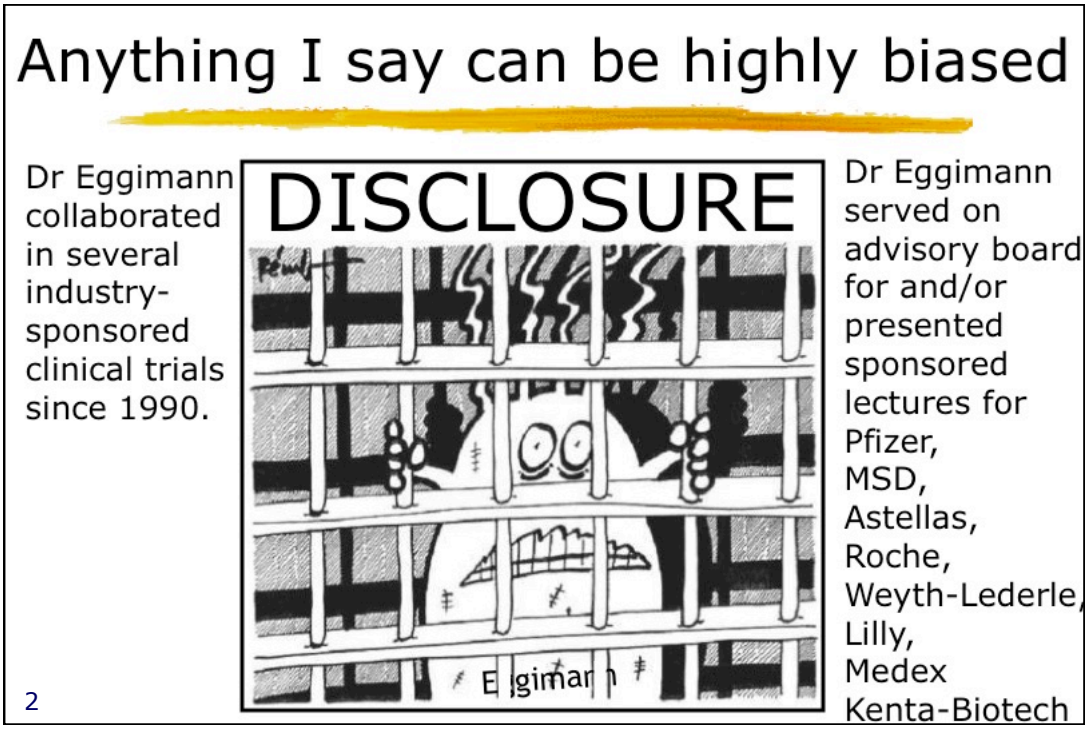
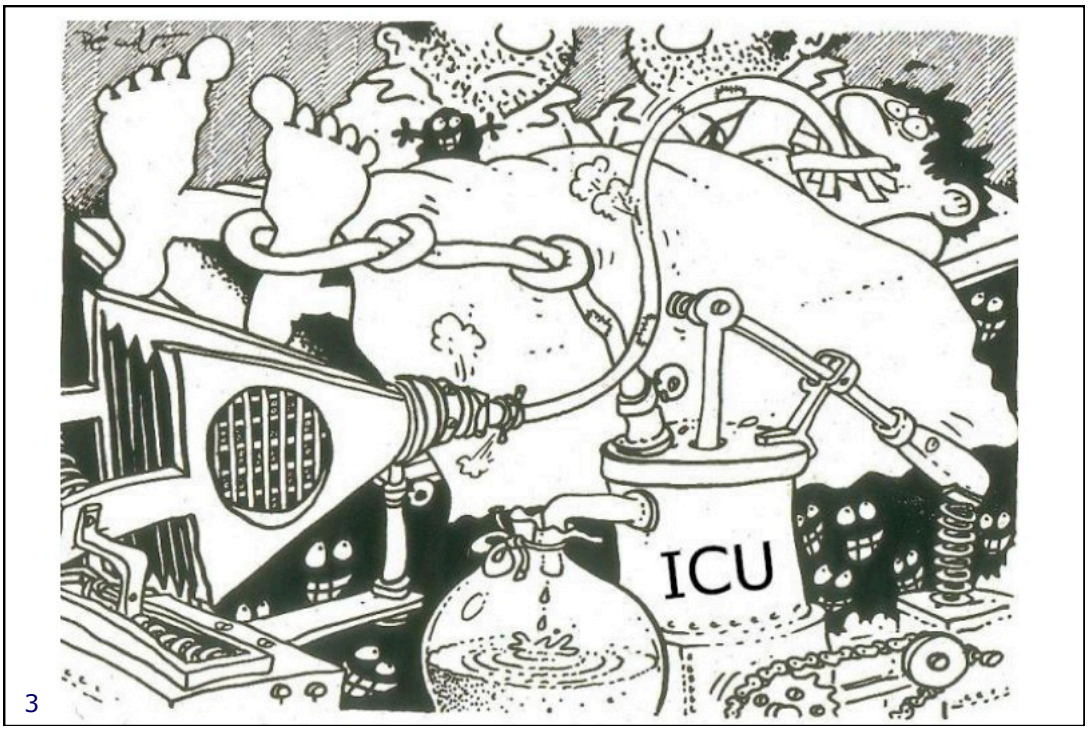
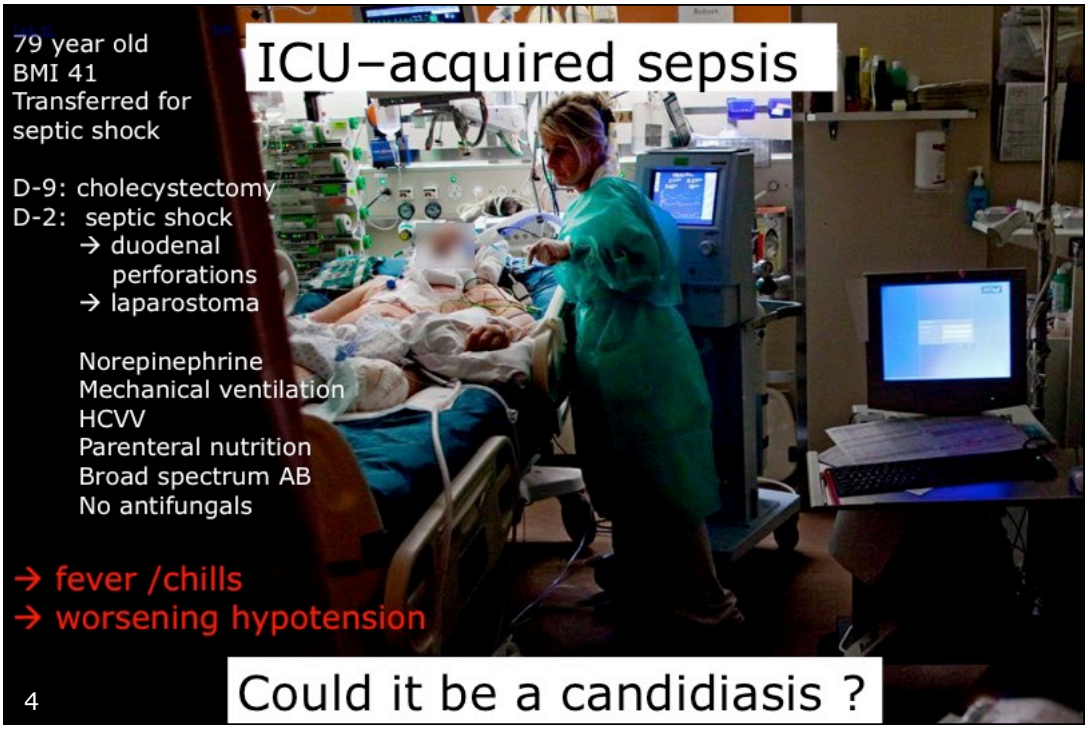
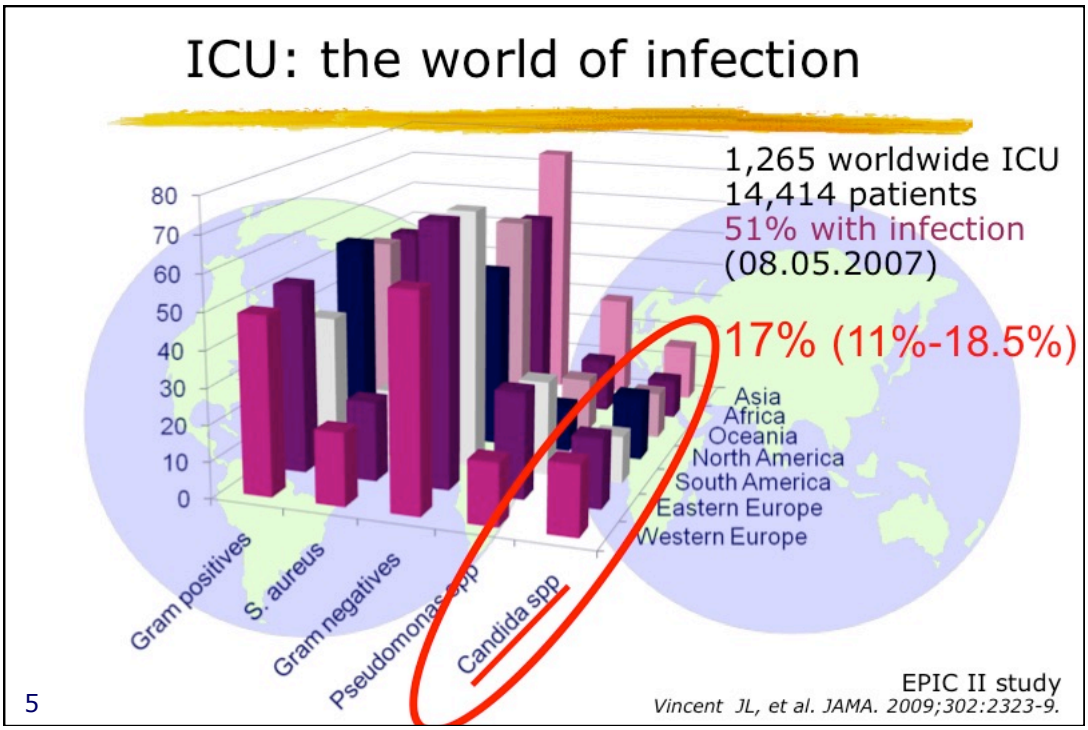
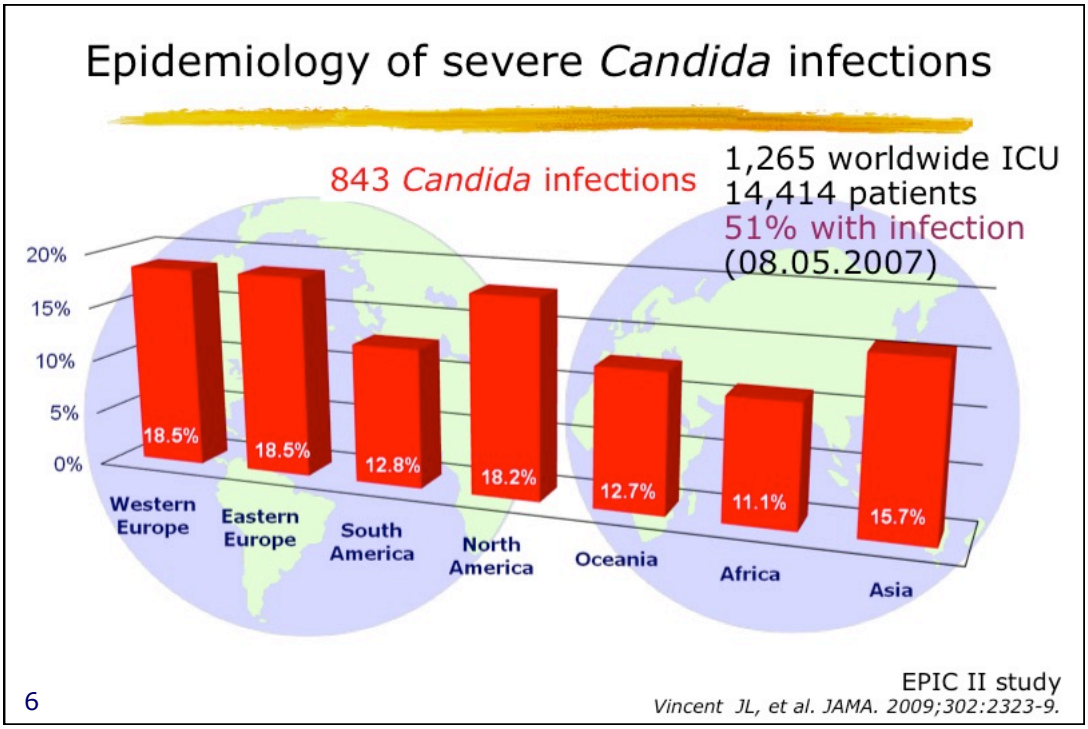

Preventing
invasive candida infections -
Where could we do better ?
Dr Philippe Eggimann, PD&MER
Service de Médecine Intensive Adulte
www.soins-intensifs.chuv.ch
Hosted by
Paul Webber
paul@webbertraining.com
CHUV
UNIL | Université de Lausanne
www.webbertraining.com
April 7, 2016


Anything I say can be highly biased
Dr Eggimann collaborated in several industry-sponsored clinical trials since 1990.
DISCLOSURE
Dr Eggimann served on advisory board for and/or presented sponsored lectures for Pfizer, MSD, Astellas, Roche, Weyth-Lederle, Lilly, Medex Kenta-Biotech
2


ICU
3


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
ICU–acquired sepsis
Could it be a candidiasis ?
4


ICU: the world of infection
1,265 worldwide ICU
14,414 patients
51% with infection
(08.05.2007)
17% (11%-18.5%)
80
70
60
50
40
30
20
10
0
Gram positives
S. aureus
Gram negatives
Pseudomonas spp
Candida spp
Asia
Africa
Oceania
North America
South America
Eastern Europe
Western Europe
EPIC II study
Vincent JL, et al. JAMA. 2009;302:2323-9.
5


Epidemiology of severe *Candida* infections
843 *Candida* infections
1,265 worldwide ICU
14,414 patients
51% with infection
(08.05.2007)
20%
15%
10%
5%
0%
18.5%
18.5%
12.8%
18.2%
12.7%
11.1%
15.7%
Western Europe
Eastern Europe
South America
North America
Oceania
Africa
Asia
EPIC II study
Vincent JL, et al. JAMA. 2009;302:2323-9.
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Epidemiology of severe *Candida* infections

843 *Candida* infections

1'265 worldwide ICU
14'414 patients
51% with infection
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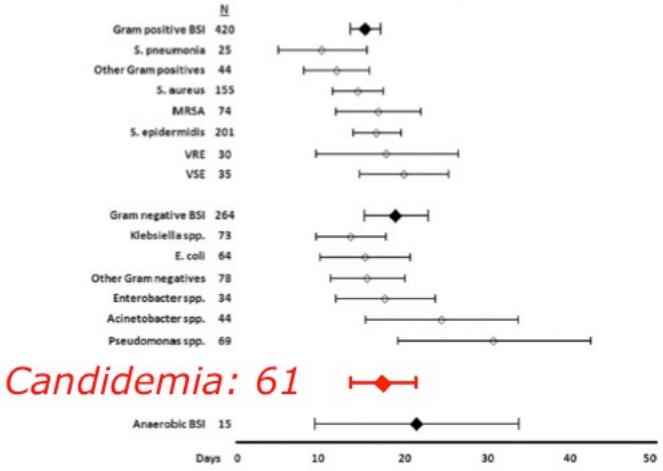

EPIC II study
Kett D et al.
CCM 2011; 39:665-70

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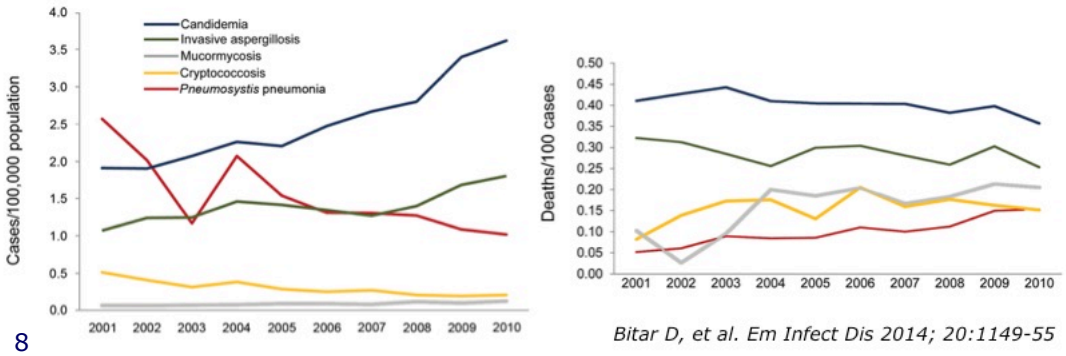
Epidemiology of severe *Candida* infections

Incidence (/1000)

Candidemia

population	0.1
hospitalized	1
ICU	10
BMT	20



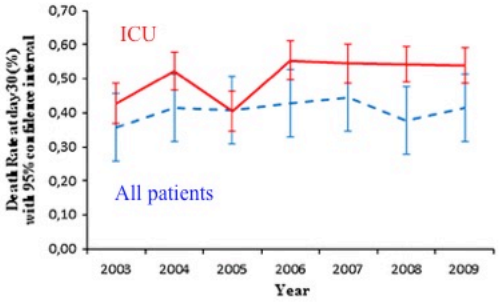
Bitar D, et al. Em Infect Dis 2014; 20:1149-55

8

Outcome of candidemia

Crude mortality
30% to 60%

2507 candidemia in Paris aera(2002-2010)

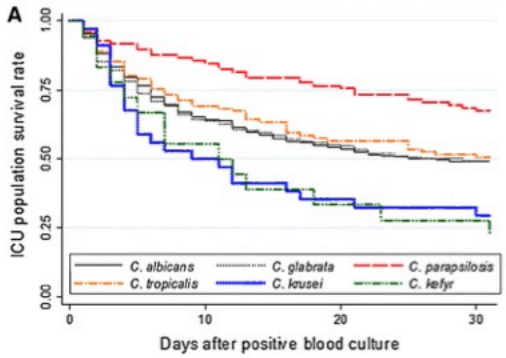


9 The French Mycosis Study Group
Lortholary O et al. ICM 2014; 40:1303-12.

Outcome of candidemia

Crude mortality
30% to 60%

1206 candidemia in ICU patients (2002-2010)

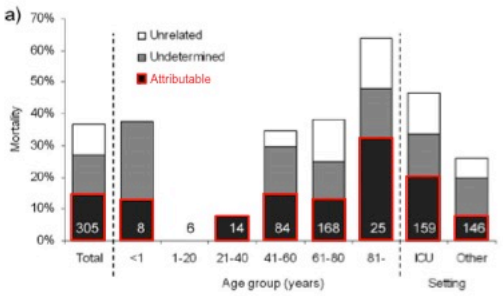


10 The French Mycosis Study Group
Lortholary O et al. ICM 2014; 40:1303-12.

Outcome of candidemia

Crude mortality
30% to 60%

Attributable mortality
25% to 40%



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

Epidemiology of severe *Candida* infections

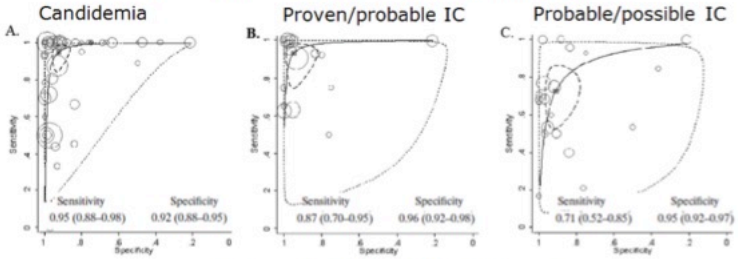
Incidence (/1000)

Candidemia

population	0.1
hospitalized	1
ICU	10
BMT	20

PCR Diagnosis of Invasive Candidiasis: Systematic Review and Meta-Analysis[▽]†

Tomer Avni,[1]* Leonard Leibovici,[1] and Mical Paul[2]



JOURNAL OF CLINICAL MICROBIOLOGY, Feb. 2011, p. 665–670

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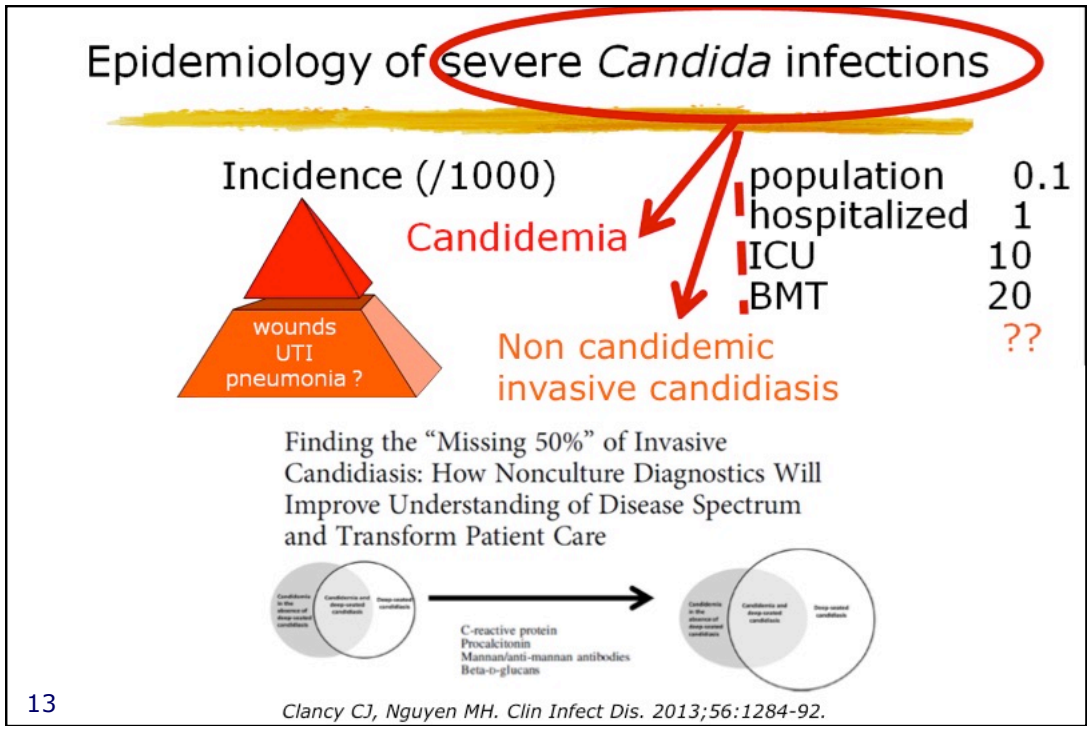
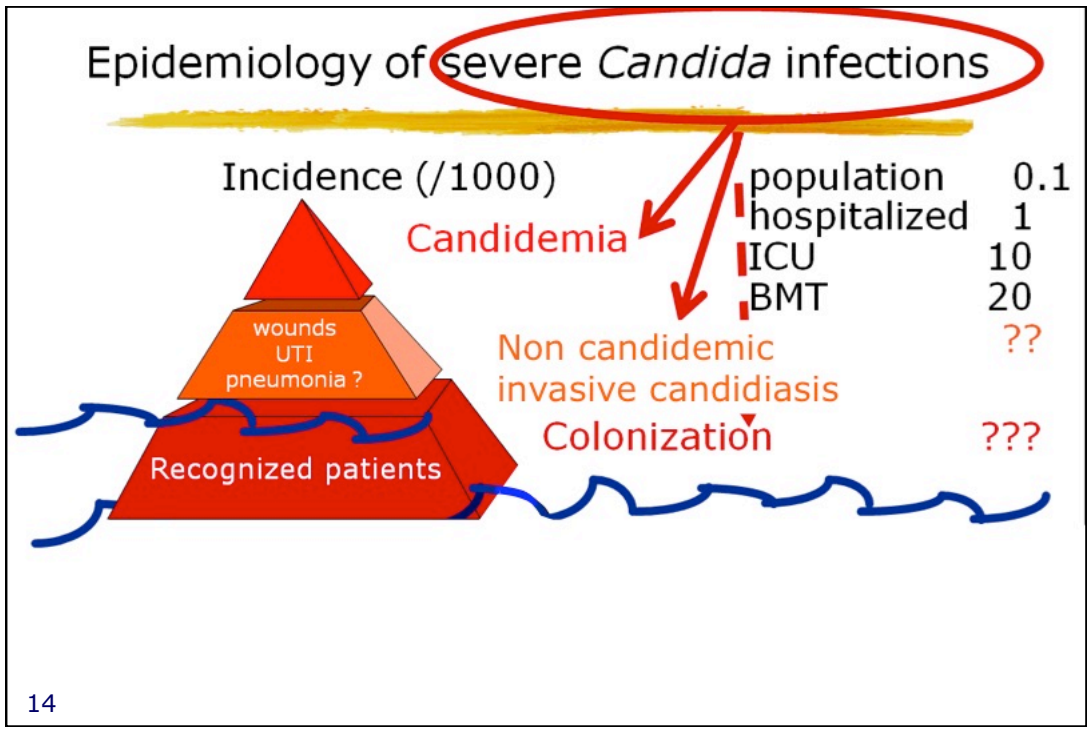

Epidemiology of severe *Candida* infections
Incidence (/1000)
Candidemia
wounds
UTI
pneumonia ?
population 0.1
hospitalized 1
ICU 10
BMT 20
Non candidemic
invasive candidiasis
??
Finding the "Missing 50%" of Invasive Candidiasis: How Nonculture Diagnostics Will Improve Understanding of Disease Spectrum and Transform Patient Care
C-reactive protein
Procalcitonin
Mannan/anti-mannan antibodies
Beta-D-glucans
13
Clancy CJ, Nguyen MH. Clin Infect Dis. 2013;56:1284-92.


Epidemiology of severe *Candida* infections
Incidence (/1000)
Candidemia
wounds
UTI
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Recognized patients
population 0.1
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ICU 10
BMT 20
Non candidemic
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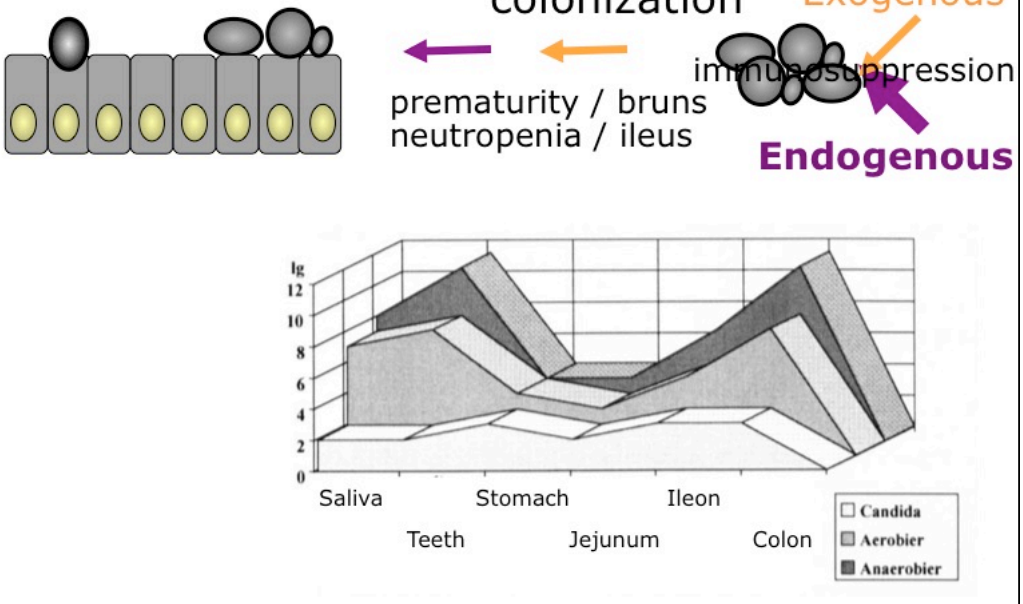
??
Colonization
???
14



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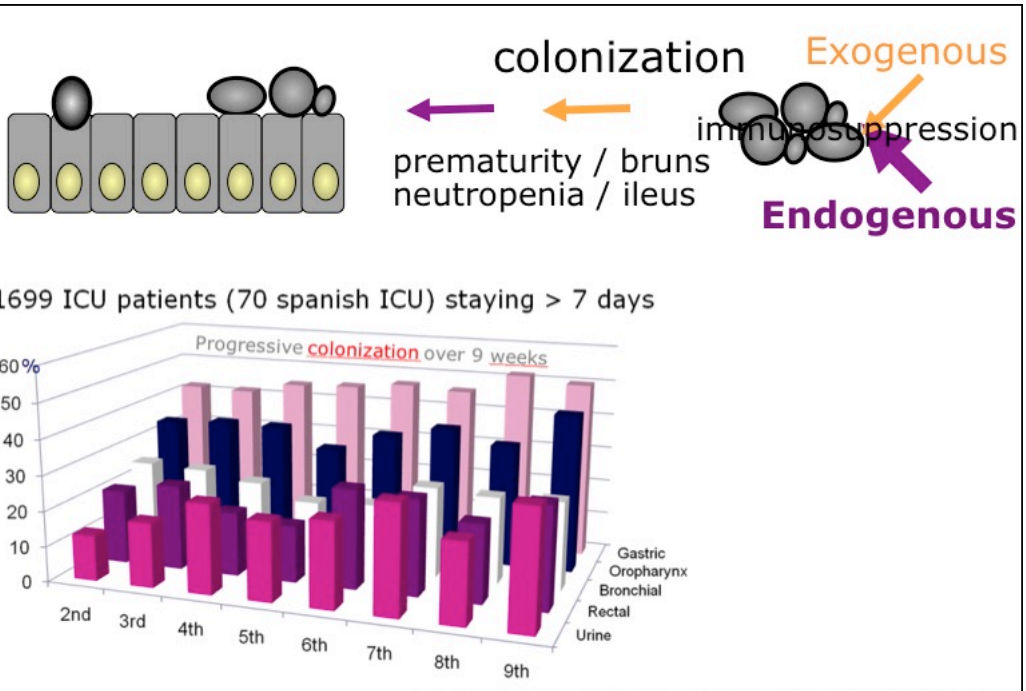
Knoke M. Mycoses. 1999;42(S1):30-4.



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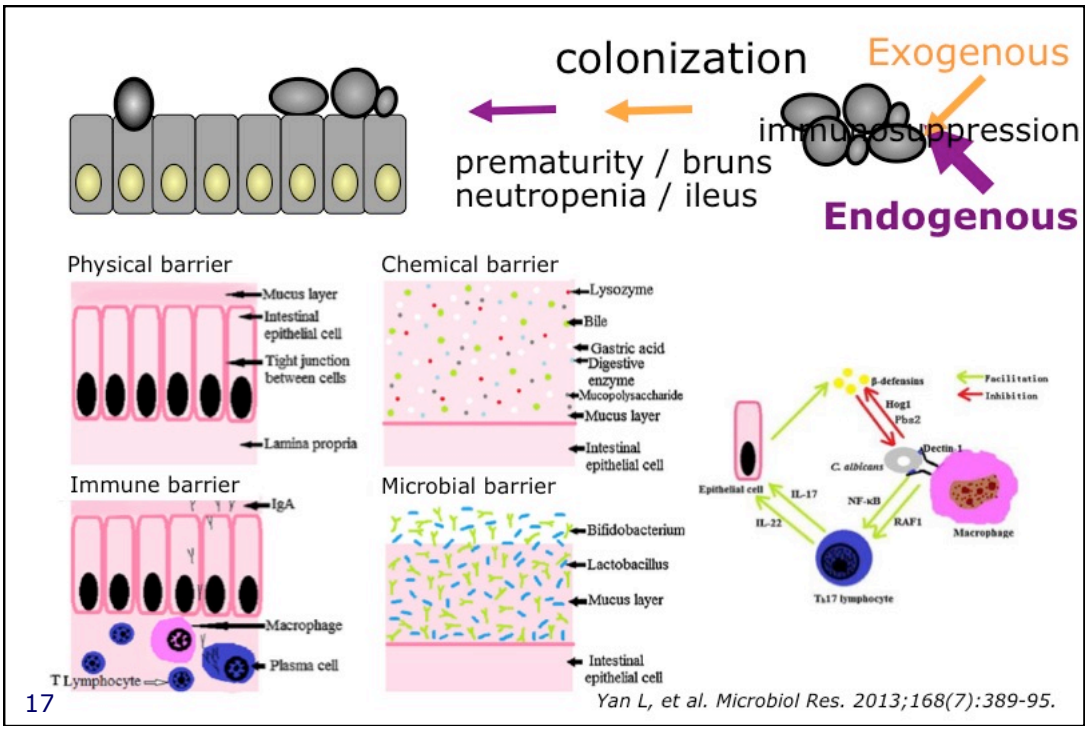
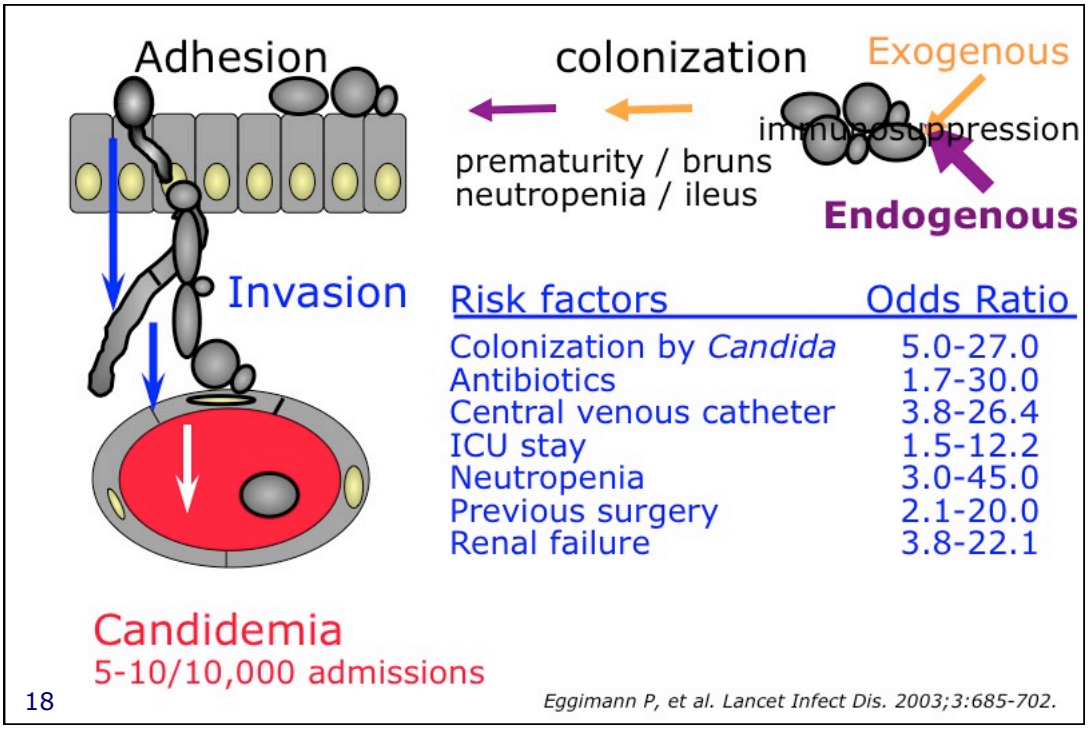
León C, et al. Eur J Clin Microbiol Infect Dis. 2009;28:233-42.



17

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



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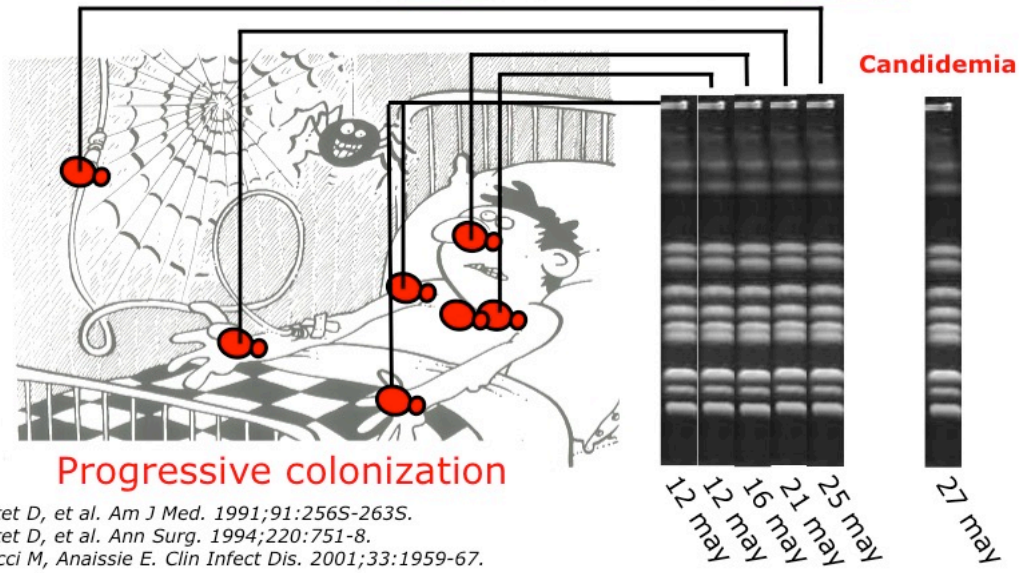
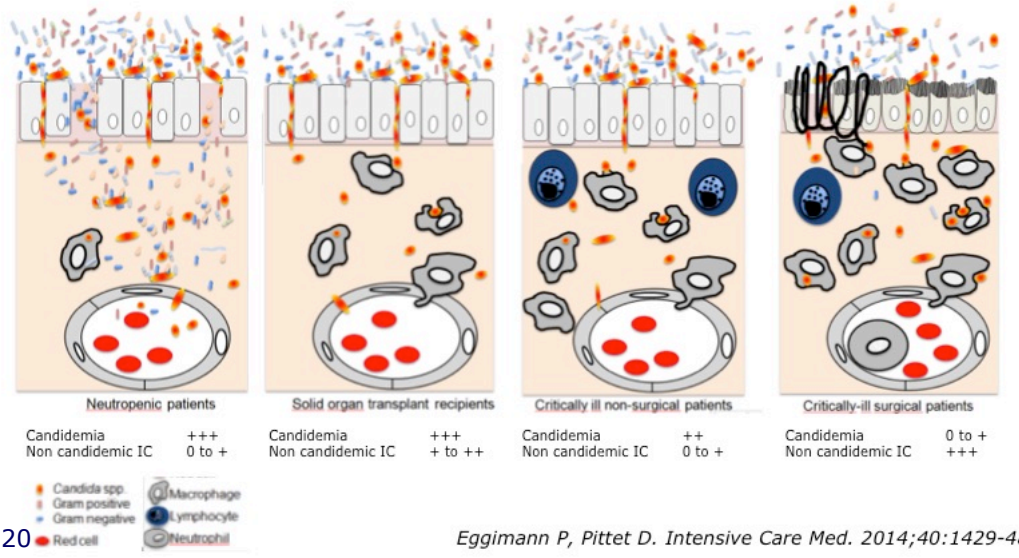
Eggimann P, et al. Lancet Infect Dis. 2003;3:685-702.

Pathophysiology of invasive candidiasis



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



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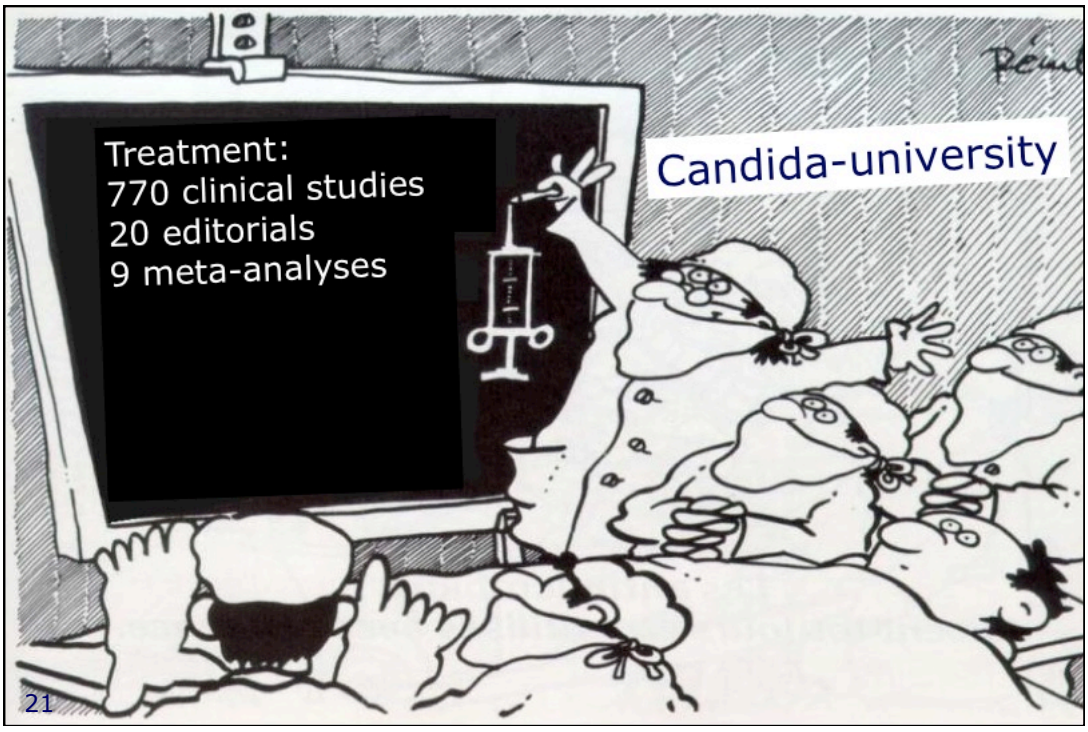
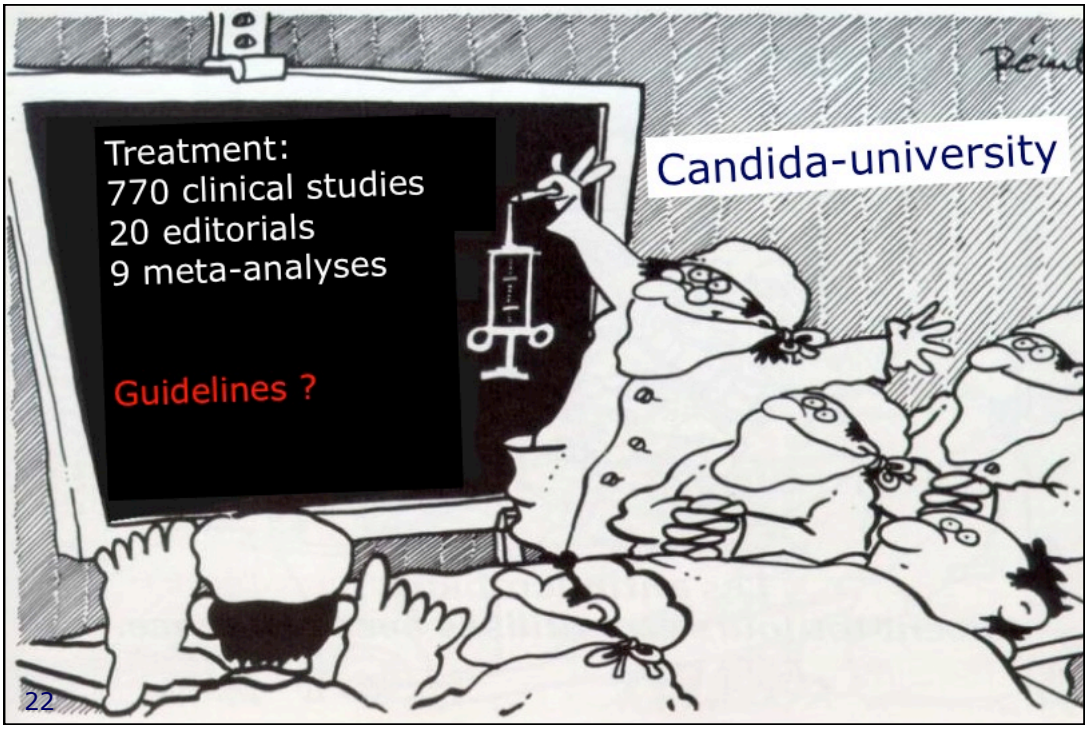
Eggimann P, Pittet D. Intensive Care Med. 2014;40:1429-48.


Treatment:
770 clinical studies
20 editorials
9 meta-analyses
Candida-university
21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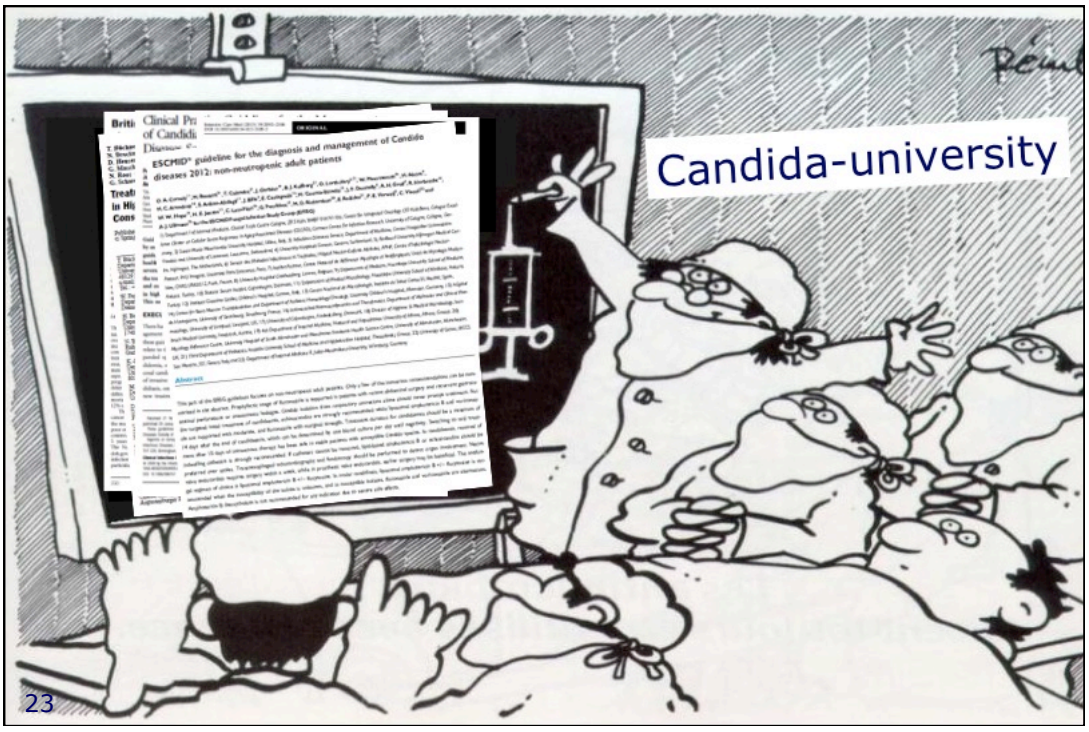
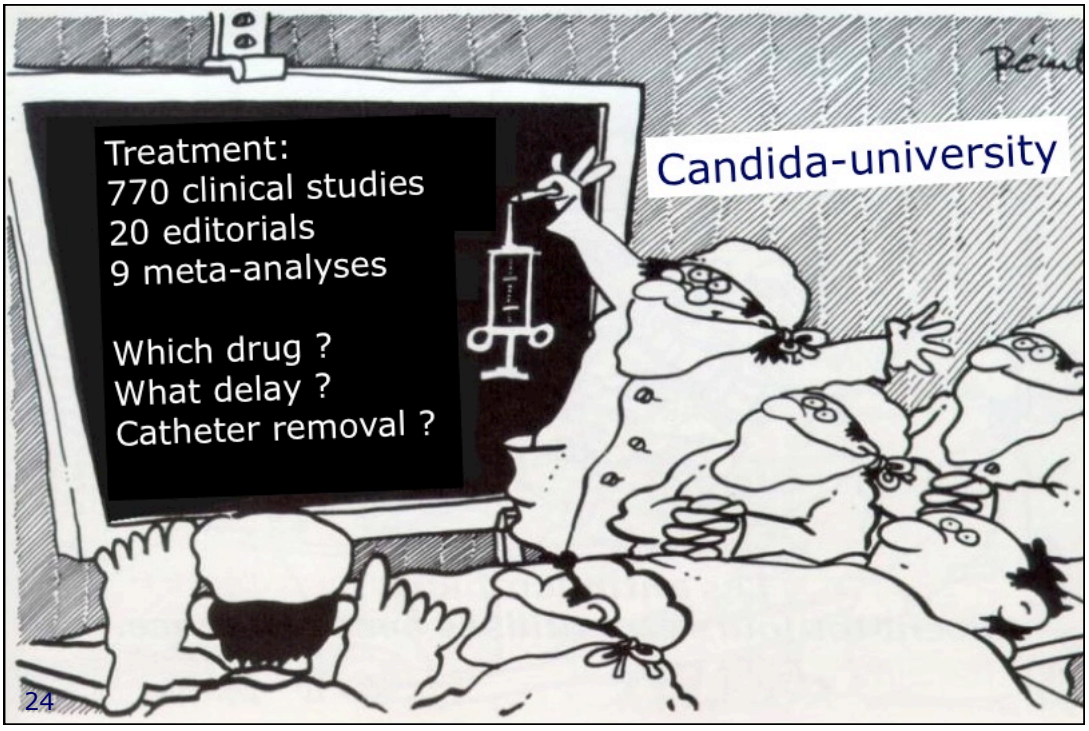
Candida-university
22


ESCMID* guideline for the diagnosis and management of Candida diseases 2012: non-neutropenic adult patients
Candida-university
23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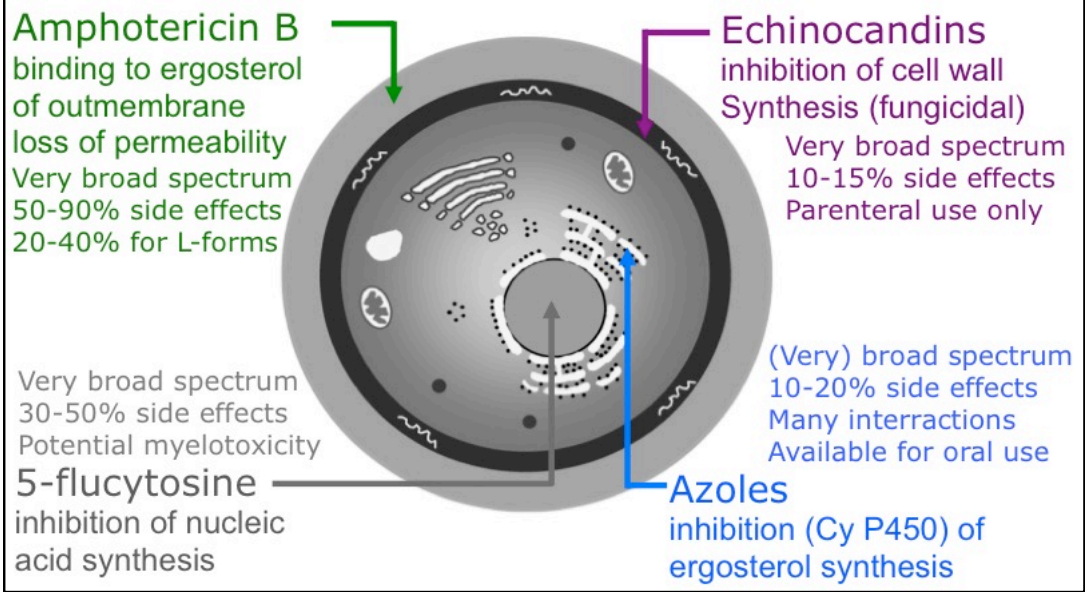
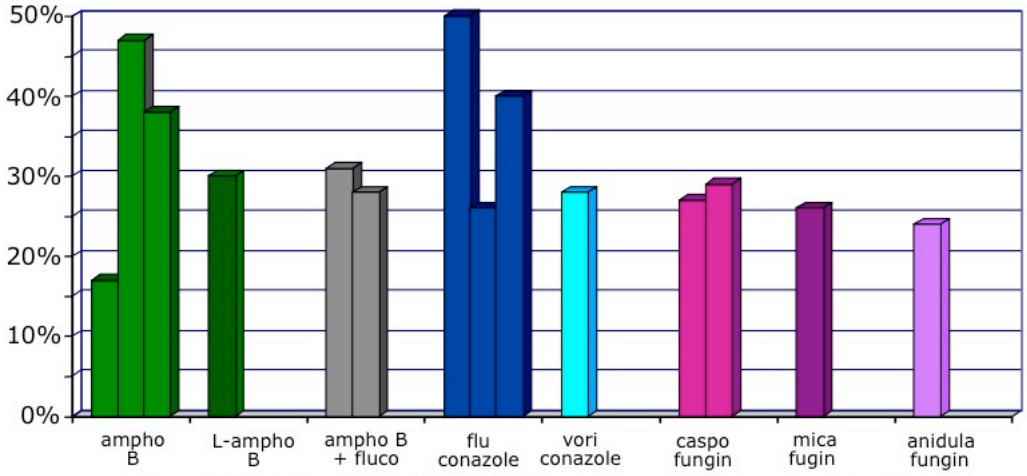
Treatment of documented candidiasis



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

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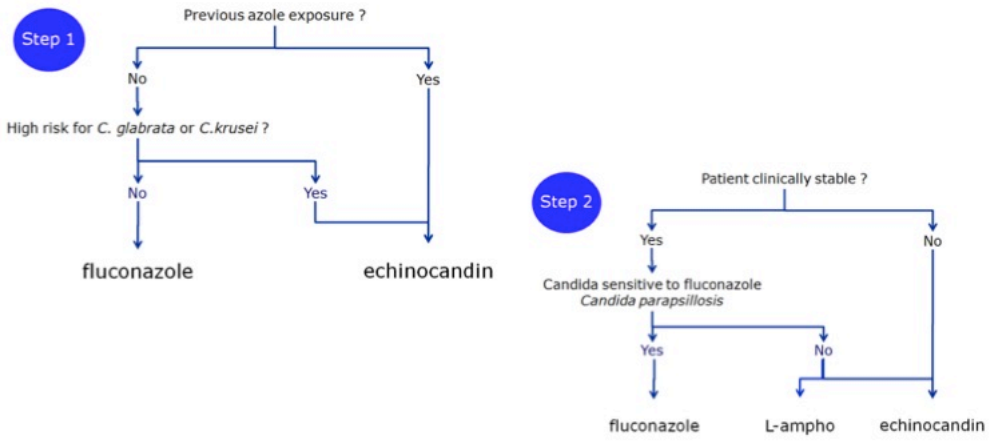
Treatment of documented candidiasis



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

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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						

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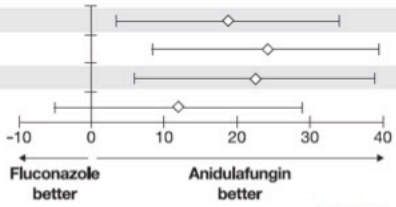
Andes DR, et al. Clin Infect Dis. 2012;54:1110-22.

Treatment of documented candidiasis

Anidulafungin compared with fluconazole for treatment of candidemia and other forms of invasive candidiasis caused by *Candida albicans*: a multivariate analysis of factors associated with improved outcome

Annette C Reboli[1*], Andrew F Shorr[2], Coleman Rotstein[3], Peter G Pappas[4], Daniel H Kett[5], Haran T Schlamm[6], Arlene L Reisman[7], Pinaki Biswas[8] and Thomas J Walsh[9]

End point	Global response n (%) Fluconazole (n = 61)	Anidulafungin (n = 74)	Absolute percent difference between treatments (95% CI)
End of IV therapy	38 (62.3)	60 (81.1)	18.8 (3.7-33.9)
End of all therapy	34 (55.7)	59 (79.7)	24.0 (8.5-39.5)
2-Week follow-up	30 (49.2)	53 (71.6)	22.4 (6.2-38.7)
6-Week follow-up	29 (47.5)	44 (59.5)	12.0 (-4.9-28.7)



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BMC Infectious Diseases 2011, **11**:261

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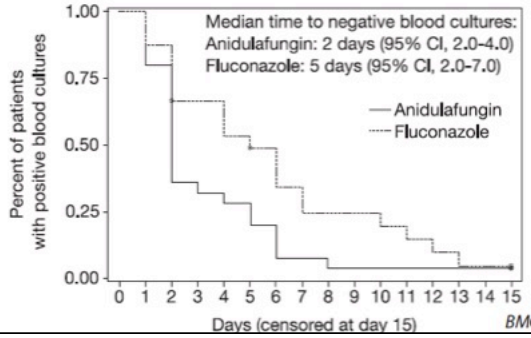

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BMC Infectious Diseases 2011, **11**:261

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	Kose 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	Kose 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$_B$	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$_B$	Noskin CID 1998	
Itraconazole	D	II$_B$	Tuil CCM 2003	
Posaconazole	D	III	No reference found	

EFISG ESCMID FUNGAL INFECTION STUDY GROUP
European Society of Clinical Microbiology and Infectious Diseases

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

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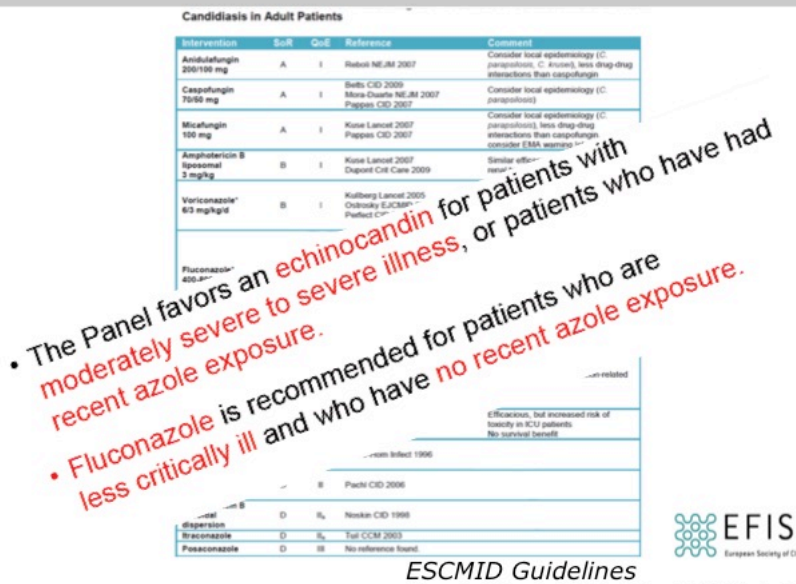
Treatment of documented candidiasis

Candidiasis in Adult Patients



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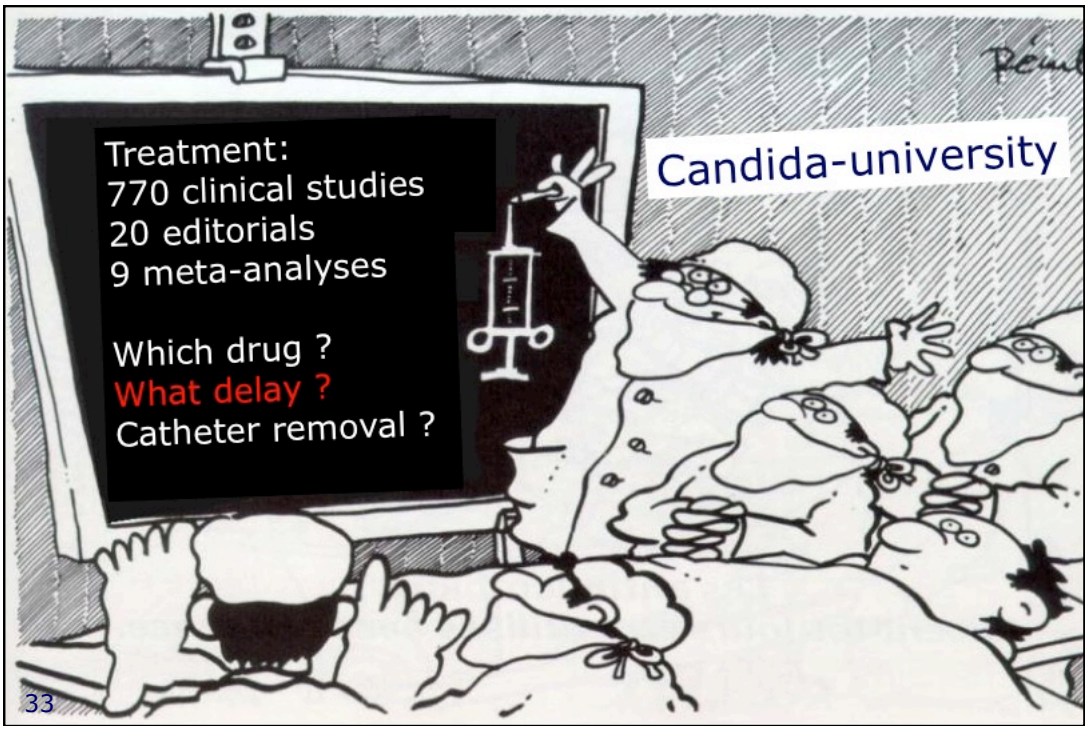
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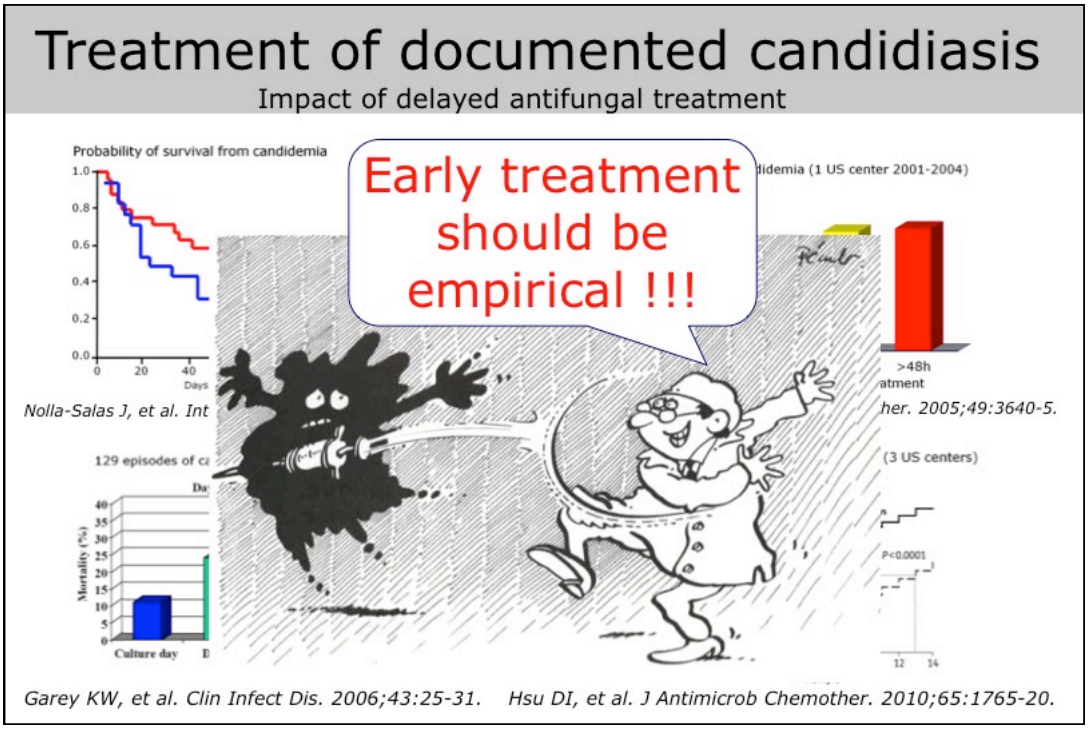
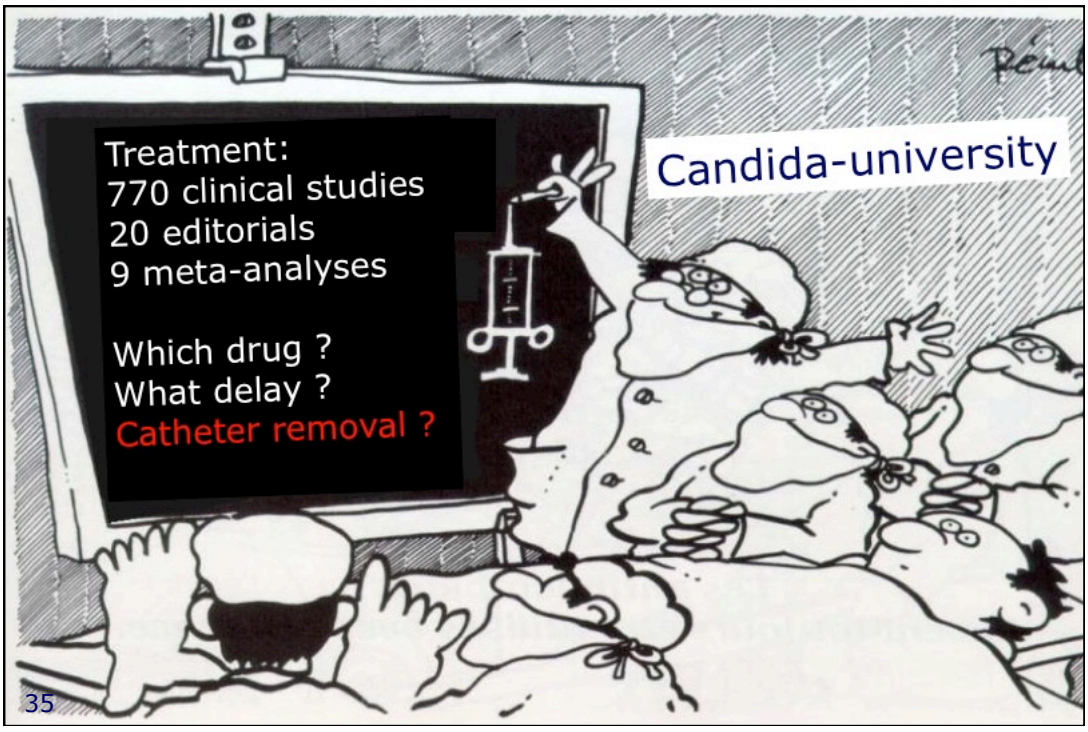
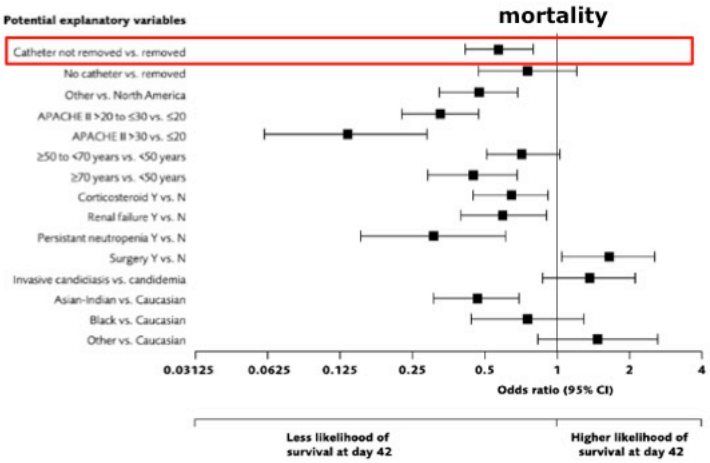

Treatment of documented candidiasis
Impact of delayed antifungal treatment
Probability of survival from candidemia
Early treatment should be empirical !!!
Nolla-Salas J, et al. Int
her. 2005;49:3640-5.
(3 US centers)
Garey KW, et al. Clin Infect Dis. 2006;43:25-31.
Hsu DI, et al. J Antimicrob Chemother. 2010;65:1765-20.



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,



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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

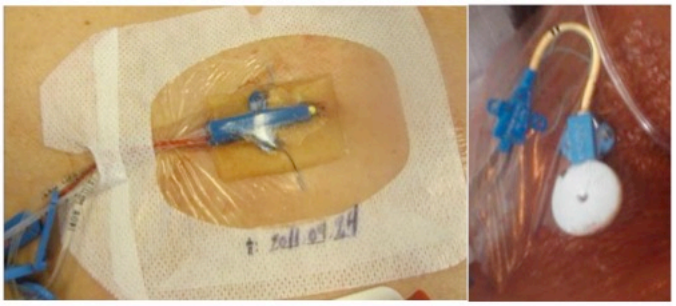
37

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)

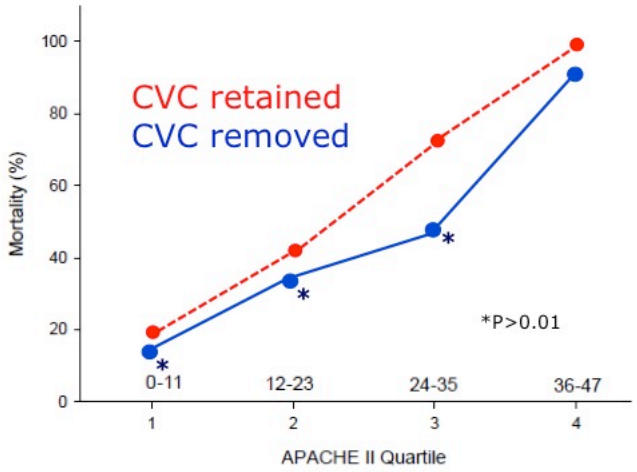


Fungines

Erard V, et al.
50th ICAAC 2010

Candidemia: catheter removal ?

7 pooled studies: 1915 candidemia



39

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

Candidemia: catheter removal ?

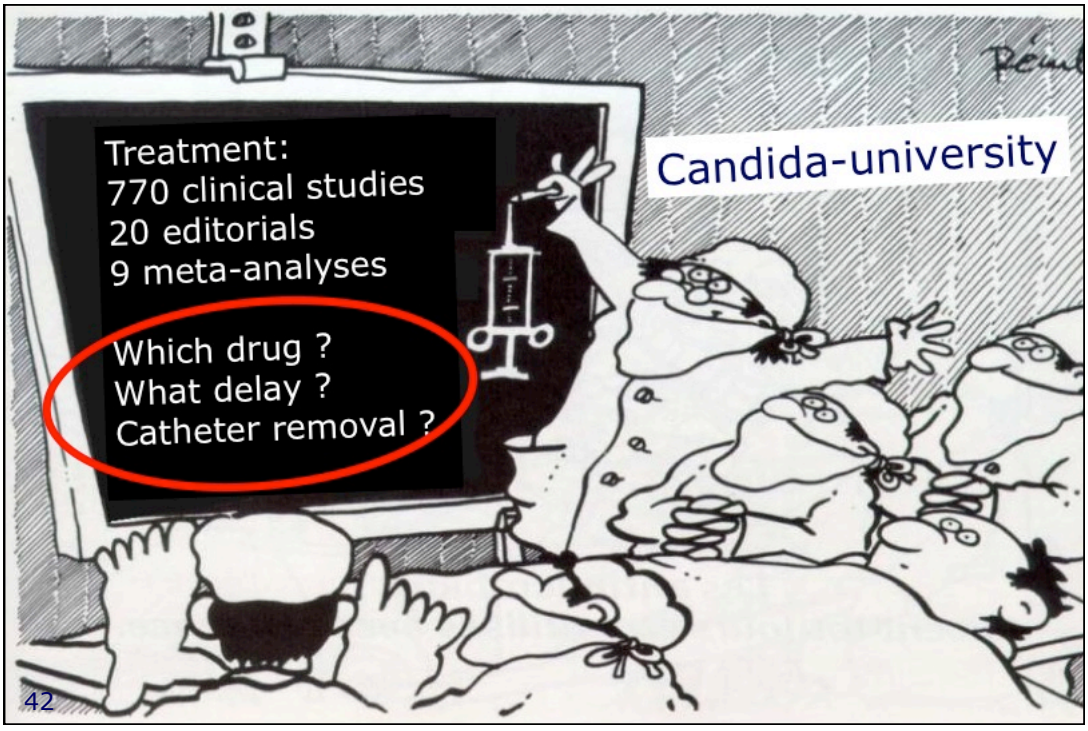
Table 7. Recommendations on Catheter Management in Candidaemia

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.

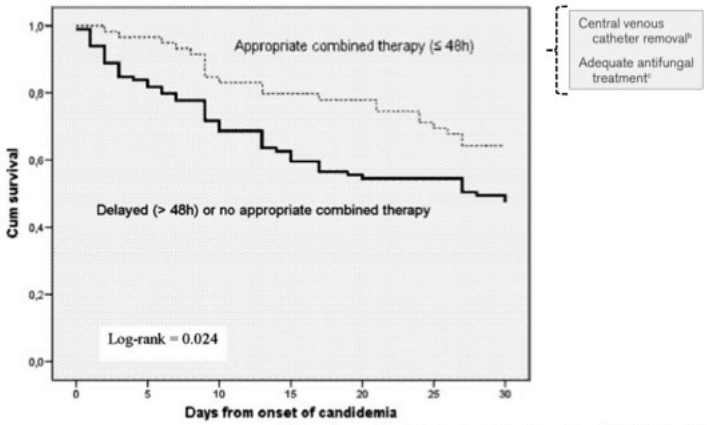
40


Candidemia: catheter removal ?
Please, remove this catheter !
41


Treatment:
770 clinical studies
20 editorials
9 meta-analyses
Which drug ?
What delay ?
Catheter removal ?
Candida-university
42

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

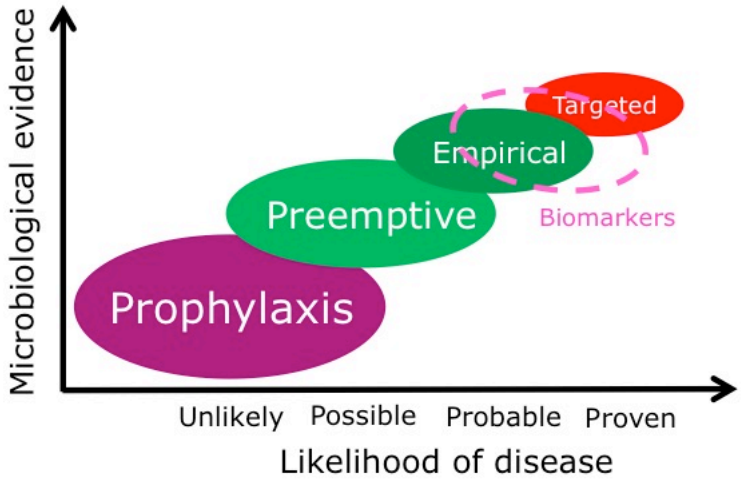
Mireia Puig-Asensio, MD[1]; Javier Pemán, MD[2]; Rafael Zaragoza, MD[3]; José Garnacho-Montero, PhD[4]; Estrella Martín-Mazuelos, MD[5], Manuel Cuenca-Estrella, MD[6] and Benito Almirante, MD[1]; on behalf of the Prospective Population Study on Candidemia in Spain (CANDIPOP) Project, Hospital Infection Study Group (GEIH) and Medical Mycology Study Group (GEMICOMED) of the Spanish Society of Infectious Diseases and Clinical Microbiology (SEIMC), and Spanish Network for Research in Infectious Diseases



43

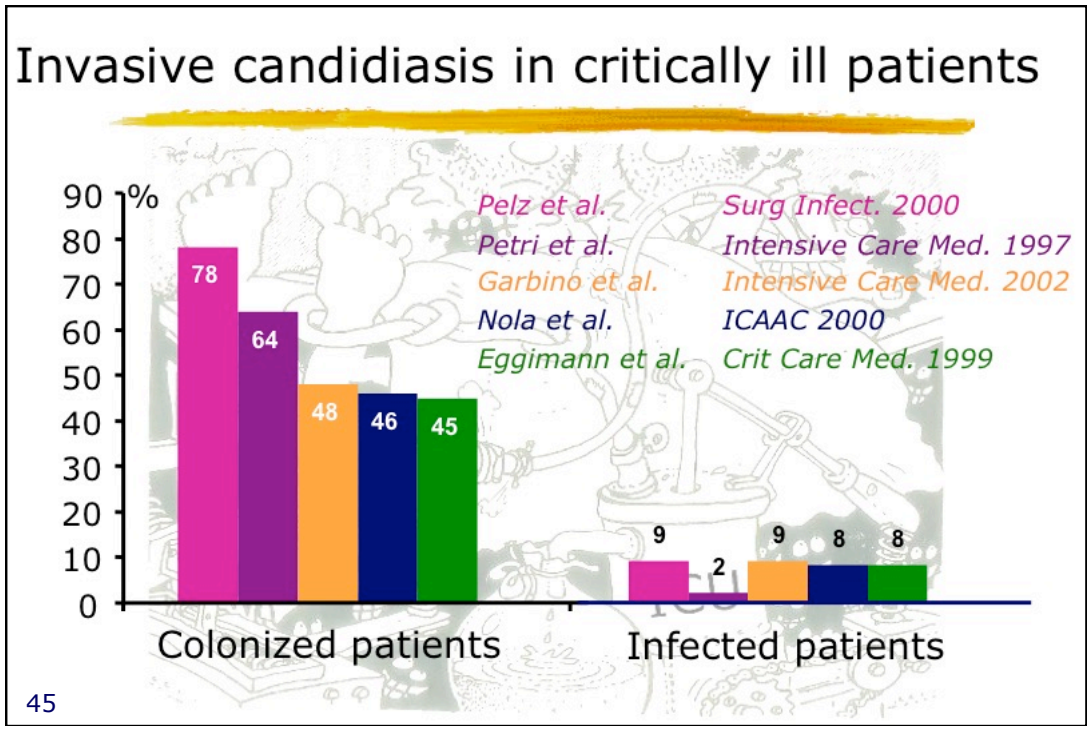
Puig-Asensio M et al. Crit Care Med. 2014;42:1423-32.

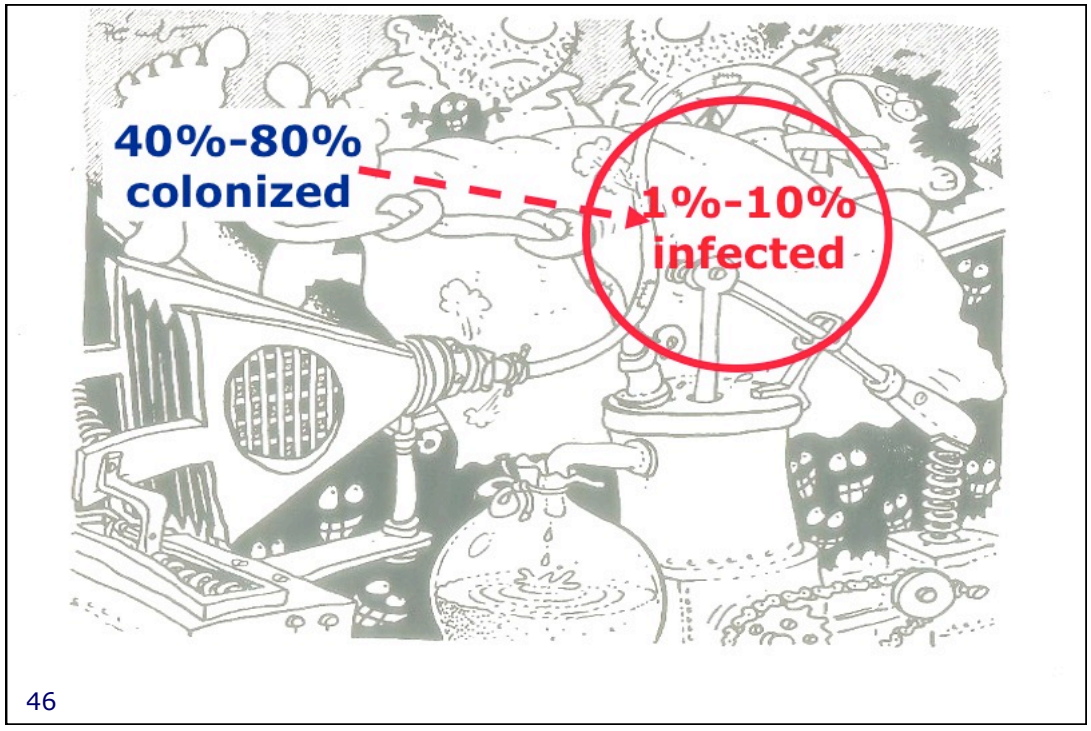
Antifungals in critically ill patients

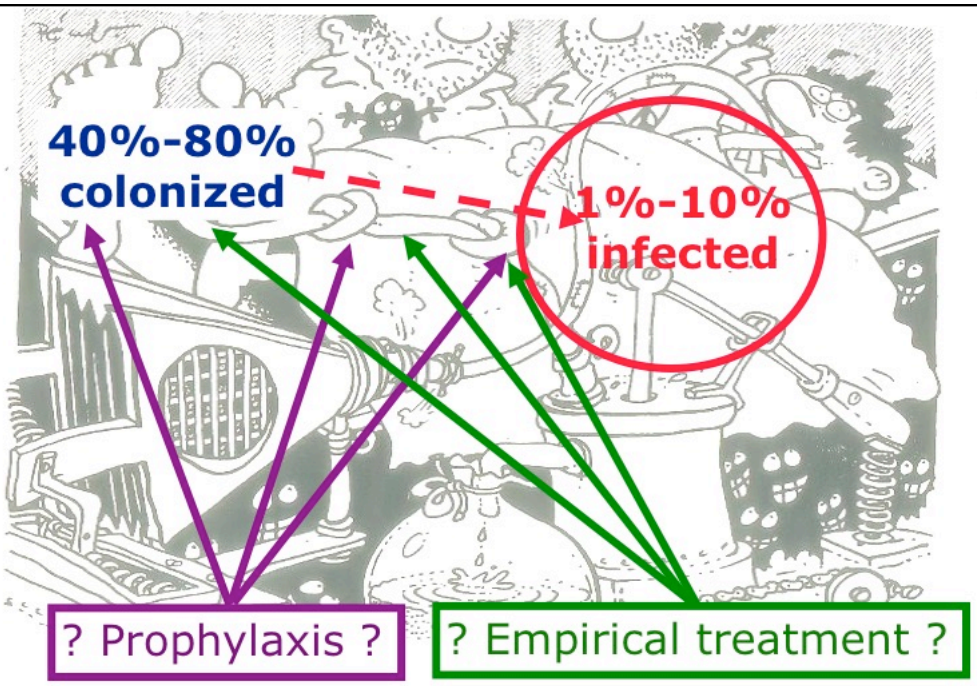


44

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


Invasive candidiasis in critically ill patients
90
80
70
60
50
40
30
20
10
0
%
78
64
48
46
45
9
2
9
8
8
Pelz et al. Surg Infect. 2000
Petri et al. Intensive Care Med. 1997
Garbino et al. Intensive Care Med. 2002
Nola et al. ICAAC 2000
Eggimann et al. Crit Care Med. 1999
Colonized patients
Infected patients
45


40%-80%
colonized
1%-10%
infected
46



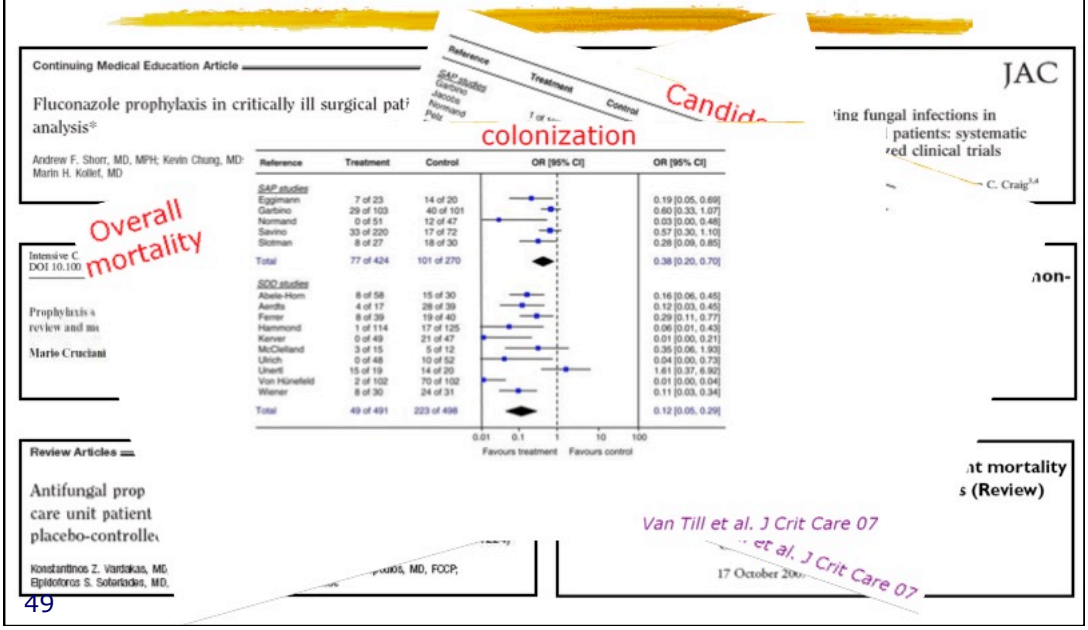
47

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
ESCMID 2014	yes, but	carfully selected pts
IDSA CID 2009/2015	yes	carfully selected pts

48

Antifungal prophylaxis in critically ill patients ?

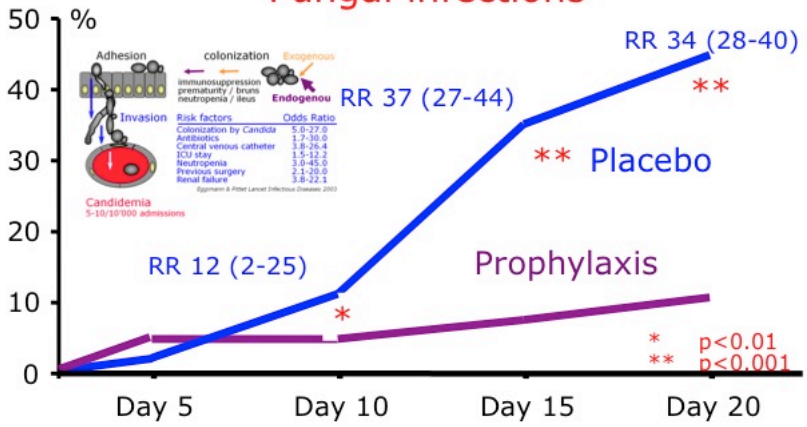


49

Antifungal prophylaxis in critically ill patients ?

Meta-analysis of randomized studies

Fungal infections



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

50

Antifungal 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*

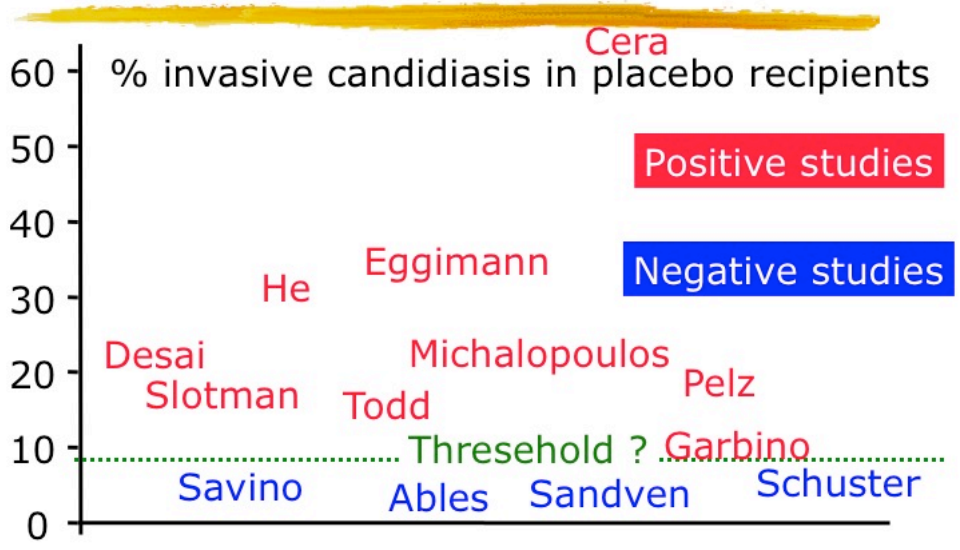
Outcome	Fluconazole Recipients (n = 122), n (%)	Placebo Recipients (n = 127), n (%)
Total failures	67 (55)	73 (57)
No resolution of fever	62 (51)	68 (54)
Documented invasive fungal infection	6 (5)†	11 (9)‡
Need for alternative antifungal agent	12 (10)	20 (16)

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

Ann Intern Med. 2008;149:83-90. www.annals.org

51

Antifungal prophylaxis in critically ill patients ?



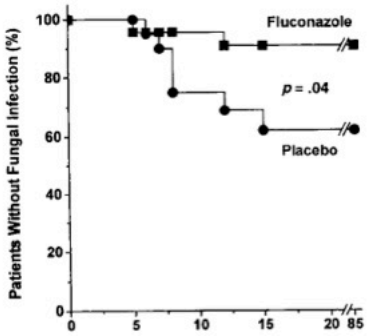
52

Prophylaxis in critically ill patients ?

Fluconazole prophylaxis prevents intra-abdominal candidiasis in high-risk surgical patients

Philippe Eggimann, MD; Patrick Francioli, MD; Jacques Bille, MD; Rémy Schneider, MD; Mei-Miau Wu, DPH; Germain Chapuis, MD; René Chiolero, MD; André Pannatier, PharmD; Julian Schilling, MD; Stefanos Geroulanos, MD, FCCM; Michel P. Glauser, MD; Thierry Calandra, MD, PhD

Recent abdominal surgery AND recurrent gastrointestinal perforations or anastomotic leakages



(Crit Care Med 1999; 27:1066–1072)

53

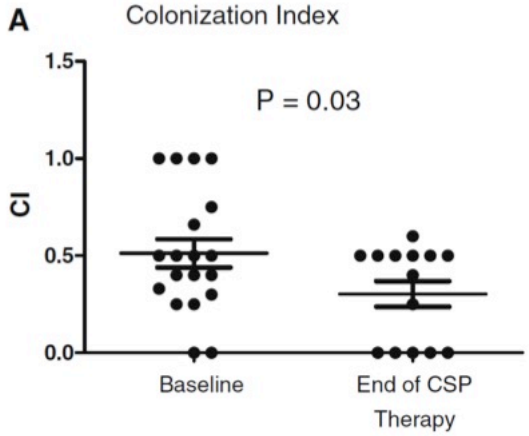
Prophylaxis: very high risk surgical patients

Laurence Senn
Philippe Eggimann
Riadh Ksontini
Andres Pascual
Nicolas Demartines
Jacques Bille
Thierry Calandra
Oscar Marchetti

Caspofungin for prevention of intra-abdominal candidiasis in high-risk surgical patients

Expected candidiasis: 6

Observed candidiasis: 0



Intensive Care Med (2009) 35:903–908

54

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 pr…			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		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.

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

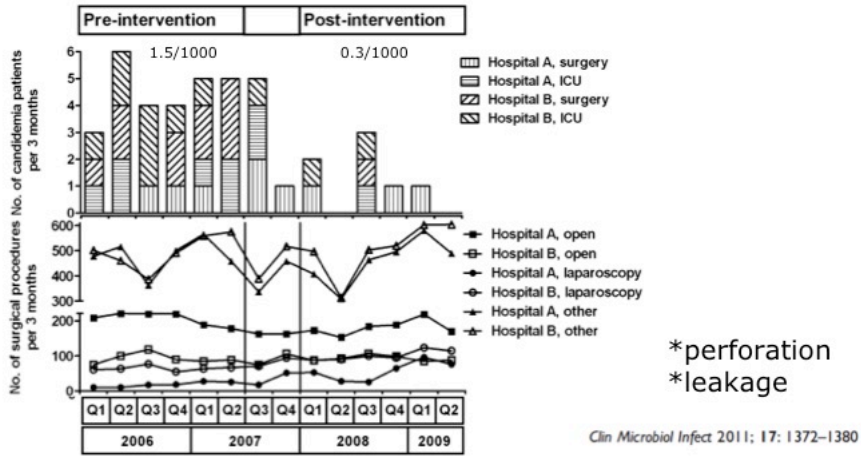
Should be restricted to selected groups of patients

55

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

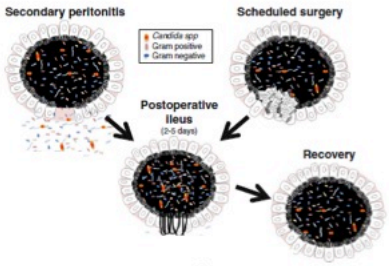
56

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…
ESCMID 2004	yes, but…
IDSA CID 2009/2015	yes, but…

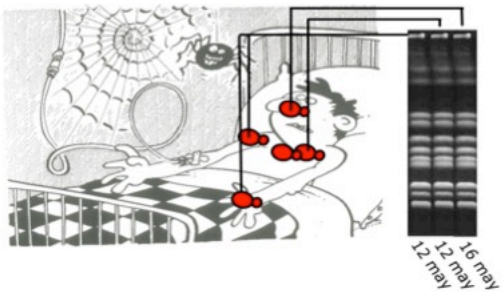
57

Empirical antifungal tx in critically ill patients ?



3 to 5 days

colonized patient
≠
infected patient

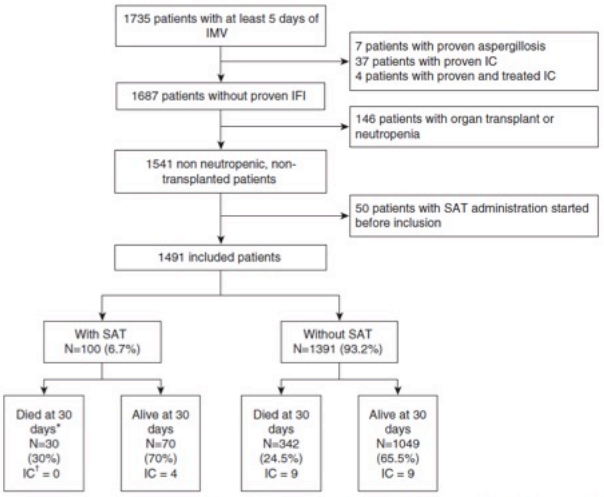


58

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

Failure of Empirical Systemic Antifungal Therapy in Mechanically Ventilated Critically Ill Patients

Sébastien Bailly[1,2], Lila Bouadma[3], Elie Azoulay[4], Maité Garrouste Orgeas[5], Christophe Adrie[6,7], Bertrand Souweine[8], Carole Schwebel[9], Danièle Maubon[10,11], Rebecca Hamidfar-Roy[9], Michael Darmon[12], Michel Wolff[3], Muriel Cornet[10,11], and Jean-François Timsit[2,3]



59

Am J Respir Crit Care Med Vol 191, Iss 10, pp 1139–1146, May 15, 2015

Failure of Empirical Systemic Antifungal Therapy in Mechanically Ventilated Critically Ill Patients

Sébastien Bailly[1,2], Lila Bouadma[3], Elie Azoulay[4], Maité Garrouste Orgeas[5], Christophe Adrie[6,7], Bertrand Souweine[8], Carole Schwebel[9], Danièle Maubon[10,11], Rebecca Hamidfar-Roy[9], Michael Darmon[12], Michel Wolff[3], Muriel Cornet[10,11], and Jean-François Timsit[2,3]

Table 2. Effect of SAT on 30-Day Mortality or Invasive Candidiasis on Different Subgroups (Sensitivity Analyses)

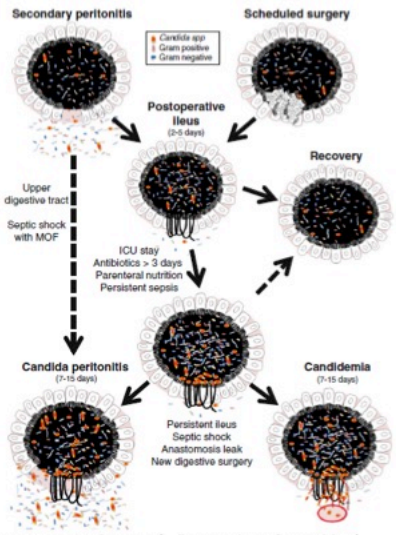
	Total (*n* = 1,491)	SAT (*n* = 100)	Death (*n* = 363)	IC (*n* = 22)	SAT Effect HR (95% CI)	*P* Value
Type of admission						
Medicine	1,251 (84)	84 (84)	314 (86)	16 (73)	0.89 (0.44	0.76
Surgery	240 (16)	16 (16)	49 (13)	6 (27)	8)	0.14
Immunosuppression						
No	1,370 (92)	86 (86)	326 (90)			0.61
Yes	121 (8)	14 (14)				0.21
Abdominal surgery or pancreatitis						
No	1,413 (95)	91				0.88
Yes	78 (5)	9				0.3
SOFA at inclusion*						
0–6	994 (67)	55 (5			(0.15–1.34)	0.15
7–23	497 (33)	45 (45			1.49 (0.69–3.25)	0.31
Candida score at inclusion*						
0–2	781 (52)	38 (38)	(55)	5 (23)	1.48 (0.67–3.26)	0.33
3–5	710 (48)	62 (62)	165 (45)	17 (77)	0.78 (0.28–2.18)	0.87
Multifocal *Candida* colonization at inclusion*						
No	1,230 (83)	66 (66)	281 (77)	17 (77)	1.08 (0.32–3.61)	0.9
Yes	261 (17)	34 (34)	82 (23)	5 (23)	1.24 (0.60–2.55)	0.56

In conclusion, this study fails to show that systematic early antifungal treatment based on risk factors of IC influence the 30-day survival without proved IC in nonneutropenic, nontransplanted patients.

60

Am J Respir Crit Care Med Vol 191, Iss 10, pp 1139–1146, May 15, 2015

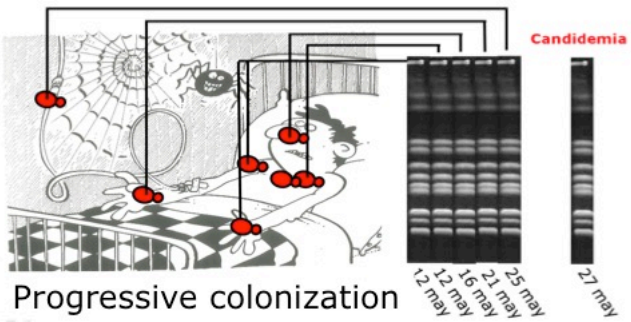
Empirical antifungal tx in critically ill patients ?



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

Invasive candidiasis:
it takes 7 to 14 days

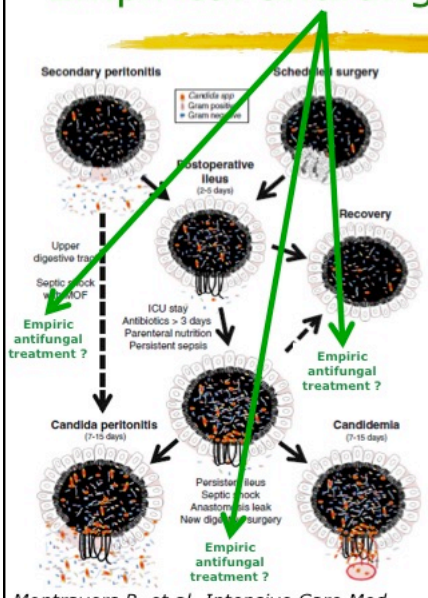
Continuous exposure to risk factors



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 ?



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

Invasive candidiasis:
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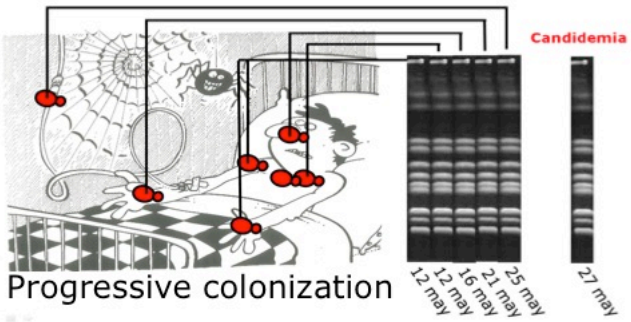

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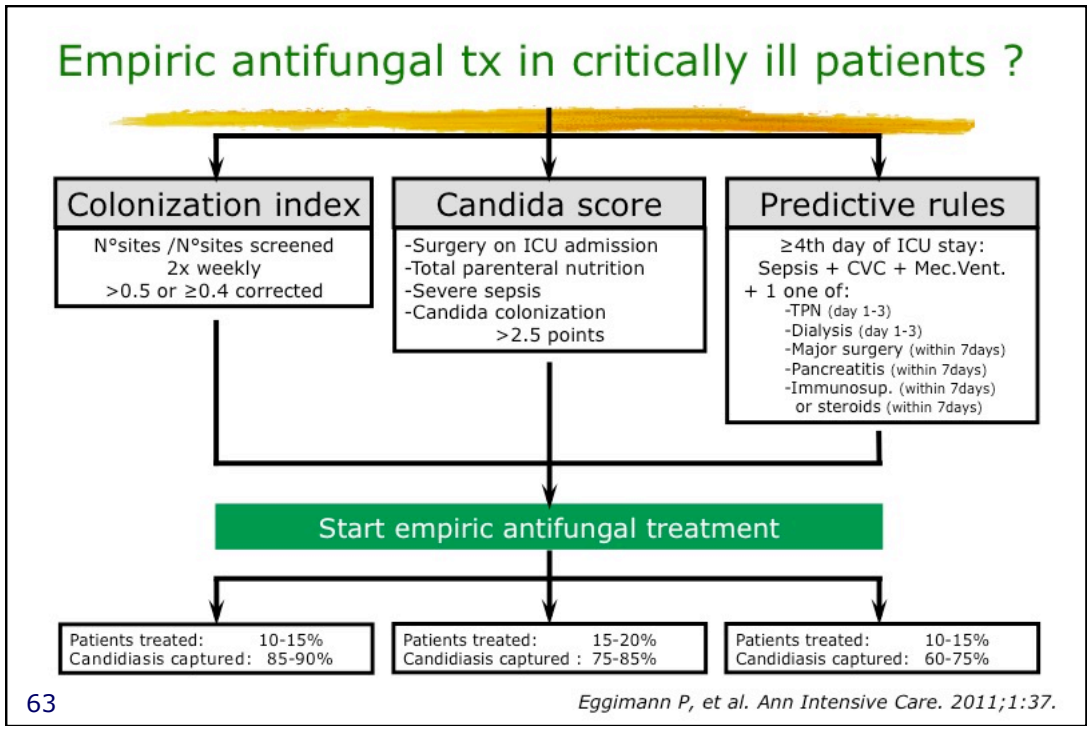
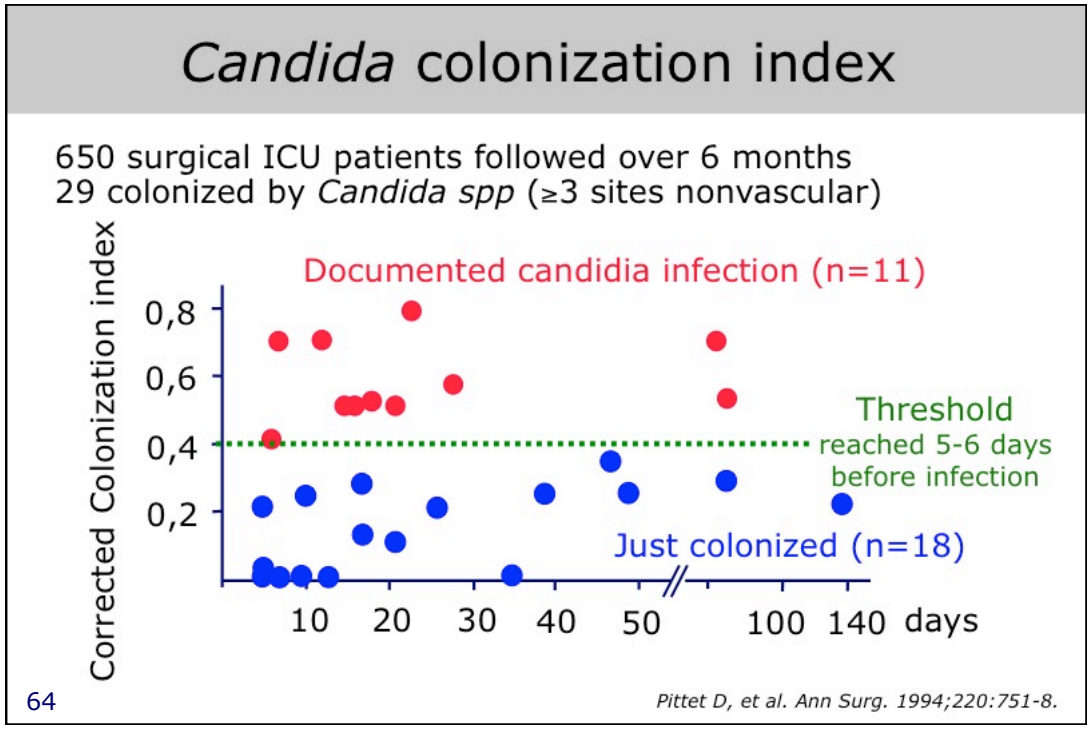

Empiric antifungal tx in critically ill patients ?
Colonization index
N°sites /N°sites screened
2x weekly
>0.5 or ≥0.4 corrected
Candida score
-Surgery on ICU admission
-Total parenteral nutrition
-Severe sepsis
-Candida colonization
>2.5 points
Predictive rules
≥4th day of ICU stay:
Sepsis + CVC + Mec.Vent.
+ 1 one of:
-TPN (day 1-3)
-Dialysis (day 1-3)
-Major surgery (within 7days)
-Pancreatitis (within 7days)
-Immunosup. (within 7days)
or steroids (within 7days)
Start empiric antifungal treatment
Patients treated: 10-15%
Candidiasis captured: 85-90%
Patients treated: 15-20%
Candidiasis captured : 75-85%
Patients treated: 10-15%
Candidiasis captured: 60-75%
63
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)
Corrected Colonization index
0,8
0,6
0,4
0,2
Documented candidia infection (n=11)
Threshold
reached 5-6 days
before infection
Just colonized (n=18)
10
20
30
40
50
100
140
days
64
Pittet D, et al. Ann Surg. 1994;220:751-8.

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
- the efficacy of antifungal prophylaxis:

} 1985 patients

To guide empirical antifungal treatment: 4 studies } 714 patients

To compare the accuracy of other tests:
- Candida score: 4 studies
- Mannans/antimannans: 2 studies
- CAGTA: 1 study
- Betaglucans: 2 studies

} 1582 patients

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.

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

Candida colonization index

Candida Colonization as a Risk Marker for Invasive Candidiasis in Mixed Medical-Surgical Intensive Care Units: Development and Evaluation of a Simple, Standard Protocol

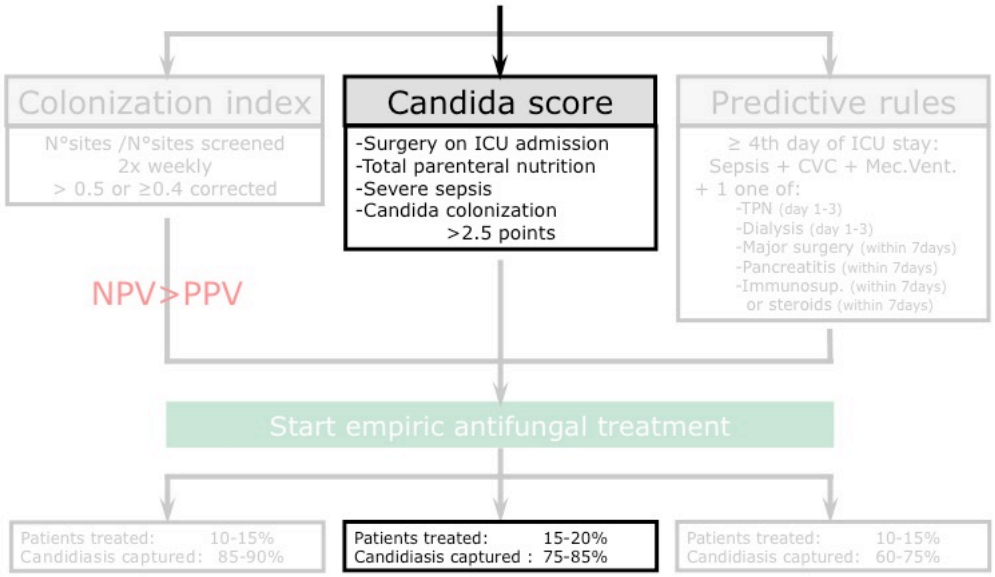
Anna F. Lau,[a*] Masrura Kabir,[a] Sharon C.-A. Chen,[a,b] E. Geoffrey Playford,[c] Deborah J. Marriott,[d] M... ...rey Lipman,[f] Emma McBryde,[g] Thomas Gottlieb,[h] Winston Cheung,[i] Ian Seppelt,[j] Jonathan Iredell,[a,k] Ta...

73/6015 (1%) IC (43 candidemia; 15 n... ...inic IC; 15 probable IC)

Negative predictive value >> positive predictive value

Variable[a]				...% confidence interval (low)	95% confidence interval (high)	Sensitivity (%)	Specificity (%)	PPV[c] (%)	NPV[d] (%)
Time point 1 (n studied = 6,015) days 3 to 4 post-ICU admis...									
At least 2 sites ...	1,671	2.25	0.0005	1.4	3.5	48	71	2	99
All 3 sit...	342	2.25	0.016	1.16	4.34	14	94	3	99
At least ... ...y density (CCI[f] ≥ 0.3)	1,549	3.7	<0.0001	2.36	5.93	58	74	3	99
At least 2 ...es heavy density	448	3.1	0.001	1.77	5.4	21	92	3	99
At least throat heavy density	1,025	3.77	<0.0001	2.39	5.94	45	82	3	99
At least perineum heavy density	703	2	0.01	1.15	3.46	22	88	2	99
At least urine heavy density	327		NS[g]						

Empiric antifungal tx in critically ill patients ?



67

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

Candida score

A bedside scoring system ("Candida score") for early antifungal treatment in nonneutropenic critically ill patients with *Candida* colonization

Cristóbal León, MD; Sergio Ruiz-Santana, MD, PhD; Pedro Saavedra, PhD; Benito Almirante, MD, PhD; Juan Nolla-Salas, MD, PhD; Francisco Álvarez-Lerma, MD, PhD; José Garnacho-Montero, MD; María Ángeles León, MD, PhD; EPCAN Study Group

Variable	Proven Candidal Infection %	*p* Value	Adjusted Odds Ratio (95% Confidence Interval)	Candida score
Surgery on ICU admission				
No	6.9			
Yes	16.5	<.001	2.71 (1.45–5.06)	+1
Total parenteral nutrition				
No	2.8			
Yes	15.5	<.001	2.48 (1.16–5.31)	+1
Severe sepsis				
No	4.5			
Yes	28.8	<.001	7.68 (4.14–14.22)	+2
Candida species colonization				
No	4.2			
Yes	12.3	<.001	3.04 (1.45–6.39)	+1

> 2.5 → 7.75 (CI 4.7 –12.7) time to develop candidiasis

68

León C, et al. Crit Care Med. 2006;34:730-7.

Candida score

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

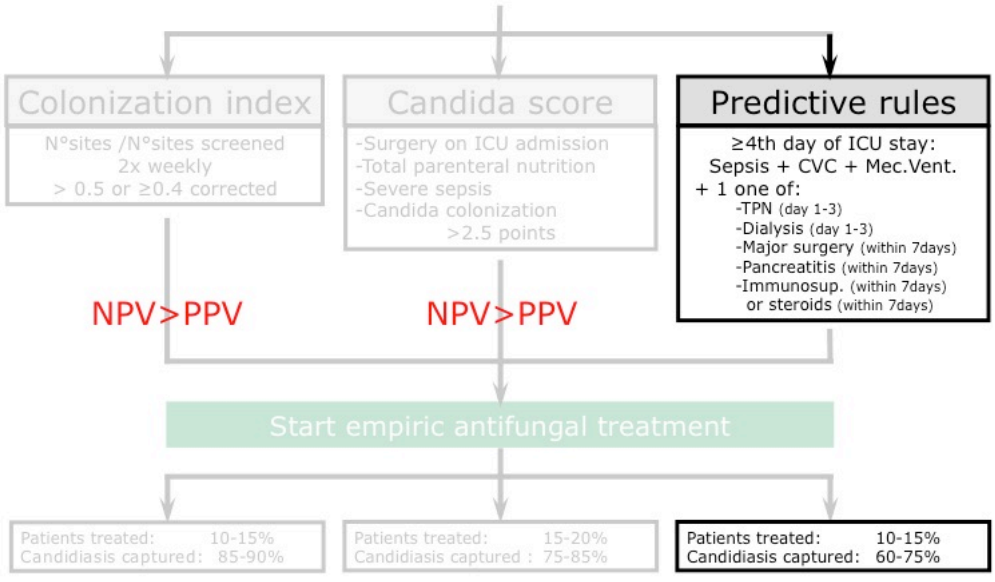
High negative predictive value

Cut-off 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)

69

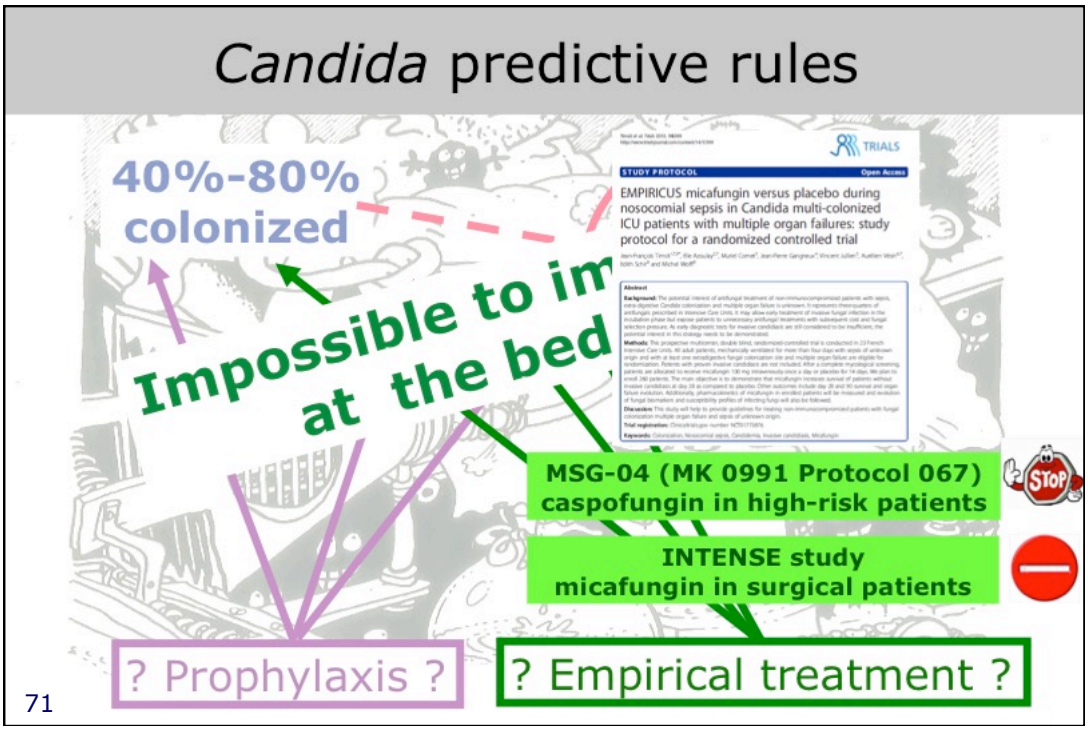
León C, et al. Crit Care Med. 2009;37:1624-33.

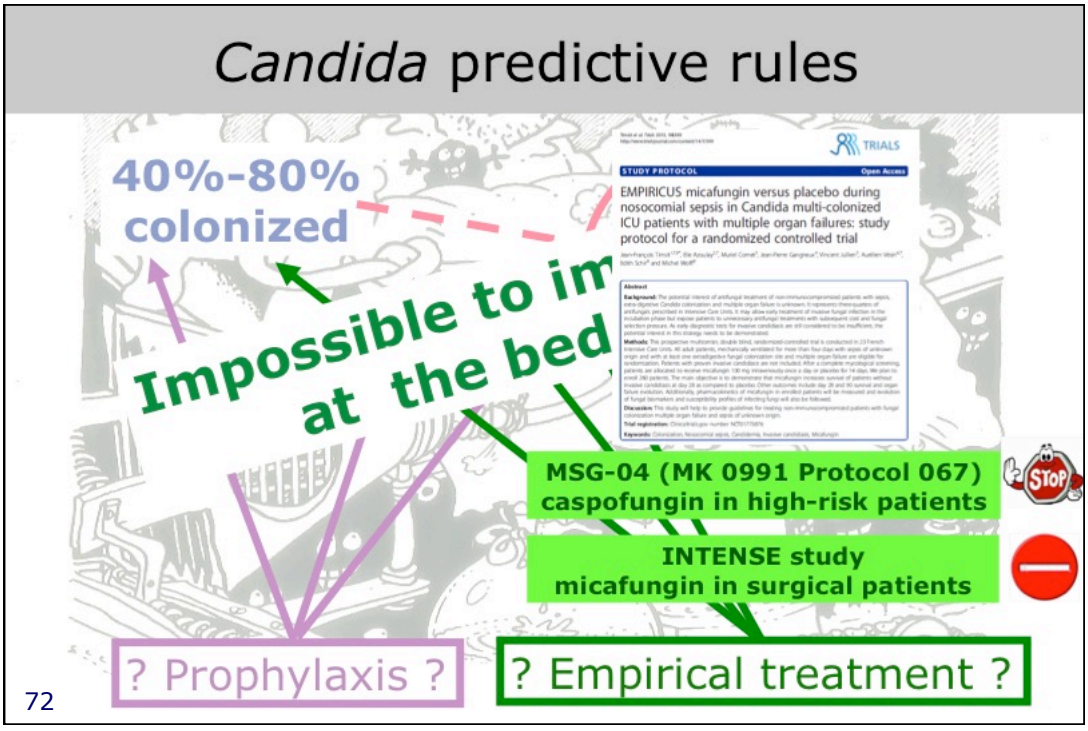
Empiric antifungal tx in critically ill patients ?



70

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


Candida predictive rules
40%-80% colonized
Impossible to im
at the bed
TRIALS
STUDY PROTOCOL
Open Access
EMPIRICUS micafungin versus placebo during nosocomial sepsis in Candida multi-colonized ICU patients with multiple organ failures: study protocol for a randomized controlled trial
MSG-04 (MK 0991 Protocol 067) caspofungin in high-risk patients
INTENSE study micafungin in surgical patients
? Prophylaxis ?
? Empirical treatment ?
71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INTENSE study micafungin in surgical patients
? Prophylaxis ?
? Empirical treatment ?
72

Empiric antifungal tx in critically ill patients ?

Colonization index
N°sites /N°sites screened
2x weekly
> 0.5 or ≥0.4 corrected

Candida score
-Surgery on ICU admission
-Total parenteral nutrition
-Severe sepsis
-Candida colonization
>2.5 points

Predictive rules
≥ 4th day of ICU stay:
Sepsis + CVC + Mec.Vent.
+ 1 one of:
-TPN (day 1-3)
-Dialysis (day 1-3)
-Major surgery (within 7days)
-Pancreatitis (within 7days)
-Immunosup. (within 7days)
or steroids (within 7days)

NPV>PPV

Start empiric antifungal treatment

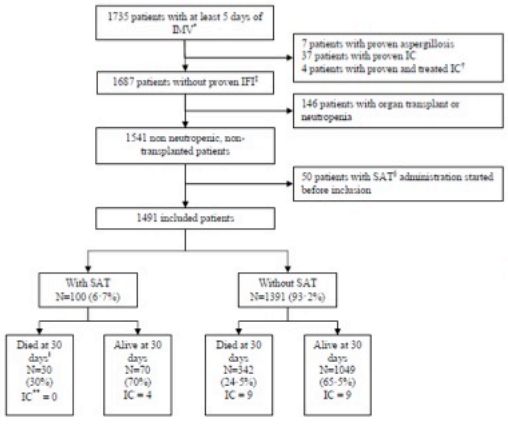
Colonization index	Candida score	Predictive rules
Patients treated: 10-15%	Patients treated: 15-20%	Patients treated: 10-15%
Candidiasis captured: 85-90%	Candidiasis captured : 75-85%	Candidiasis captured: 60-75%

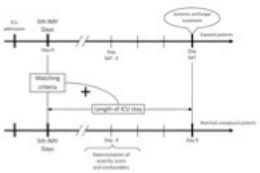
73

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

Failure of Empirical Systemic Antifungal Therapy in Mechanically-ventilated Critically Ill Patients

Sebastien Bailly , Lila Bouadma , Elie Azoulay , Maité Garrouste Orgeas , Bertrand Souweine , Carole Schwebel , Danièle Maubon , Rebecca Hamidfar-Roy , Michael Darmon , Michel Wolff , Muriel Cornet , and Jean-Francois Timsit





		SAT All (N=1491)	SAT Untreated (N=1391)	SAT Treated (N=100)	p value*
Variables at ICU Admission					
Age		65 (53 - 76)	65 (53 - 76)	63 (54 - 75)	0.65
Sex (Male)		950 (64)	898 (65)	52 (52)	0.01
Center					<.01
	A	745 (50)	679 (49)	66 (66)	
	B	486 (33)	465 (33)	21 (21)	
	C,D,E	260 (17)	247 (18)	13 (13)	
ICU admission					0.04
	Medicine	1251 (84)	1167 (84)	84 (84)	
	Elective surgery	85 (6)	84 (6)	1 (1)	
	Emergency surgery	155 (10)	140 (10)	15 (15)	

74

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Table 2: Effect of SAT on 30-day mortality or invasive candidiasis on different sub-groups (sensitivity analyz

		Total N=1491	SAT N=100	Death N=363	IC		
Type of admission	Medicine	1251 (84)	84 (84)				
	Surgery	240 (16)					
Immunosuppression	No						
							0.21
Abdominal surger							0.88
pancrea						1.05 [0.57 ; 1.95]	
					4 (18)	3.92 [0.3 ; 52.14]	0.3
				177 (49)	11 (50)	0.44 [0.15 ; 1.34]	0.15
			45 (45)	186 (51)	11 (50)	1.49 [0.69 ; 3.25]	0.31
		781 (52)	38 (38)	198 (55)	5 (23)	1.48 [0.67 ; 3.26]	0.33
	[3-5]	710 (48)	62 (62)	165 (45)	17 (77)	0.78 [0.28 ; 2.18]	0.87
M							0.9
colonization at inclusion*	No	1230 (83)	66 (66)	281 (77)	17 (77)	1.08 [0.32 ; 3.61]	
	Yes	261 (17)	34 (34)	82 (23)	5 (23)	1.24 [0.60 ; 2.55]	0.56

Experimented clinicians failed to identify ICU patients susceptible to benefit from empirical antifungal treatment

75

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Empiric antifungal tx in critically ill patients ?

Coloniz

N°sites /

> 0.5 o

rules

stay:

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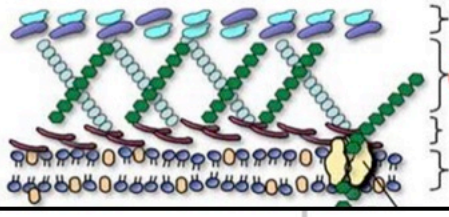
Biomarkers of candidiasis in critically ill patients



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

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

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

76

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)

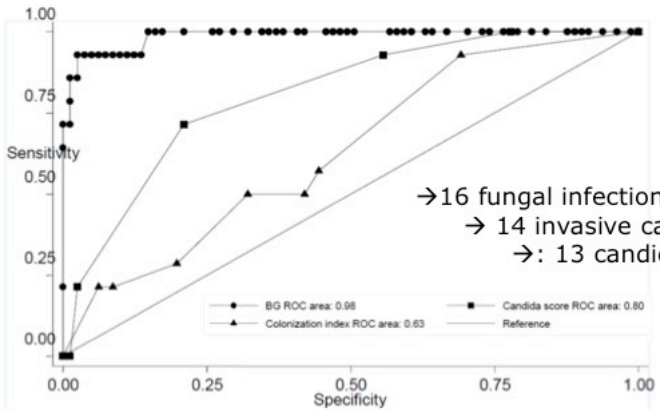
[1]Infectious Diseases Service, Department of Medicine, [2]Institute of Microbiology, and [6]Adult Intensive Care Service, Lausanne University Hospital, Lausanne, Switzerland; [3]Division of Infectious Diseases and Hospital Epidemiology and [4]Intensive Care Service, Basel University Hospital, Basel,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

77

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)



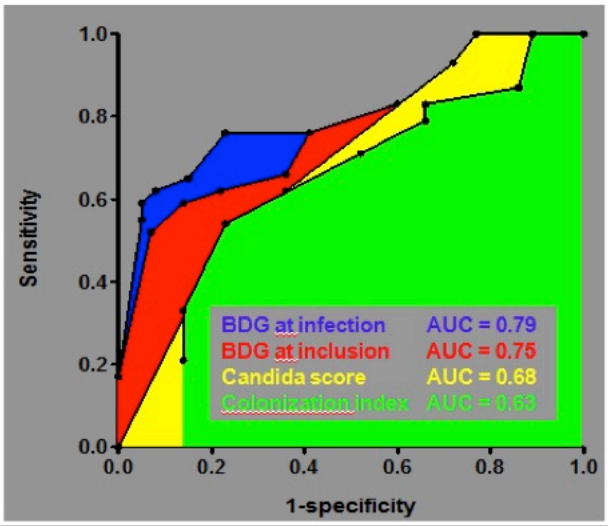
→16 fungal infections
→ 14 invasive candidiasis
→: 13 candidemia

78

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

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Funginos

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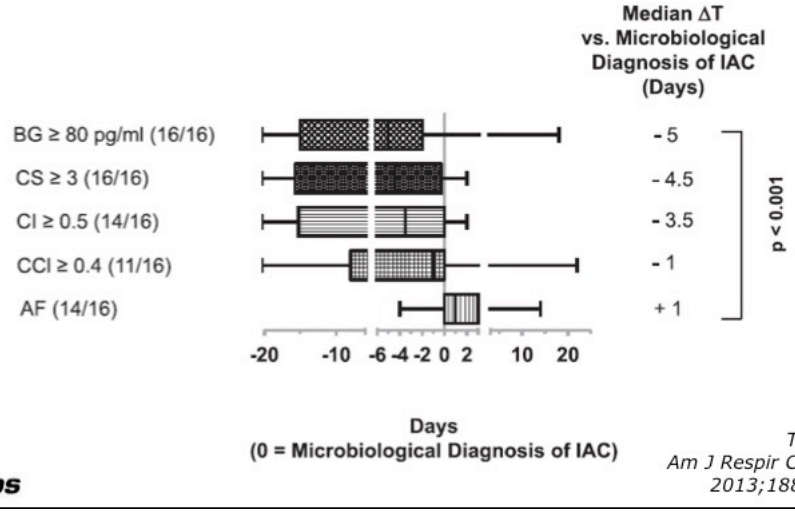

Tissot F, et al. Am J Respir Crit Care Med. 2013;188:1100-1109.

Funginos

Beta-glucan in critically ill patients

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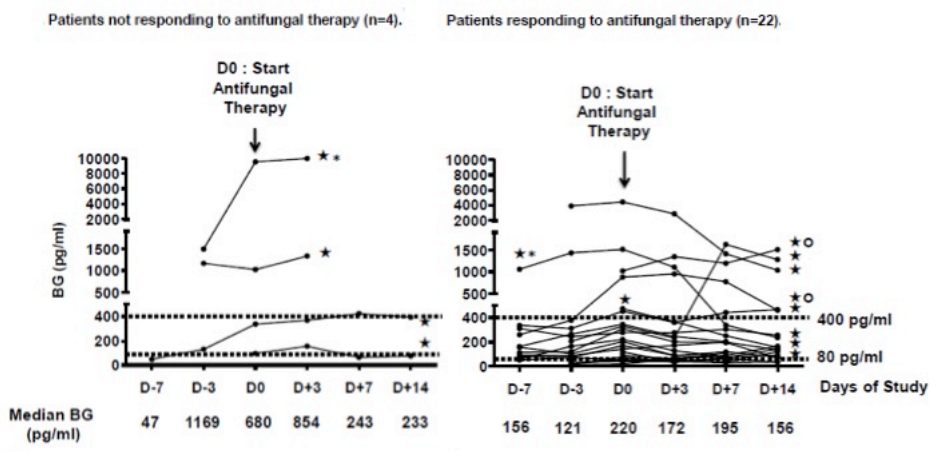
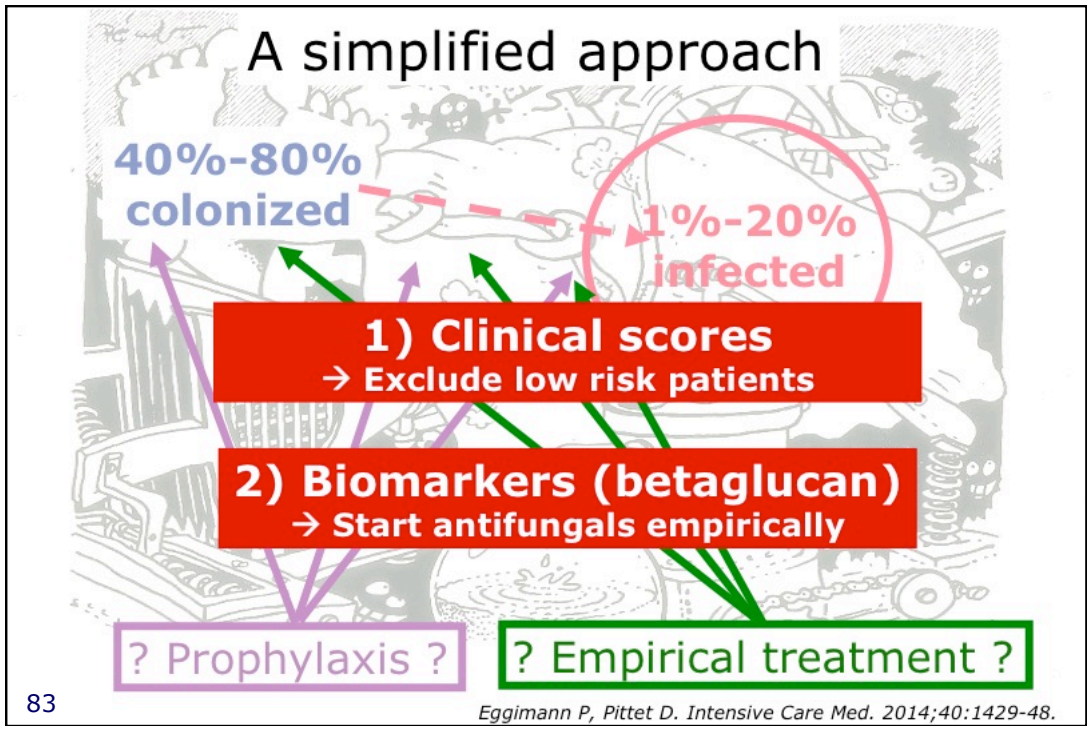
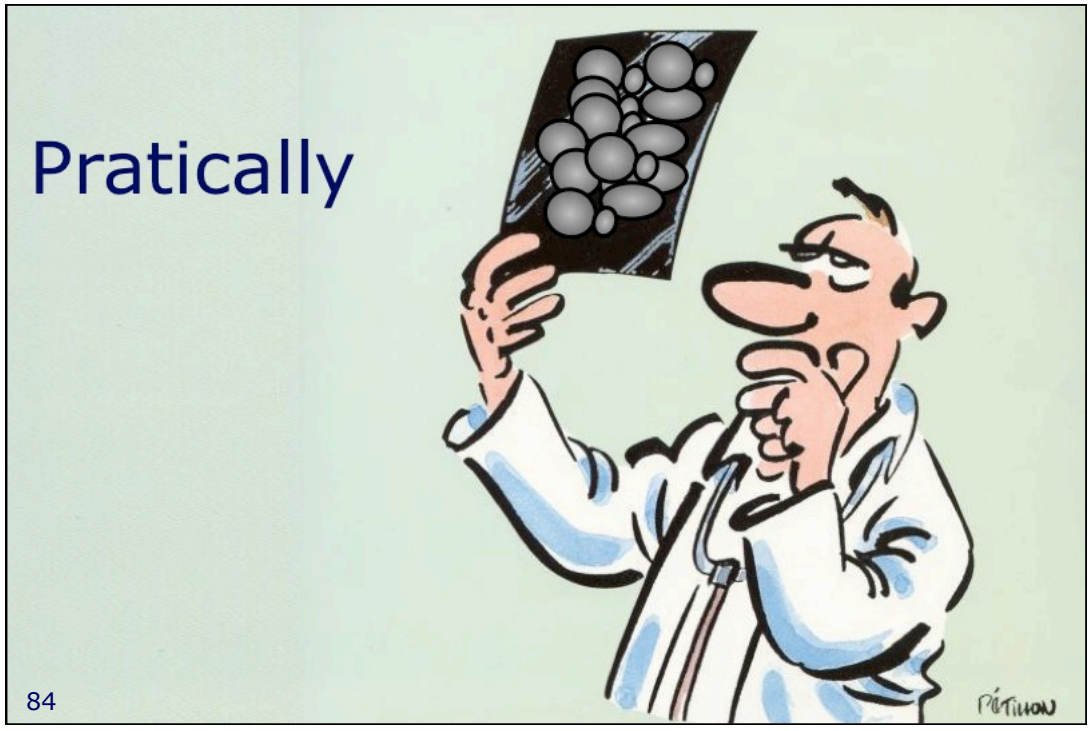
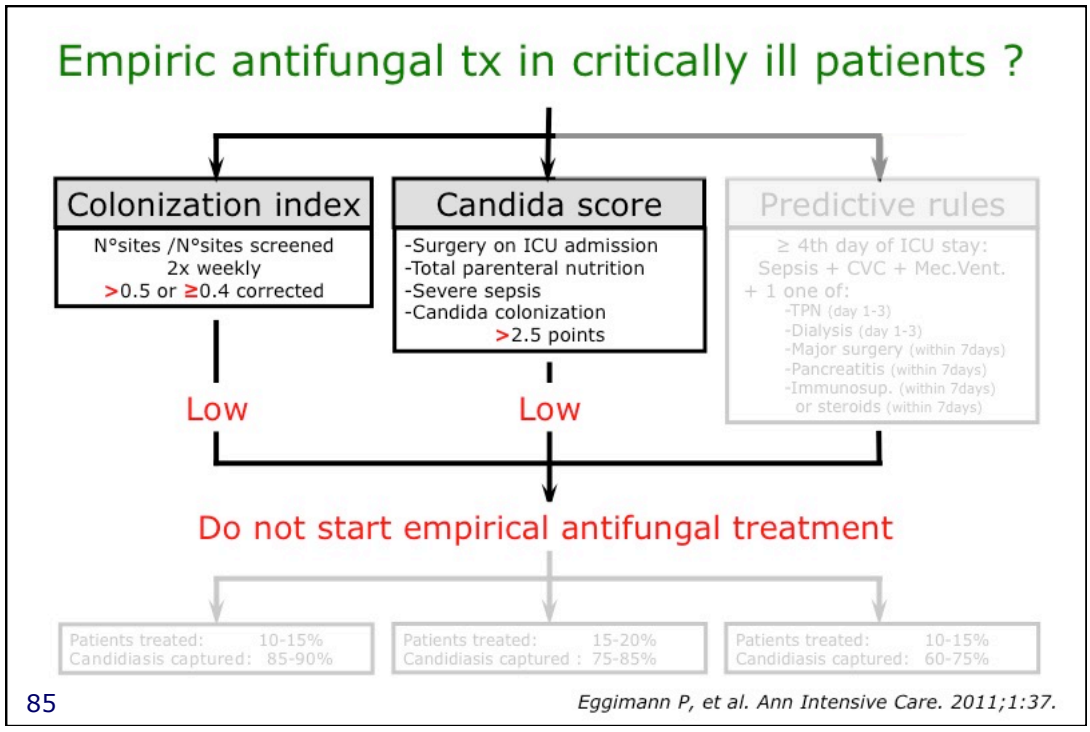


Tissot F, et al. ICAAC 2010.


A simplified approach
40%-80% colonized
1%-20% infected
1) Clinical scores
→ Exclude low risk patients
2) Biomarkers (betaglucan)
→ Start antifungals empirically
? Prophylaxis ?
? Empirical treatment ?
83
Eggimann P, Pittet D. Intensive Care Med. 2014;40:1429-48.


Pratically
84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Candida score
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-Total parenteral nutrition
-Severe sepsis
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>2.5 points
Predictive rules
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-Pancreatitis (within 7days)
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or steroids (within 7days)
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Low
Do not start empirical antifungal treatment
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85
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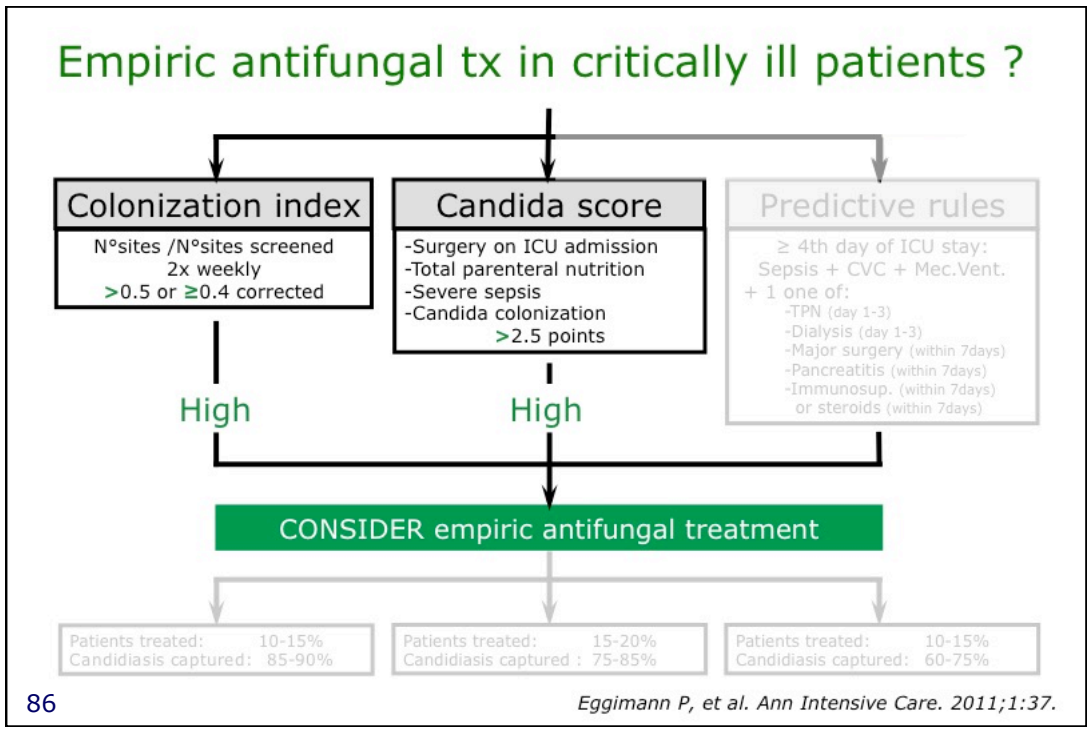
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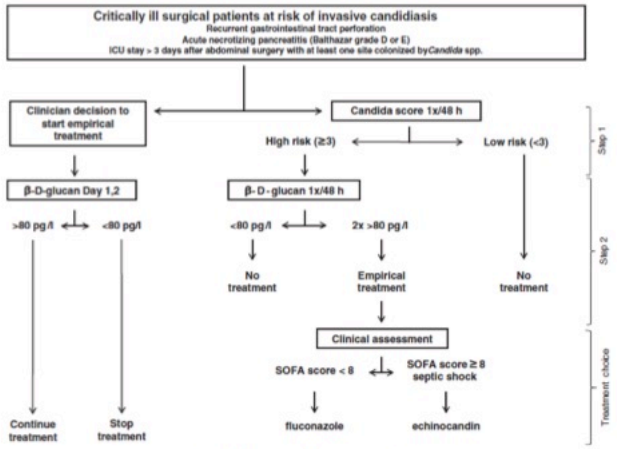
86
Eggimann P, et al. Ann Intensive Care. 2011;1:37.

Empiric antifungal tx in critically ill patients ?

The Role of Biomarkers for Starting Antifungals in the Intensive Care Unit

Jean-Luc Pagani, MD, Jean-Pierre Revelly, MD, Yok-Ai Que, MD, PhD, and Philippe Eggimann, MD



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(*Clin Pulm Med* 2015;00:000–000)

Empiric antifungal tx in critically ill patients ?

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88

(*Clin Pulm Med* 2015;00:000–000)

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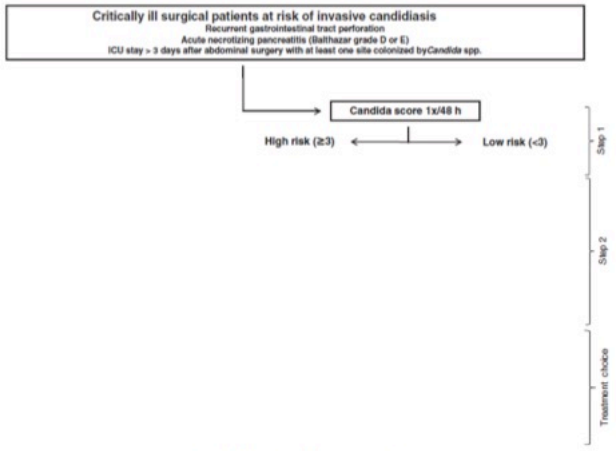

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(*Clin Pulm Med* 2015;00:000–000)

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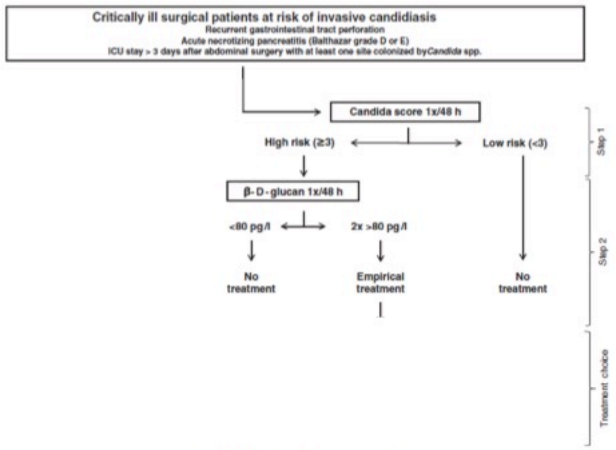

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(*Clin Pulm Med* 2015;00:000–000)

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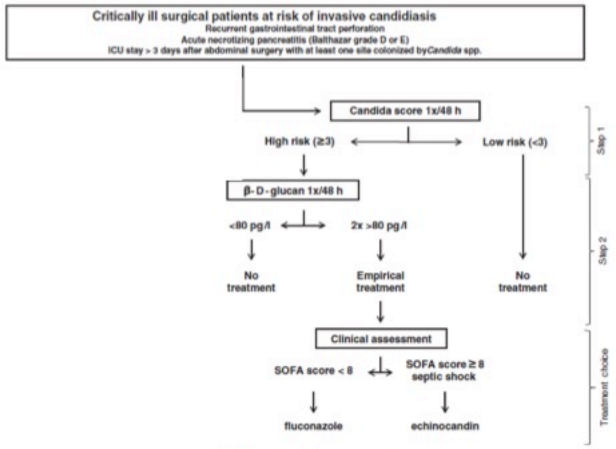

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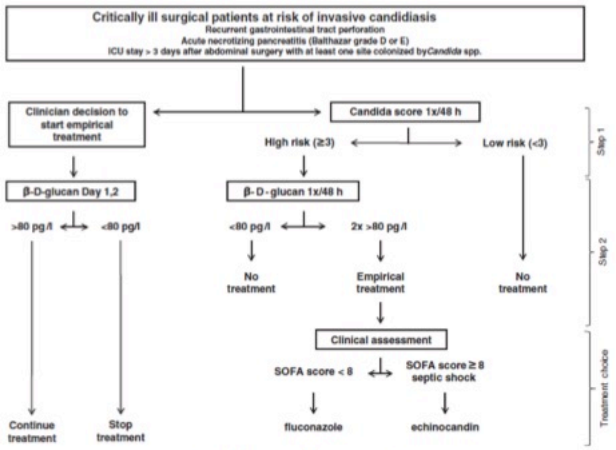

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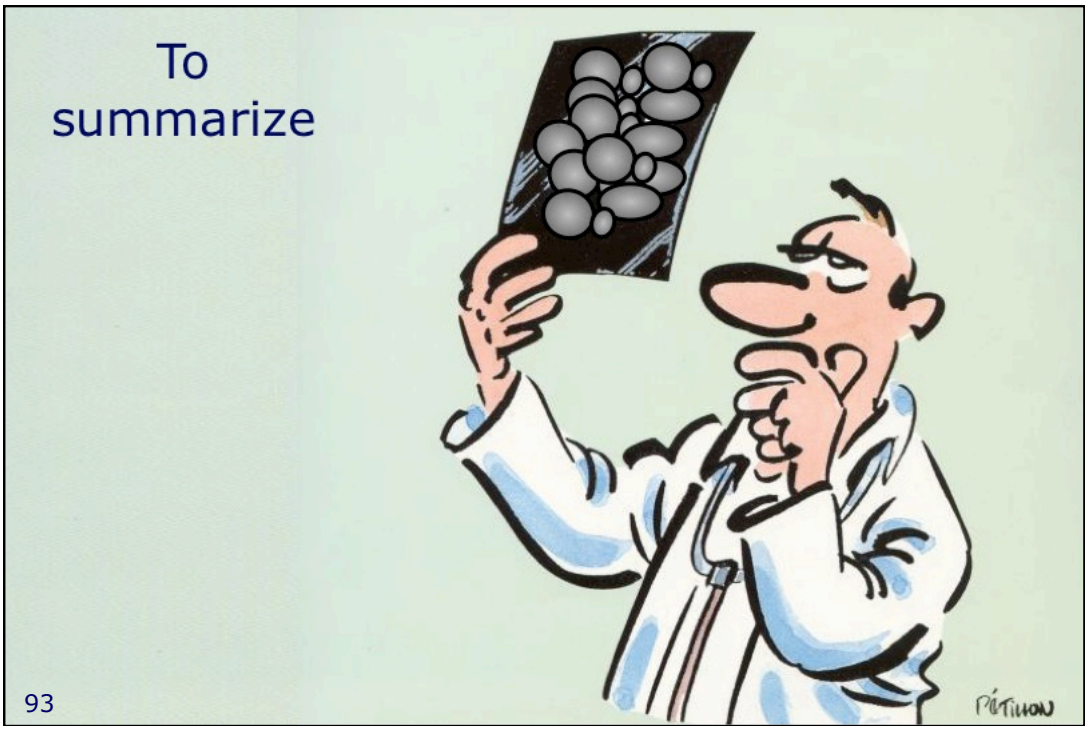
To summarize
93
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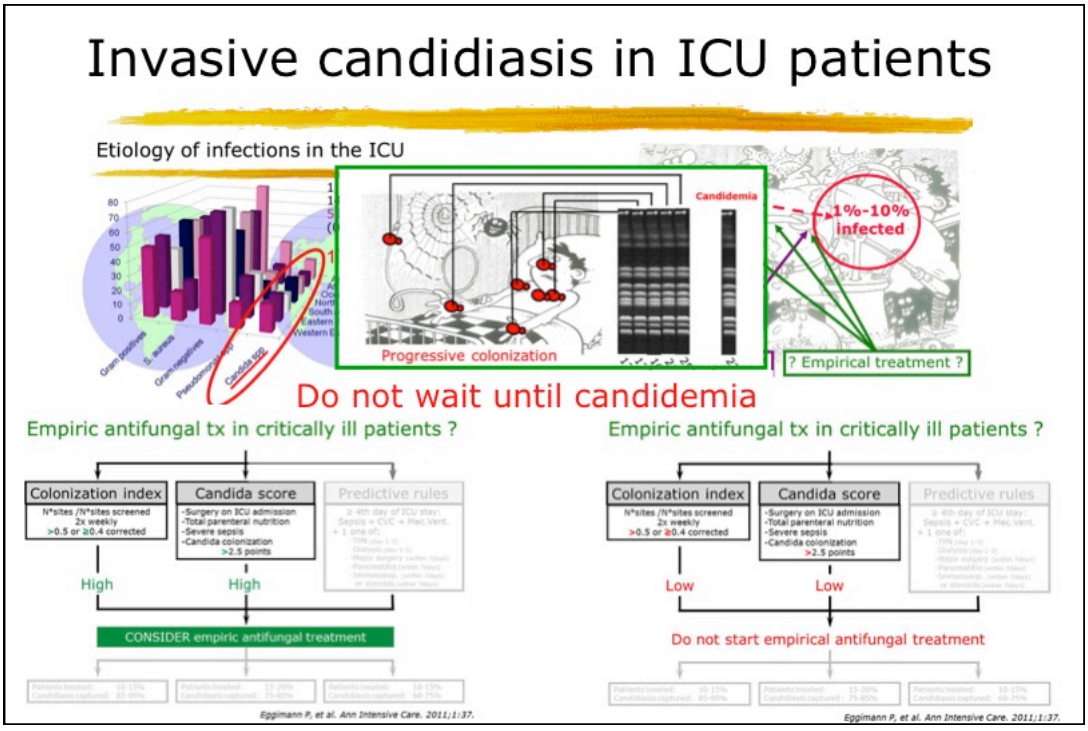
Invasive candidiasis in ICU patients
Etiology of infections in the ICU
Candidemia
1%-10% infected
Progressive colonization
? Empirical treatment ?
Do not wait until candidemia
Empiric antifungal tx in critically ill patients ?
Colonization index
Candida score
Predictive rules
High
High
CONSIDER empiric antifungal treatment
Empiric antifungal tx in critically ill patients ?
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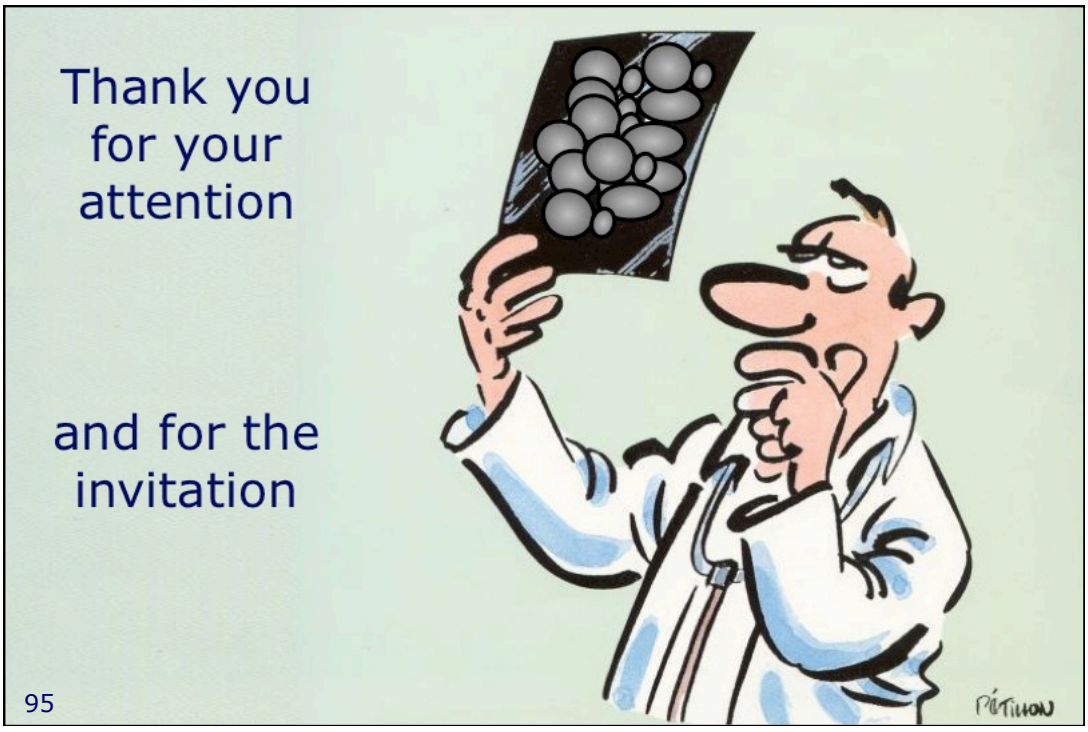
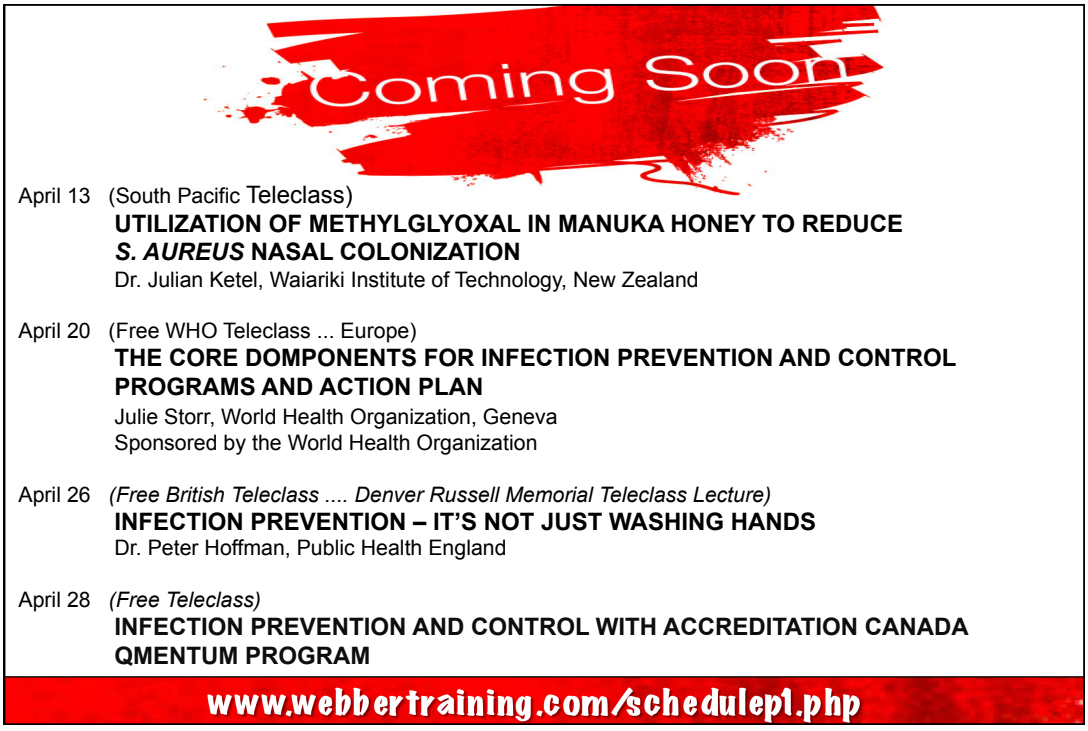
Candida score
Predictive rules
Low
Low
Do not start empirical antifungal treatment

Preventing Invasive Candida Infections – Where Could We Do Better?
Dr. Philippe Eggimann, Centre Hospitalier Universitaire Vaudois, Switzerland
A Webber Training Teleclass





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