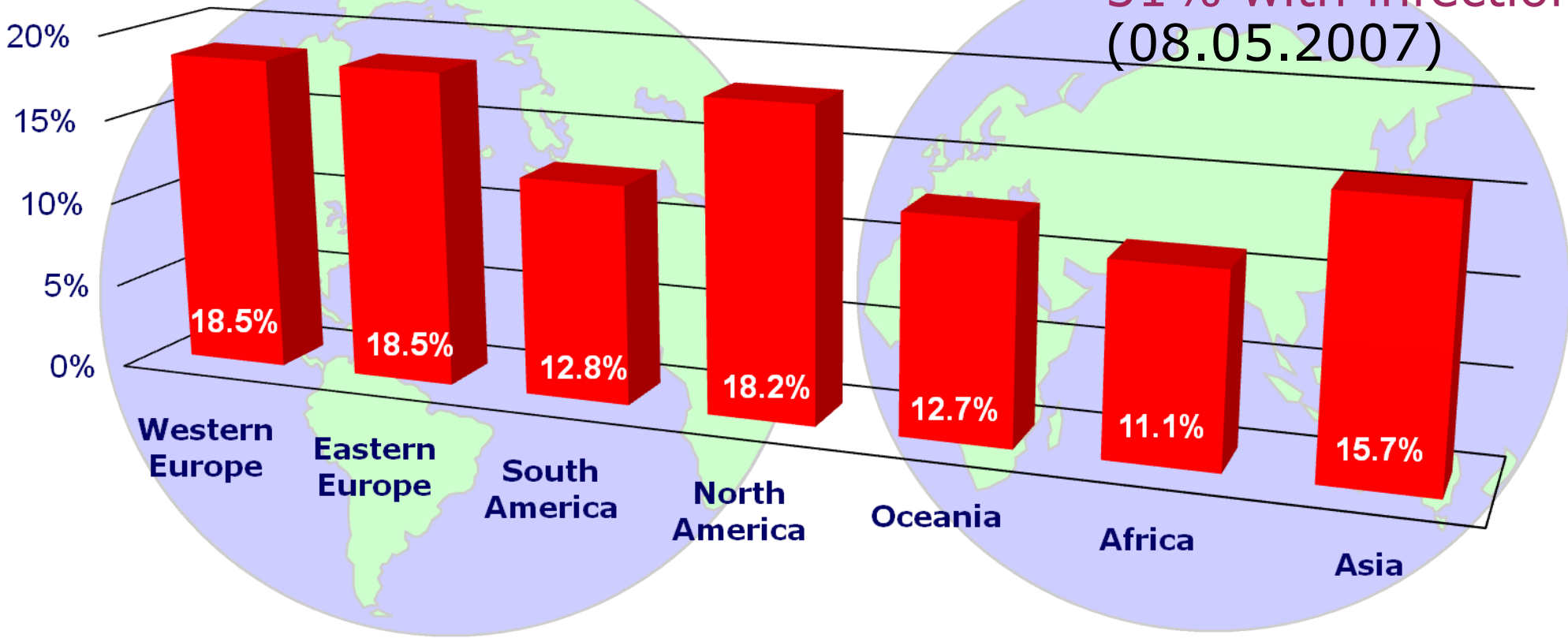
EPIC II study

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

Epidemiology of severe *Candida* infections

843 *Candida spp*

1,265 worldwide ICU
14,414 patients
51% with infection
(08.05.2007)



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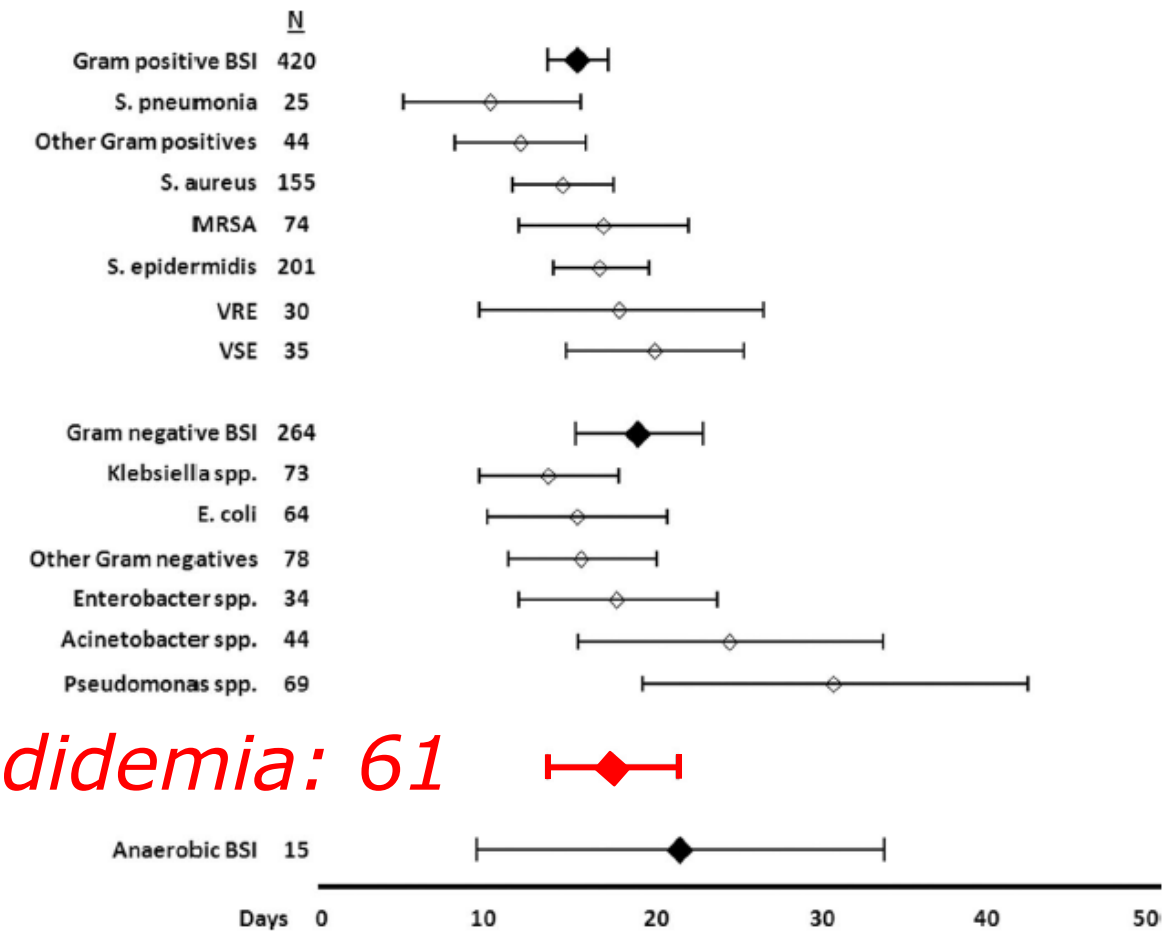
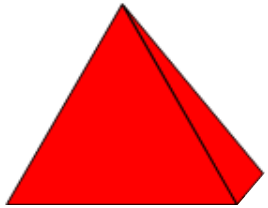


EPIC II study
Kett D et al.
CCM 2011; 39:665-70

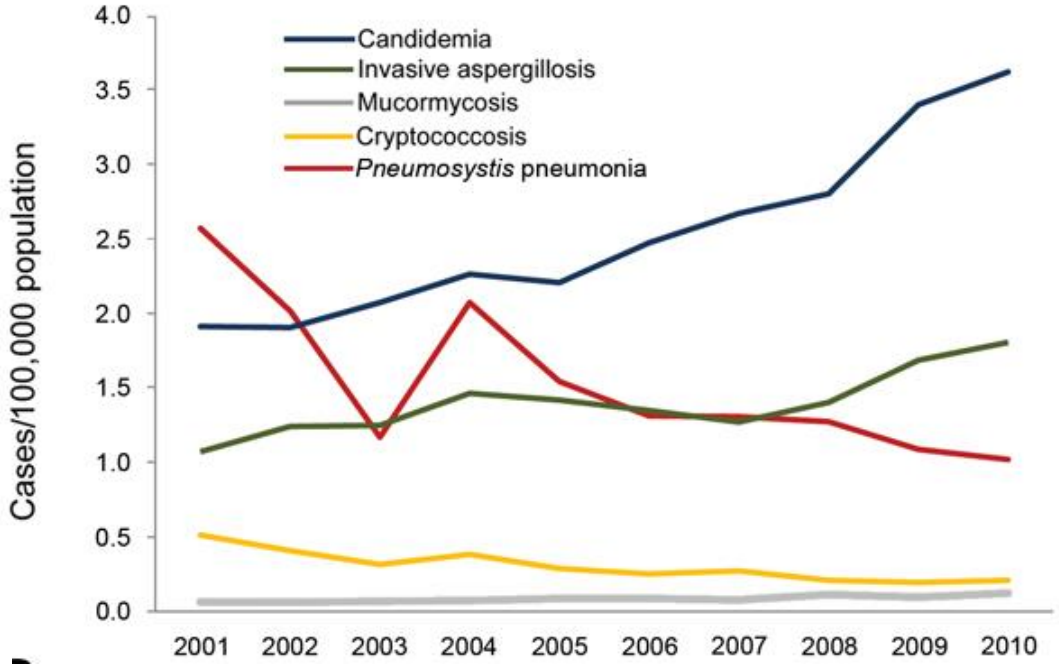
Epidemiology of severe *Candida* infections

Incidence (/1000)



Candidemia

population	0.1
hospitalized	1
ICU	10
BMT	20

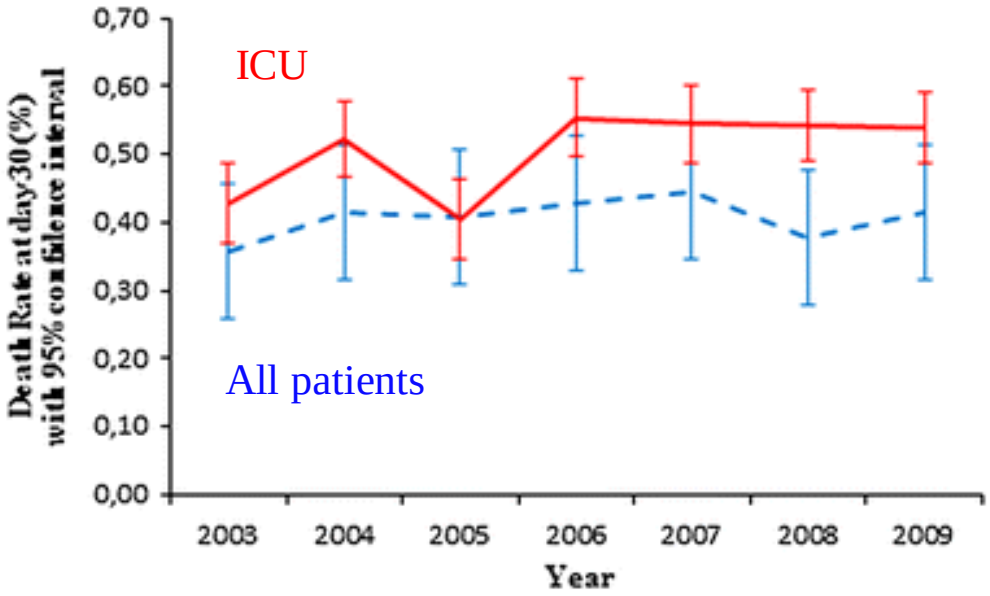


Bitar D, et al. Em Infect Dis 2014; 20:1149-55

Outcome of candidemia

Crude mortality
30% to 60%

2507 candidemia in Paris aera(2002-2010)

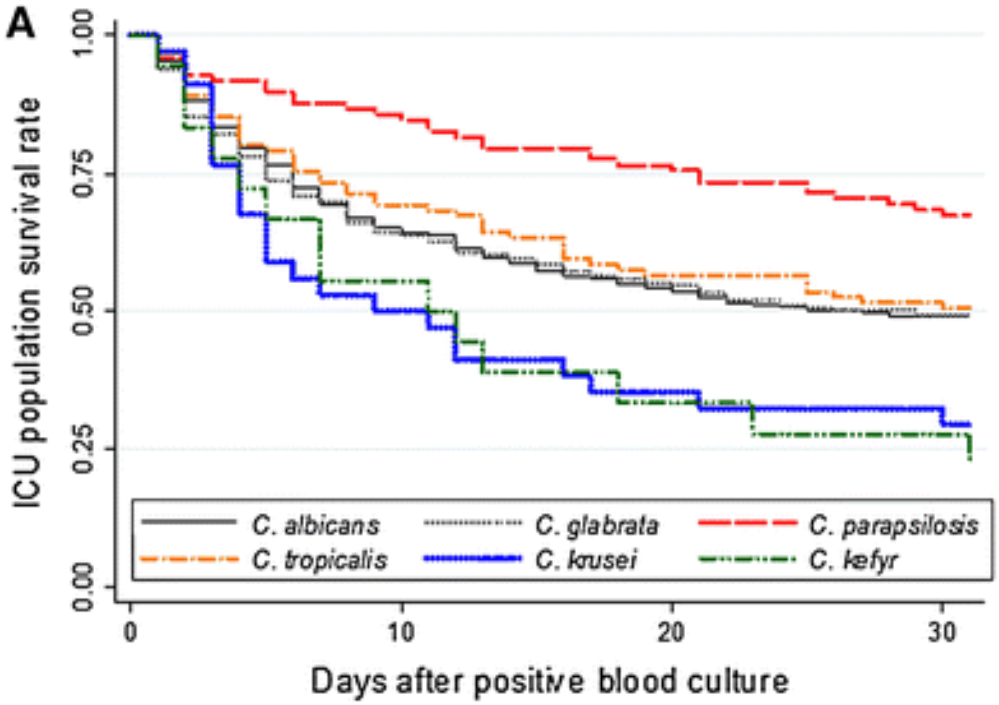


The French Mycosis Study Group
Lortholary O et al. ICM 2014; 40:1303-12.

Outcome of candidemia

Crude mortality
30% to 60%

1206 candidemia in ICU patients (2002-2010)



The French Mycosis Study Group
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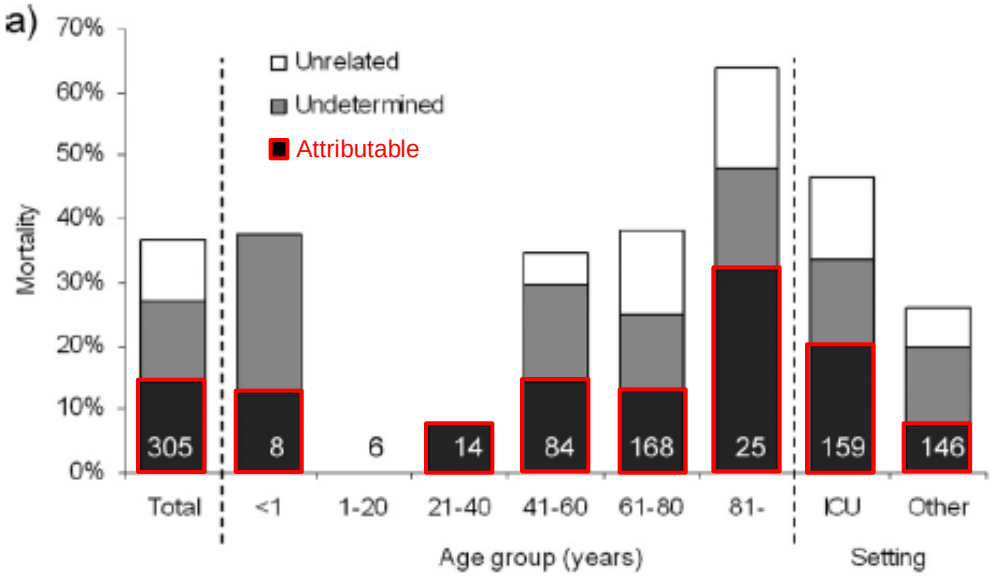
Outcome of candidemia

Crude mortality
30% to 60%

Attributable mortality
25% to 40%



Arendrup MC, et al. J Clin Microbiol. 2011;49:3300-8.

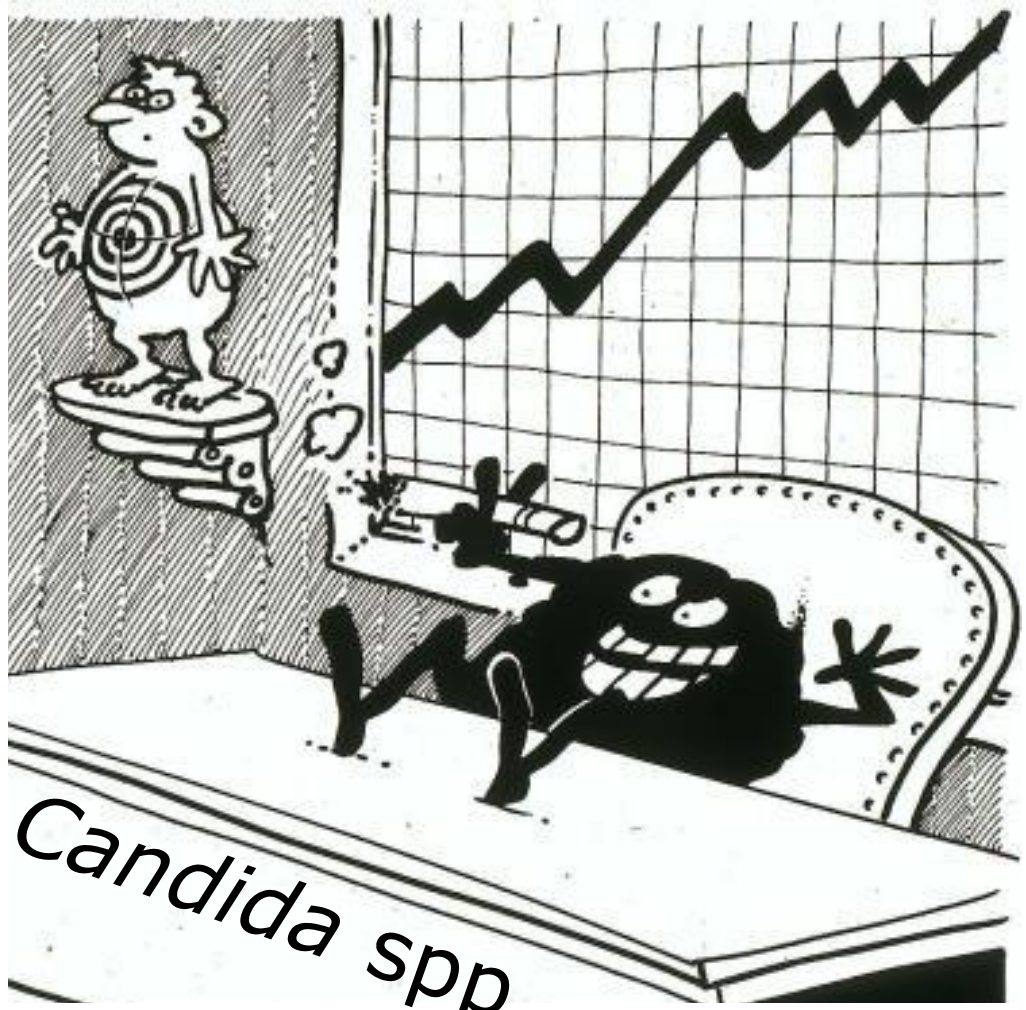
Outcome of candidemia

Crude mortality
30% to 60%

Attributable mortality
25% to 40%

Increased of length of stay
8 to 25 days

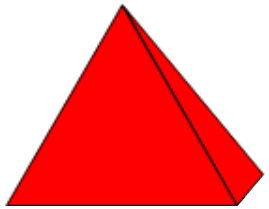
Increased costs
5,000 to 40,000 Euros



Wey SB, et al. Arch Intern Med. 1988;148:2462-5. Voss A, et al. Infection. 1997;25:8-11.
Blot et al. Am J Med. 2002;113:480-5. Wisplinghoff H, et al. Clin Infect Dis. 2004; 39:309-17.
Guldlaugsson O, et al. Clin Infect Dis. 2003; 37:1172-7. Zaoutis TE, et al. Clin Infect Dis. 2005; 41:1232-9.

Epidemiology of severe *Candida* infections

Incidence (/1000)



Candidemia

population	0.1
hospitalized	1
ICU	10
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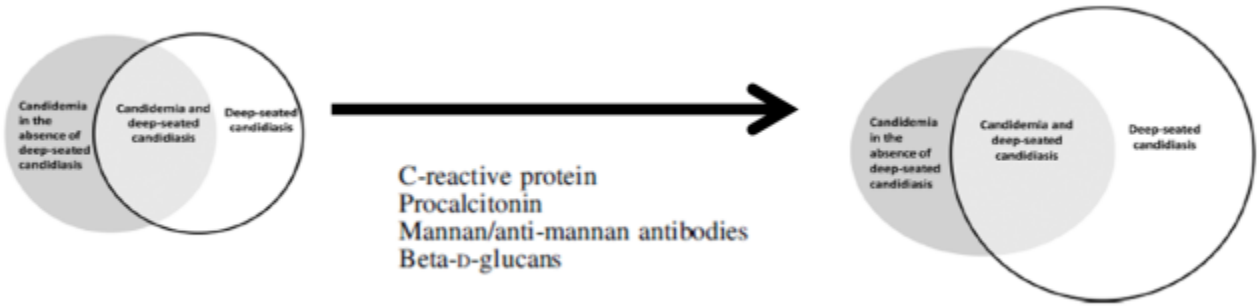
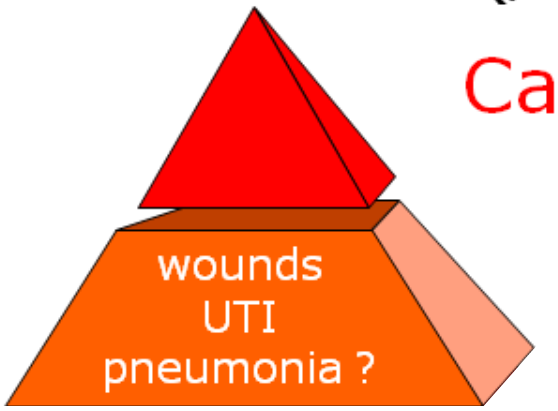
Finding the "Missing 50%" of Invasive Candidiasis: How Nonculture Diagnostics Will Improve Understanding of Disease Spectrum and Transform Patient Care



Clancy CJ, Nguyen MH. Clin Infect Dis. 2013;56:1284-92.

Epidemiology of severe *Candida* infections

Incidence (/1000)



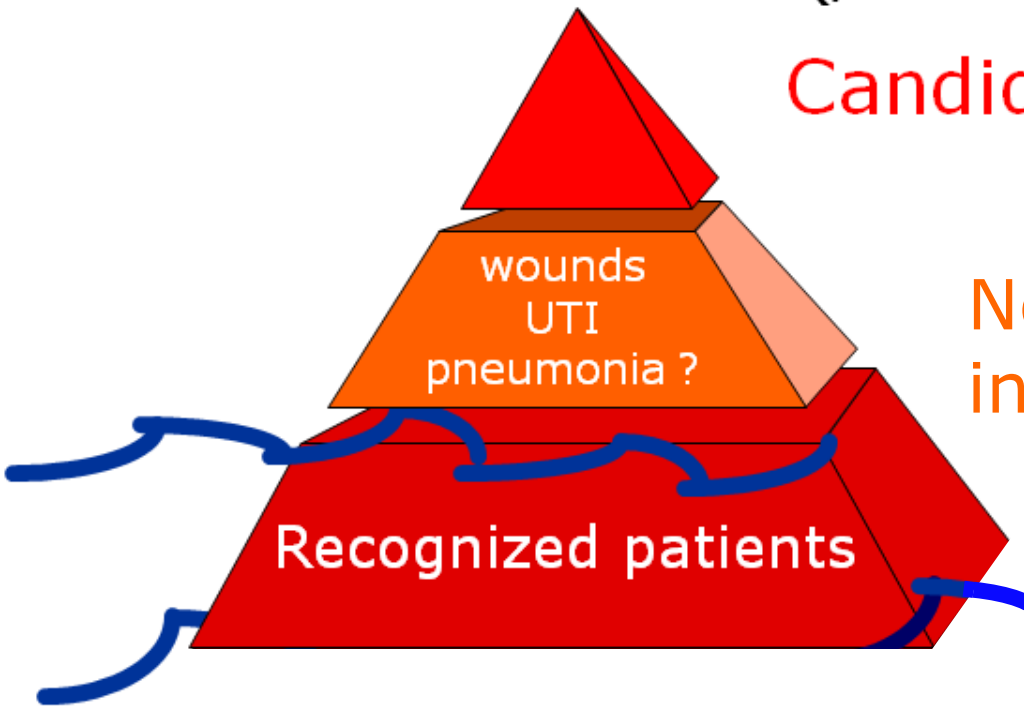
Candidemia

population	0.1
hospitalized	1
ICU	10
BMT	20

Non candidemic invasive candidiasis ??

Epidemiology of severe *Candida* infections

Incidence (/1000)

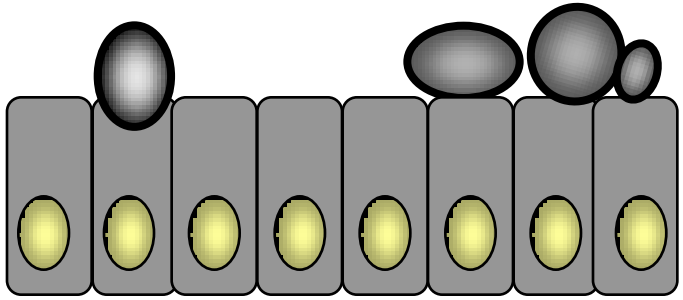


Candidemia

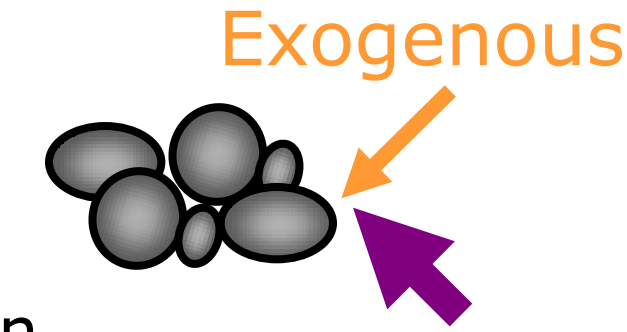
population	0.1
hospitalized	1
ICU	10
BMT	20

Non candidemic invasive candidiasis ??

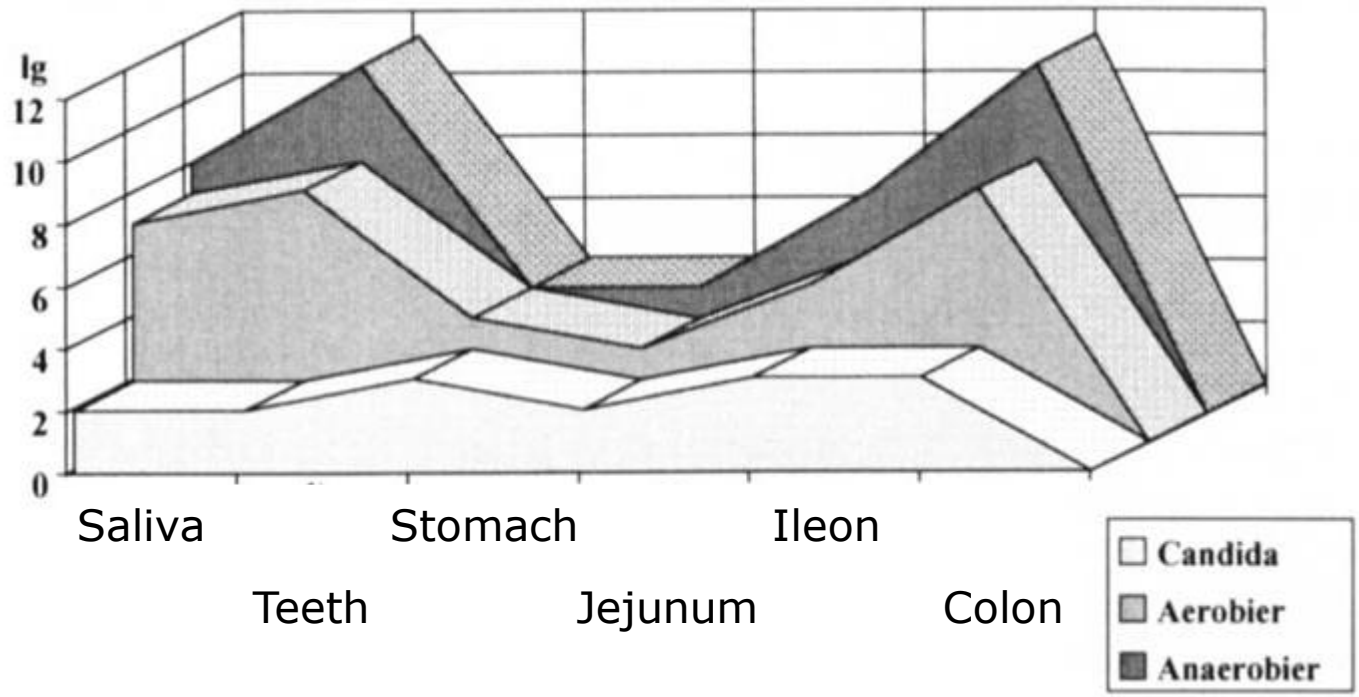
Colonization ???



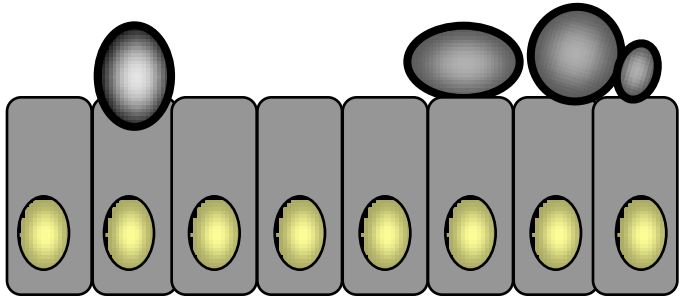
colonization



immunosuppression
prematurity / bruns
neutropenia / ileus

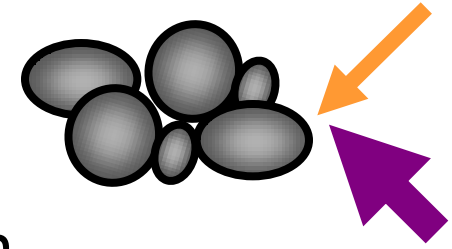


Knoke M. Mycoses. 1999;42(S1):30-4.



colonization

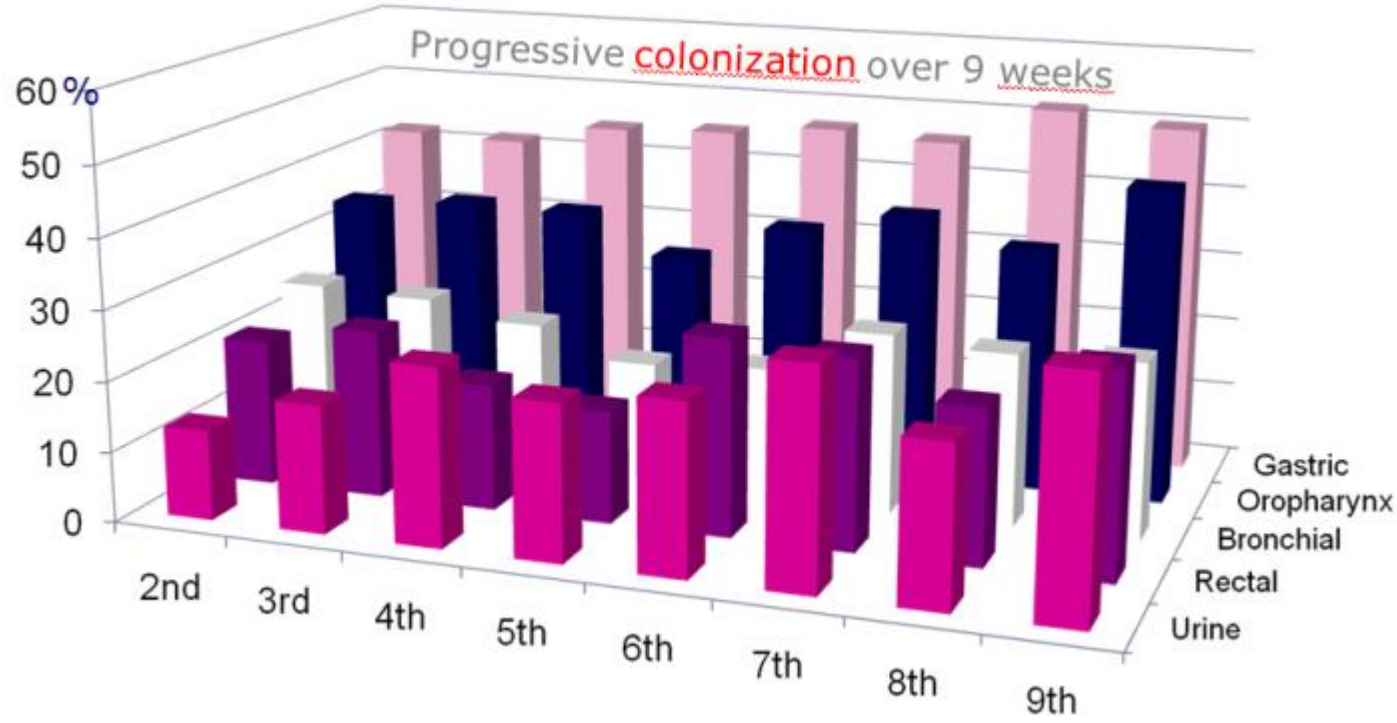
Exogenous



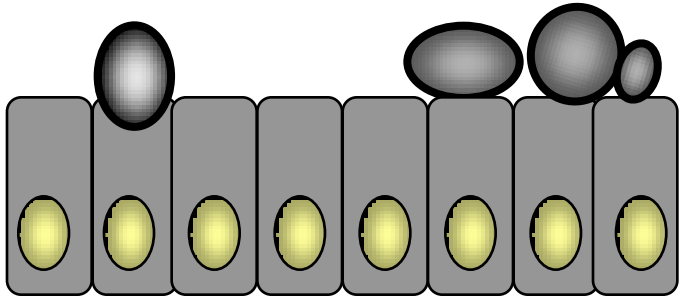
Endogenous

immunosuppression
prematurity / bruns
neutropenia / ileus

1699 ICU patients (70 spanish ICU) staying > 7 days

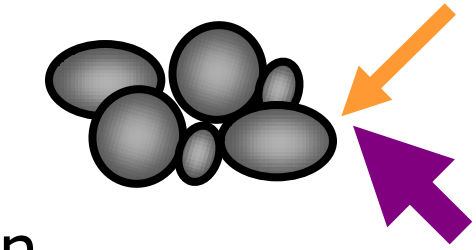


León C, et al. Eur J Clin Microbiol Infect Dis. 2009;28:233-42.



colonization

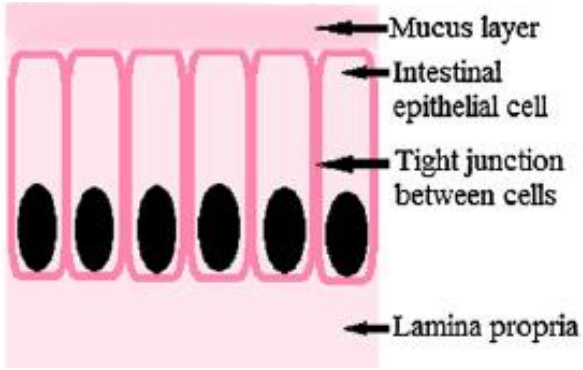
Exogenous



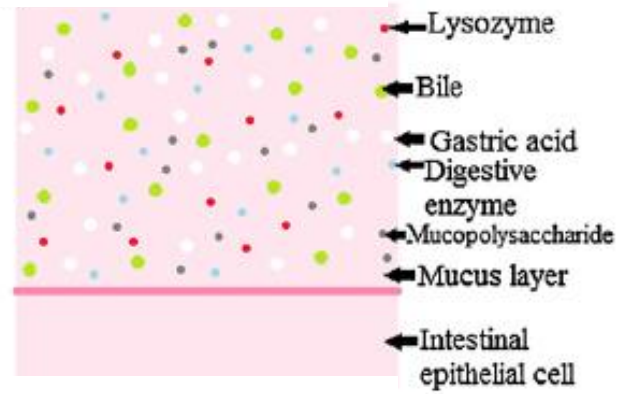
Endogenous

immunosuppression
prematurity / bruns
leus

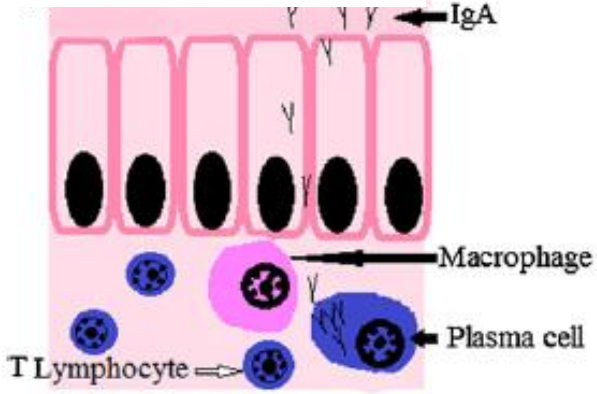
Physical barrier



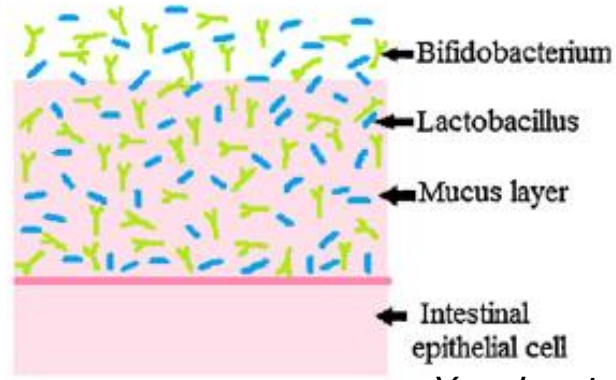
Chemical barrier

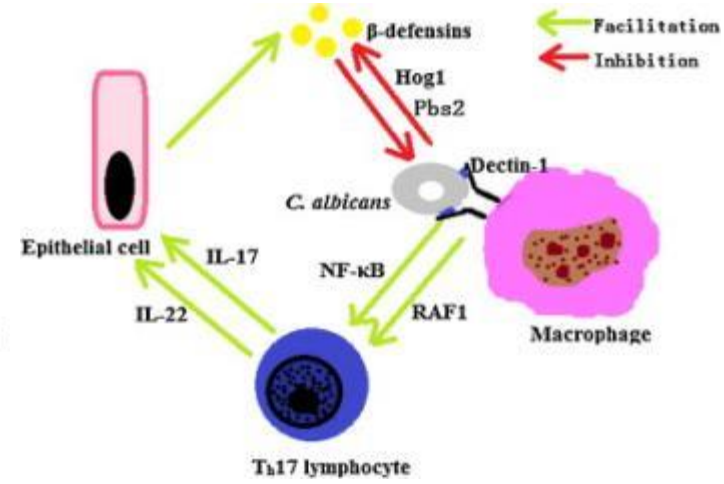


Immune barrier

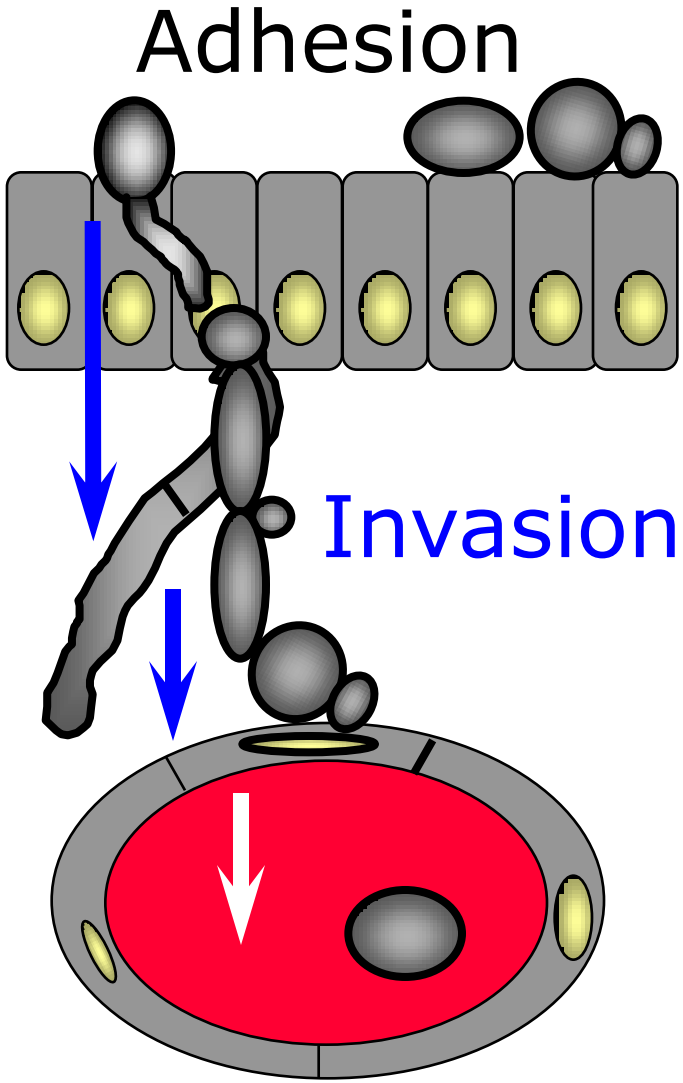


Microbial barrier

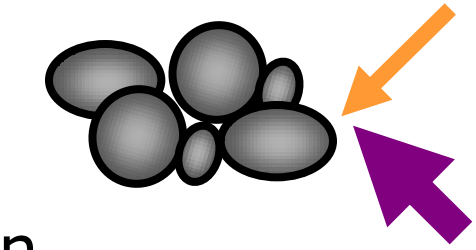




Yan L, et al. Microbiol Res. 2013;168(7):389-95.



colonization



Endogenous

immunosuppression
prematurity / bruns
neutropenia / ileus

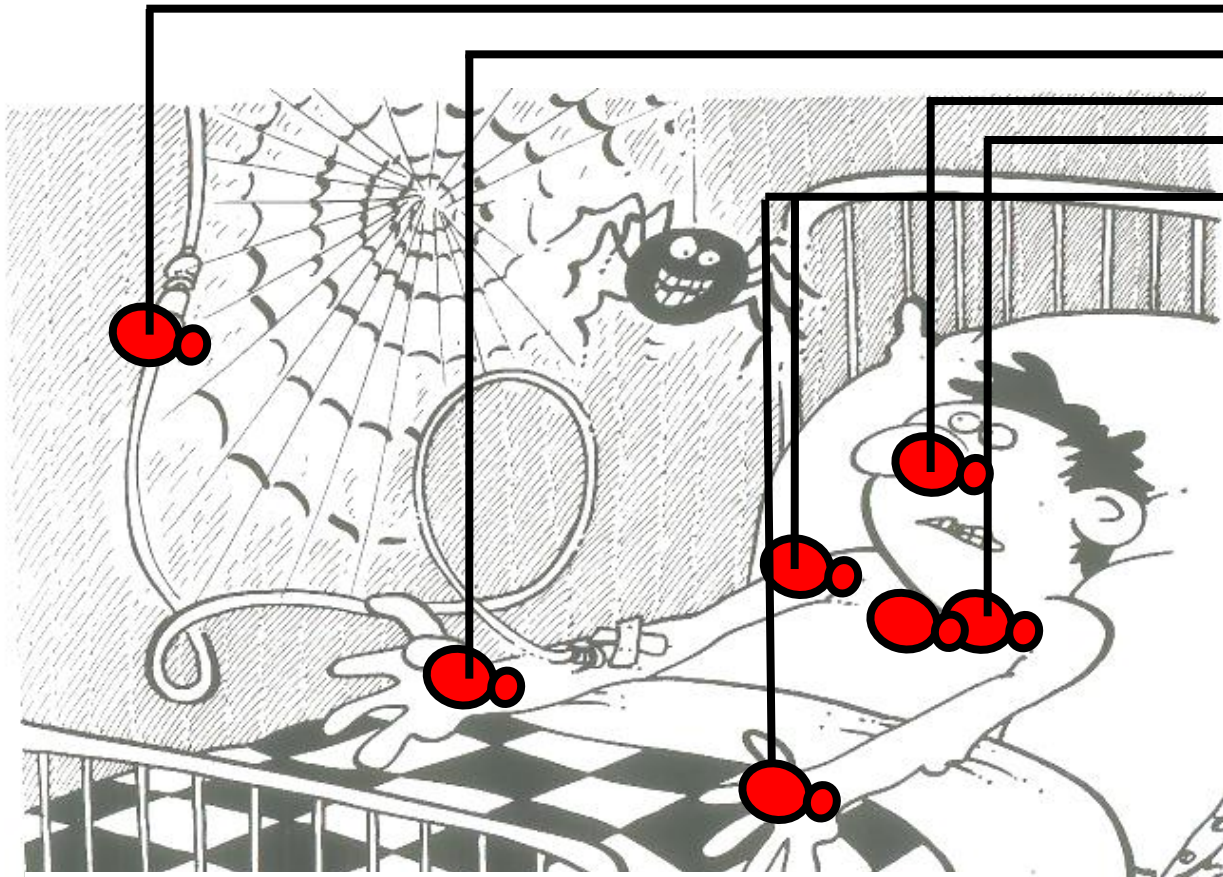
Risk factors	Odds Ratio
Colonization by *Candida*	5.0-27.0
Antibiotics	1.7-30.0
Central venous catheter	3.8-26.4
ICU stay	1.5-12.2
Neutropenia	3.0-45.0
Previous surgery	2.1-20.0
Renal failure	3.8-22.1

Candidemia

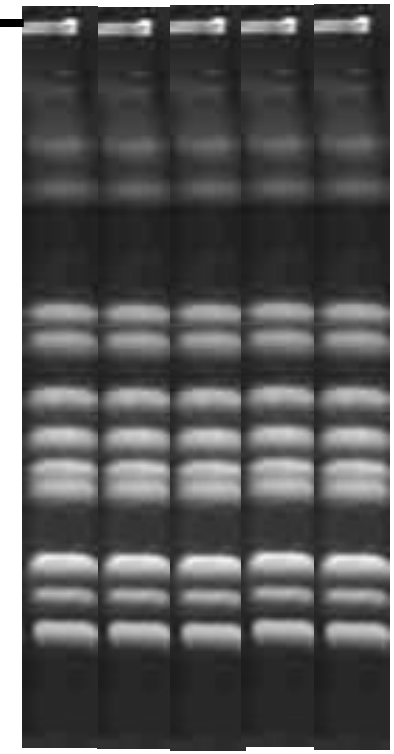
5-10/10,000 admissions

Eggimann P, et al. Lancet Infect Dis. 2003;3:685-702.

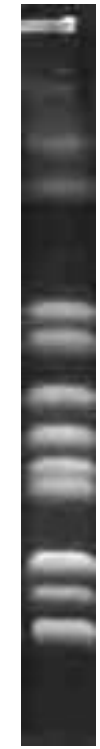
Pathophysiology of invasive candidiasis



Progressive colonization



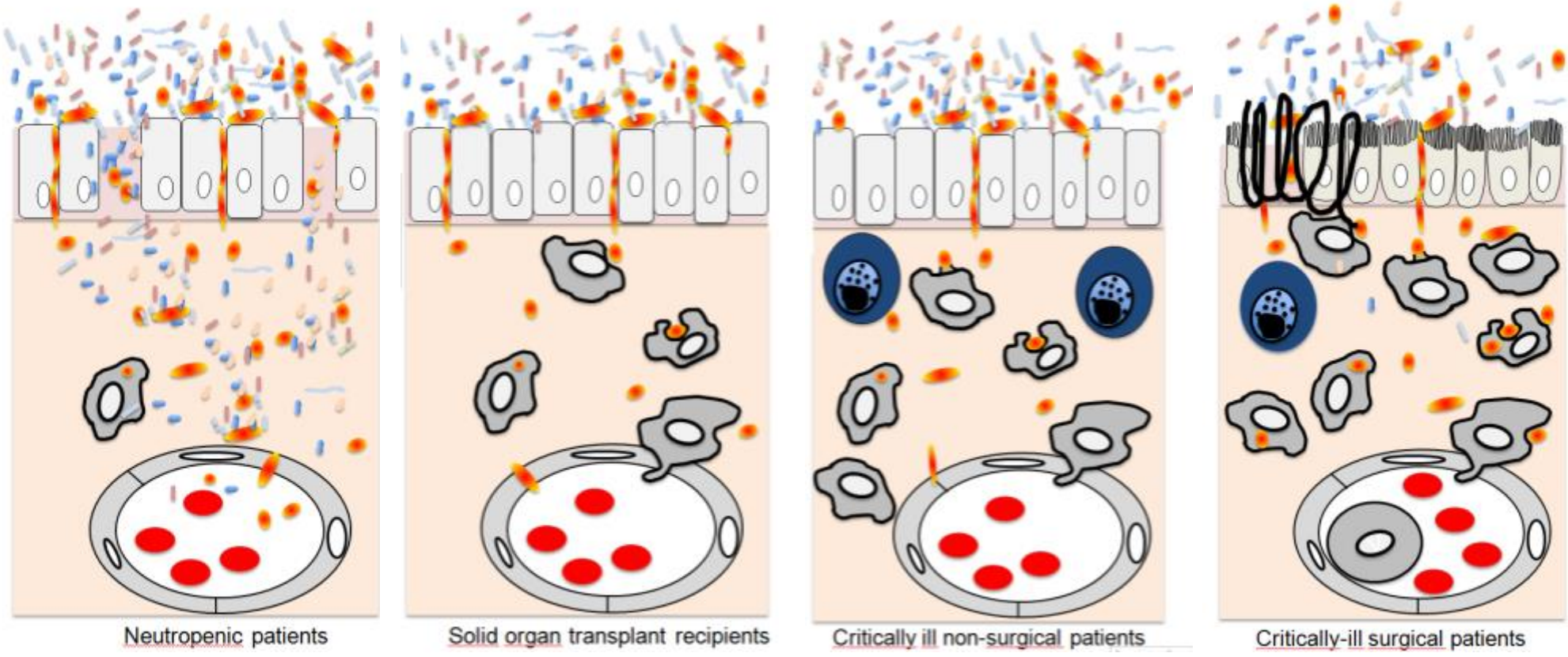
Candidemia



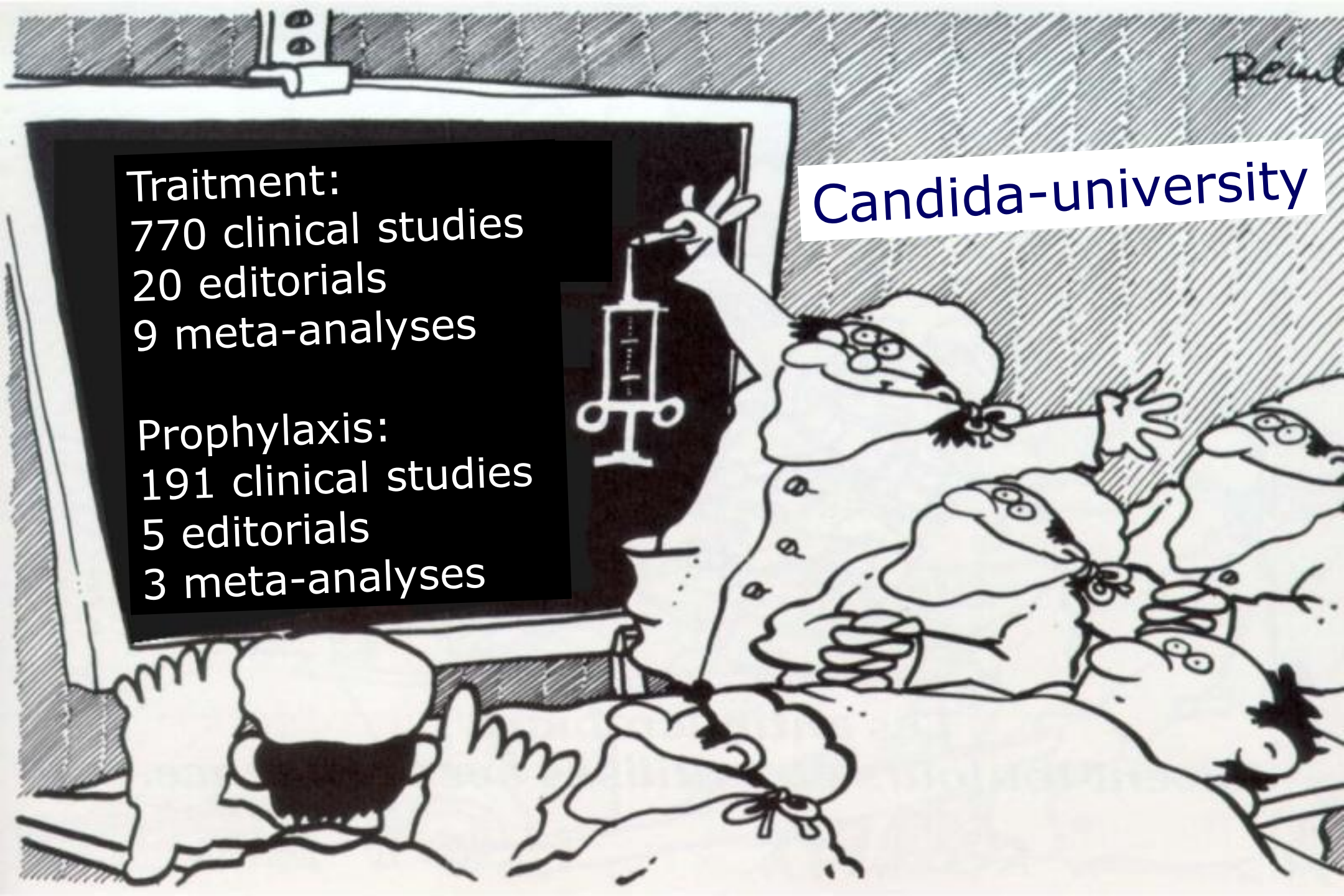
12 may
12 may
16 may
21 may
25 may
27 may

Pittet D, et al. Am J Med. 1991;91:256S-263S.
Pittet D, et al. Ann Surg. 1994;220:751-8.
Nucci M, Anaissie E. Clin Infect Dis. 2001;33:1959-67.

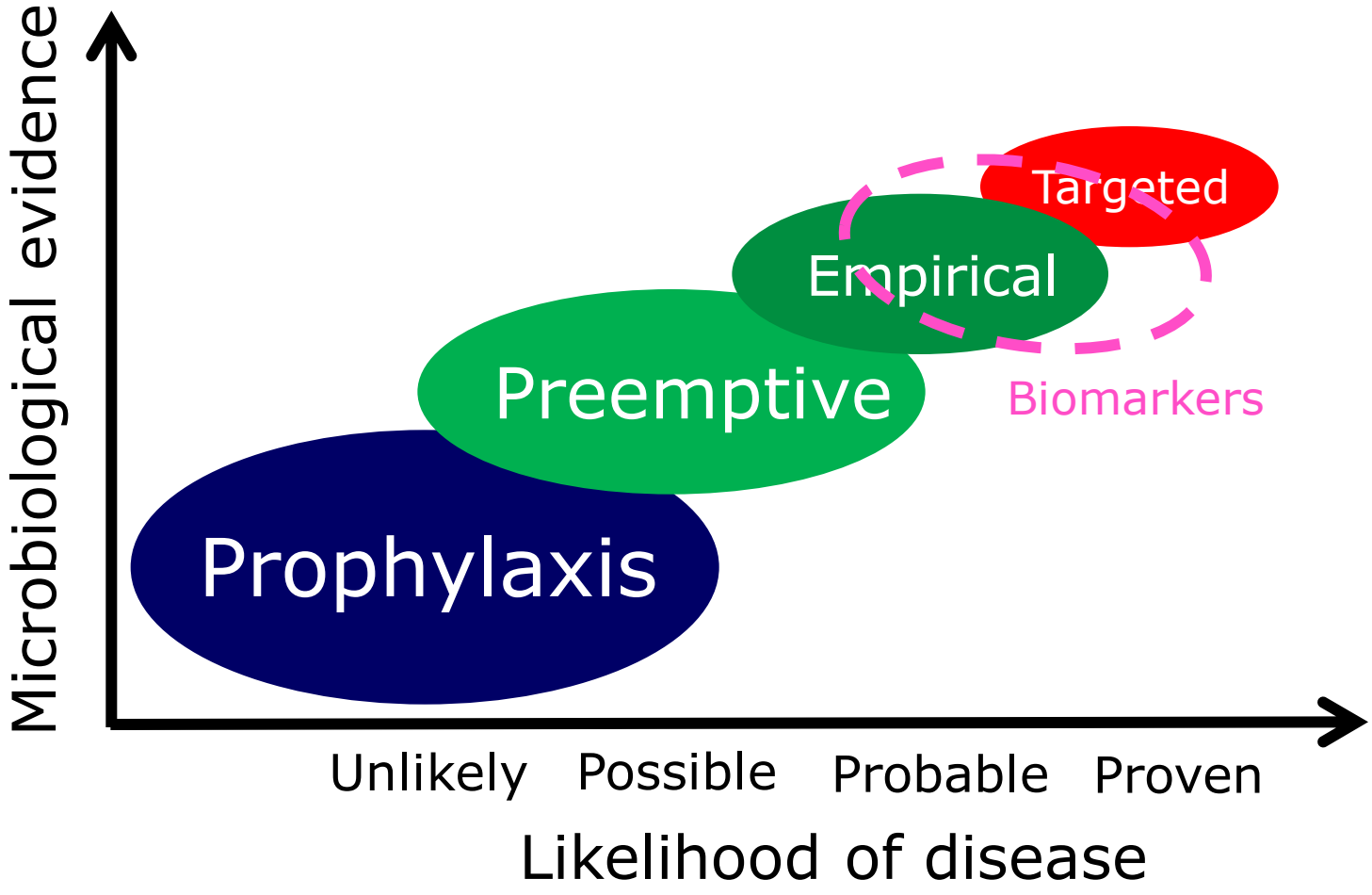
Pathophysiology of invasive candidiasis



Eggimann P, Pittet D. Intensive Care Med. 2014;40:1429-48.

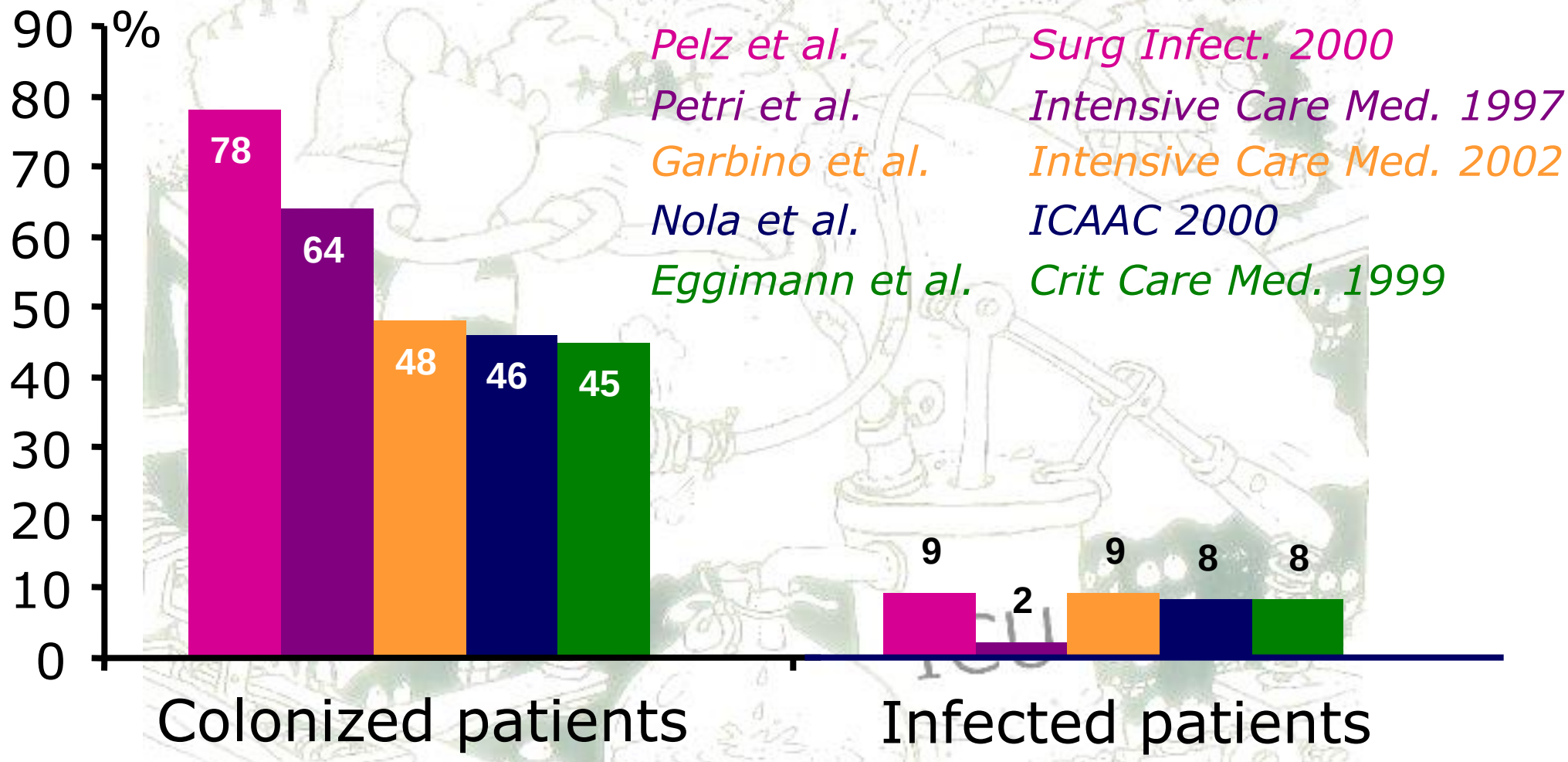

Traitment:
770 clinical studies
20 editorials
9 meta-analyses
Prophylaxis:
191 clinical studies
5 editorials
3 meta-analyses
Candida-university

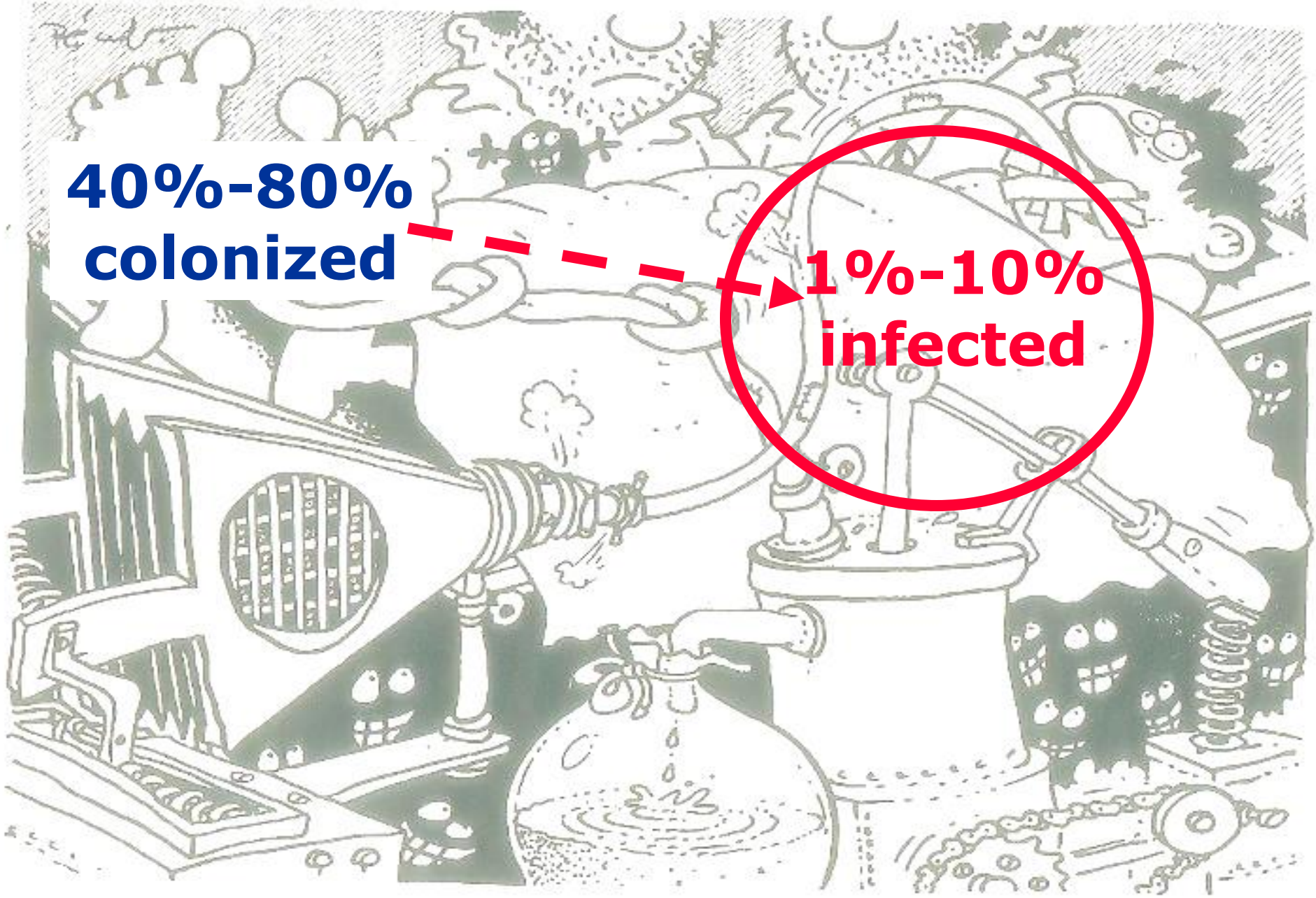
Antifungals in critically ill patients

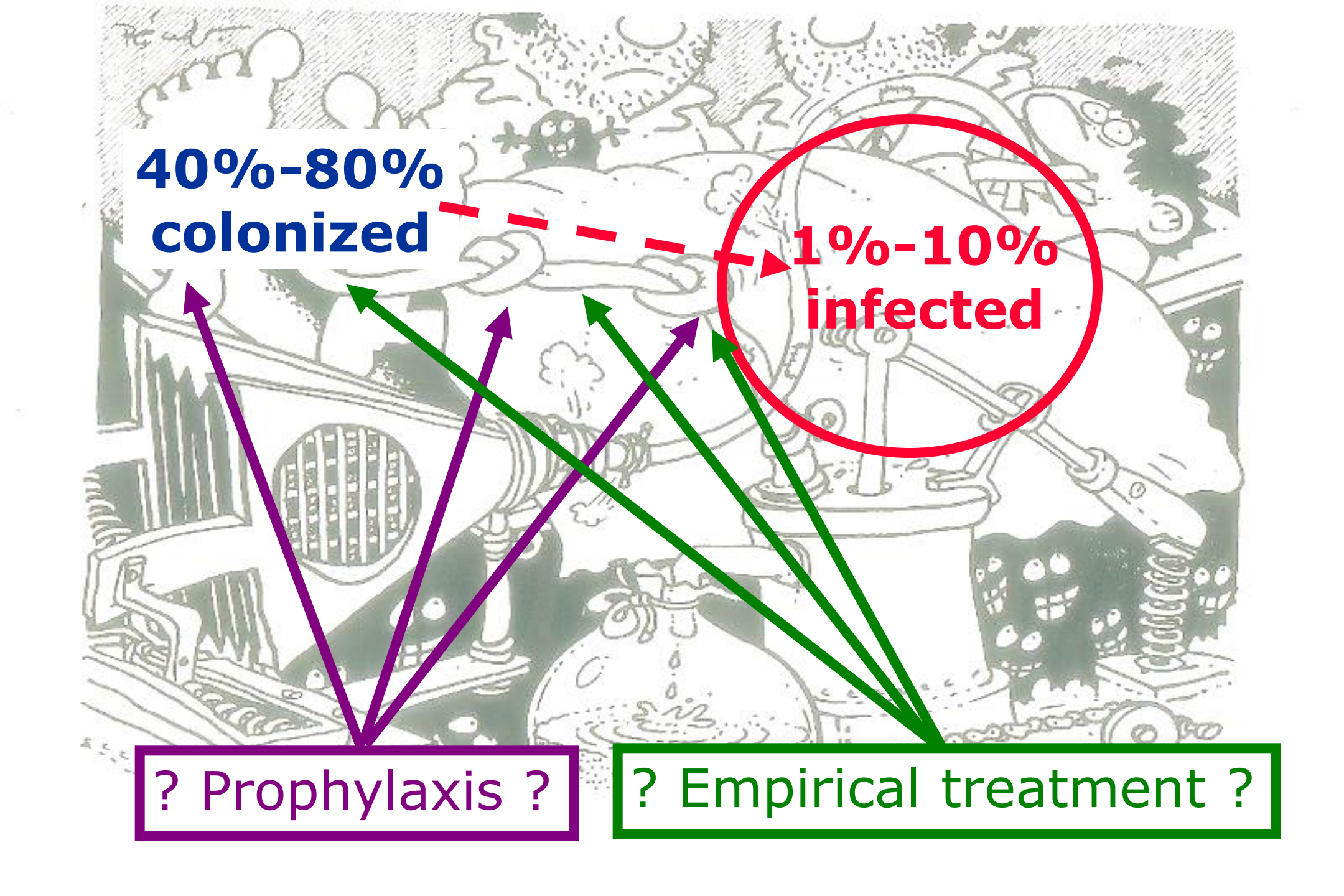


Eggimann, Bille, Marchetti, Annals of Intensive Care 2011, 1:37

Invasive candidiasis in critically ill patients




40%-80%
colonized
1%-10%
infected

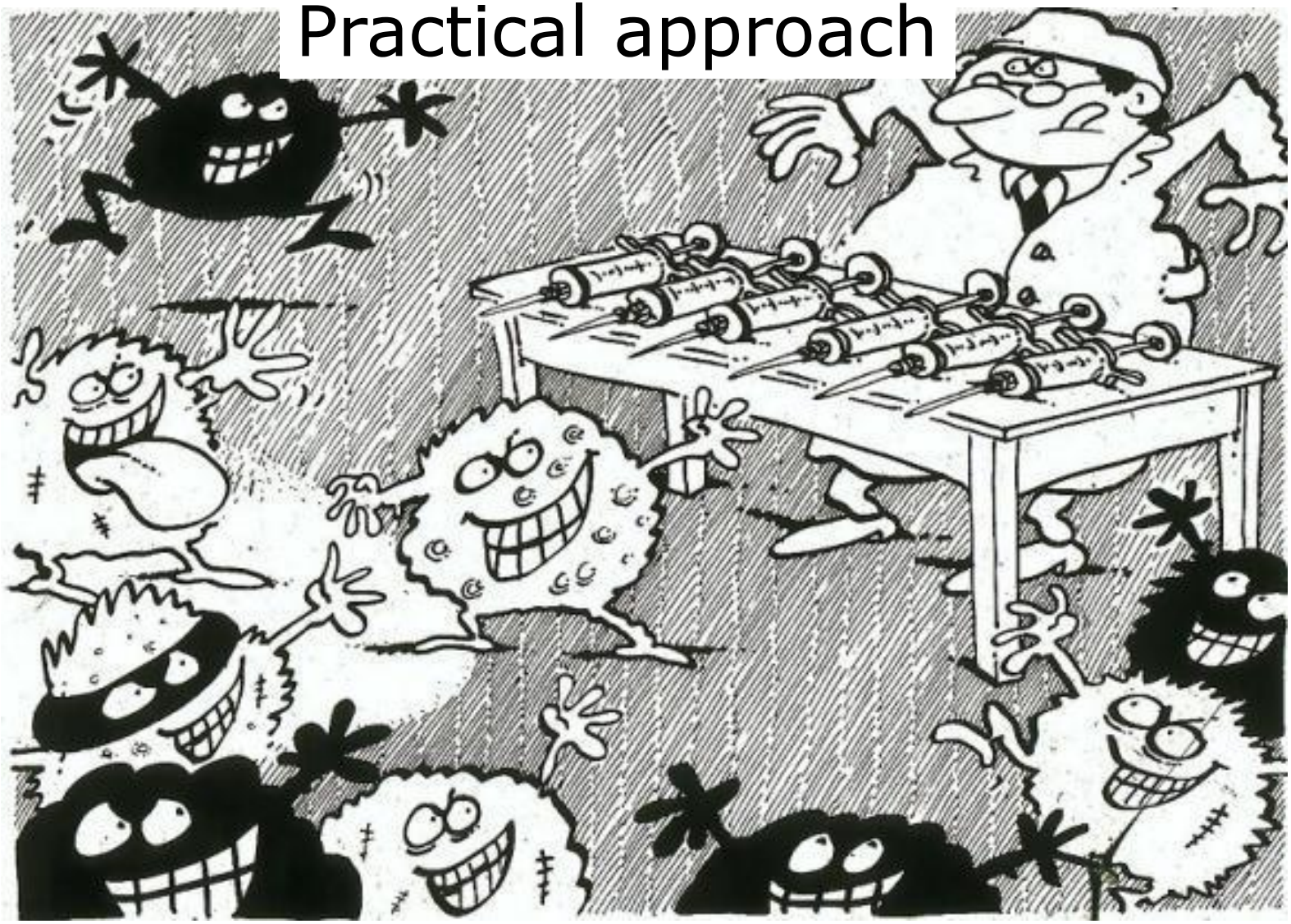

40%-80%
colonized
1%-10%
infected
? Prophylaxis ?
? Empirical treatment ?

Invasive candidiasis: the real challenge

Guidelines	Preemptive Empirical	Prophylaxis
BSAC CID 1994	yes	∅
Edwards CID 1997	∅	∅ data
Vincent ICM 1998	∅	SDD ?
Rex CID 2000	∅	yes, but
Buchner EJCMID 2002	yes	at risk patients
Denning Lancet ID 2003	∅	∅
Pappas CID 2004	∅	carfully selected pts
SFAR/SPILF/SRLF 2004	yes, but	∅ indication
FUNGINOS 2006	yes, but	carfully selected pts
IDSA CID 2009	yes	carfully selected pts

Severe candida infections in critically ill patients

Practical approach



Should this patient received antifungals ?

Colonization par yeasts (*Candida* spp) ?

NO
or
no information

Documented high risk group

YES

Prophylaxis

Eggimann & Garbino & Pittet Lancet Infectious Diseases 2003

Antifungal prophylaxis in critically ill patients ?

Continuing Medical Education Article

Fluconazole prophylaxis in critically ill surgical pati
analysis*

Andrew F. Shorr, MD, MPH; Kevin Chung, MD;
Marin H. Kollef, MD

JAC

ing fungal infections in
patients: systematic
ed clinical trials

C. Craig[3,4]

Overall mortality

Intensive C
DOI 10.100

Prophylaxis
review and m

Mario Cruciani

ion-

Review Articles

Antifungal prop
care unit patient
placebo-controlle

Konstantinos Z. Vardakas, MD
Elpidoforos S. Soteriades, MD,

ıt mortality
s (Review)

Van Till et al. J Crit Care 07

et al. J Crit Care 07

17 October 20

Reference | Treatment | Control

SAP studies
Garbino
Jacobs
Normand
Pelz

Candid

colonization

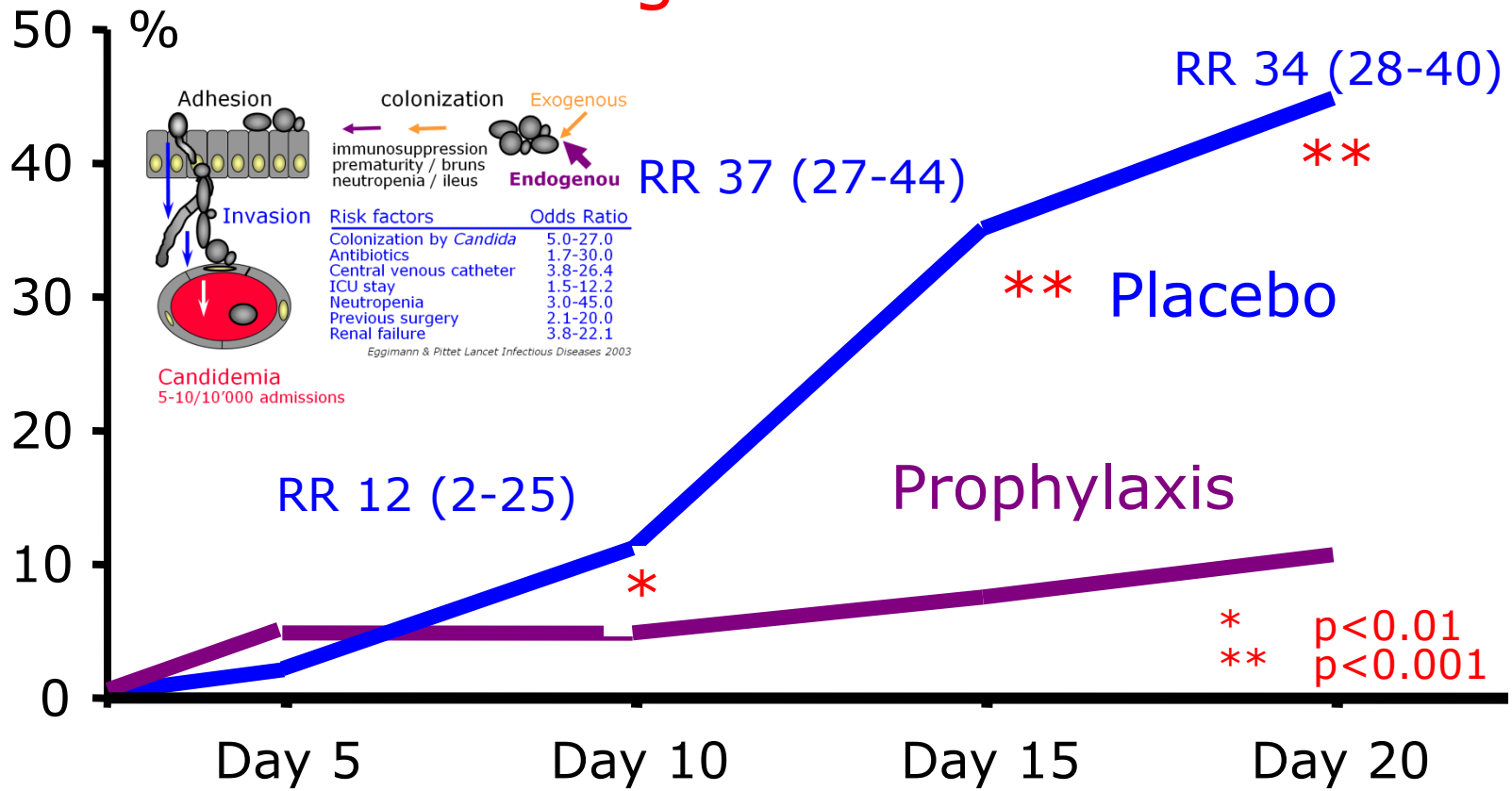
Reference	Treatment	Control	OR [95% CI]	OR [95% CI]
SAP studies				
Eggimann	7 of 23	14 of 20		0.19 [0.05, 0.69]
Garbino	29 of 103	40 of 101		0.60 [0.33, 1.07]
Normand	0 of 51	12 of 47		0.03 [0.00, 0.48]
Savino	33 of 220	17 of 72		0.57 [0.30, 1.10]
Slotman	8 of 27	18 of 30		0.28 [0.09, 0.85]
Total	77 of 424	101 of 270		0.38 [0.20, 0.70]
SDD studies				
Abele-Horn	8 of 58	15 of 30		0.16 [0.06, 0.45]
Aerdts	4 of 17	28 of 39		0.12 [0.03, 0.45]
Ferrer	8 of 39	19 of 40		0.29 [0.11, 0.77]
Hammond	1 of 114	17 of 125		0.06 [0.01, 0.43]
Kerver	0 of 49	21 of 47		0.01 [0.00, 0.21]
McClelland	3 of 15	5 of 12		0.35 [0.06, 1.93]
Ulrich	0 of 48	10 of 52		0.04 [0.00, 0.73]
Unertl	15 of 19	14 of 20		1.61 [0.37, 6.92]
Von Hünefeld	2 of 102	70 of 102		0.01 [0.00, 0.04]
Wiener	8 of 30	24 of 31		0.11 [0.03, 0.34]
Total	49 of 491	223 of 498		0.12 [0.05, 0.29]

0.01 0.1 1 10 100
Favours treatment Favours control

Prophylaxis in critically ill patients ?

Meta-analysis of randomized studies

Fungal infections



Cruciani M, et al. ICM; 31: 1356-61

Prophylaxis in critically ill patients ?

Empirical Fluconazole versus Placebo for Intensive Care Unit Patients

A Randomized Trial

Mindy G. Schuster. MD: John E. Edwards Jr.. MD: Jack D. Sobel. MD: Rabih O. Darouiche. MD: Adolf W. Karchmer. MD: Susan Hadley. MD:

Table 4. Reasons for Failure at the End of the Primary Observation Period*

Outcome	Fluconazole Recipients (n = 122), n (%)	Placebo Recipients (n = 127), n (%)
Total failures	67 (55)	73 (57)
No resolution of fever	62 (51)	68 (54)
Documented invasive fungal infection	6 (5)†	11 (9)‡
Need for alternative antifungal agent	12 (10)	20 (16)

fungal infection, no discontinuation because of toxicity, and no need for a nonstudy, systemic antifungal medication (as assessed

Prophylaxis in critically ill patients ?

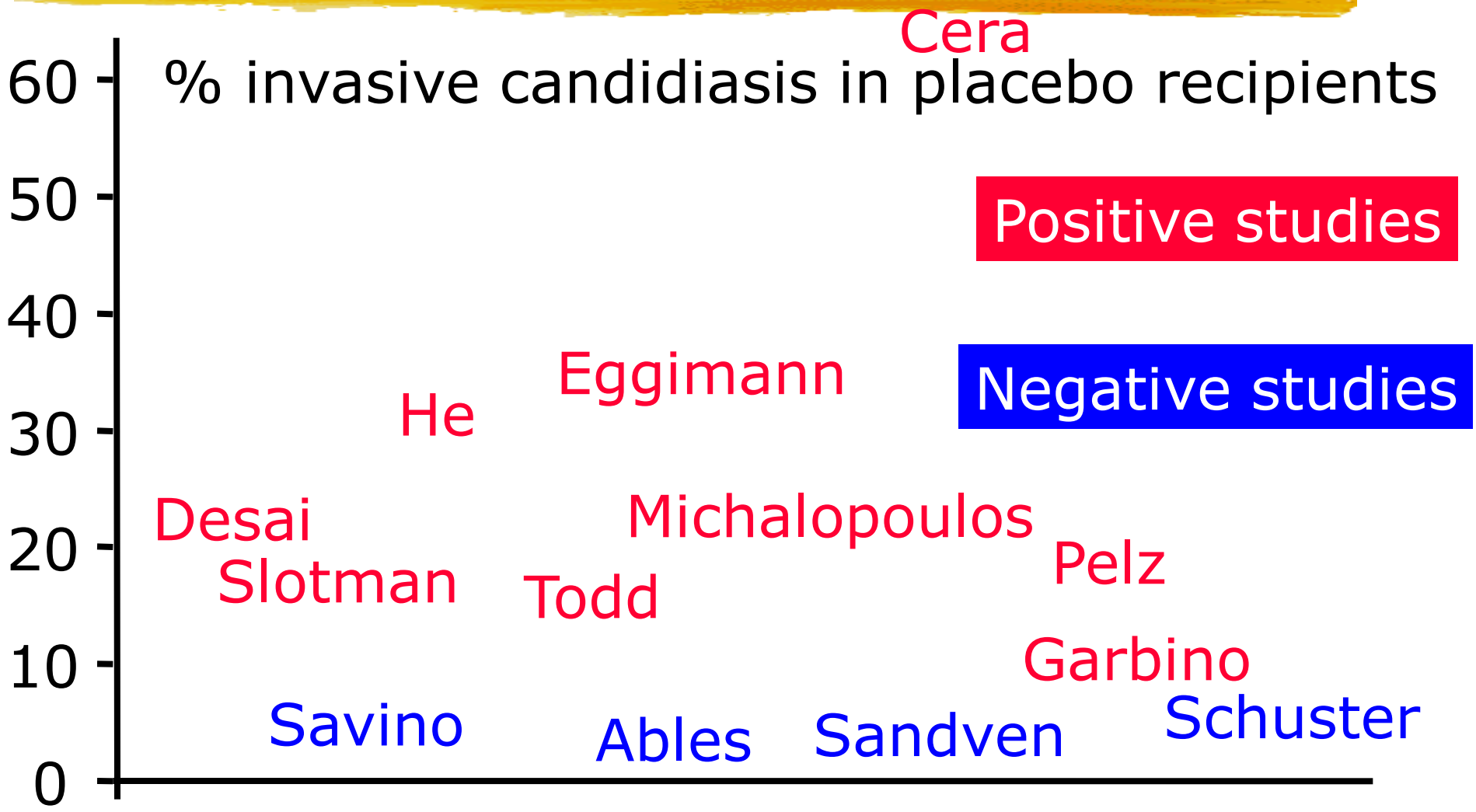


Table 3. Recommendations on Antifungal Prophylaxis in ICU Patients

Population	Intention	Intervention	SoR	QoE	Reference	Comment
Recent abdominal surgery AND recurrent gastrointestinal perforations or anastomotic leakages	To prevent intraabdominal *Candida* infection	Fluconazole 400mg/d	B	I	Eggimann CCM 1999	Placebo N=43
		Caspofungin 70/50mg/d	C	II_u	Senn ICM 2009	Single arm N=19
Critically ill surgical patients with an expected length of ICU stay ≥ 3d	To delay the time to fungal infection	Fluconazole 400mg/d	C	I	Pelz Ann Surg 2001	Placebo N=260
Ventilated for 48h and expected to be ventilated for another ≥72h	To prevent invasive candidiasis / candidaemia	Fluconazole 100mg/d	C	I	Garbino ICM 2002	Placebo N=204 SDD used
Ventilated, hospitalized for ≥3d, received antibiotics, CVC, and ≥1 of: parenteral nutrition, dialysis, major surgery, pancreatitis, systemic steroids, immunosuppression	To prevent invasive candidiasis / candidaemia	Ca		II_a	Ostrosky SHEA 2011	Placebo N=186 EORTC/MSG criteria used
Surgical ICU patients	To pre			I	Slotman Arch Surg 1987	Placebo N=57
Critically ill patients with risk factors for invasive candidiasis / candidaemia		ole mg/d	D	I	Havlicek Int Surg 2008	Open N=147
Surgical ICU with catabolism	emia	Nystatin 4 Mio IU/d	D	I	Cerra Arch Surg 1992	Placebo N=46

The table displays the published efore other available antifungal agents are not mentioned here.
SoR, Strength of recommendation; quality of evidence; ICU, intensive care unit; CVC, central venous catheter; IU, international units.

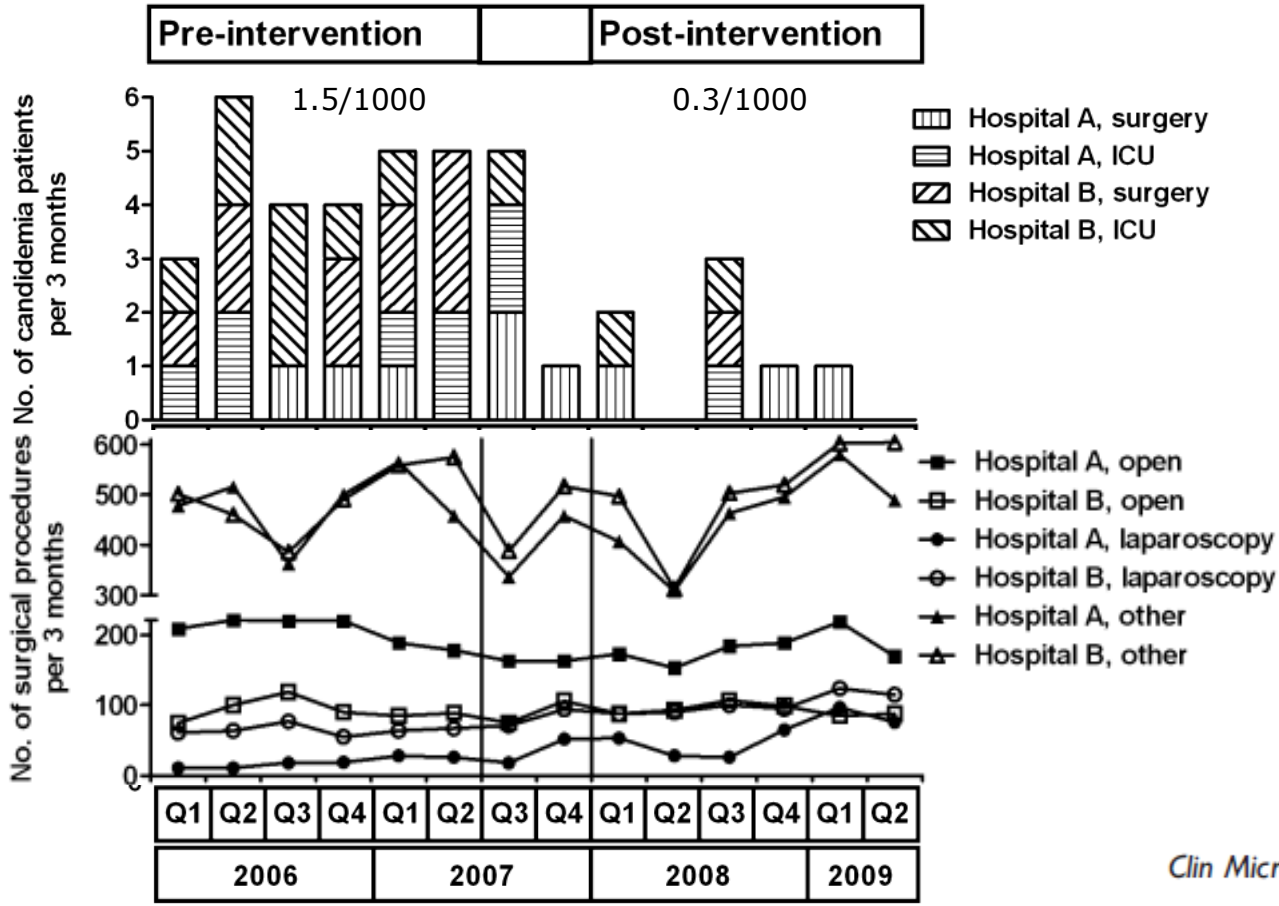
Should be restricted to selected groups of patients

Clin Microbiol Infect 2012; **18** (Suppl. 7): 19–37

Prophylaxis: very high risk surgical patients

Decreasing candidaemia rate in abdominal surgery patients after introduction of fluconazole prophylaxis*

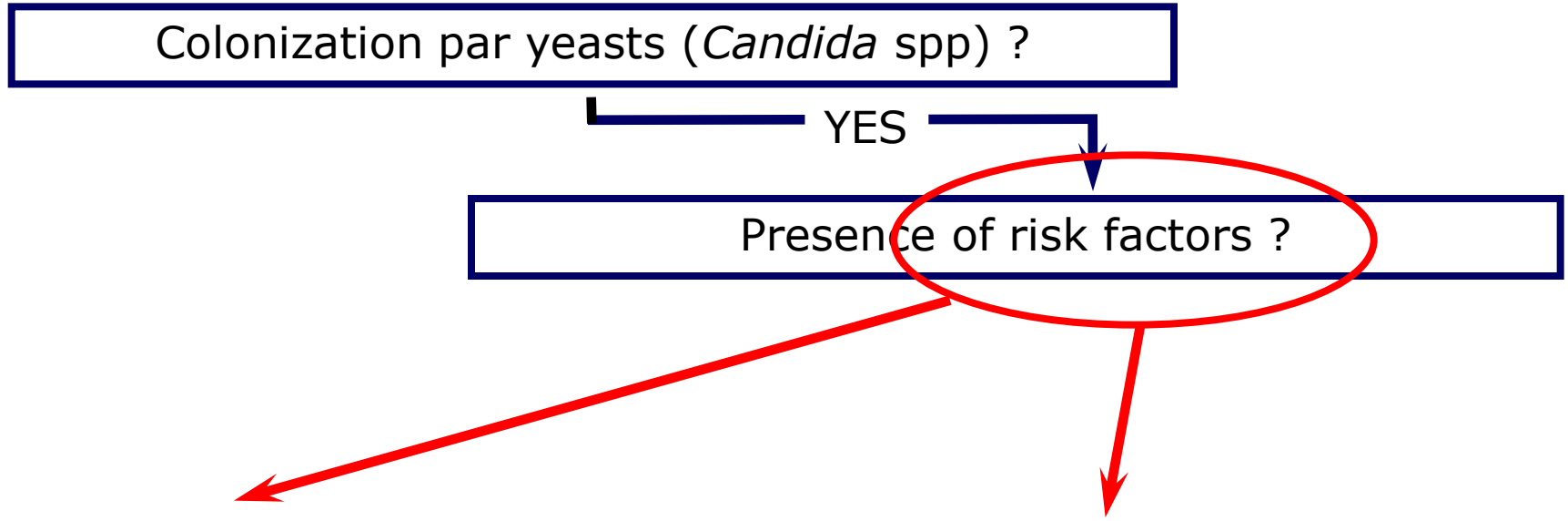
B. J. Holzknecht[1†], J. Thorup[2], M. C. Arendrup[3], S. E. Andersen[4], M. Steensen[5], P. Hesselfeldt[6], J. M. Nielsen[7] and J. D. Knudsen[1]



*perforation
*leakage

Clin Microbiol Infect 2011; **17**: 1372–1380

Should this patient received antifungals ?



broad spectrum antibiotics
immunosuppression
major abdominal surgery
anastomotic leakage
burns (>50%)
major trauma (ISS > 20)
candiduria (urologic surgery)
solid organ transplant
colonization > 2 sites

central venous access
diarrhea or absence of transit
parenteral nutrition
ICU stay > 7 days
prematurity
cancer/neutropenia
reinal failure/CVVH
candiduria $>10^5$

Eggimann & Pittet Lancet Infectious Diseases 2003

Should this patient received antifungals ?

Colonization par yeasts (*Candida* spp) ?

YES

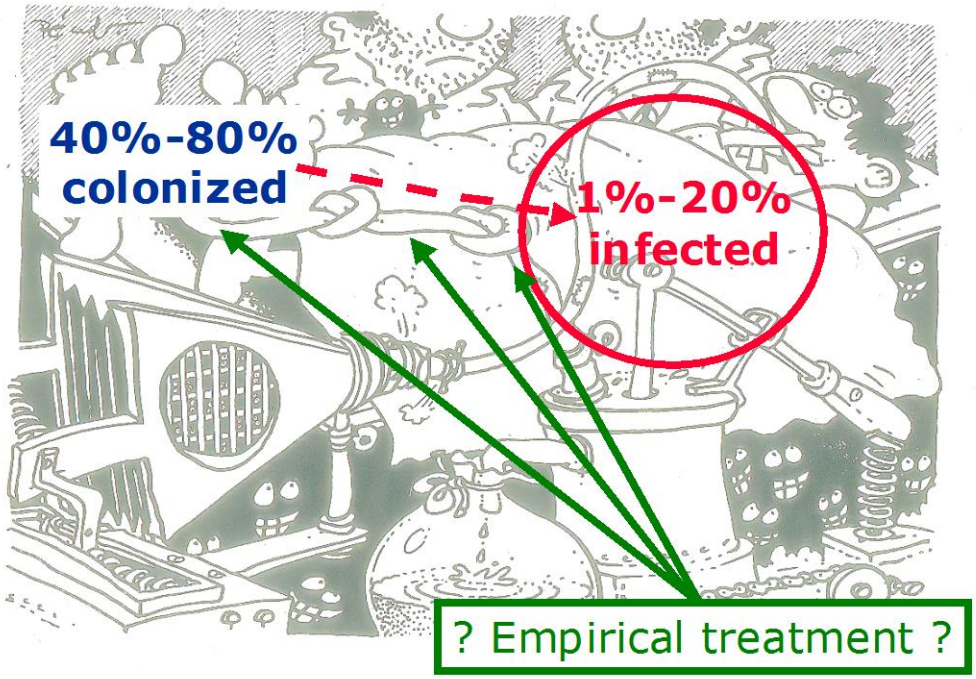
Presence of risk factors ?

YES

Patient unstable or septic

YES

Empirical treatment

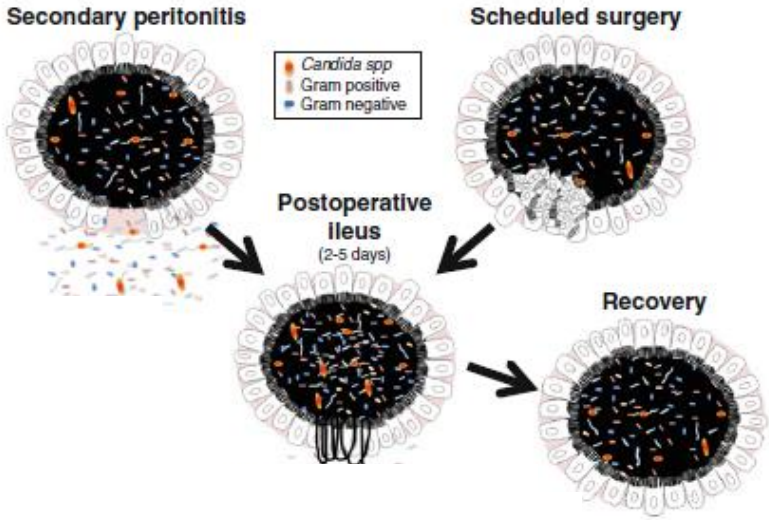


Eggimann & Pittet Lancet Infectious Diseases 2003

Empirical antifungal tx in critically ill patients ?

Guidelines	Preemptive treatment
BSAC CID 1994	yes
Edwards CID 1997	∅
Vincent ICM 1998	∅
Rex CID 2000	∅
Buchner EJCMID 2002	yes
Denning Lancet ID 2003	∅
Pappas CID 2004	∅
SFAR/SPILF/SRLF 2004	yes, but…
FUNGINOS 2006	yes, but…
IDSA CID 2009	yes, but…

Empirical antifungal tx in critically ill patients ?

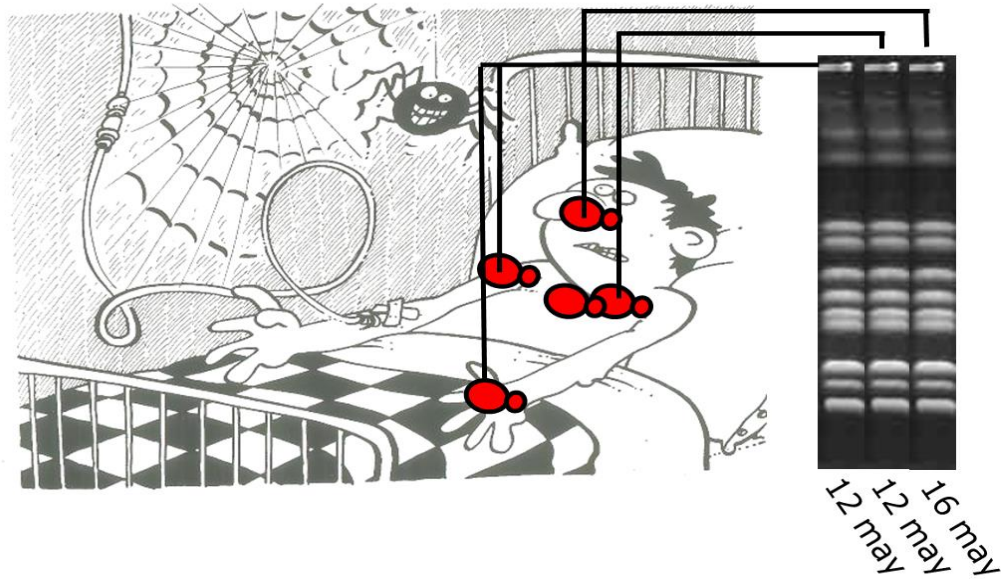


3 to 5 days

colonized patient

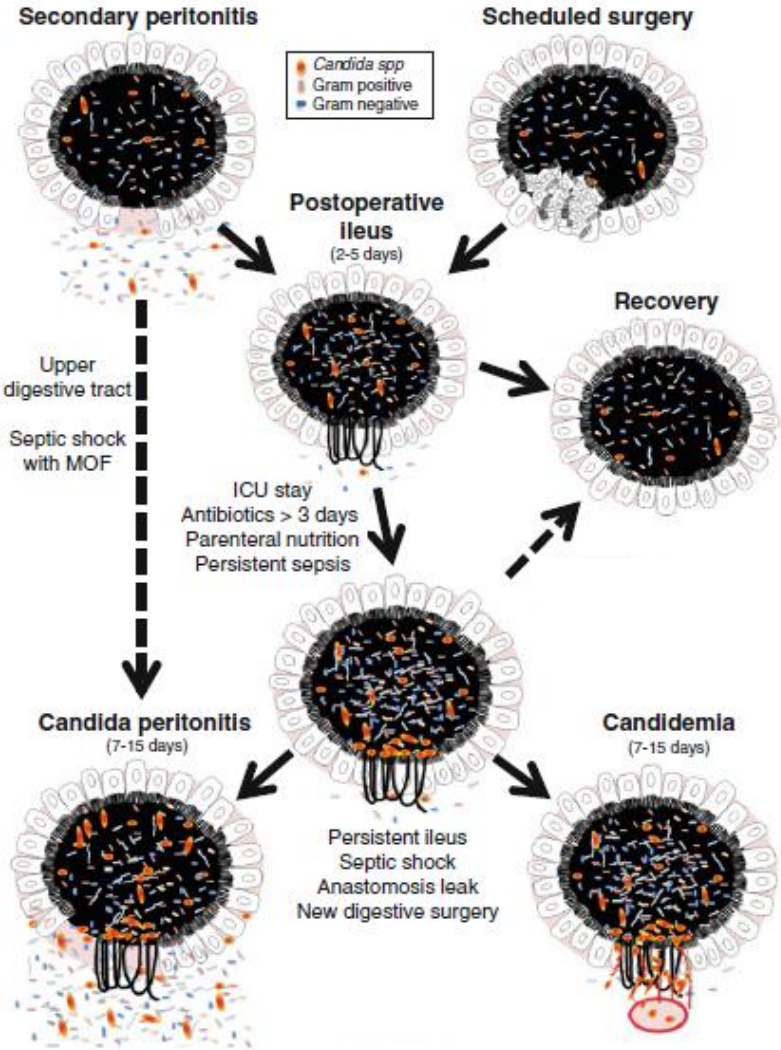
≠

infected patient



Montravers P, et al. Intensive Care Med. 2013;39:2226-30.

Empirical antifungal tx in critically ill patients ?



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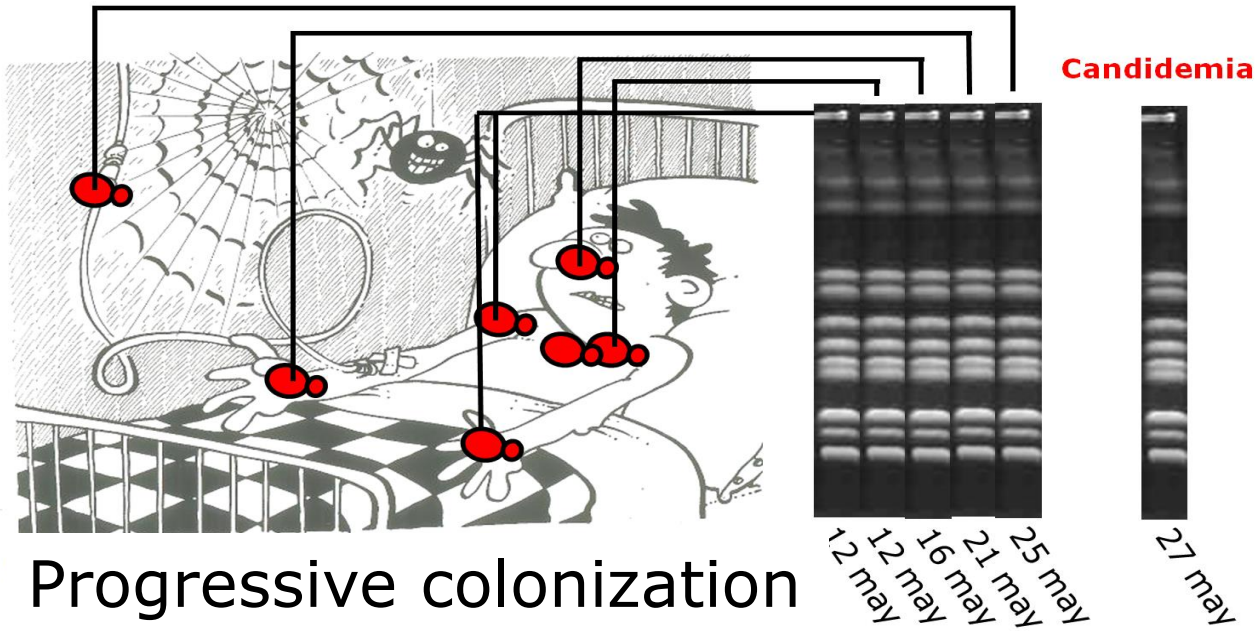
Invasive candidiasis:
it takes 7 to 14 days

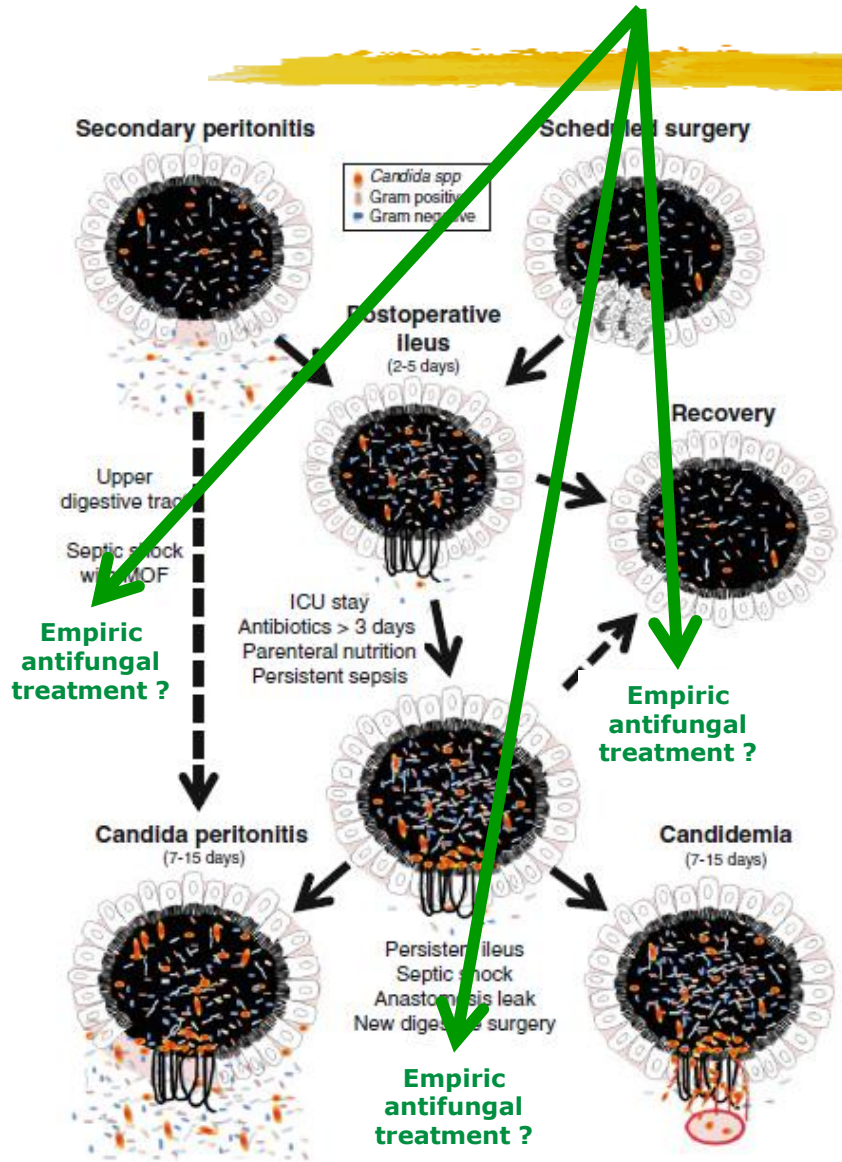
Continuous exposure to risk factors



Progressive colonization

Pittet D, et al. Am J Med. 1991;91:256S-263S.
Pittet D, et al. Ann Surg. 1994;220:751-8.
Nucci M, Anaissie E. Clin Infect Dis. 2001;33:1959-67.

Empirical antifungal tx in critically ill patients ?



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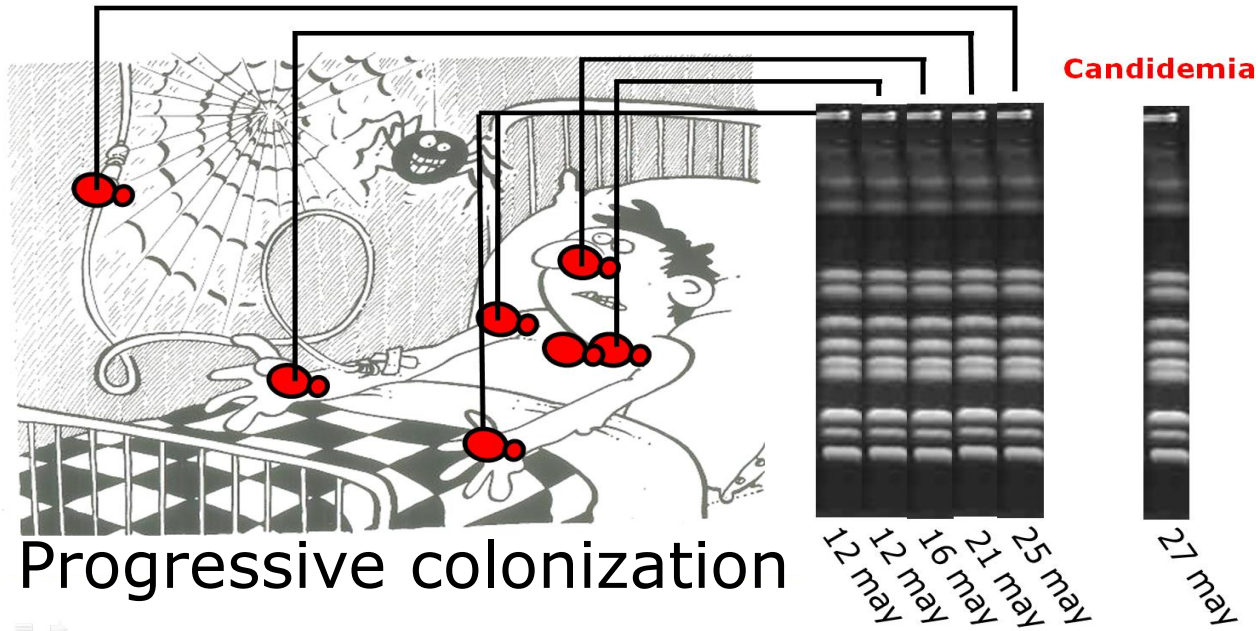

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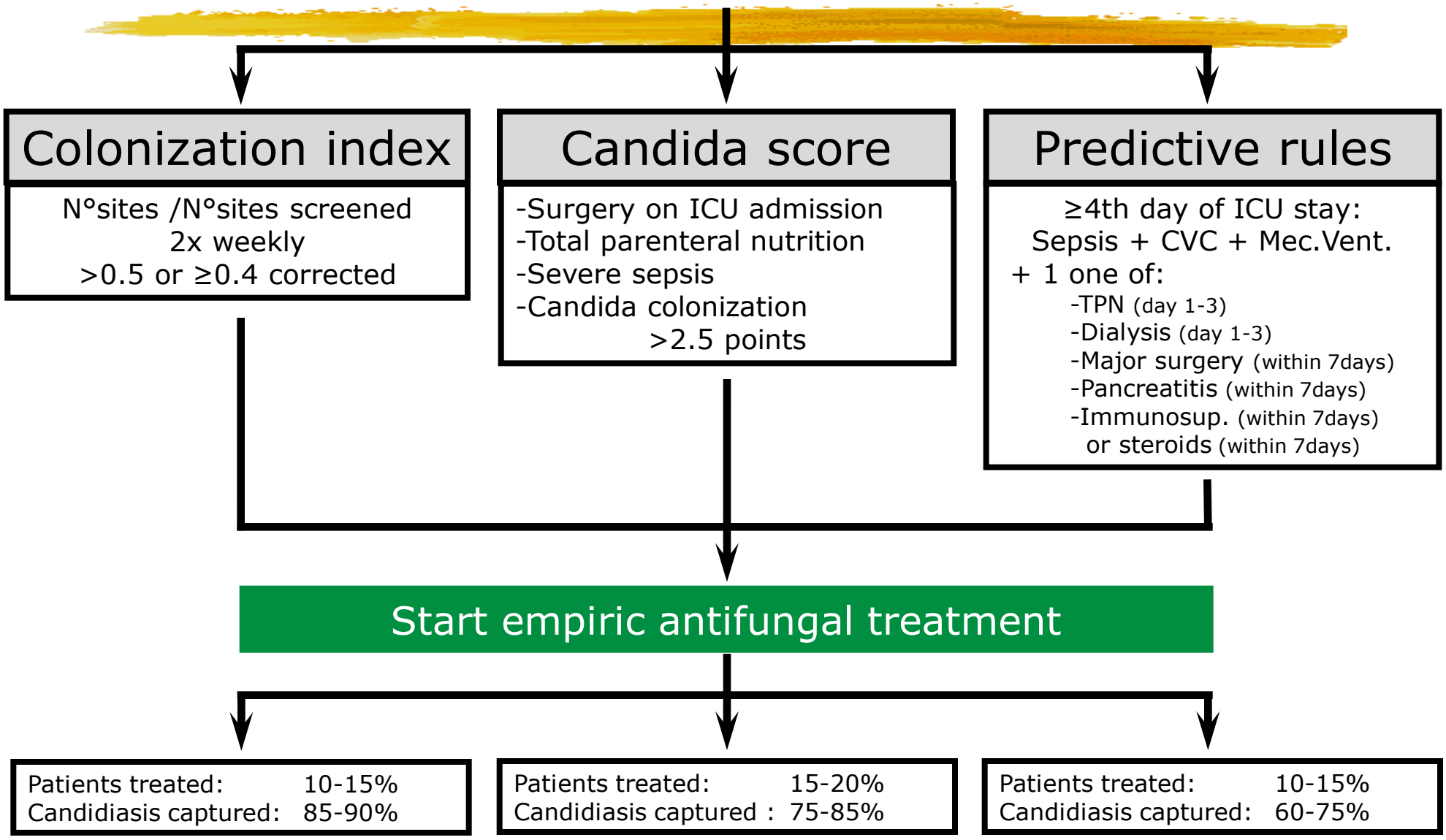
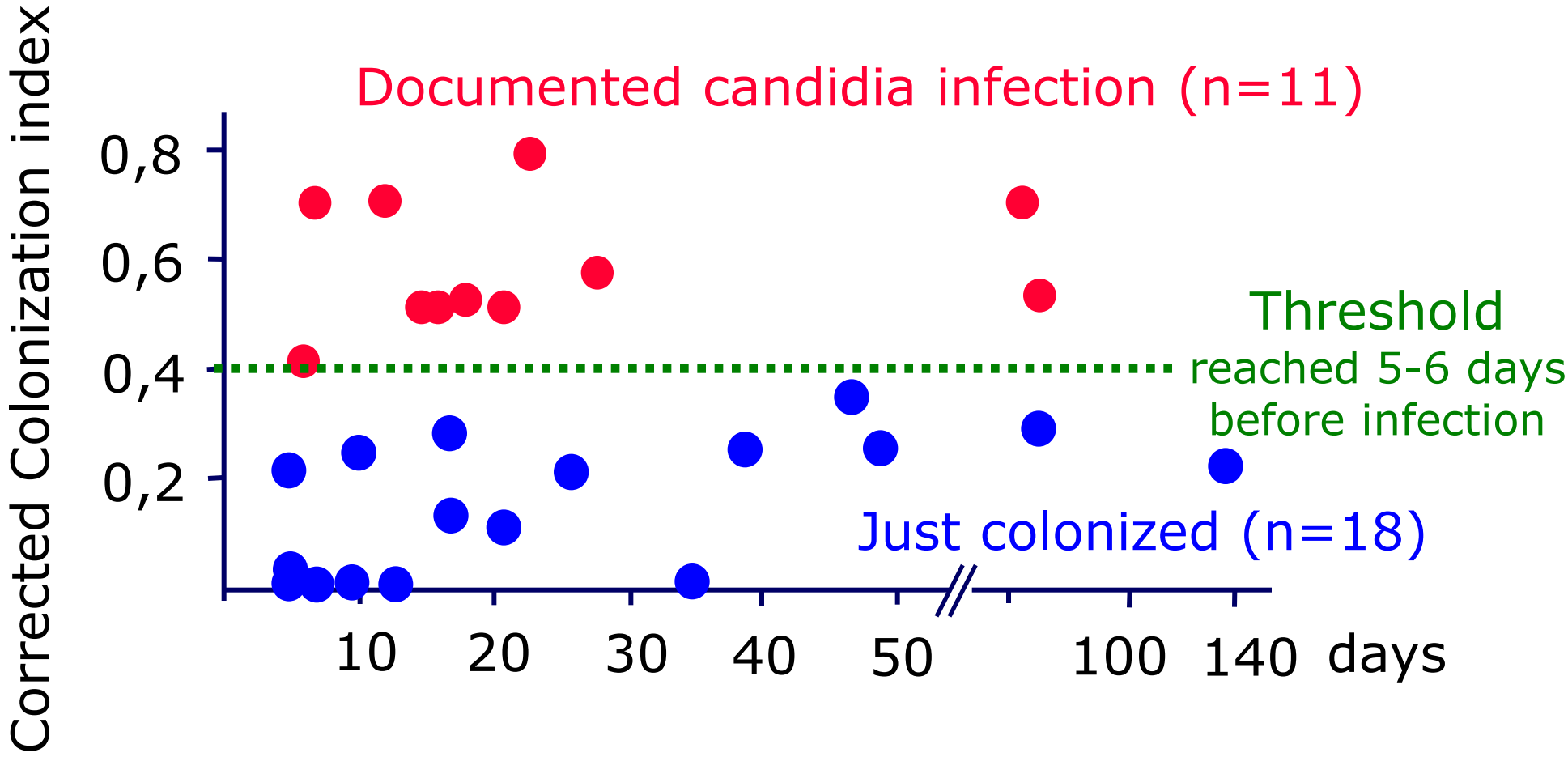


Eggimann P, et al. Ann Intensive Care. 2011;1:37.

Candida colonization index

650 surgical ICU patients followed over 6 months
29 colonized by *Candida spp* (≥3 sites nonvascular)



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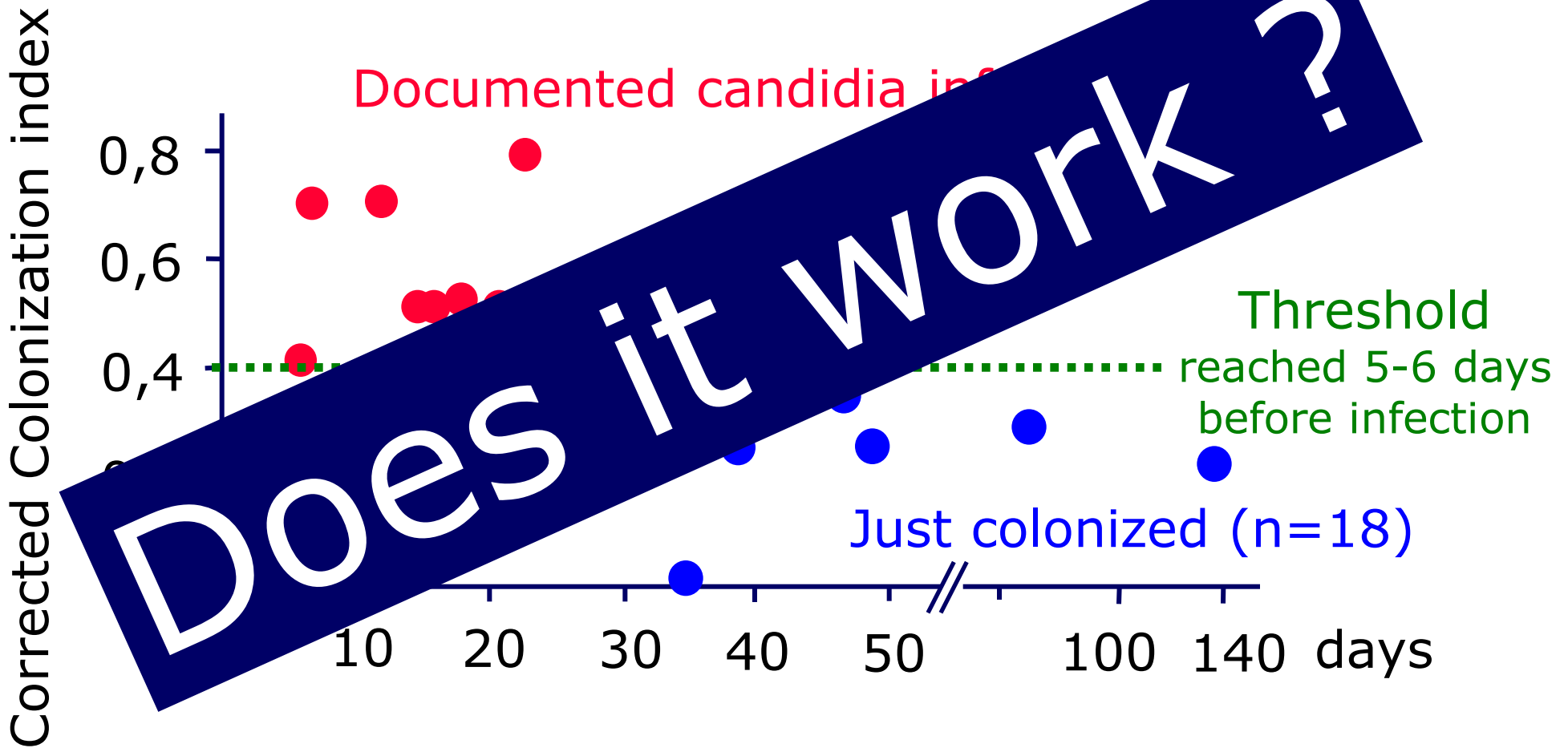
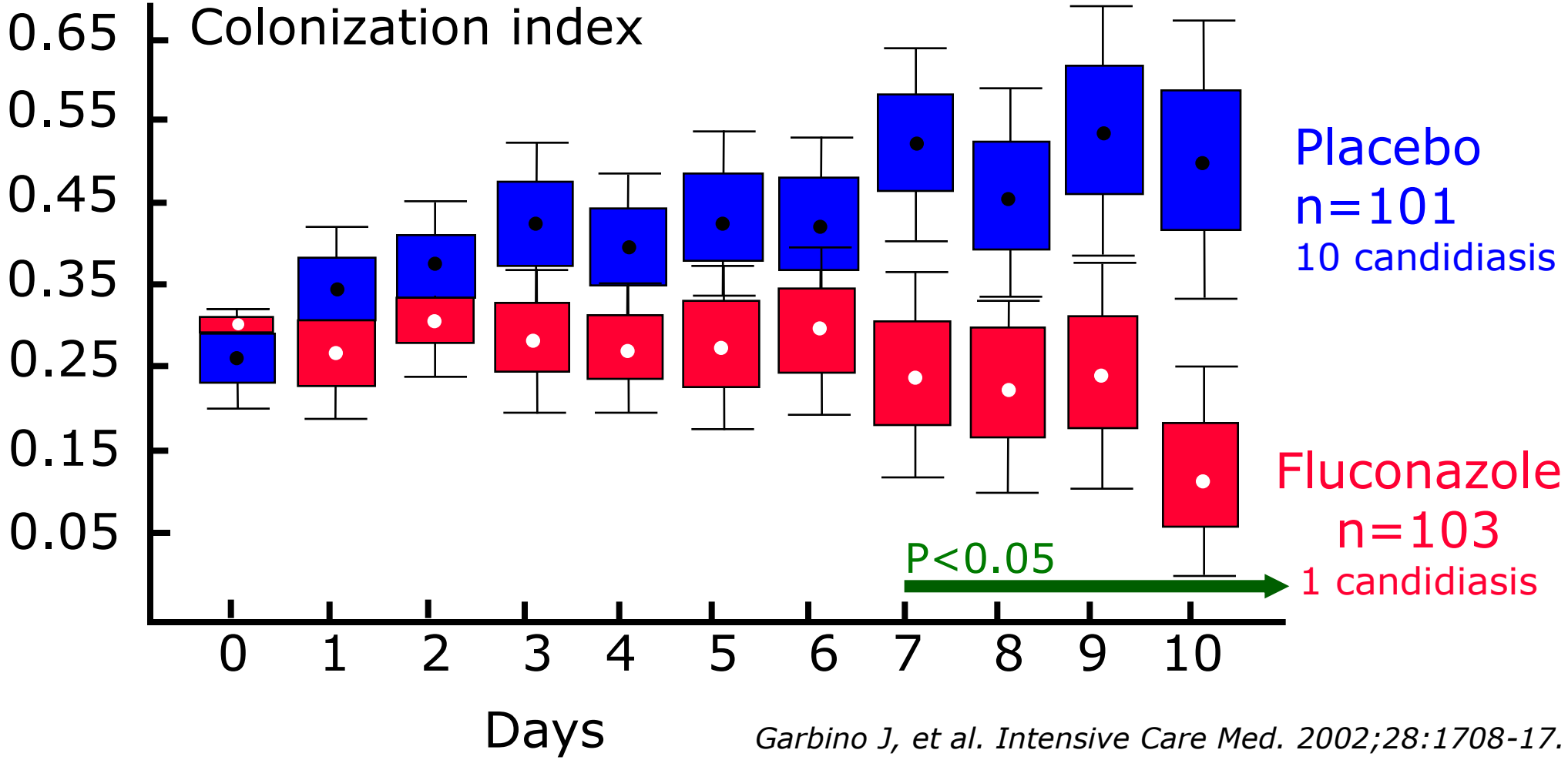


Does it work ?

Pittet D, et al. Ann Surg. 1994;220:751-8.

Candida colonization index

220 mixed ICU patients, ventilated for >4 days
randomized to fluconazole 100 mg/d or placebo



Garbino J, et al. Intensive Care Med. 2002;28:1708-17.

Candida colonization index

Candida colonization index and subsequent infection in critically ill surgical patients: 20 years later
--Manuscript Draft--

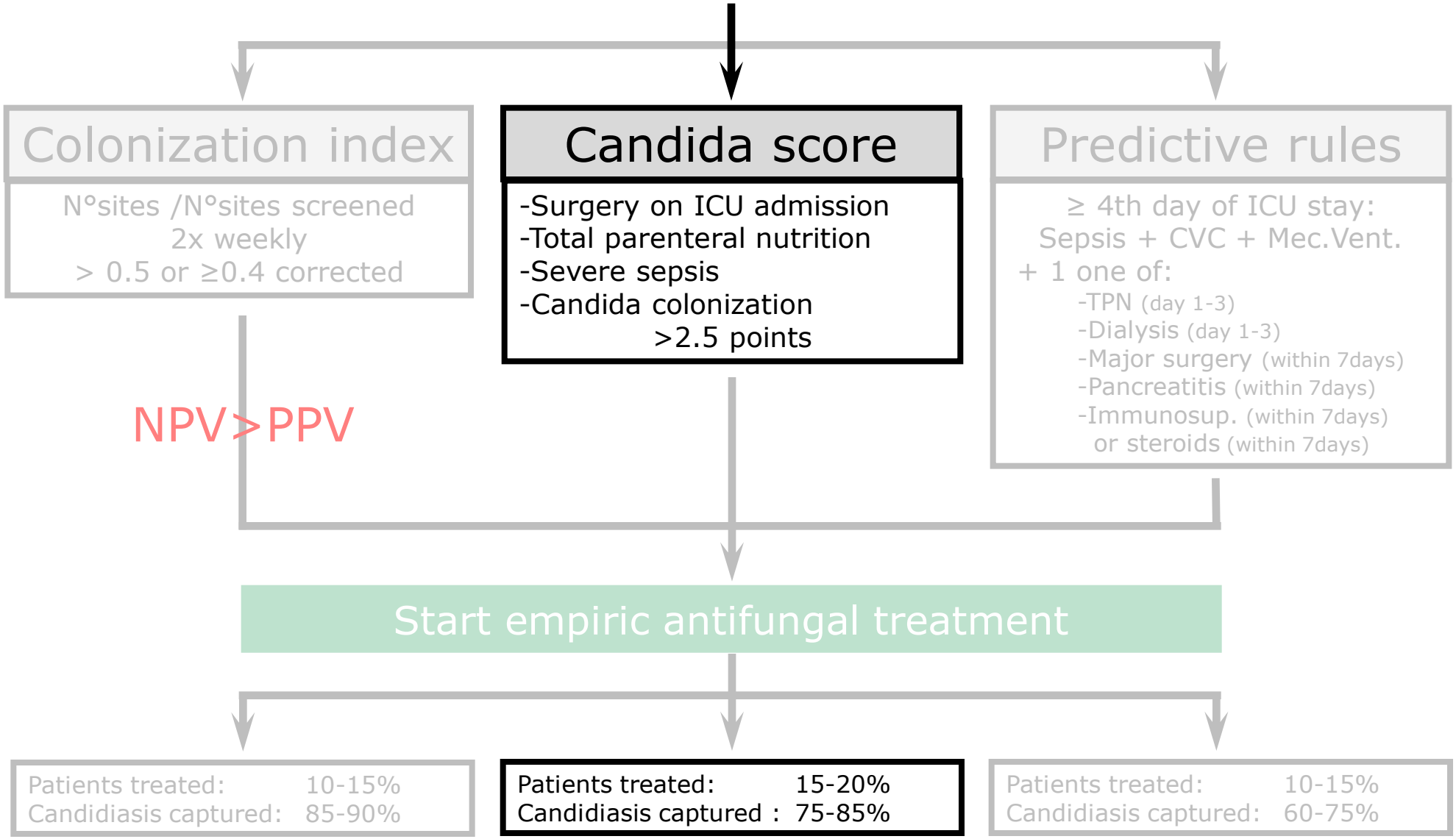
Assessment of		
- the risk of invasive candidiasis:	7 studies	
- the value of candiduria:	5 studies	1985 patients
- the efficacy of antifungal prophylaxis:	6 studies	
To guide empirical antifungal treatment:	3 studies	714 patients
To compare the accuracy of other tests:		
- Candida score	4 studies	1582 patients
- Mannans/antimannans	2 studies	
- CAGTA	1 study	
- Betaglucans	2 studies	

Negative predictive value >> positive predictive value

Despite its limited bedside practicality and before confirmation of potentially more accurate predictors, such as specific biomarkers, the CI remains an important way to characterize the dynamics of colonization, which increases early in patients who develop invasive candidiasis.

Eggimann P, Pittet D. Intensive Care Med. 2014;40:1429-48.

Empiric antifungal tx in critically ill patients ?



Eggimann P, et al. Ann Intensive Care. 2011;1:37.

Candida score

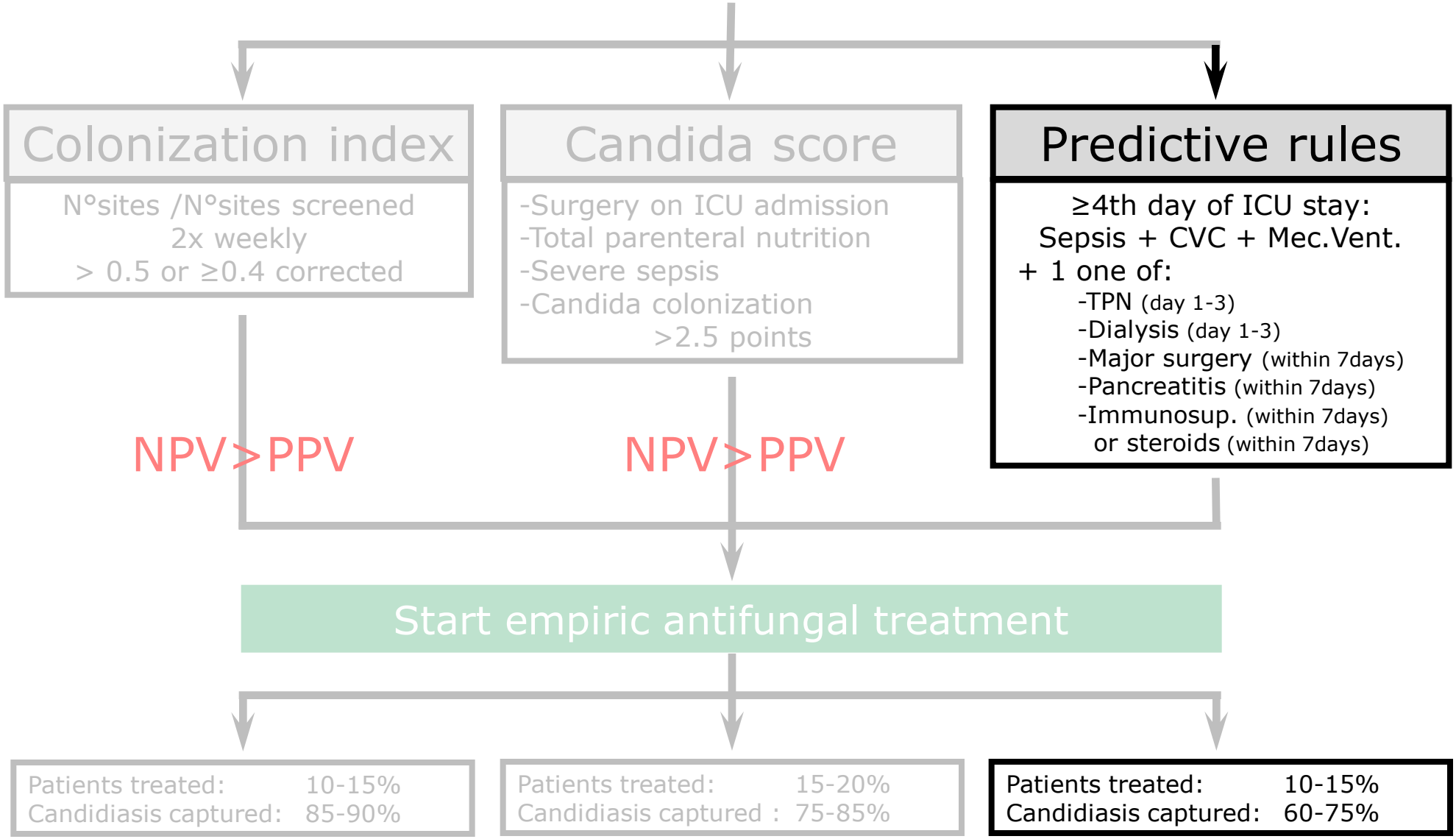
1007 ICU patients (36 units) staying >7 days
58 candidiasis (5.8%)

High negative predictive value

Score 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)

León C, et al. Crit Care Med. 2009;37:1624-33.

Empiric antifungal tx in critically ill patients ?



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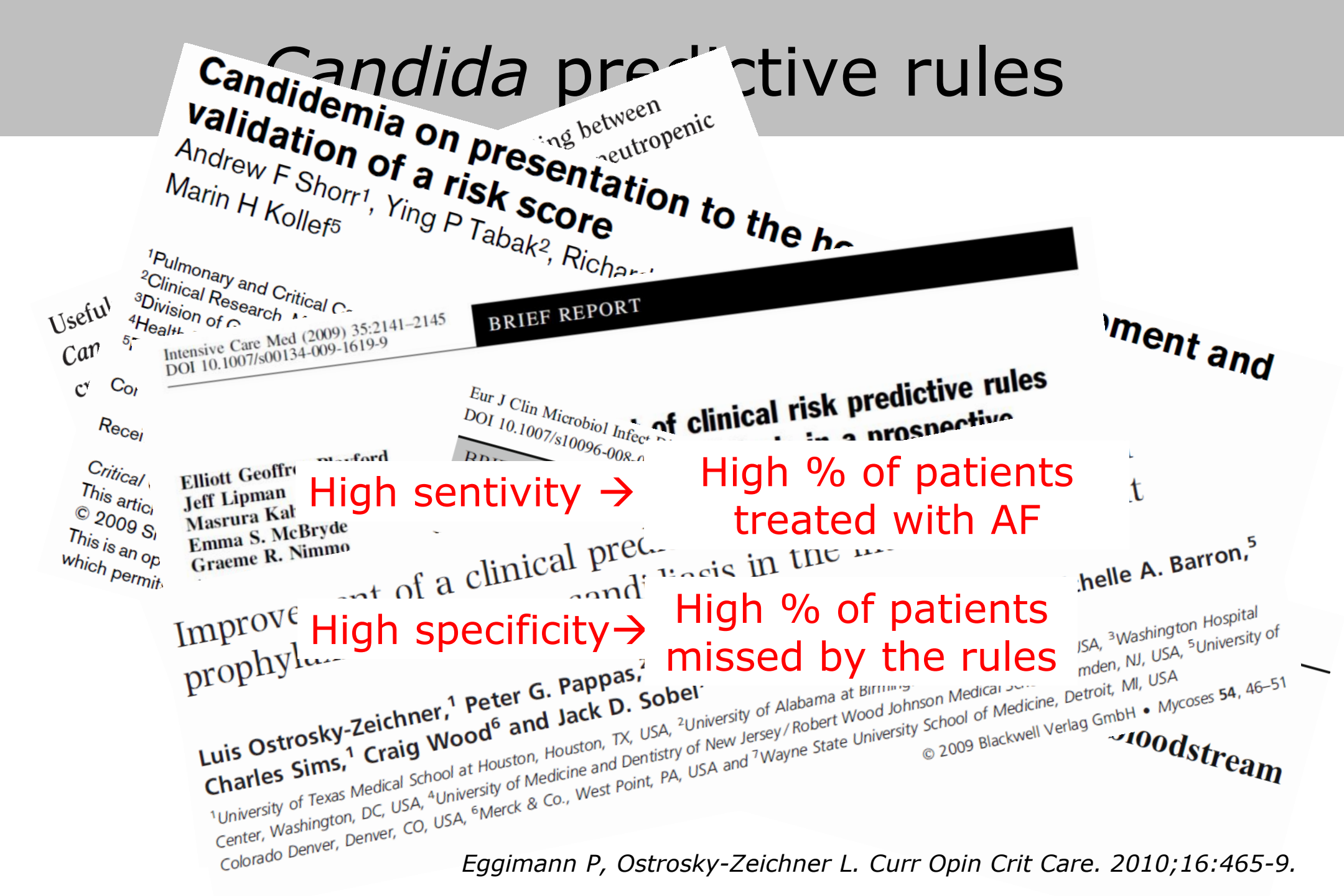
Candida predictive rules



High sentivity → High % of patients treated with AF

High specificity→ High % of patients missed by the rules

Eggimann P, Ostrosky-Zeichner L. Curr Opin Crit Care. 2010;16:465-9.

Candida predictive rules

40%-80% colonized

Impossible to implement at the bedside

MSG-04 (MK 0991 Protocol 067)
caspofungin in high-risk patients

INTENSE study
micafungin in surgical patients

? Prophylaxis ?

? Empirical treatment ?

Empiric antifungal tx in critically ill patients ?

Coloniz

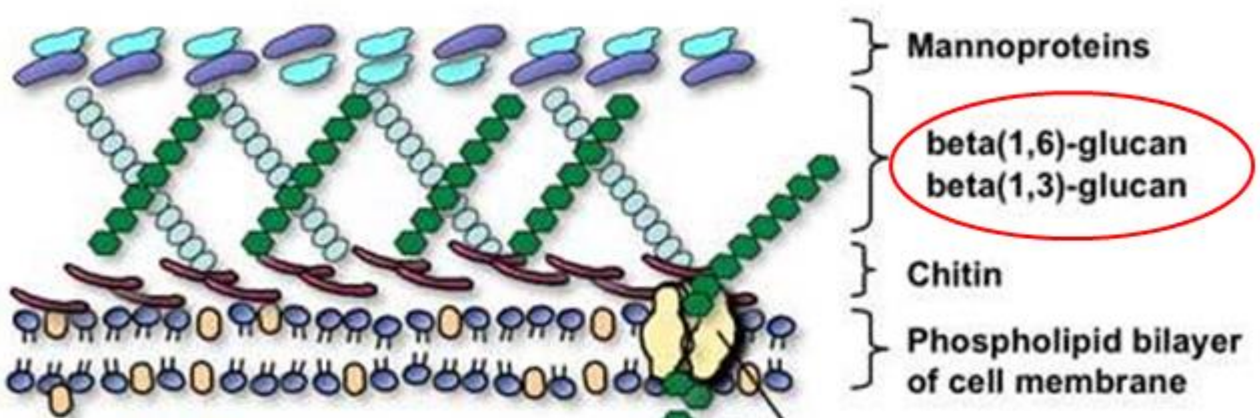
N°sites /
2
> 0.5 o

rules

stay:
ec.Vent.

thin 7days)
n 7days)
in 7days)
7days)

Biomarkers of candidiasis in critically ill patients



Patients treated:	10-15%
Candidiasis captured:	85-90%

Patients treated:	15-20%
Candidiasis captured :	75-85%

Patients treated:	10-15%
Candidiasis captured:	60-75%

Eggimann P, et al. Ann Intensive Care. 2011;1:37.

Biomarkers of candidiasis in critically ill patients

Posteraro *et al. Critical Care* 2011, **15**:R249
http://ccforum.com/content/15/5/R249

CRITICAL CARE

RESEARCH Open Access

Early diagnosis of candidemia in intensive care unit patients with sepsis: a prospective comparison of (1→3)-β-D-glucan assay, *Candida* score, and colonization index

Brunella Posteraro[1], Gennaro De Pascale[2], Mario Tumbarello[3*], Riccardo Torelli[1], Mariano Alberto Pennisi[2], Giuseppe Bello[2], Riccardo Maviglia[2], Giovanni Fadda[1], Maurizio Sanguinetti[1] and Massimo Antonelli[2]

Posteraro B, et al. Crit Care. 2011;15(5):R249.

β-Glucan Antigenemia Anticipates Diagnosis of Blood Culture–Negative Intraabdominal Candidiasis

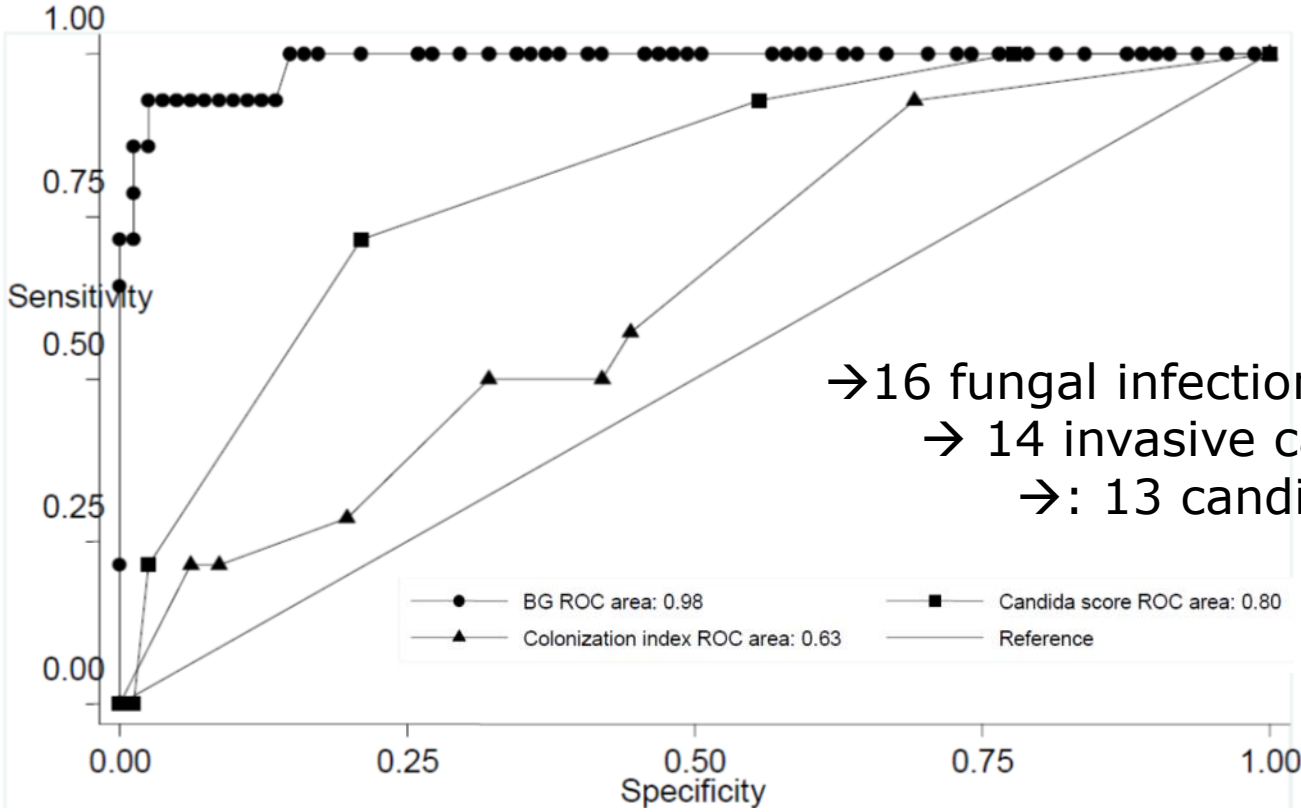
Frederic Tissot[1], Frederic Lamoth[1], Philippe M. Hauser[2], Christina Orasch[1,3], Ursula Flückiger[3], Martin Siegemund[4], Stefan Zimmerli[5], Thierry Calandra[1], Jacques Bille[2], Philippe Eggimann[6*], Oscar Marchetti[1*], and the Fungal Infection Network of Switzerland (FUNGINOS)

[1]Infectious Diseases Service, Department of Medicine, [2]Institute of Microbiology, and [6]Adult Intensive Care Service, Lausanne University Hospital, Lausanne, Switzerland; [3]Division of Infectious Diseases and Hospital Epidemiology and [4]Intensive Care Service, Basel University Hospital, Basel, Switzerland; and [5]Institute for Infectious Diseases, University of Bern, Bern, Switzerland

Tissot F, et al. Am J Respir Crit Care Med. 2013;188:1100-1109.

Biomarkers of candidiasis in critically ill patients

95 roman ICU patients developping sepsis >5th day of stay
(diag : medical 61; surgical: 12 trauma:22)

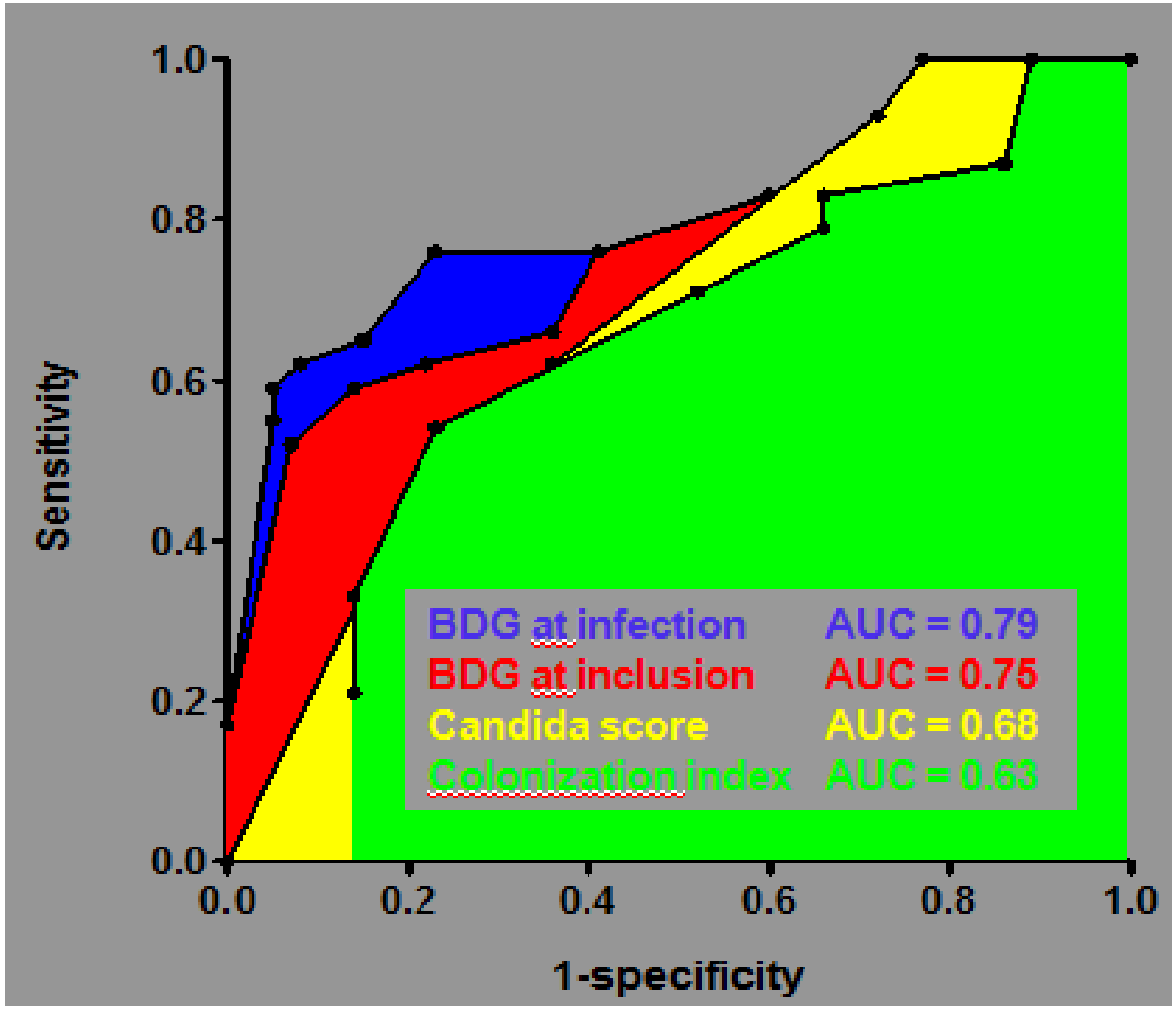


→16 fungal infections
→ 14 invasive candidiasis
→: 13 candidemia

Posteraro B, et al. Crit Care. 2011;15(5):R249.

Biomarkers of candidiasis in critically ill patients

89 swiss ICU patients at very high risk of candidiasis
(recurrent GI tract perforation / necrotizing pancreatitis)



29 invasive candidiasis

Tissot F, et al.
Am J Respir Crit Care Med.
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Fungal Infection Network of Switzerland

Biomarkers of candidiasis in critically ill patients

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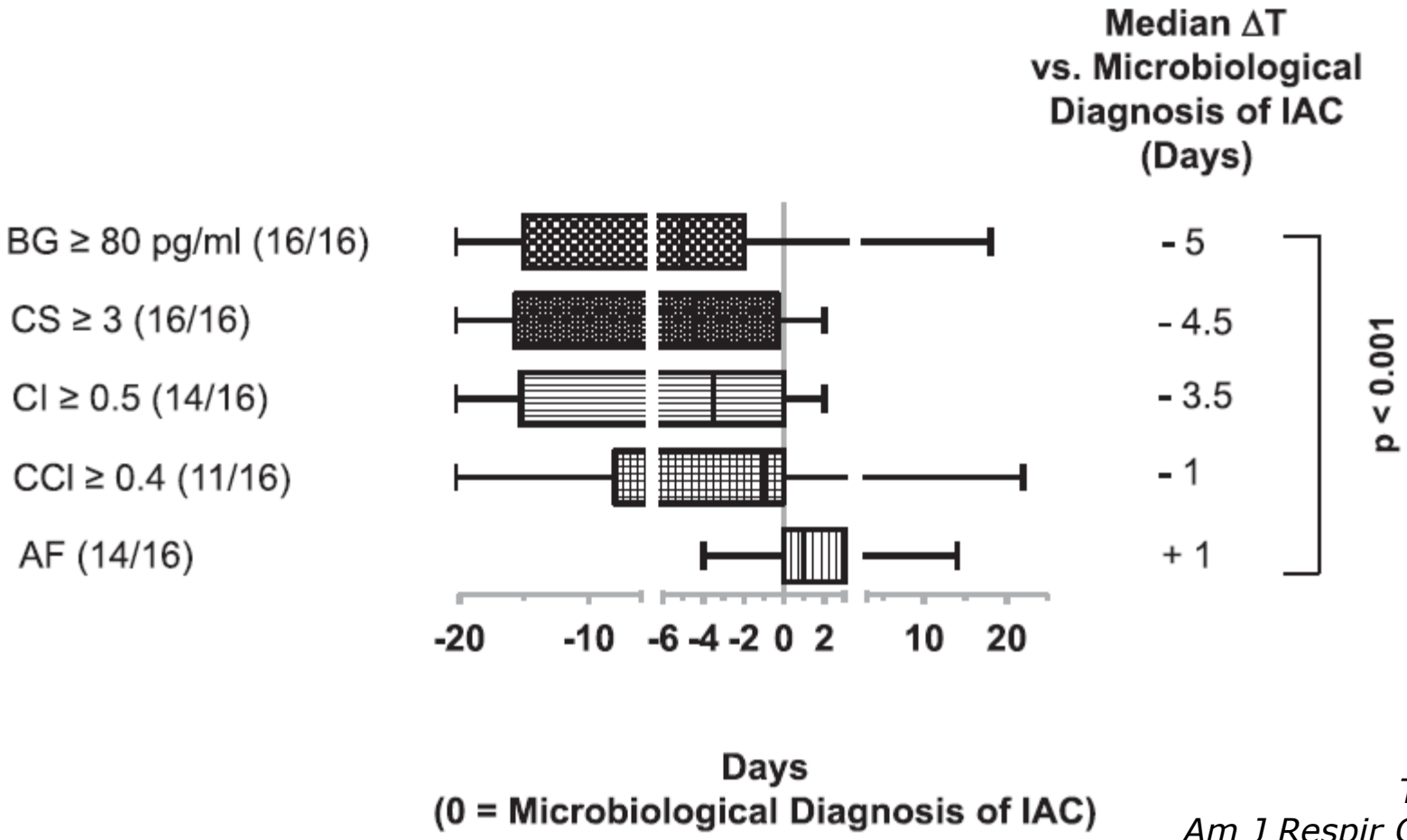

Tissot F, et al.
Am J Respir Crit Care Med.
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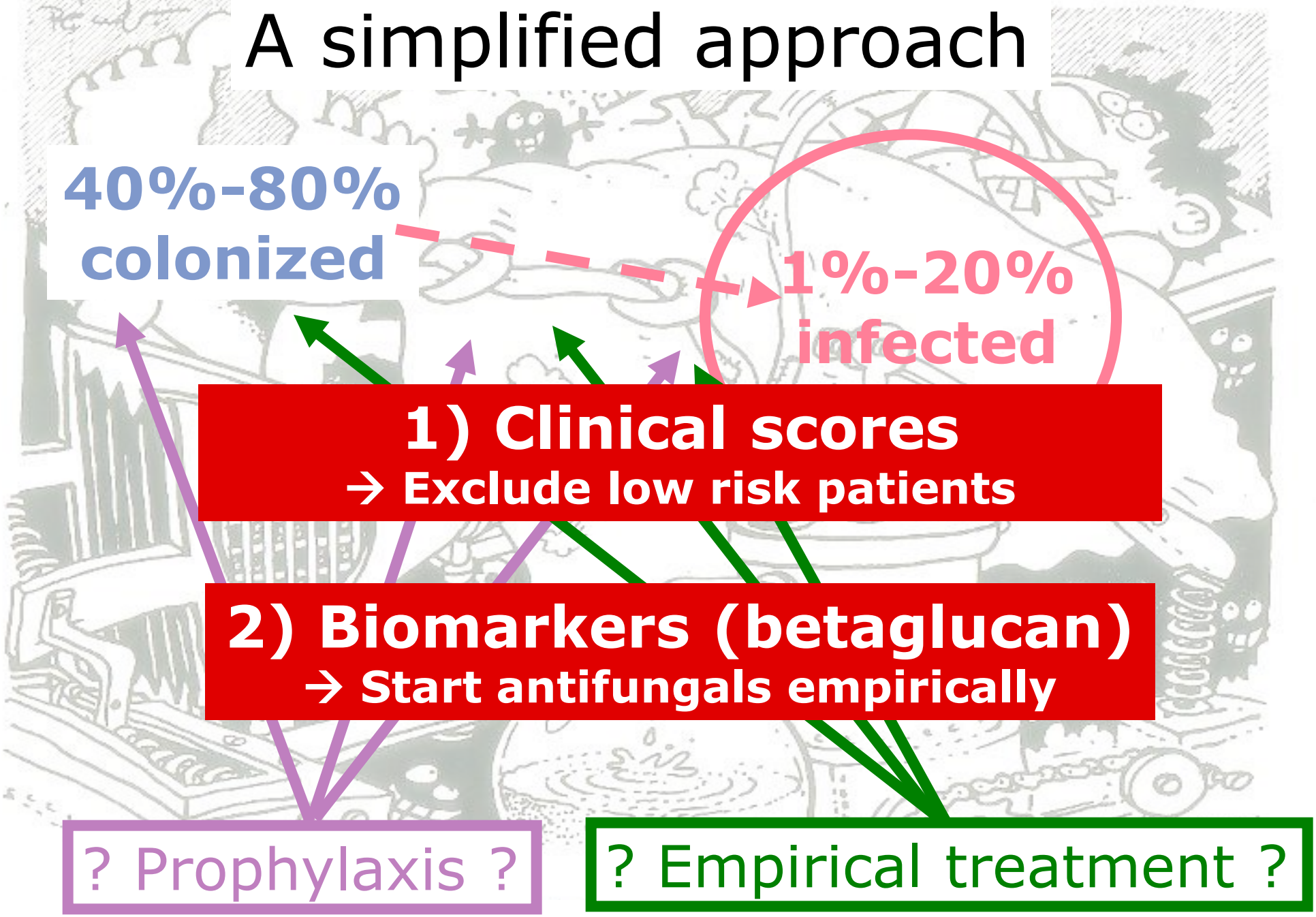
The near future

A simplified approach



Eggimann P, Pittet D. Intensive Care Med. 2014;40:1429-48.

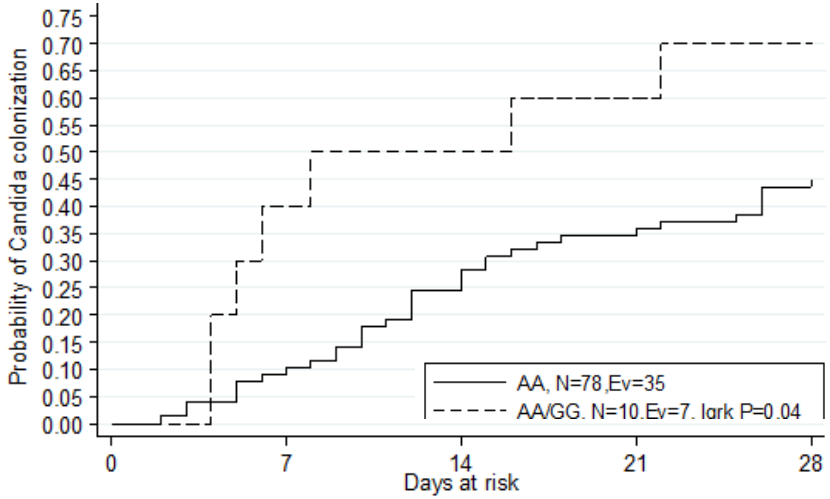
The future

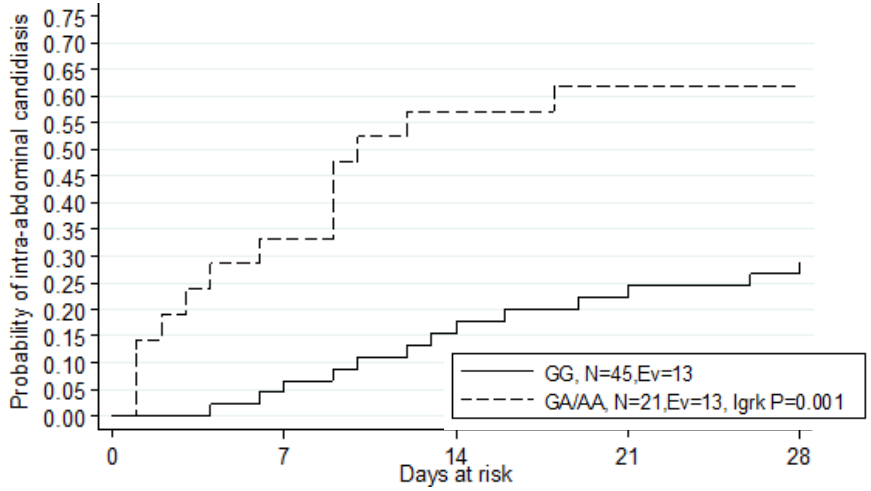
Genetic markers in patients with candidiasis

89 surgical ICU patients (recurrent GI tract perforation /severe pancreatitis)
→ 29 developed invasive candidiasis (2 candidemia)

Gene (nt|aa change) rs number	Multivariate analysis HR (95%CI)	Cox P [a]
	***Candida* colonization [b] (N=88)**	
TLR4 *rs4986790*, AA/AG vs. GG	3.39 (1.45-7.93)	0.006
SP-A2 *rs17886395*, CC/GC vs. GG	1.87 (0.93-3.74)	0.08
Male sex	1.27 (0.67-2.43)	0.5
Age (years)	0.99 (0.97-1.01)	0.4

Gene (nt|aa change) rs number	Multivariate analysis HR (95%CI)	Cox P [a]
	Intra-abdominal candidiasis * [c] (N=69)	
TNF-α *rs1800629*, GA/AA vs. GG	4.31 (1.85-10.1)	0.0007
DEFB1 *rs1800972*, GG/CG vs. CC	3.21 (1.36-7.59)	0.008
SAPS II score [d]	2.41 (1.01-5.75)	0.05
Male sex	2.27 (0.97-5.30)	0.06

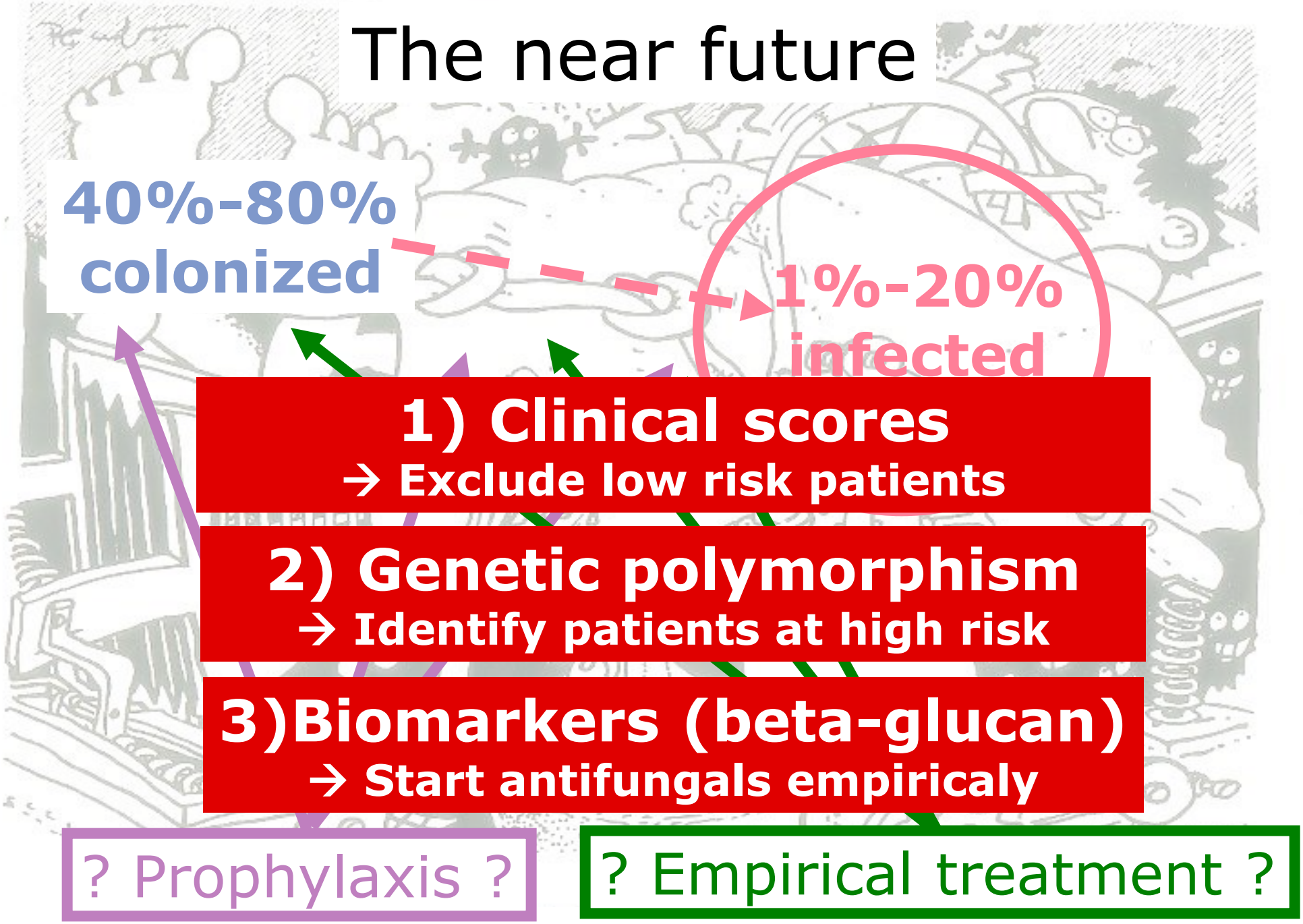




Funginos

Wójtowicz A, et al. Crit Care Med. 2014;42:e304-8.

The near future



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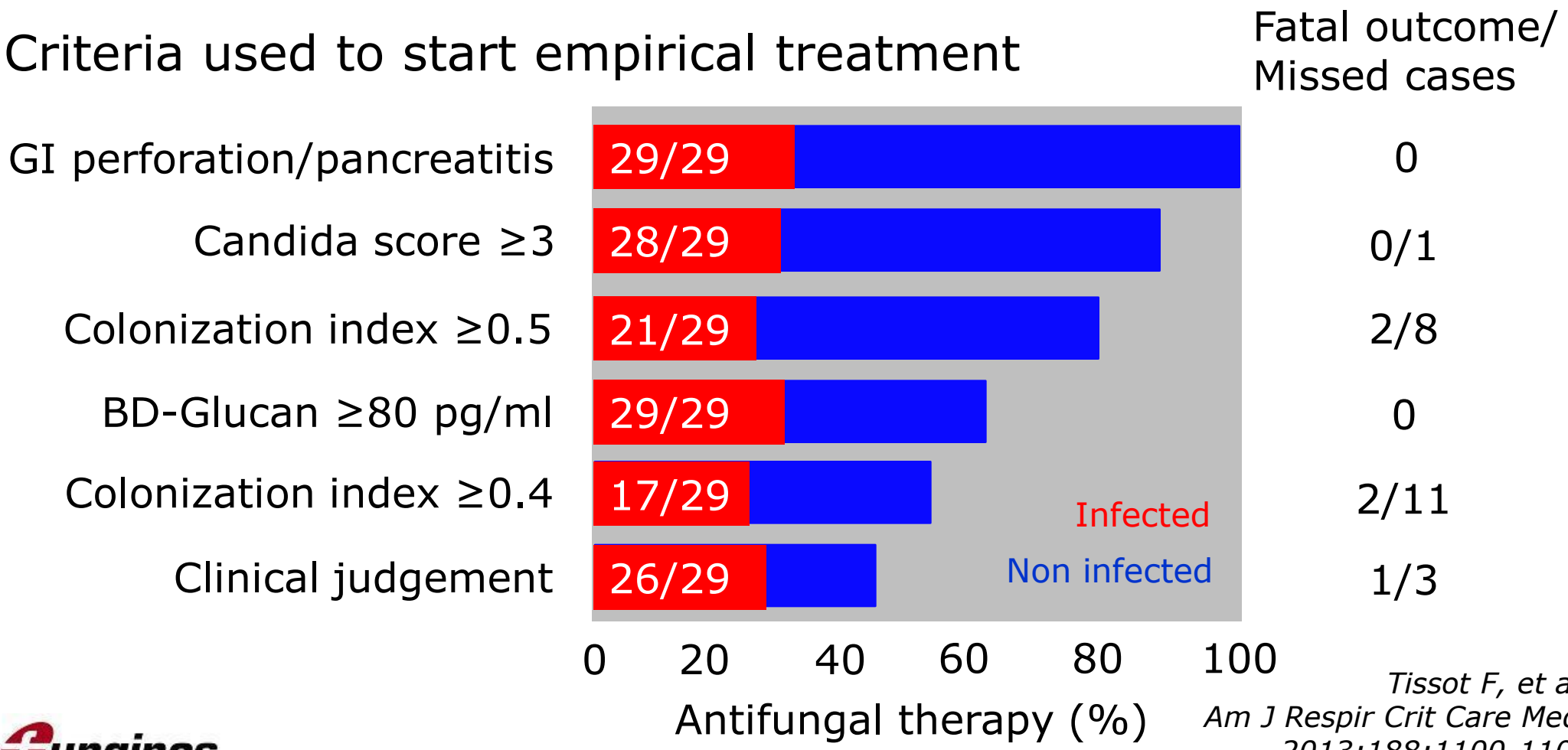
Empirical antifungal tx in critically ill patients ?

My proposal for the current bedside approach

Empirical antifungal tx in critically ill patients ?

89 ICU patients at very high risk of candidiasis
(recurrent GI tract perforation / necrotizing pancreatitis)



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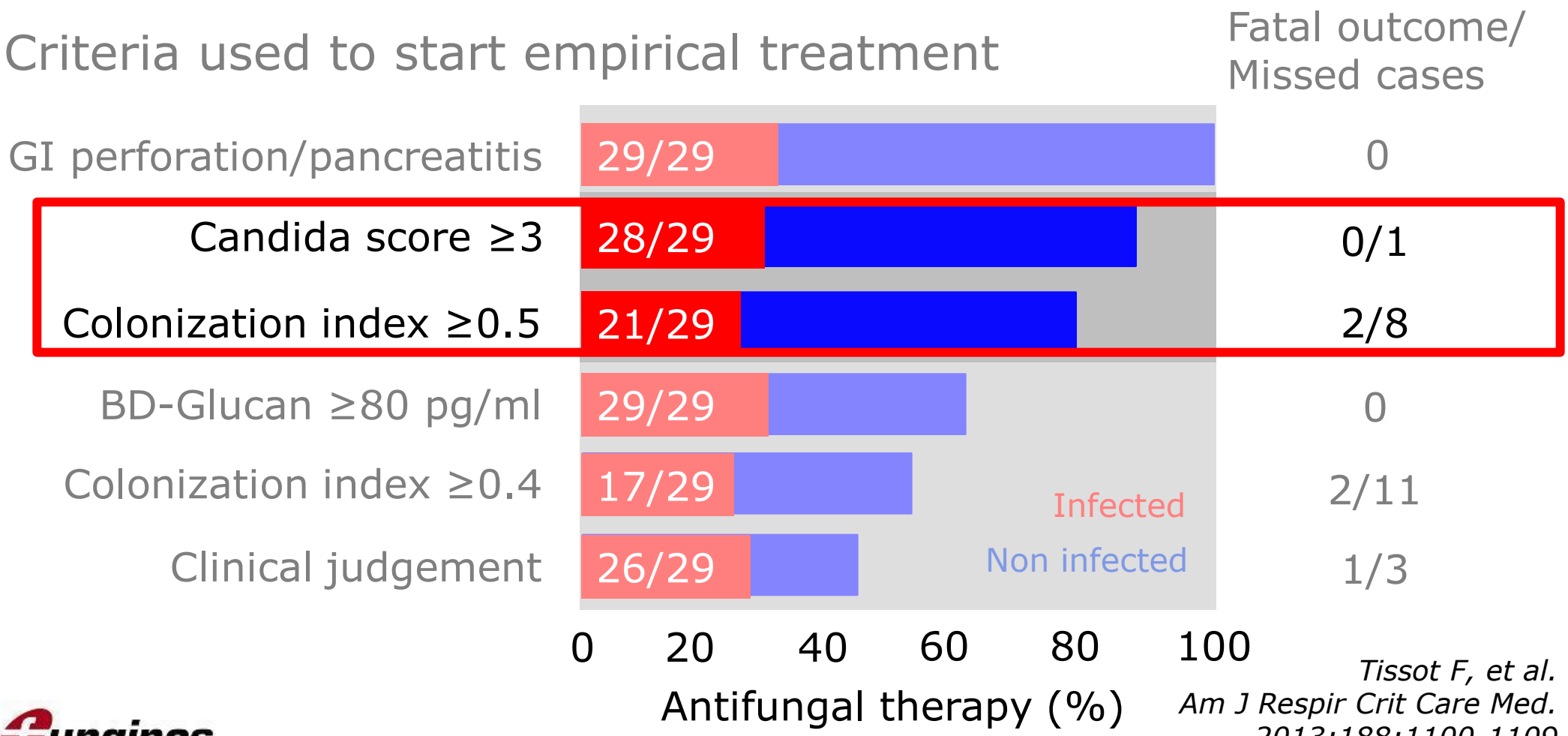

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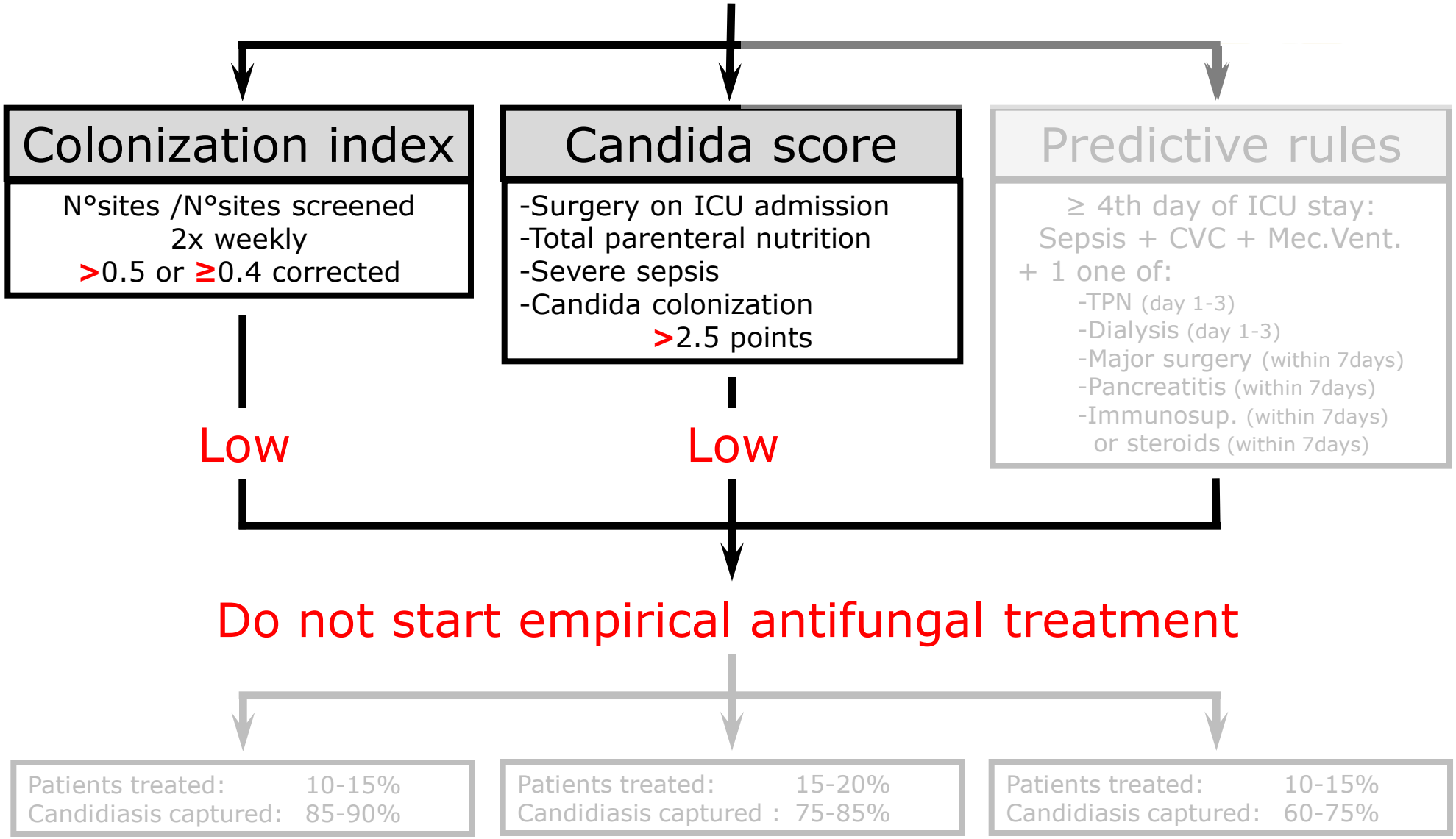
Empiric antifungal tx in critically ill patients ?



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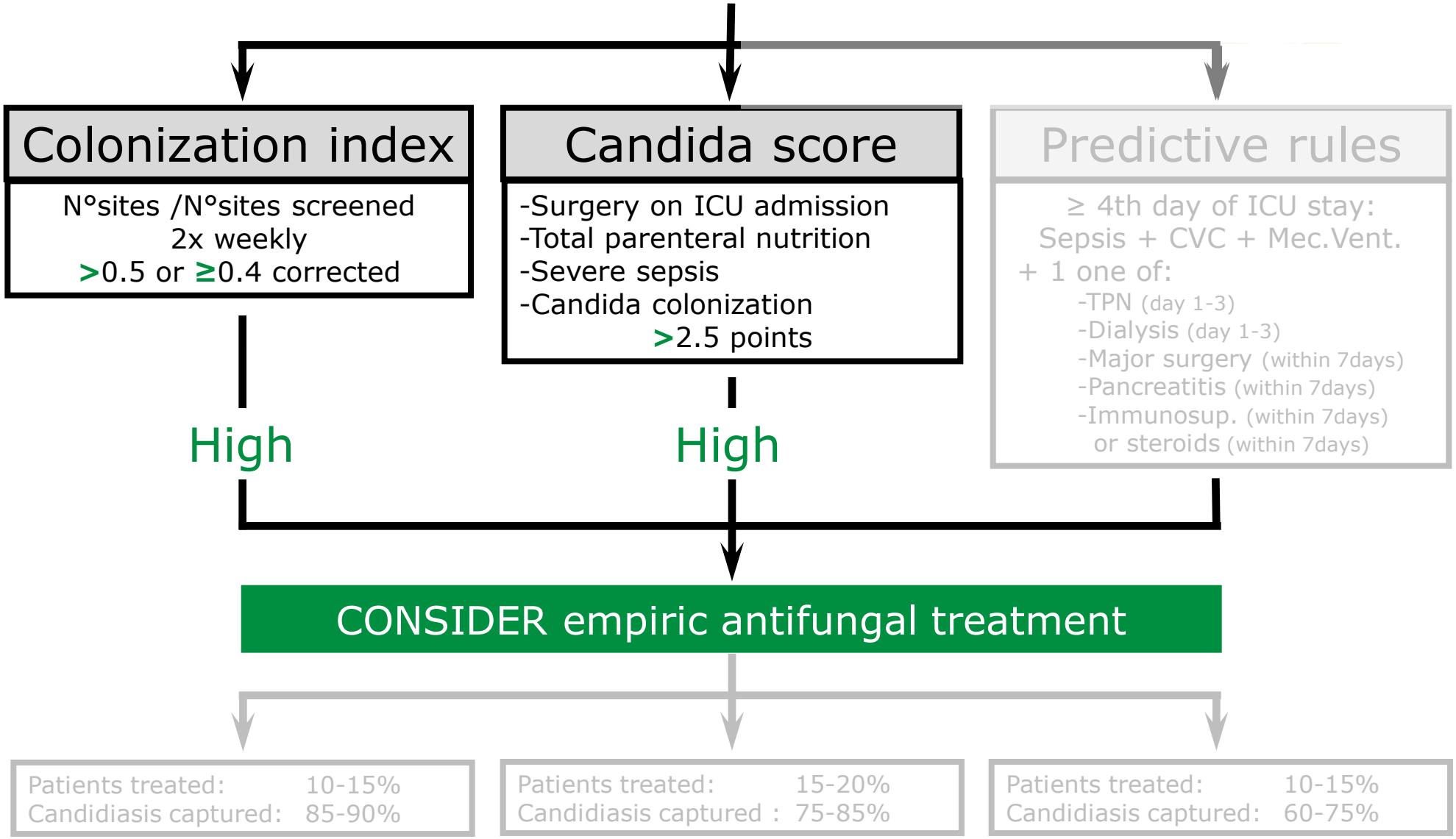

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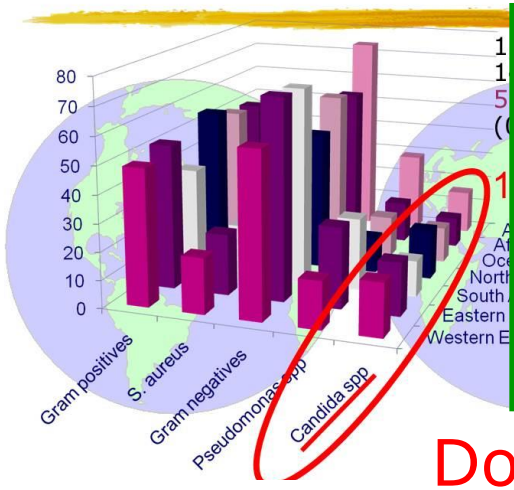
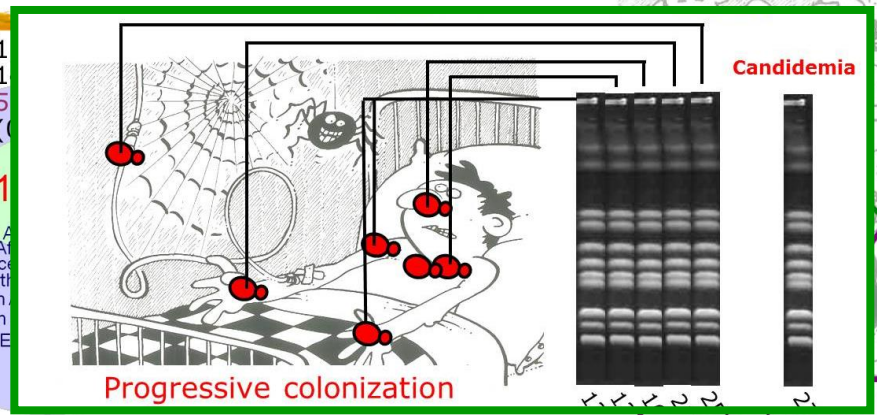
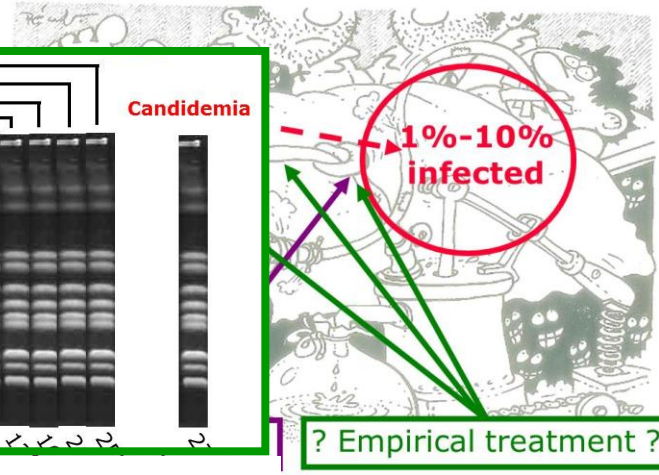
To summarize

Invasive candidiasis in ICU patients

Etiology of infections in the ICU

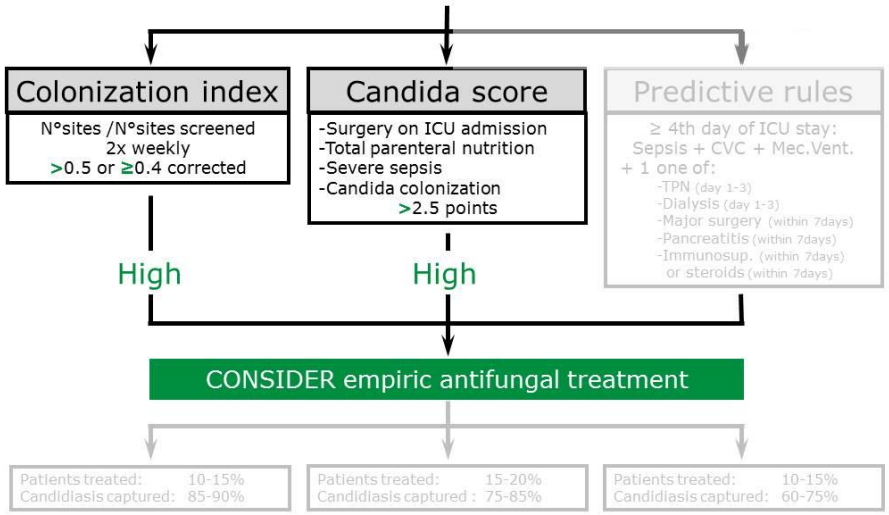






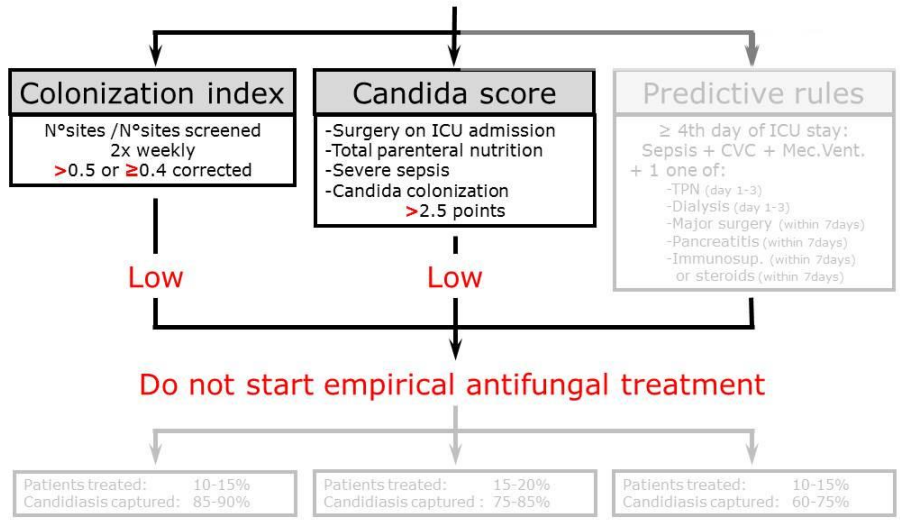
Do not wait until candidemia

Empiric antifungal tx in critically ill patients ?



Eggimann P, et al. Ann Intensive Care. 2011;1:37.

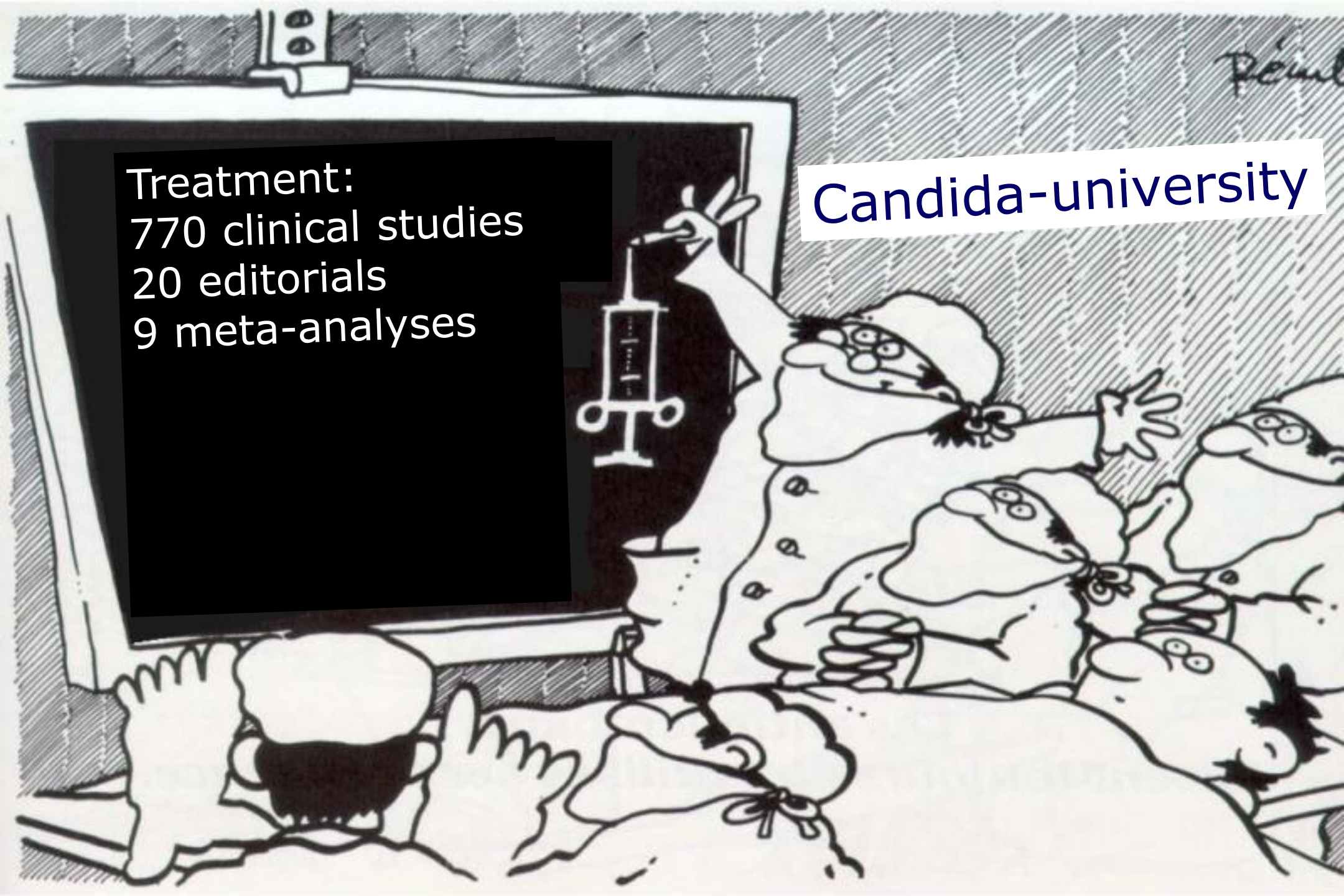
Empiric antifungal tx in critically ill patients ?

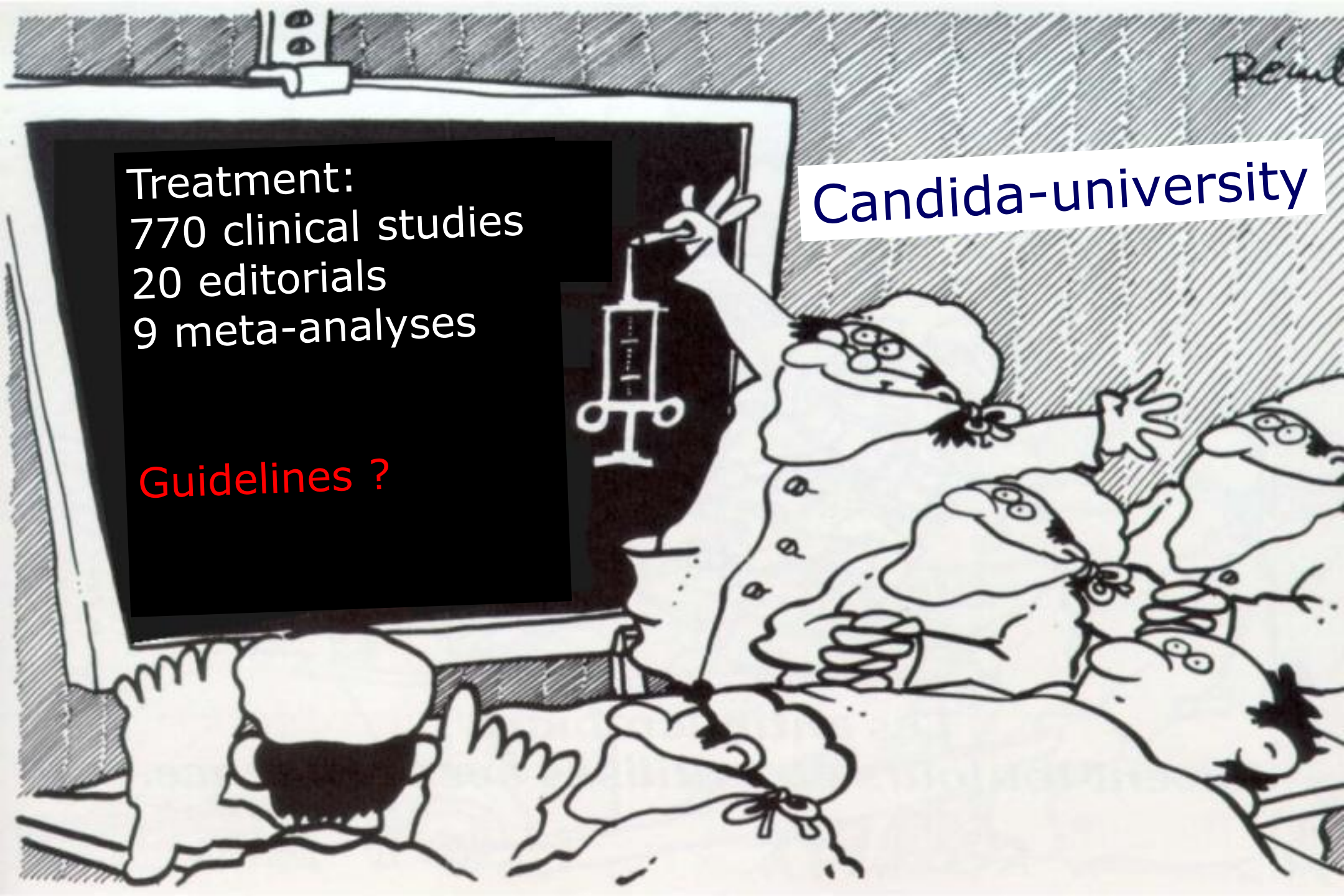


Eggimann P, et al. Ann Intensive Care. 2011;1:37.

Thank you
for your
attention

and for the
invitation


Treatment:
770 clinical studies
20 editorials
9 meta-analyses
Candida-university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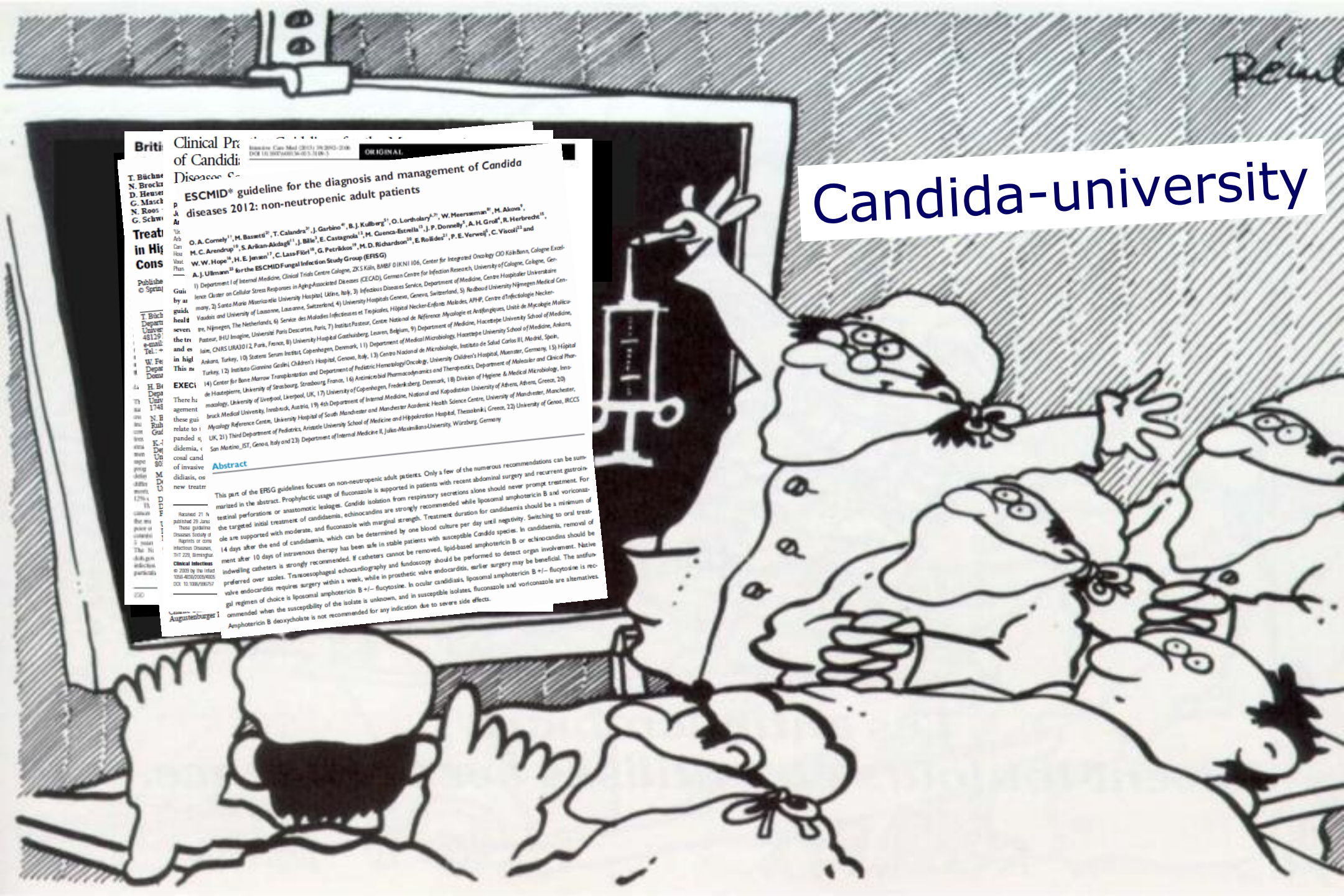
Guidelines ?
Candida-university



ORIGINAL

ESCMID* guideline for the diagnosis and management of Candida diseases 2012: non-neutropenic adult patients

O. A. Cornely[1,7], M. Bassetti[27], T. Calandra[31], J. Garbino[40], B. J. Kullberg[51], O. Lortholary[8,31], W. Meersseman[41], M. Akova[2], M. C. Arendrup[10], S. Arikan-Akdagli[11], J. Bille[3], E. Castagnola[12], M. Cuenca-Estrella[13], J. P. Donnelly[5], A. H. Groll[6], R. Herbrecht[15], W. W. Hope[16], H. E. Jensen[17], C. Lass-Flörl[18], G. Petrikkos[19], M. D. Richardson[20], E. Roilides[21], P. E. Verweij[5], C. Viscoli[22] and A. J. Ullmann[23] for the ESCMID Fungal Infection Study Group (EFISG)

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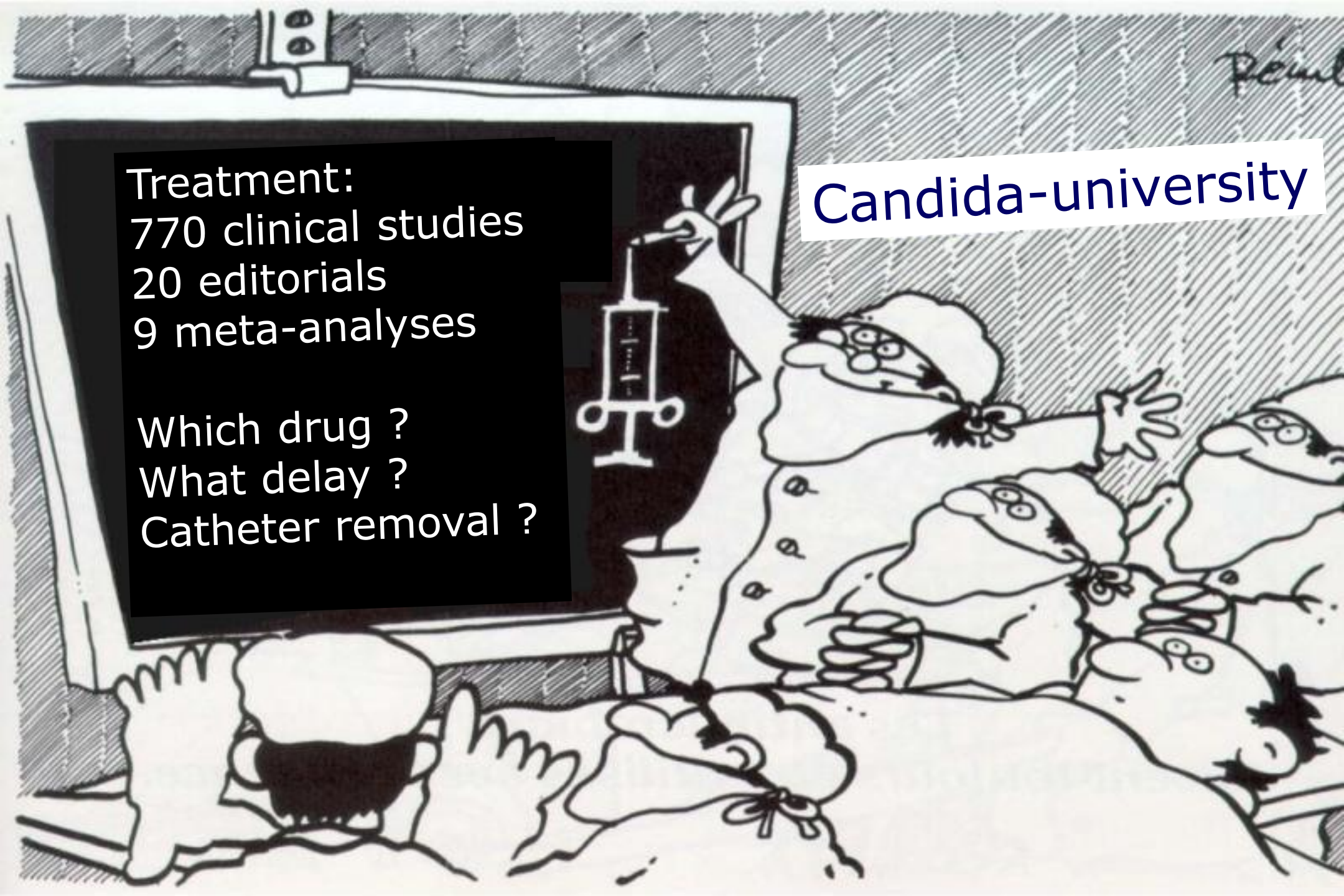
Abstract

This part of the EFISG guidelines focuses on non-neutropenic adult patients. Only a few of the numerous recommendations can be summarized in the abstract. Prophylactic usage of fluconazole is supported in patients with recent abdominal surgery and recurrent gastrointestinal perforations or anastomotic leakages. *Candida* isolation from respiratory secretions alone should never prompt treatment. For the targeted initial treatment of candidaemia, echinocandins are strongly recommended while liposomal amphotericin B and voriconazole are supported with moderate, and fluconazole with marginal strength. Treatment duration for candidaemia should be a minimum of 14 days after the end of candidaemia, which can be determined by one blood culture per day until negativity. Switching to oral treatment after 10 days of intravenous therapy has been safe in stable patients with susceptible *Candida* species. In candidaemia, removal of indwelling catheters is strongly recommended. If catheters cannot be removed, lipid-based amphotericin B or echinocandins should be preferred over azoles. Transoesophageal echocardiography and fundoscopy should be performed to detect organ involvement. Native valve endocarditis requires surgery within a week, while in prosthetic valve endocarditis, earlier surgery may be beneficial. The antifungal regimen of choice is liposomal amphotericin B +/– flucytosine. In ocular candidiasis, liposomal amphotericin B +/– flucytosine is recommended when the susceptibility of the isolate is unknown, and in susceptible isolates, fluconazole and voriconazole are alternatives. Amphotericin B deoxycholate is not recommended for any indication due to severe side effects.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Candida-university

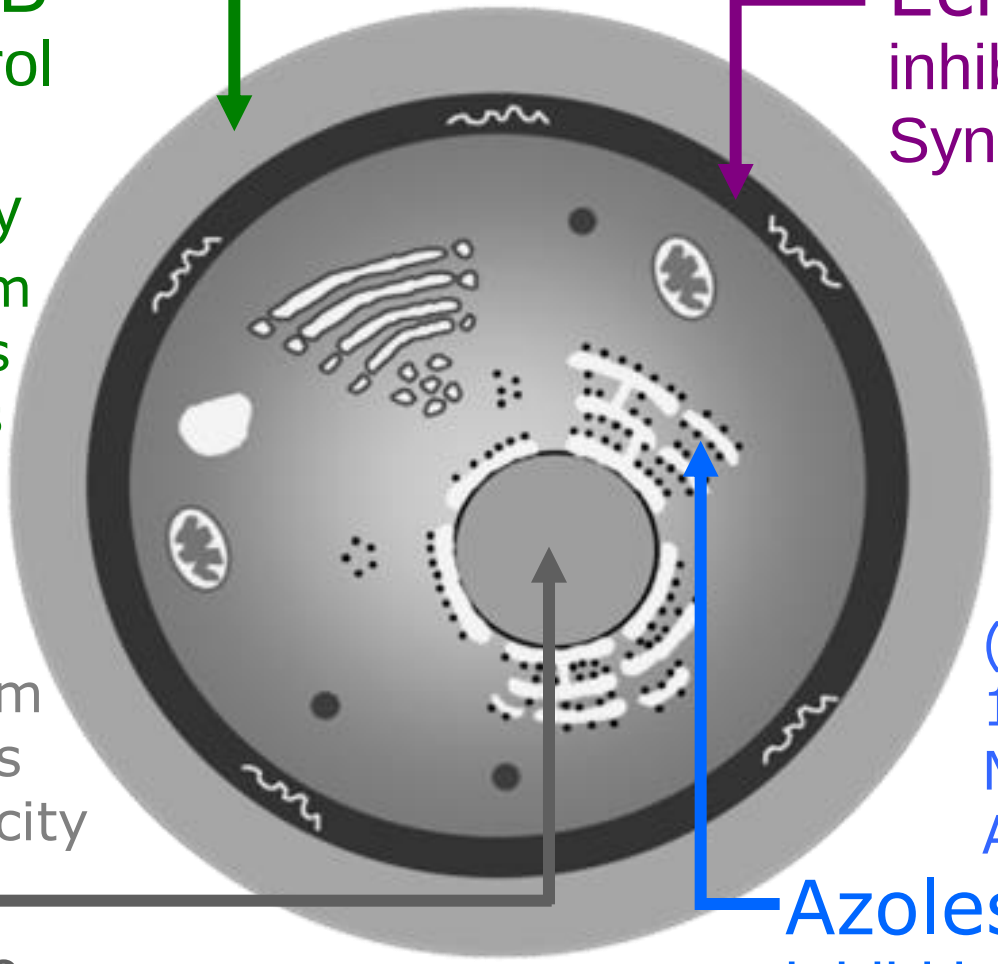
Treatment of documented candidiasis

Amphotericin B
binding to ergosterol
of outmembrane
loss of permeability

Very broad spectrum
50-90% side effects
20-40% for L-forms

Echinocandins
inhibition of cell wall
Synthesis (fungicidal)

Very broad spectrum
10-15% side effects
Parenteral use only



Very broad spectrum
30-50% side effects
Potential myelotoxicity

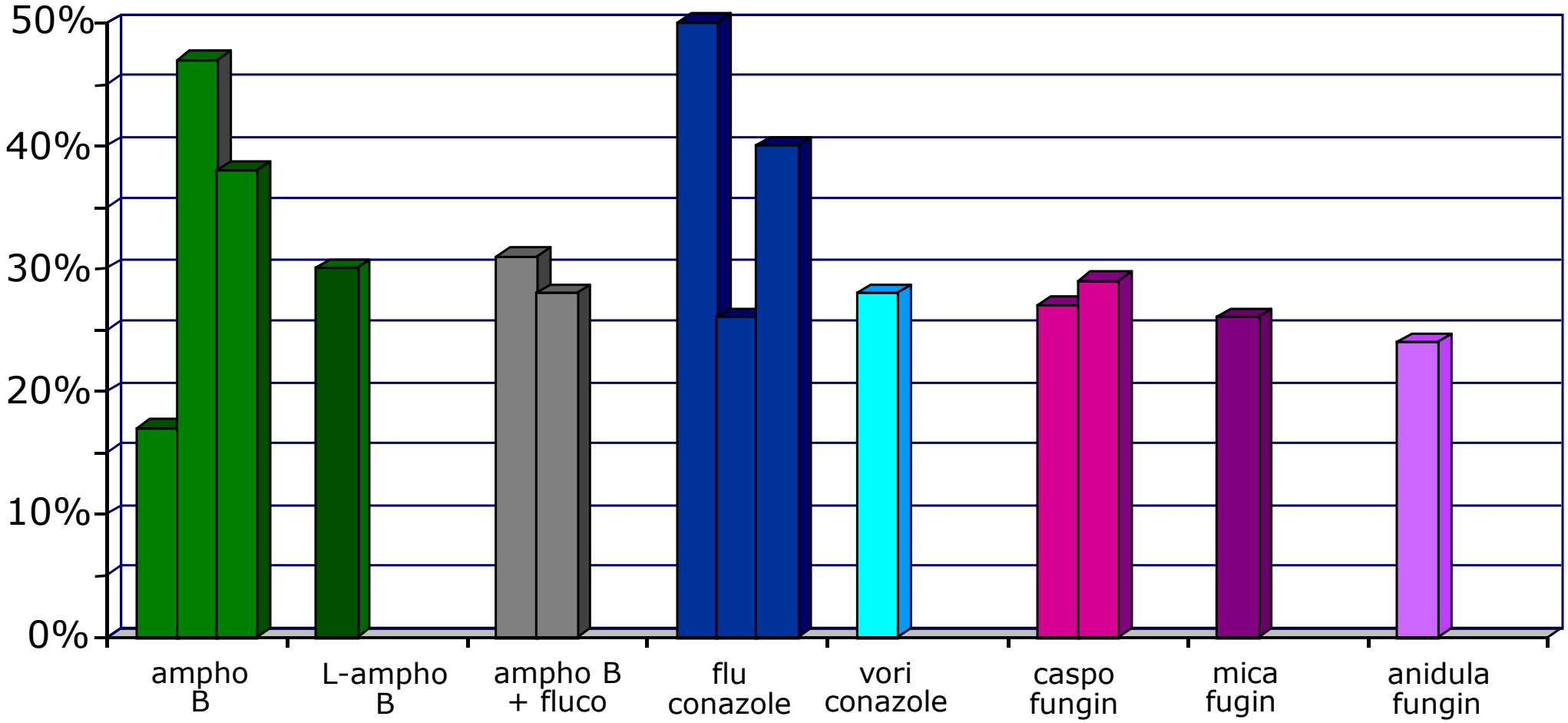
5-flucytosine
inhibition of nucleic
acid synthesis

(Very) broad spectrum
10-20% side effects
Many interractions
Available for oral use

Azoles
inhibition (Cy P450) of
ergosterol synthesis

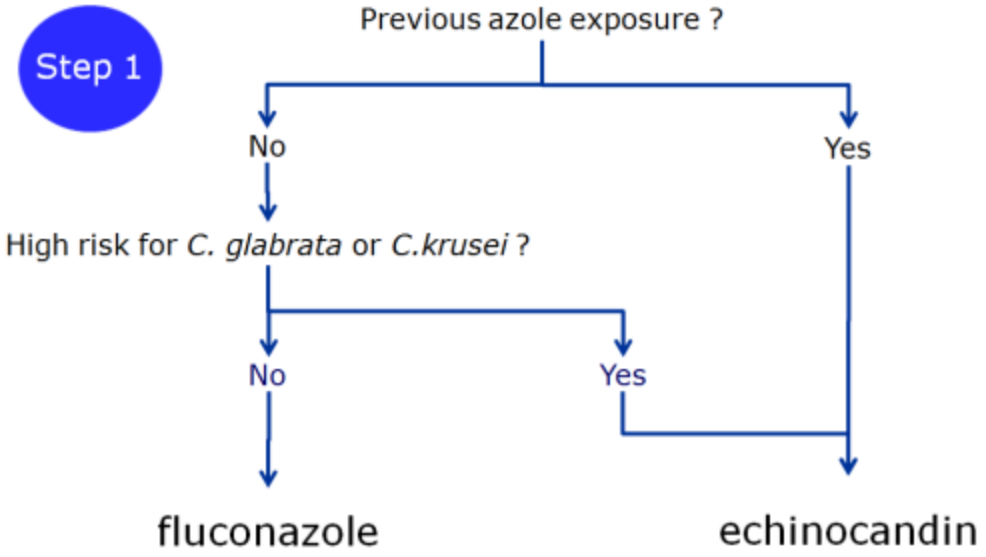
Treatment of documented candidiasis

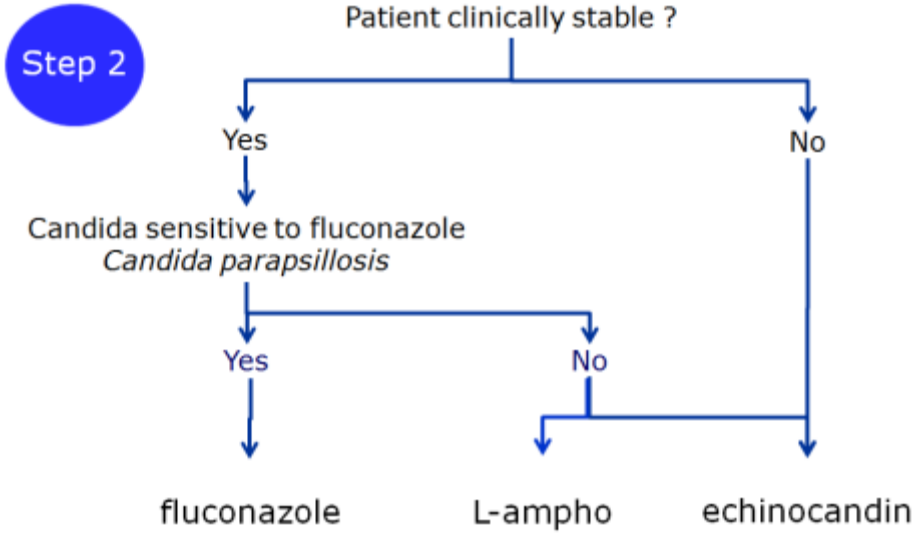
Failure rates in randomized adult studies 1994 to 2007



Rex NEJM 1994; Phillips CIF 1997; Mora-Duarte NEJM 02; Rex CID 03; Kullberg Lancet 05; Pappas CID 07; Kuse Lancet 07; Reboli NEJM 07

Treatment of documented candidiasis





IDSA Guidelines

Pappas PG, et al. Clin Infect Dis. 2009;48:503–35.

Treatment of documented candidiasis

Pooled data from 7 randomized adult studies 1994 to 2007

		Mortality				Success		
Organisms[a]	Factor	*P*	OR	95% CI	Factor	*P*	OR	95% CI
All organisms (n = 978)	Age	.02	1.01	1.00–1.02	APACHE II	.0001	0.94	.93–.96
	APACHE II score	.0001	1.11	1.08–1.14	Echinocandin	.01	2.33	1.27–4.35
	Immunosuppressive therapy	.001	1.69	1.18–2.44	CVC removed	.001	1.69	1.23–2.33
	Candida tropicalis	.01	1.64	1.11–2.39	Study	NS		
	Echinocandin	.02	0.65	.45–.94				
	CVC removed	.0001	0.50	.35–.72				
	Study	NS						
Candida albicans (n = 408)	APACHE II score	.0001	1.09	1.05–1.13	APACHE II score	.005	0.92	.92–.99
	Immunosuppressive therapy	.002	2.22	1.30–3.70	Echinocandin	.005	3.70	1.49–9.09
	Surgery	.05	0.58	.34–.98	Study	NS		
	Malignancy	.03	1.89	1.05–3.45				
	Echinocandin	.03	0.55	.32–.95				
	CVC removed	.01	0.52	.31–.90				
	Study	NS						

Andes DR, et al. Clin Infect Dis. 2012;54:1110-22.

Treatment of documented candidiasis

Candidiasis in Adult Patients

Intervention	SoR	QoE	Reference	Comment
Anidulafungin 200/100 mg	A	I	Reboli NEJM 2007	Consider local epidemiology (*C. parapsilosis, C. krusei*), less drug-drug interactions than caspofungin
Caspofungin 70/50 mg	A	I	Betts CID 2009 Mora-Duarte NEJM 2007 Pappas CID 2007	Consider local epidemiology (*C. parapsilosis*)
Micafungin 100 mg	A	I	Kuse Lancet 2007 Pappas CID 2007	Consider local epidemiology (*C. parapsilosis*), less drug-drug interactions than caspofungin, consider EMA warning label
Amphotericin B liposomal 3 mg/kg	B	I	Kuse Lancet 2007 Dupont Crit Care 2009	Similar efficacy as micafungin, higher renal toxicity than micafungin
Voriconazole* 6/3 mg/kg/d	B	I	Kullberg Lancet 2005 Ostrosky EJCMID 2003 Perfect CID 2003	Limited spectrum compared to echinocandins, drug-drug interactions, limitation of IV formulation in renal impairment, consider therapeutic drug monitoring
Fluconazole* 400-800 mg	C	I	Anaissie CID 1996 Rex NEJM 1994 Rex CID 2003 Philips EJCMID 1997 Reboli NEJM 2007 Tuil CCM 2003 Abele-Horn Infect 1996 Leroy CCM 2009 Gafter-Gvili Mayo Clin Proc 2008	Limited spectrum, Inferiority to anidulafungin (especially in the subgroup with high APACHE scores), may be better than echinocandins against *C. parapsilosis*
Amphotericin B lipid complex 5 mg/kg	C	II_a	Anaissie ICAAC 1995 Ito CID 2005	
Amphotericin B deoxycholate 0.7–1.0 mg/kg	D	I	Ullmann CID 2006 Bates CID 2001 Anaissie CID 1996 Rex NEJM 1994 Philips EJCMID 1997 Mora-Duarte NEJM 2002	Substantial renal and infusion-related toxicity
Amphotericin B deoxycholate plus fluconazole	D	I	Rex CID 2003	Efficacious, but increased risk of toxicity in ICU patients No survival benefit
Amphotericin B deoxycholate plus 5-fluorocytosine	D	II	Abele-Horn Infect 1996	
Efungumab plus lipid-associated amphotericin B	D	II	Pachl CID 2006	
Amphotericin B colloidal dispersion	D	II_a	Noskin CID 1998	
Itraconazole	D	II_a	Tuil CCM 2003	
Posaconazole	D	III	No reference found.	

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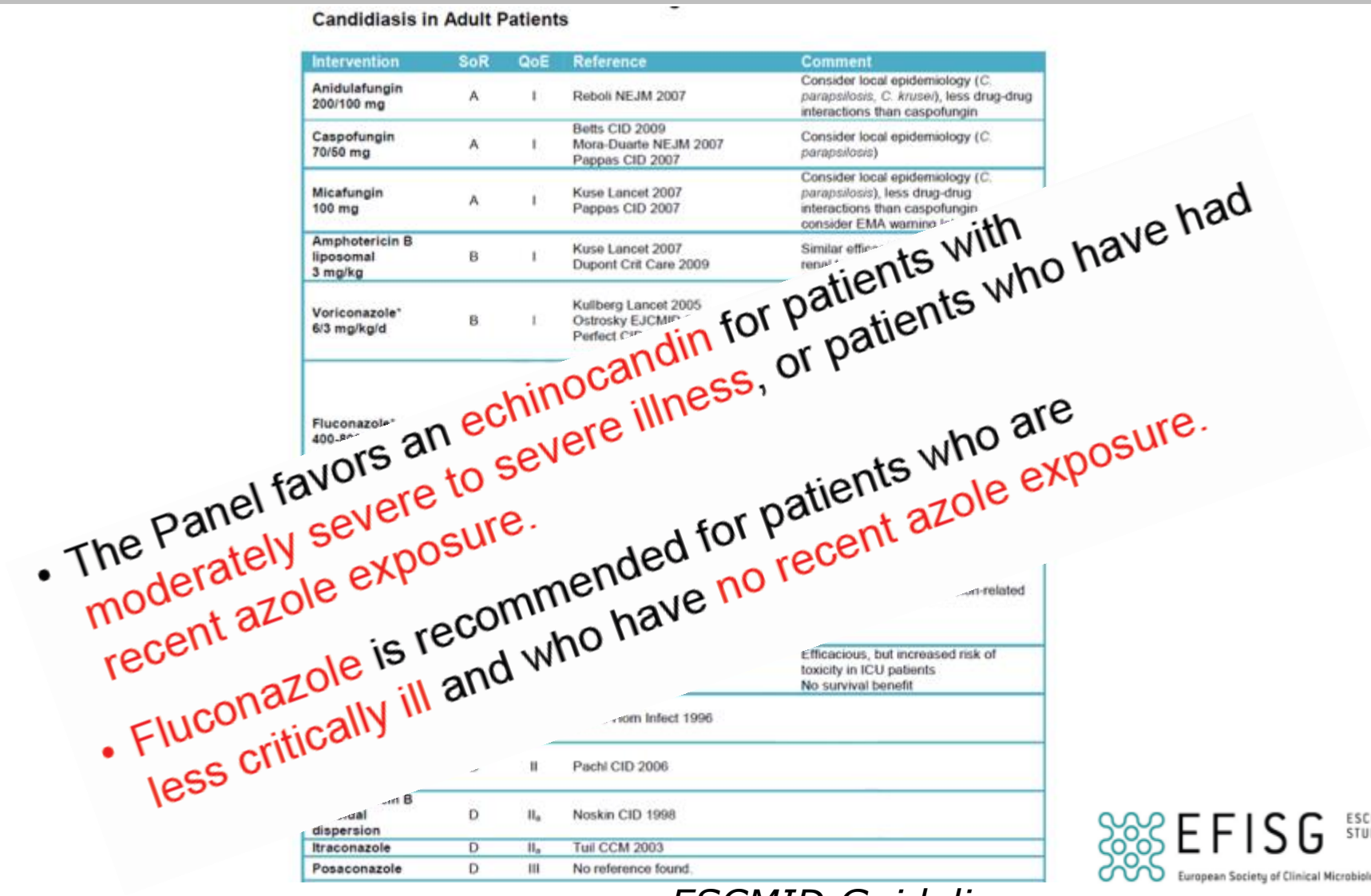
European Society of Clinical Microbiology and Infectious Diseases

ESCMID Guidelines

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

Treatment of documented candidiasis



Candidiasis in Adult Patients

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Amphotericin B liposomal 3 mg/kg	B	I	Kuse Lancet 2007 Dupont Crit Care 2009	Similar effi renal
Voriconazole* 6/3 mg/kg/d	B	I	Kullberg Lancet 2005 Ostrosky EJCMI Perfect	
Fluconazole* 400-8				-related
				Efficacious, but increased risk of toxicity in ICU patients No survival benefit
			om Infect 1996	
		II	Pachl CID 2006	
al dispersion	D	II_a	Noskin CID 1998	
Itraconazole	D	II_a	Tuil CCM 2003	
Posaconazole	D	III	No reference found.	

- The Panel favors an echinocandin for patients with moderately severe to severe illness, or patients who have had recent azole exposure.
- Fluconazole is recommended for patients who are less critically ill and who have no recent azole exposure.

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European Society of Clinical Microbiology and Infectious Diseases

ESCMID Guidelines

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

Treatment of documented candidiasis

Intensive Care Med (2014) 40:1489–1498
DOI 10.1007/s00134-014-3400-y

ORIGINAL

Arnaldo L. Colombo
Thais Guimarães
Teresa Sukienik
Alessandro C. Pasqualotto
Ricardo Andreotti
Flavio Queiroz-Telles
Simone A. Nouér
Marcio Nucci

Prognostic factors and historical trends in the epidemiology of candidemia in critically ill patients: an analysis of five multicenter studies sequentially conducted over a 9-year period

Table 5 Factors associated with 30-day mortality[a] among 640 ICU patients with candidemia by multivariate analysis

Variable	Odds ratio	95 % Confidence interval	*p* value
Receipt of corticosteroids	4.00	1.98–8.13	<0.001
Period 1	2.49	1.22–5.08	0.01
APACHE II score[b]	1.05	1.01–1.09	0.03
Age	1.03	1.01–1.05	0.003
Treatment with an echinocandin	0.20	0.07–0.58	0.003

Treatment of documented candidiasis

Intensive Care Med (2014) 40:1303–1312
DOI 10.1007/s00134-014-3408-3

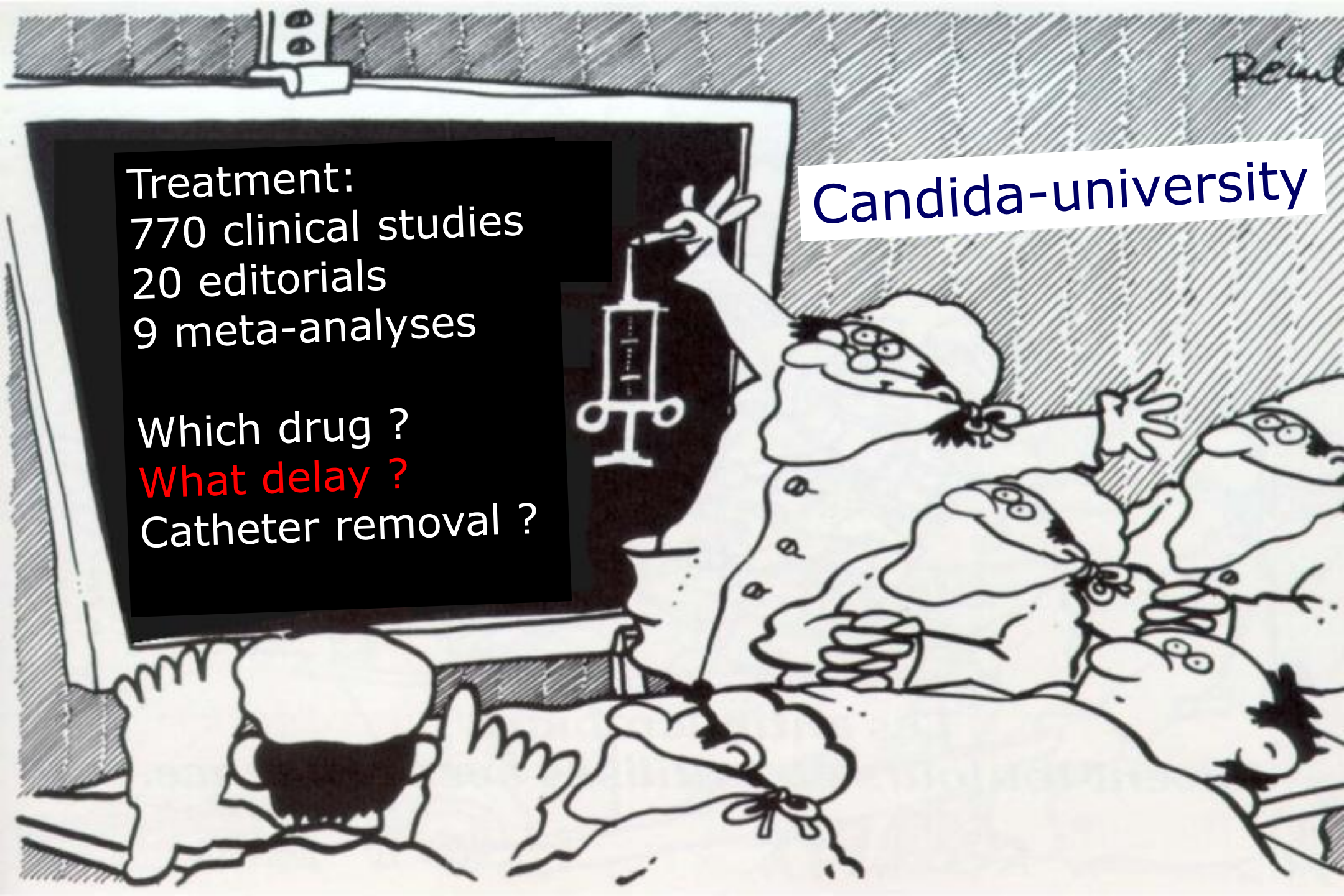
ORIGINAL

Olivier Lortholary
Charlotte Renaudat
Karine Sitbon
Yoann Madec
Lise Denoeud-Ndam
Michel Wolff
Arnaud Fontanet
Stéphane Bretagne
Françoise Dromer
The French Mycosis Study Group

Worrisome trends in incidence and mortality of candidemia in intensive care units (Paris area, 2002–2010)

Table 2 Risk factors for death in adult patients hospitalized in intensive care unit (ICU) with incident candidemia due to a single isolate (logistic regression), YEASTS program, Paris area, October 2002 to September 2010

	Death before day 30			Death before day 8			Death between day 8 and day 30		
	Adj. OR	95 % CI	*p*	Adj. OR	95 % CI	*p*	Adj. OR	95 % CI	*p*
Male gender							0.71	0.51–0.99	0.043
Age categories									
<45 years	1		0.0001				1		0.0003
45–64 years	1.66	1.09–2.53					2.32	1.38–3.89	
65–79 years	2.49	1.60–3.56					3.19	1.88–5.43	
≥80 years	3.09	1.73–5.49					2.91	1.45–5.83	
Arterial catheter	1.39	1.01–1.92	0.0430				1.47	1.02–2.11	0.0371
Surgery within 30 days	0.62	0.46–0.84	0.0017				0.54	0.39–0.76	0.0004
Species									
C. albicans	1		0.0013	1		0.0031			
C. grabrata	0.65	0.43–0.98		0.58	0.34–1.02				
C. parapsilosis	0.43	0.25–0.76		0.18	0.06–0.52				
C. tropicalis	0.99	0.61–1.63		1.00	0.53–1.86				
C. krusei	1.78	0.71–4.47		1.55	0.57–4.23				
C. kefyr	3.88	1.14–13.26		2.79	0.84–9.21				
Preexposure to caspofungin	3.83	1.29–11.35	0.0153	3.54	1.09–11.53	0.0357			
First-line treatment									
Fluconazole	1		0.0003	1		<0.0001			
Echinocandin	1.23	0.85–1.80		0.98	0.59–1.61				
Other treatment	1.11	0.69–1.79		0.81	0.42–1.56				
No treatment	4.34	2.23–8.45		11.04	5.72–21.30				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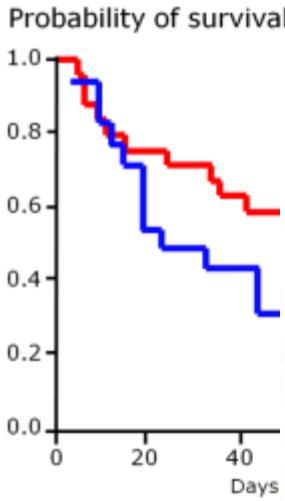
What delay ?
Catheter removal ?
Candida-university

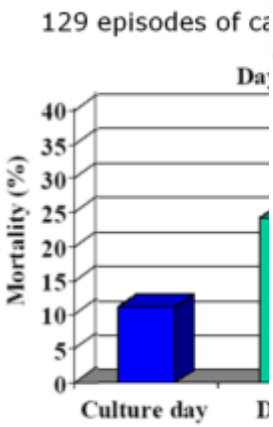
Treatment of documented candidiasis

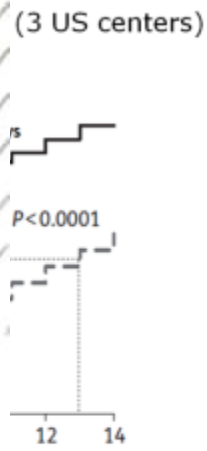
Impact of delayed antifungal treatment



Nolla-Salas J, et al. Int

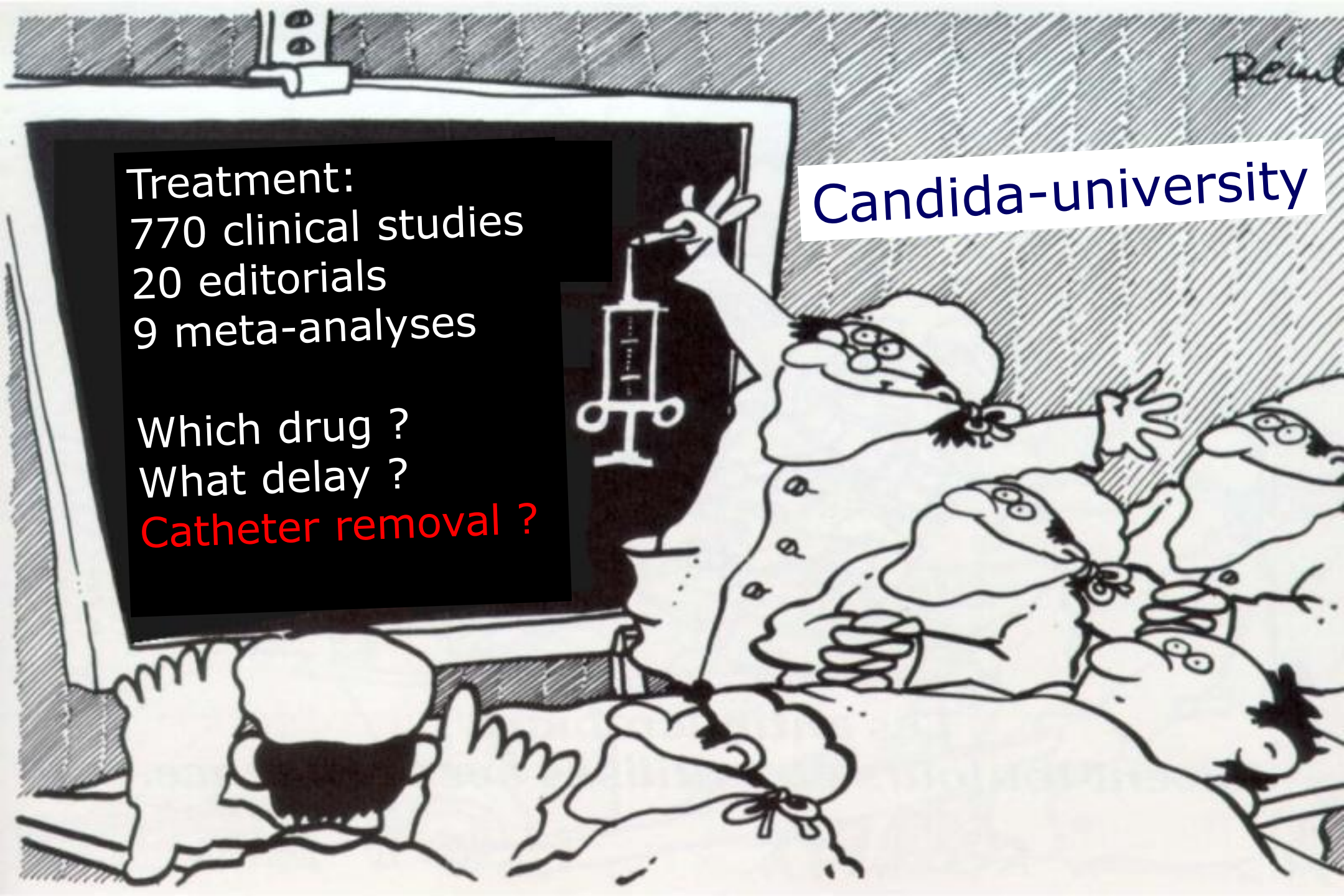
her. 2005;49:3640-5.





Garey KW, et al. Clin Infect Dis. 2006;43:25-31.

Hsu DI, et al. J Antimicrob Chemother. 2010;65:1765-20.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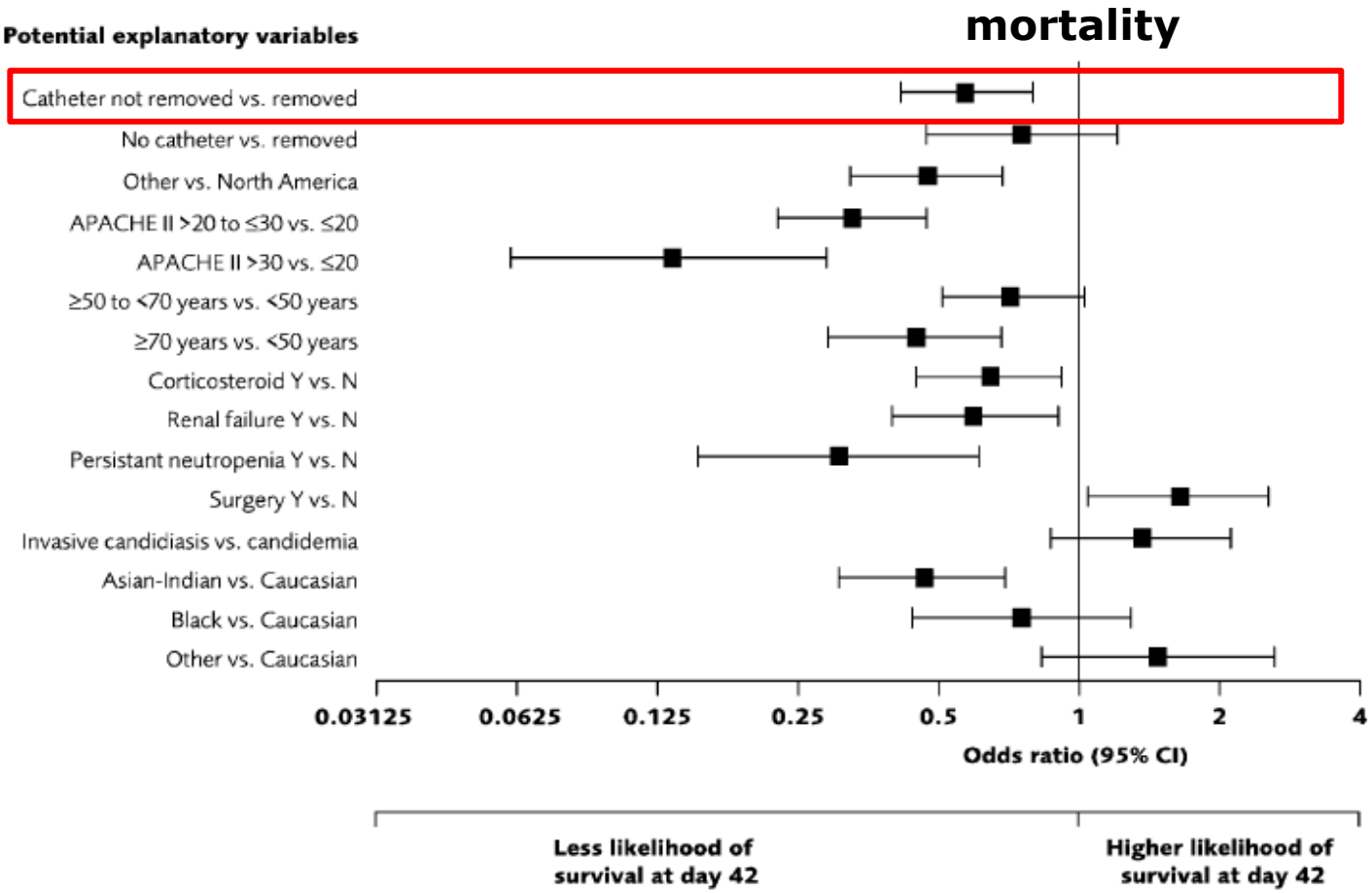
Candidemia: catheter removal ?

2 pooled studies:
1109 candidemia

Both survival and treatment success were significantly less likely for the non-removal of catheter versus removal,



Horn DL, et al. Eur J Clin Microbiol Infect Dis. 2010;29:223-9.

Candidemia: catheter removal ?

2 pooled studies:
842 candidemia

Early Removal of Central Venous Catheter in Patients with Candidemia Does Not Improve Outcome: Analysis of 842 Patients from 2 Randomized Clinical Trials

Table 5. Multivariate Analysis of the Effect of Early Removal of the Central Venous Catheter (CVC) on Treatment Success and Survival at 28 and 42 Days after Treatment Initiation in 842 Patients with Candidemia

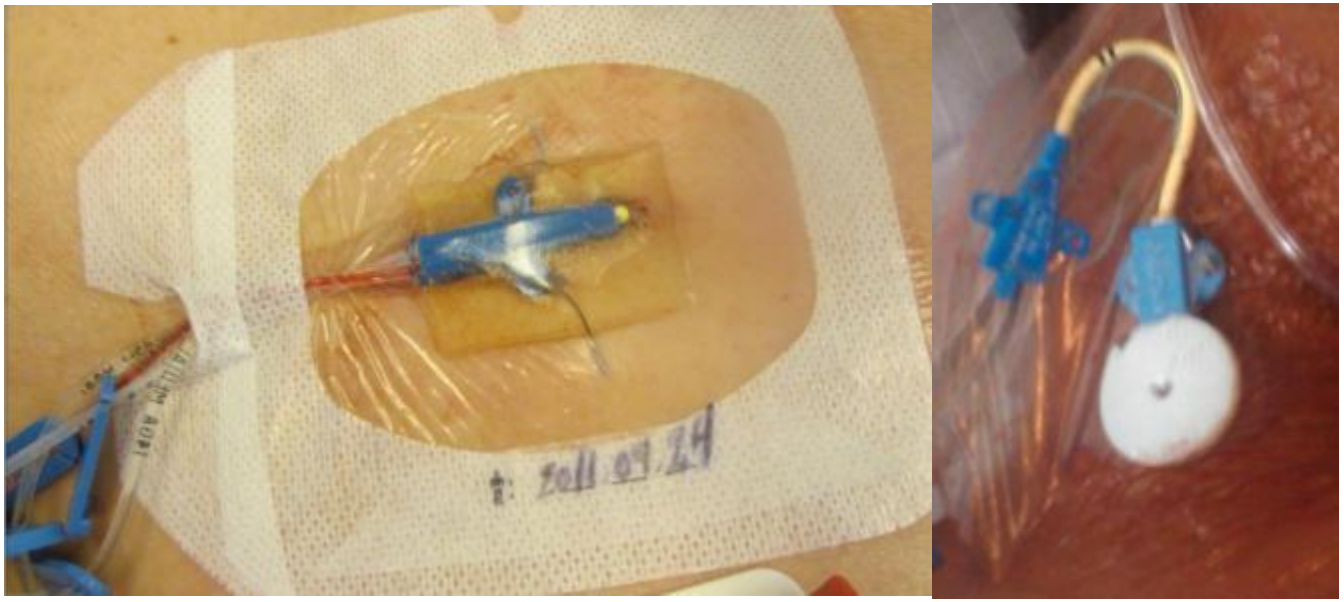
	Treatment success		Survival at 28 days		Survival at 42 days	
Variable	OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*
CVC removal within 24 h after treatment initiation						
CVC removal	NT	NT	1.15 (0.79–1.67)	.45	1.19 (0.84–1.67)	.33
Persistent neutropenia	NT	NT	0.36 (0.15–0.88)	.03	0.38 (0.16–0.90)	.03
Higher APACHE II score	NT	NT	0.90[a] (0.88–0.93)	<.001	0.91[a] (0.89–0.93)	<.001
Liver failure	NT	NT	0.23 (0.07–0.72)	.01	NT	NT
Surgery	NT	NT	1.46 (0.87–2.47)	.16	1.97 (1.23–3.18)	.005
Older age	NT	NT	0.98[a] (0.97–0.99)	.02	0.98[a] (0.97–0.99)	.02

Nucci M, et al. Clin Infect Dis. 2011;51:295-303.

Candidemia: catheter removal ?

Swiss fungal network 2004-2006: 566 candidemia
hospital mortality 232 (41%)
attributable mortality 45 (8%)

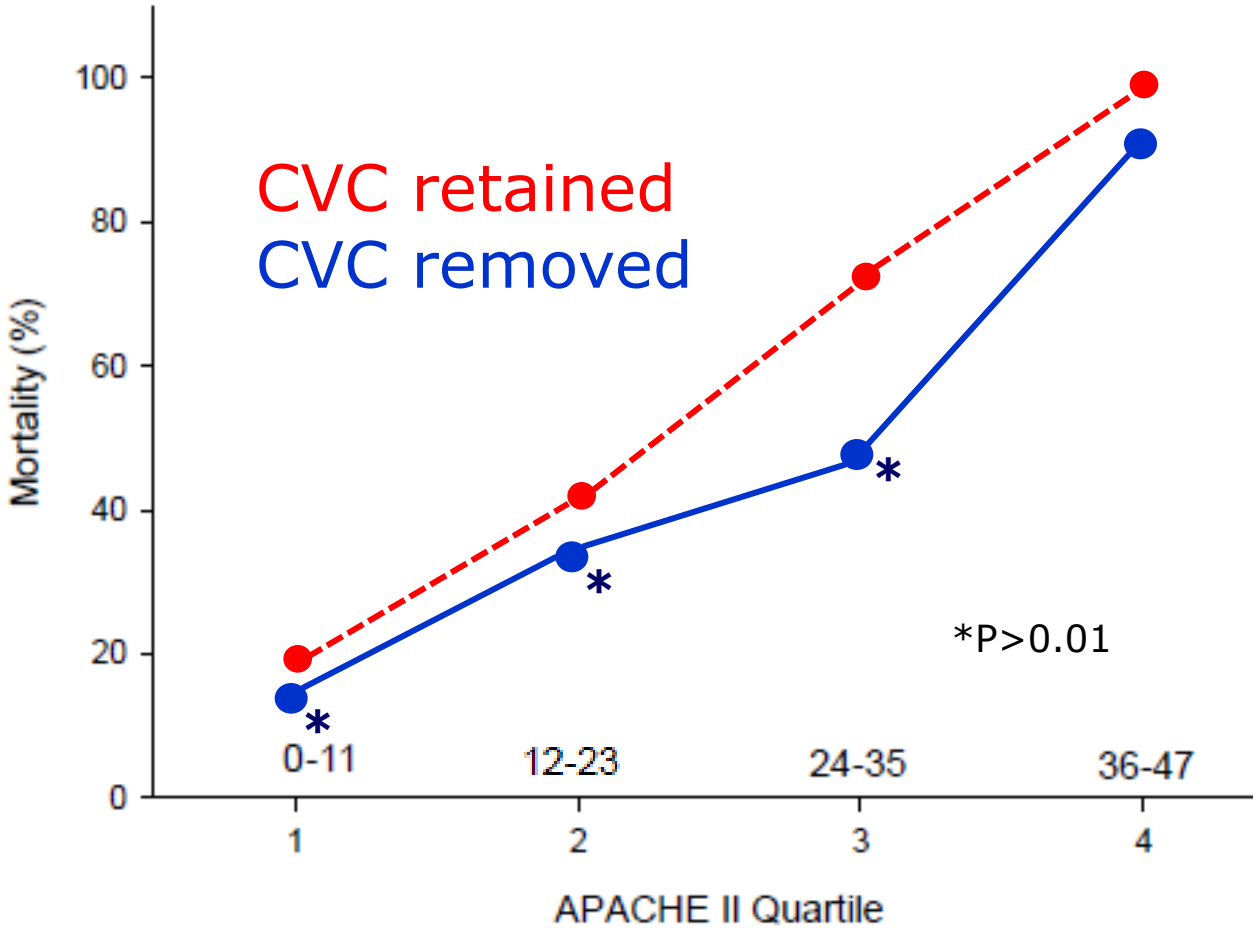
OR for death CVC retained : 4.07 (1.5–10.6)
antifungals> 72 h : 1.41 (0.9-4.52)



Erard V, et al.
50th ICAAC 2010

Candidemia: catheter removal ?

7 pooled studies: 1915 candidemia



Andes DR, et al. Clin Infect Dis. 2012;54:1110-22.

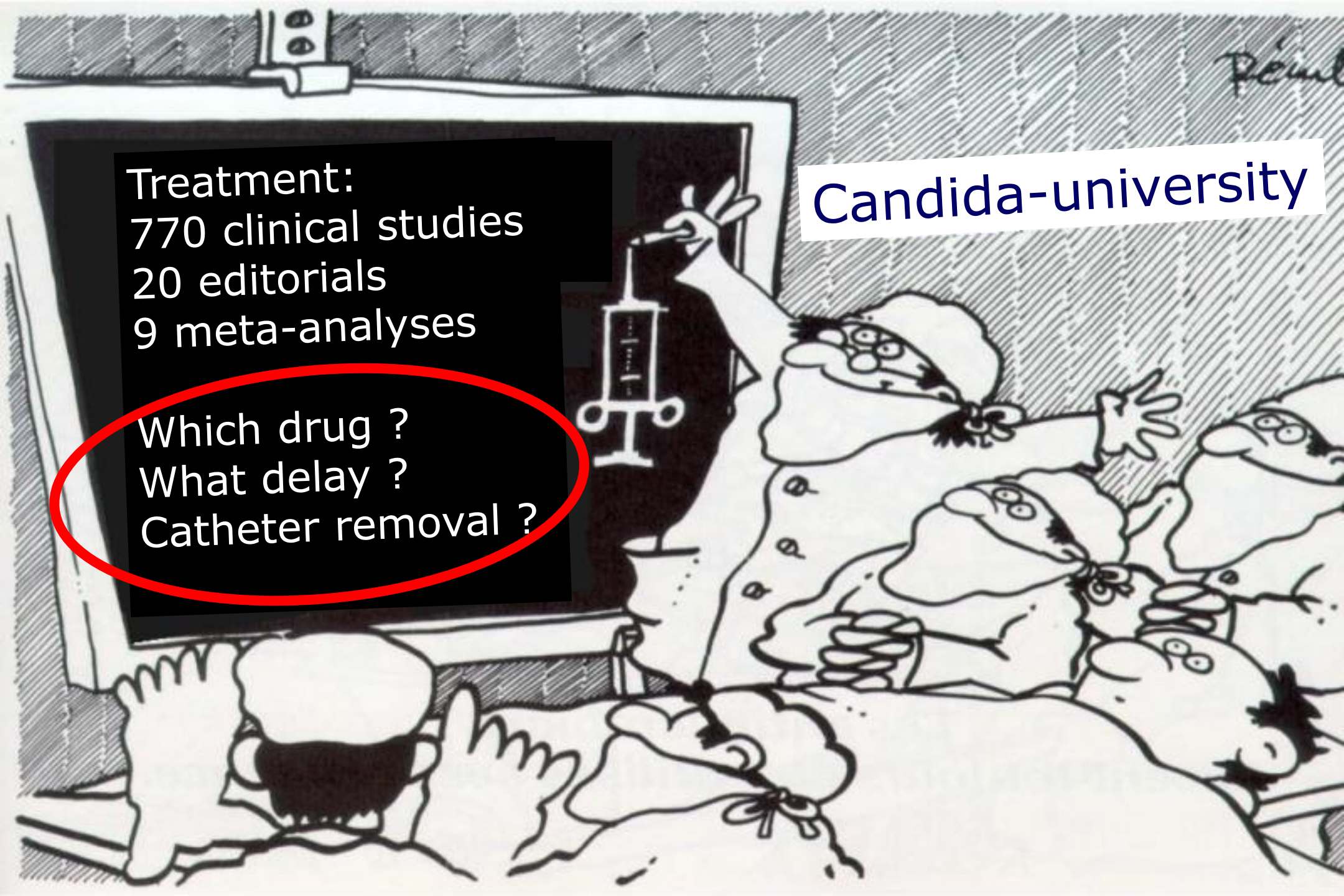
Candidemia: catheter removal ?

Table 7. Recommendations on Catheter Management in Candidaemia

Population	Intervention	SoR	QoE	Reference
Central venous catheter can be removed	Remove indwelling lines (not over a guidewire)	A	II_r	Andes CID 2012
Central venous catheter cannot be removed	Echinocandin, liposomal amphotericin B, or amphotericin B lipid complex	B	II_r	Andes CID 2012 Kucharikova AAC 2010 Kuhn AAC 2002 Mukherjee IJAA 2009 Nucci CID 2010 Rex CID 1995
	Azole, or amphotericin B deoxycholate	D	II_r	Almirante JCM 2005 Andes CID 2012 Leroy CCM 2009 Liu J Infect 2009 Rodriguez CMI 2007 Weinberger JHI 2005
Interventions are intended to clear candidaemia and to improve survival.				

ESCMID Guidelines
Cornely OA, et al. Clin Microbiol Infect. 2012;18: 19-37.

Candidemia: catheter removal ?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Candida-university

Impact of Therapeutic Strategies on the Prognosis of Candidemia in the ICU

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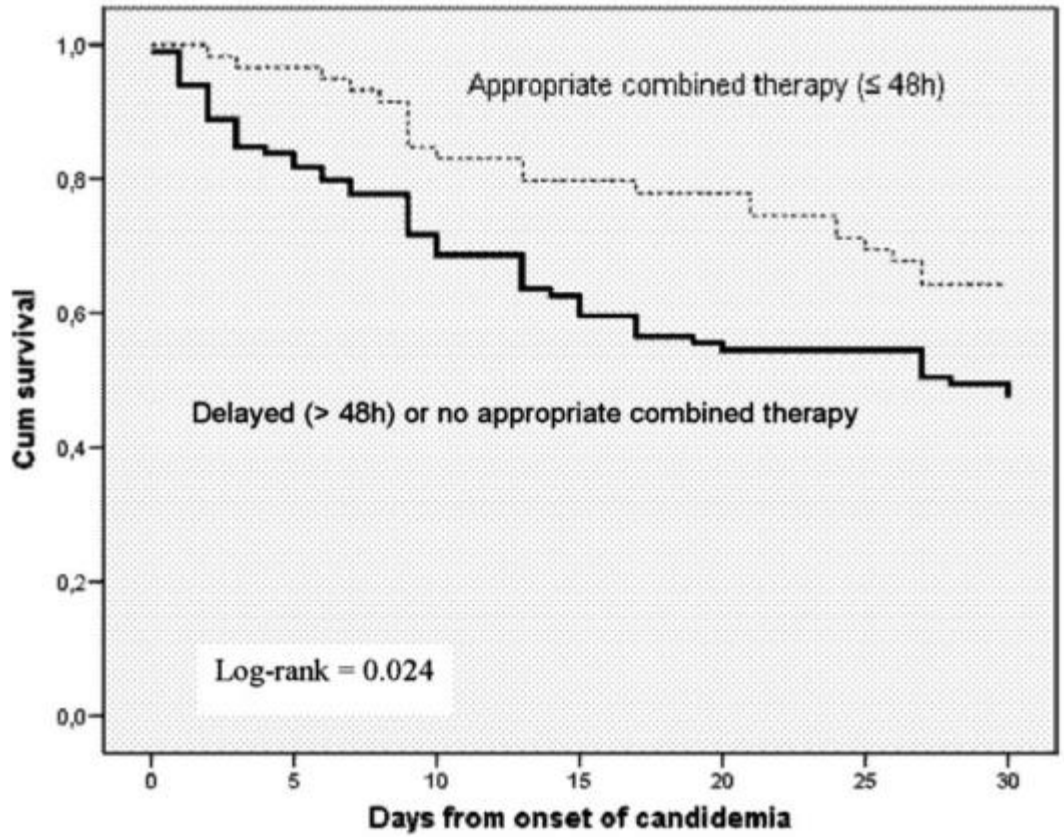

- Central venous catheter removal[b]
- Adequate antifungal treatment[c]

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