Antifungal Stewardship

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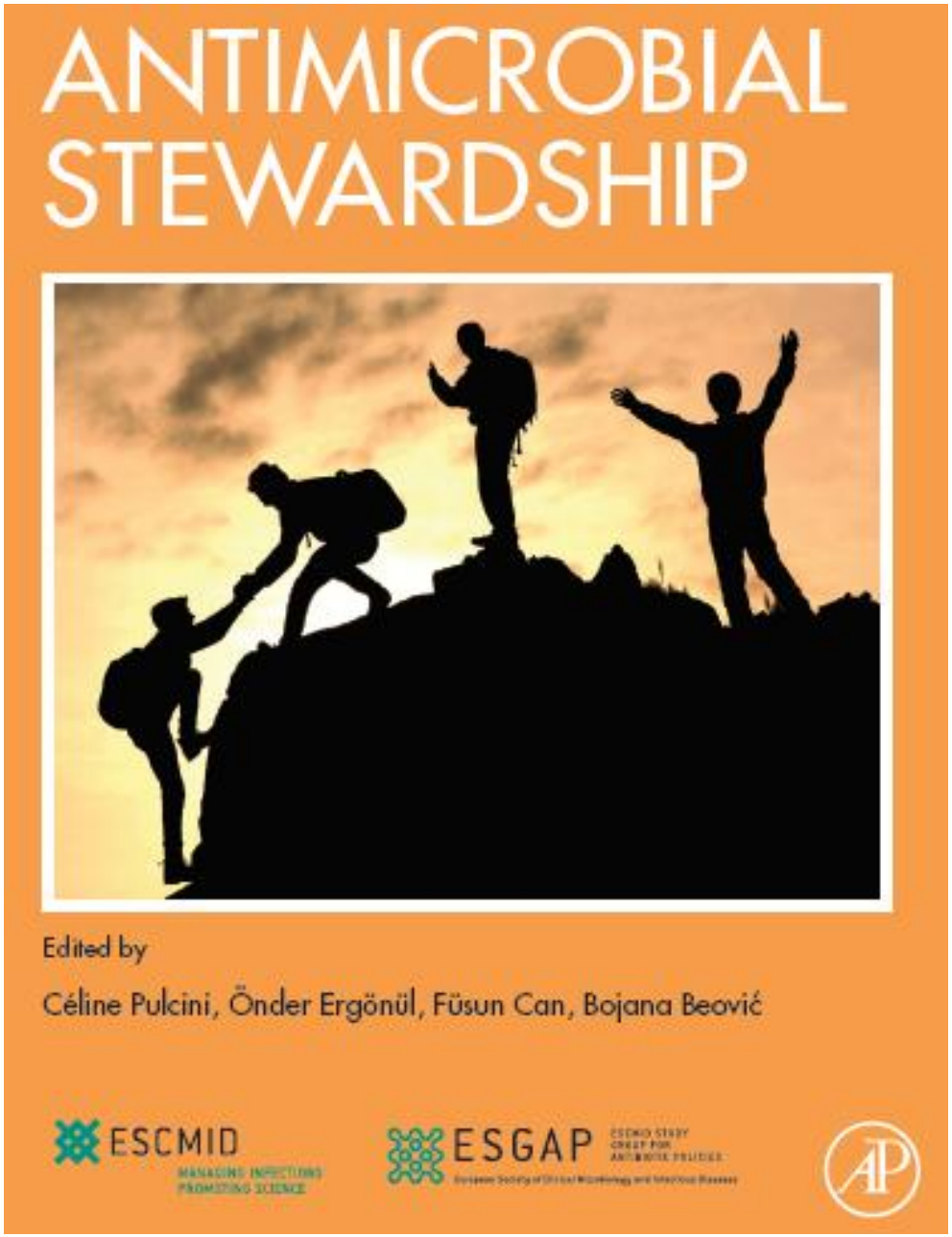
Koç University, School of Medicine, Istanbul
6 October 2017, ESGAP course, Istanbul

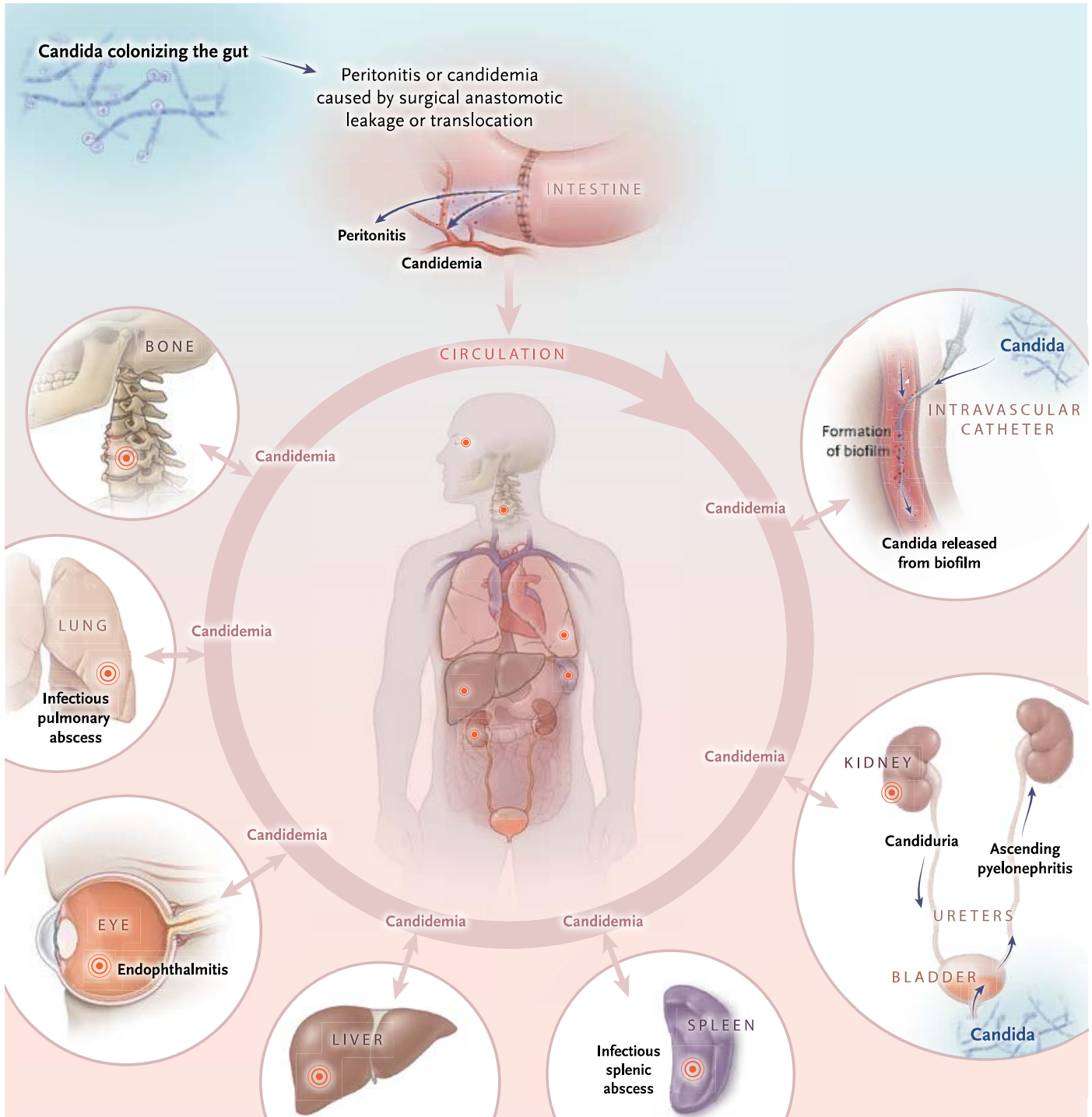


Antifungal Stewardship

Ozlem K. Azap* and Önder Ergönül**
*Başkent University, Ankara, Turkey
**Koç University, Istanbul, Turkey

Objectives

- What do we know?
  - Invasive Candida and Aspergillosis
  - Impact of infection
- How can we make progress?
  - Contribution of antibiotic stewardship
  - How can we implement AFS?
  - Suggestions



Invasive candidiasis:

candidemia and deep-seated tissue candidiasis.

Fatality up to 40% despite antifungal therapy

Kullberg & Arendrup NEJM 2015.

Nosocomial Bloodstream Infections in United States Hospitals: A Three-Year Analysis

Michael B. Edmond, Sarah E. Wallace, Donna K. McClish, Michael A. Pfaller, Ronald N. Jones, and Richard P. Wenzel

From the Divisions of Quality Health Care and Infectious Diseases, Department of Internal Medicine, and Department of Biostatistics, Virginia Commonwealth University School of Medicine, Richmond, Virginia, and the Division of Medical Microbiology, Department of Pathology, University of Iowa College of Medicine, Iowa City, Iowa

Table 1. Rank order of nosocomial bloodstream pathogens and the associated crude mortality among 49 hospitals throughout the United States.

Rank	Pathogen	No. of isolates	%	Crude mortality (%)
1	Coagulase-negative staphylococci	3,908	31.9	21
2	*Staphylococcus aureus*	1,928	15.7	25
3	Enterococci	1,354	11.1	32
4	*Candida* species	934	7.6	40
5	*Escherichia coli*	700	5.7	24
6	*Klebsiella* species	662	5.4	27
7	*Enterobacter* species	557	4.5	28
8	*Pseudomonas* species	542	4.4	33
9	*Serratia* species	177	1.4	26
10	Viridans streptococci	173	1.4	23

CID 1999

Candida spp.: At a Glance

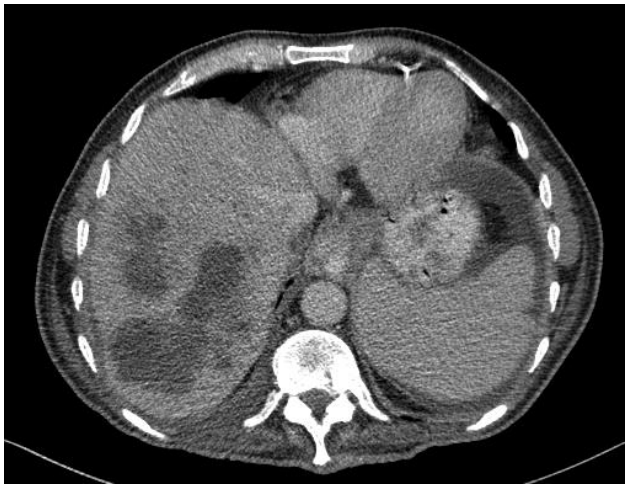
	Features	Antifungal resistance
C. albicans	Responsible for about 50% of Candidemia	Fluconazole 1-2%
C. parapsilosis	Biofilm Skin contamination Fatality is < than *C.albicans* Southern Europe	MIC of echinocandins are high
C. glabrata	Elderly, HIV+ Northern Europe	Dose related resistance for azoles
C. tropicalis	More common among cancer pts	Less R to Fluconazole
C. krusei	Less common Fatality is > *C.albicans*	R to fluconazole Echinocandins considered

Azap O, Ergonul O, AFS, 2017

Resistance of Candida Spp

Table 3. General patterns of susceptibility of *Candida* species.

Species	Fluconazole	Itraconazole	Voriconazole	Posaconazole	Flucytosine	Amphotericin B	Candins
Candida albicans	S	S	S	S	S	S	S
Candida tropicalis	S	S	S	S	S	S	S
Candida parapsilosis	S	S	S	S	S	S	S to R[a]
Candida glabrata	S-DD to R	S-DD to R	S-DD to R	S-DD to R	S	S to I	S
Candida krusei	R	S-DD to R	S	S	I to R	S to I	S
Candida lusitaniae	S	S	S	S	S	S to R	S



Candida glabrata MIC (2 March 2015)

1.	Voriconazole	0.023 micg/mL
2.	Flucanazole	1.5 micg/mL
3.	Posaconazole	0.5 micg/mL
4.	Micafungin	<0.02 micg/mL
5.	Caspofungin	2 micg/mL
6.	Anidulafungin	<0.02 micg/mL
7.	Amphotericin B	4 micg/mL

Candida parapsilosis MIC (Blood culture; 9 March 2015)

1.	Voriconazole	0.064 micg/mL
2.	Flucanazole	2 micg/mL
3.	Posaconazole	0.094 micg/mL
4.	Micafungin	<0.006 micg/mL
5.	Caspofungin	1.5 micg/mL
6.	Anidulafungin	<0.003 micg/mL
7.	Amphotericin B	0.38 micg/mL
8.	Itraconazole	2 micg/mL

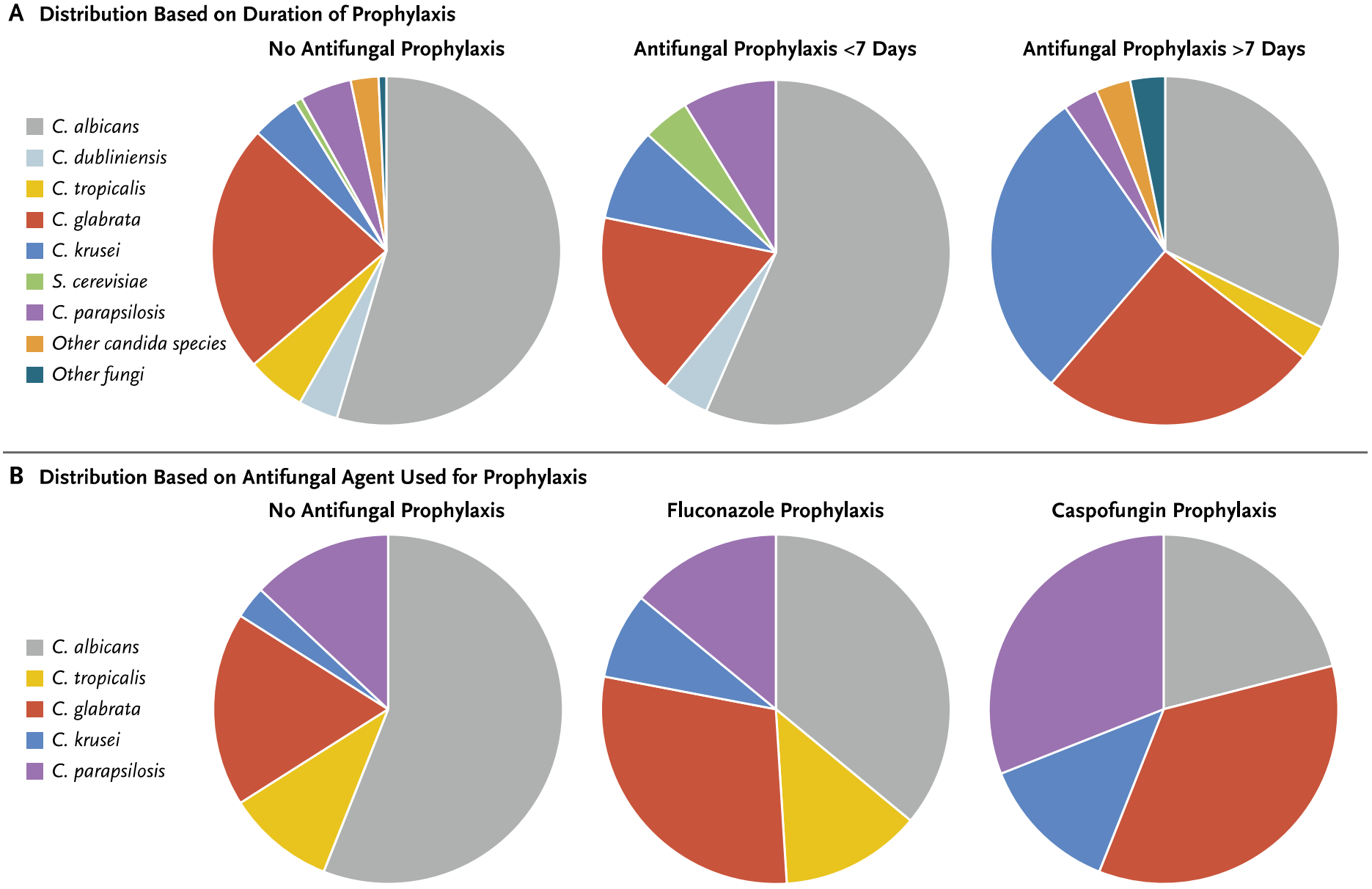
Invasive *Candida* infections in surgical patients in intensive care units: a prospective, multicentre survey initiated by the European Confederation of Medical Mycology (ECMM) (2006–2008)

L. Klingspor[1], A. M. Tortorano[2], J. Peman[3], B. Willinger[4], P. Hamal[5], B. Sendid[6], A. Velegraki[7], C. Kibbler[8], J. F. Meis[9,10], R. Sabino[11], M. Ruhnke[12], S. Arikan-Akdagli[13], J. Salonen[14] and I. Dóczi[15]

TABLE 3. Species distribution of 807 *Candida* isolates in 779 patients

Candida species	Number of isolates	(%)
C. albicans	436	54.0
C. parapsilosis	149	18.5
C. glabrata	111	13.8
C. tropicalis	49	6.0
C. krusei	20	2.5
C. lusitaniae	14	1.7
C. dubliniensis	9	1.2
C. guillermondii	5	0.6
C. äferrii	4	0.4
Other[a]	9	1.2
Total	807	100

[a]*C. pelliculosa*, $n = 3$; *C. haemoloni*, $n = 2$; *C. kefyr*, $n = 2$; *C. lambica*, $n = 1$; *C. humicola*, $n = 1$.



Kullberg & Arendrup
NEJM 2015.

Table 1. Risk Factors for Invasive Candidiasis.*

Critical illness, with particular risk among patients with long-term ICU stay
Abdominal surgery, with particular risk among patients who have anastomotic leakage or have had repeat laparotomies
Acute necrotizing pancreatitis
Hematologic malignant disease
Solid-organ transplantation
Solid-organ tumors
Neonates, particularly those with low birth weight, and preterm infants
Use of broad-spectrum antibiotics
Presence of central vascular catheter, total parenteral nutrition
Hemodialysis
Glucocorticoid use or chemotherapy for cancer
Candida colonization, particularly if multifocal (colonization index >0.5 or corrected colonization index >0.4)

Kullberg & Arendrup
NEJM 2015.

Invasive *Candida* infections in surgical patients in intensive care units: a prospective, multicentre survey initiated by the European Confederation of Medical Mycology (ECMM) (2006–2008)

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TABLE 1. European Confederation of Medical Mycology prospective study of *Candida* infections in 779 surgical patients in ICU from 14 countries

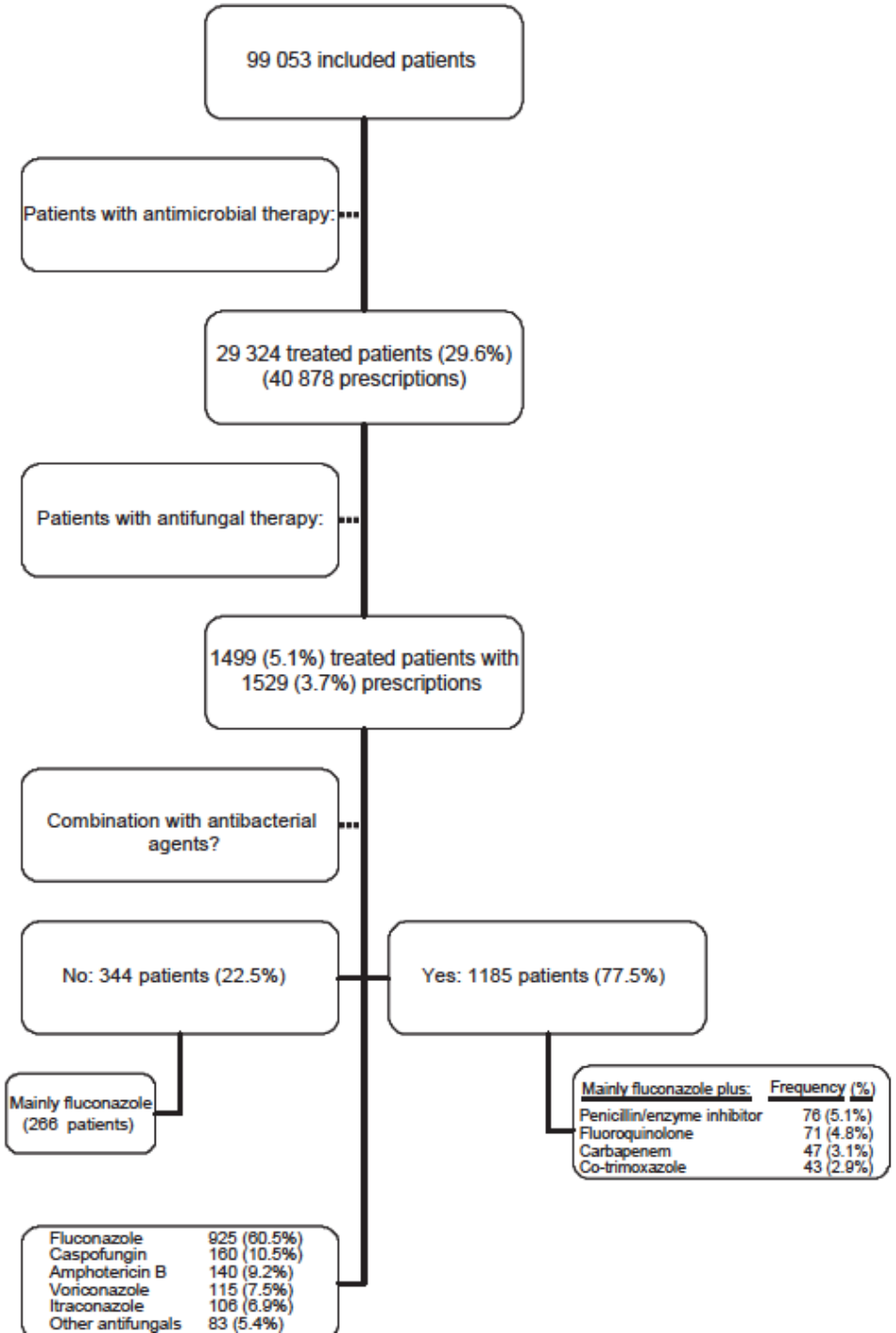
Country	Cases	(%)	Country	Cases	(%)
Austria	97	12.5	Italy	216	27.7
Czech Republic	77	9.9	the Netherlands	18	2.3
Finland	10	1.3	Portugal	6	0.8
France	55	7.1	Spain	96	12.3
Germany	13	1.7	Sweden	101	13.0
Greece	41	5.3	Turkey	11	0.4
Hungary	5	0.6	UK	33	4.2

Type of preceding surgery	
Abdominal	401 (51.5)
Thoracic	156 (20.0)
Vascular	49 (6.3)
Neurosurgery	64 (8.2)
Orthopaedic	12 (1.5)
Multiple trauma	54 (6.9)
Solid organ transplant	26 (3.3)
Other	17 (2.2)
Repeated surgery	166/752 (21.3)

Clin Microbiol Infect 2015; **21**: 87.e1–87.e10

Antifungal therap ...e ESAC point-prevalence surve...

P. Zarb[1], B. Amadeo[2], A. Mull... on behalf of the ESAC-3 hospital care subproject group



Zarb, CMI 2012

Clinical Questions

- Initial therapy: overuse or underuse?
  - Which is the optimal drug?
- Diagnosis
  - Biomarkers
  - Candida score
- Susceptibility testing
- How to treat in organ failure?
- When to apply step-down strategy?
- How to implement PK/PD
- Cost-effectivity?

Unnecessary Treatments

- Treatment for colonization (!)

Intensive Care Med (2009) 35:1526–1531
DOI 10.1007/s00134-009-1482-8

ORIGINAL

W. Meersseman
K. Lagrou
I. Spriet
J. Maertens
E. Verbeken
W. E. Peetermans
E. Van Wijngaerden

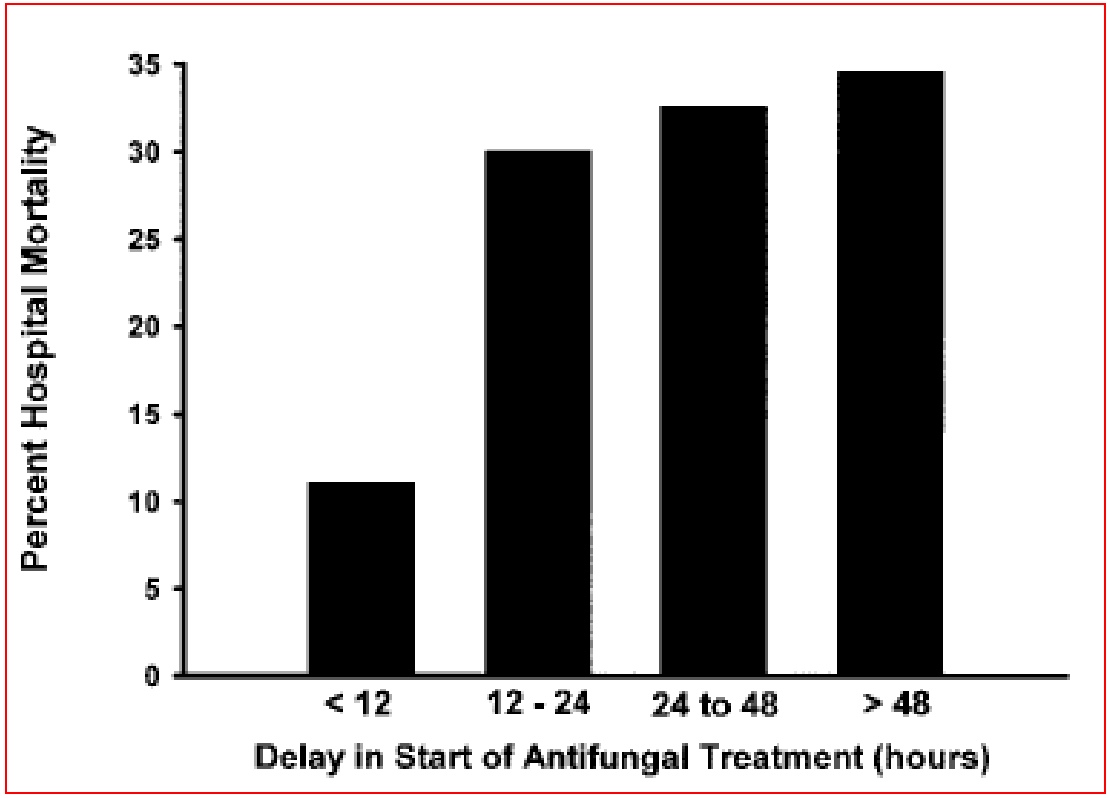
Significance of the isolation of *Candida* species from airway samples in critically ill patients: a prospective, autopsy study

- Low risk patients
- Longer than necessary

ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Sept. 2005, p. 3640–3645
0066-4804/05/$08.00+0 doi:10.1128/AAC.49.9.3640–3645.2005

Vol. 49, No. 9

Delaying the Empiric Treatment of *Candida* Bloodstream Infection until Positive Blood Culture Results Are Obtained: a Potential Risk Factor for Hospital Mortality



Morrell, et al. AAC 2015.

Delayed Detection in ICU

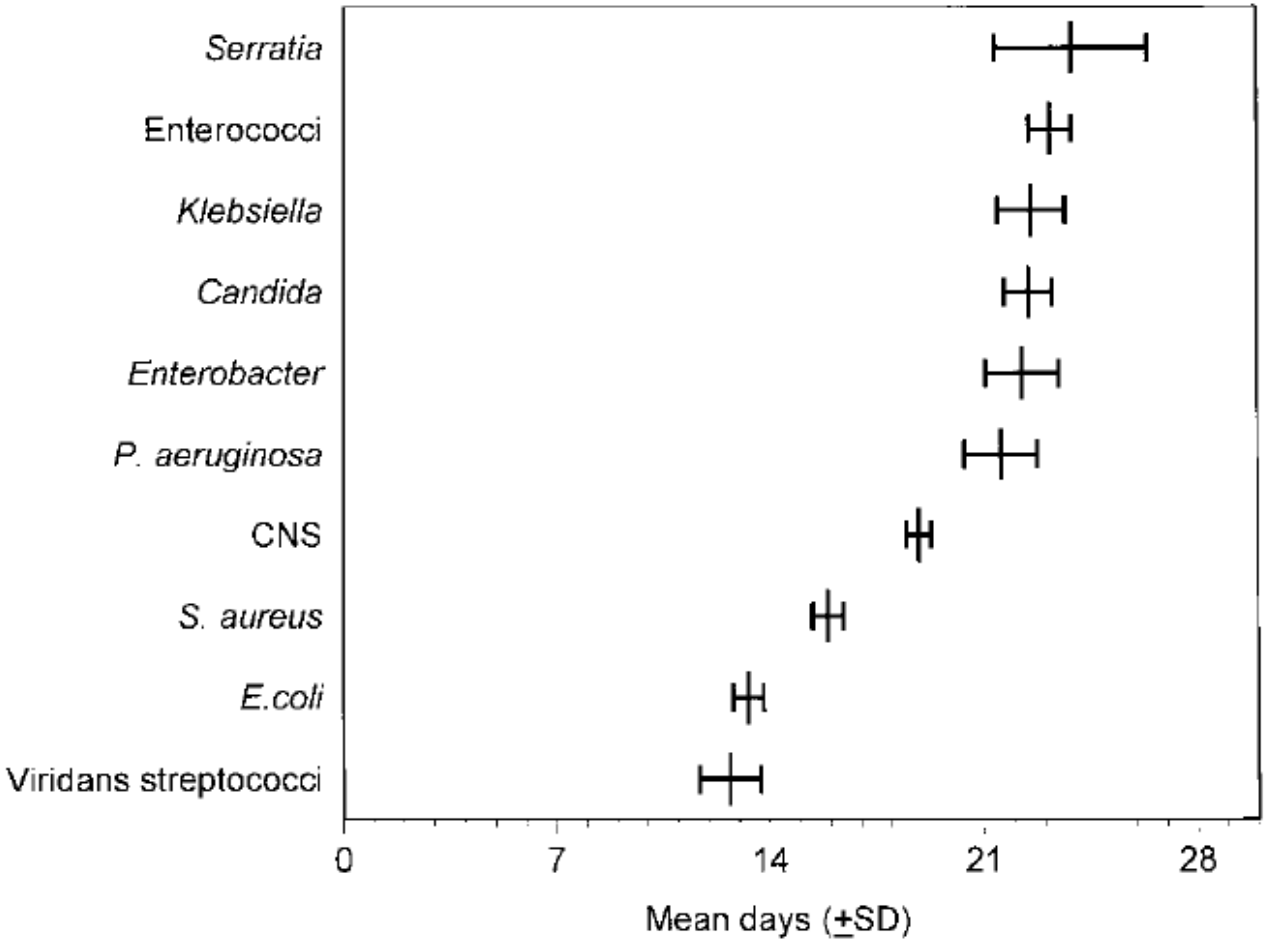
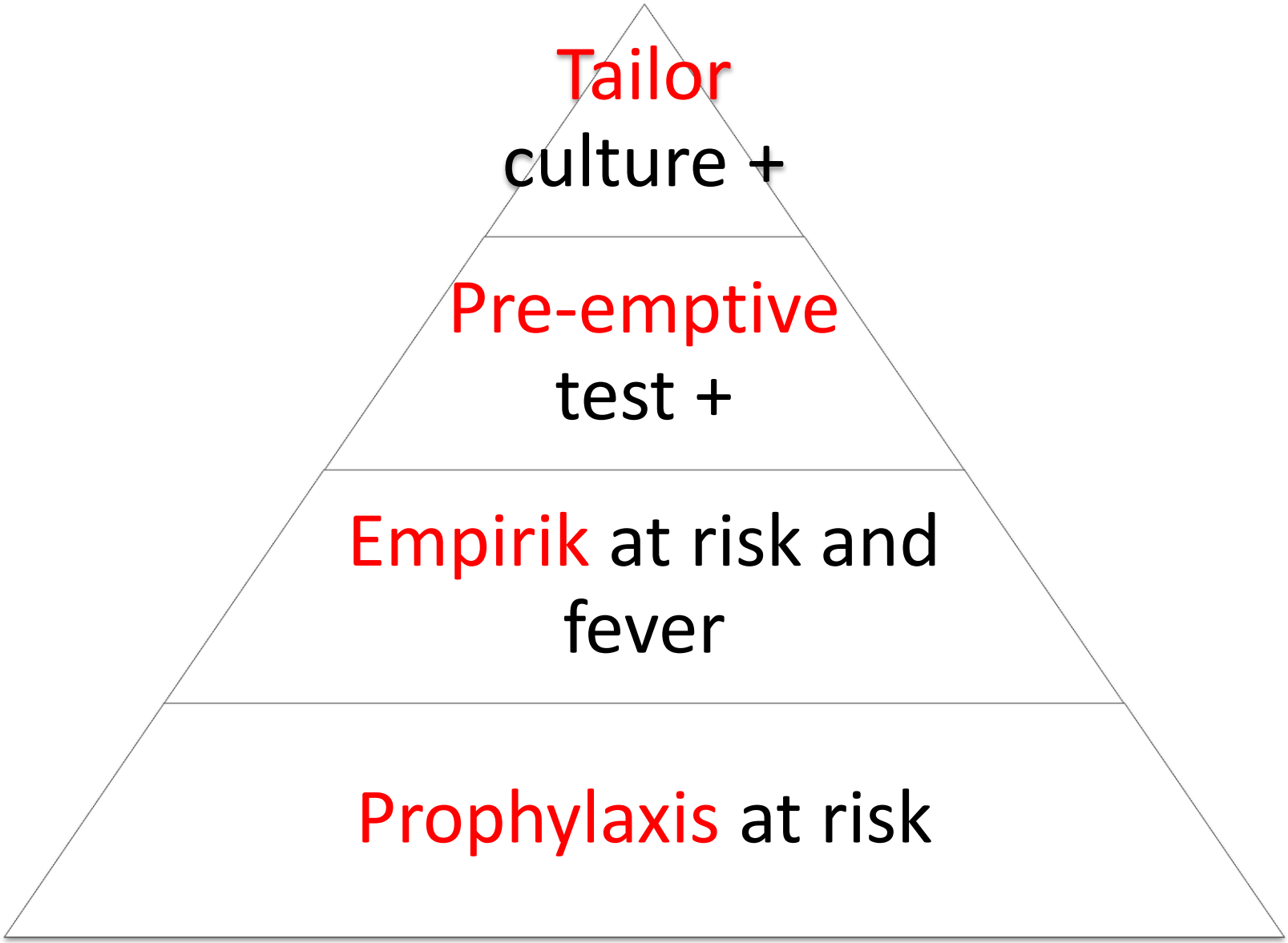


Figure 2. Time from hospital admission to bacteremia by pathogen (mean ± SD) among 49 sentinel hospitals throughout the United States. CNS = coagulase-negative staphylococci; *E. coli* = *Escherichia coli; P. aeruginosa* = *Pseudomonas aeruginosa; S. aureus* = *Staphylococcus aureus.*

Edmond, CID, 1999


Tailor
culture +
Pre-emptive
test +
Empirik at risk and
fever
Prophylaxis at risk

Diagnosis

- **Blood Culture**
  - Only diagnostic approach that allows subsequent susceptibility testing.
  - Blood culture sensitivity: 21-71% reported in autopsy studies.
  - Blood cultures: slow turn-around times and revealed late .
  - Positive blood cultures should prompt the immediate initiation of therapy and a search for metastatic foci.
- **β-d-glucan**
  - Could be false positive.
  - The major benefit is negative predictive value.
- **Mannan/Anti-mannan**
  - Maybe in hepatosplenic candidiasis
- **PCR**
  - not well standardized yet

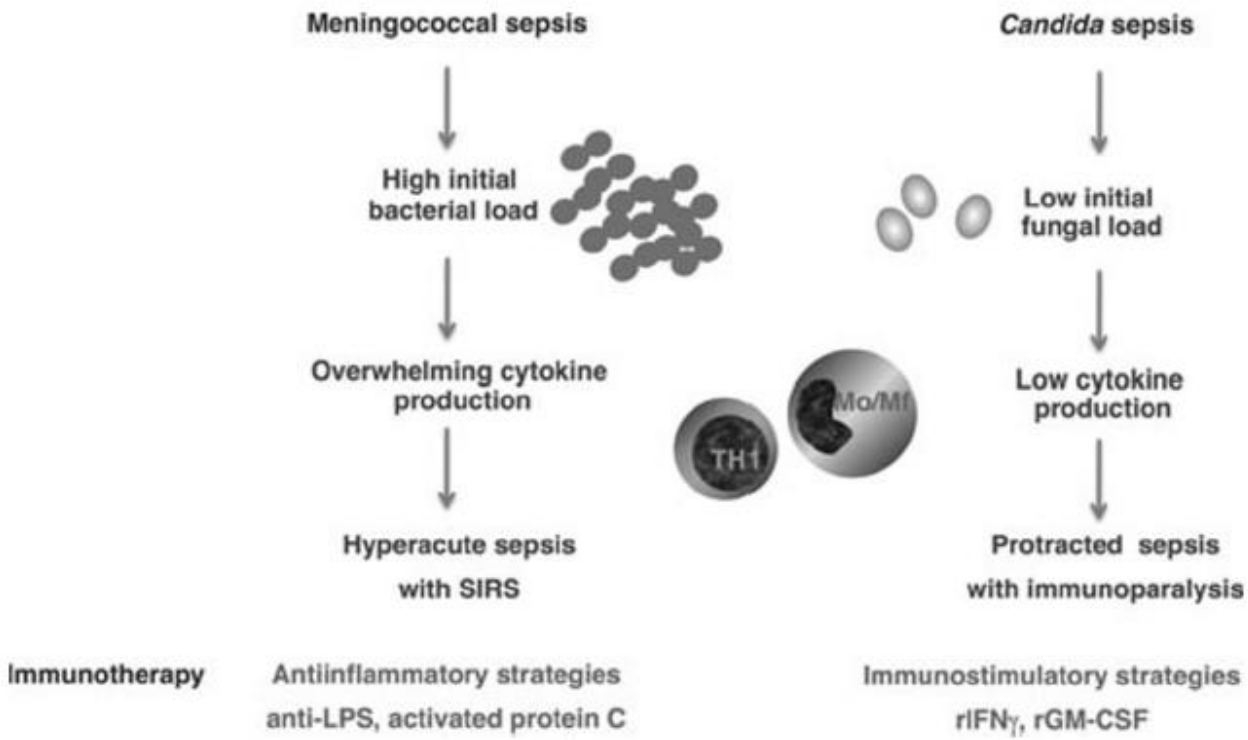


FIG. 2. The role of proinflammatory cytokines during sepsis: whereas proinflammatory cytokines are overwhelmingly released during acute meningococcal sepsis, the concentrations found during systemic candidiasis are much lower. This is partly because of differences in microbial load in the two infections. It is therefore late-stage immunoparalysis, rather than the acute cytokine storm, that is the main immunological disturbance in systemic candidiasis, and the patient would benefit from enhancement of the host defence. LPS, lipopolysaccharide; Mo/Mf, monocyte/macrophage; rGM-CSF, recombinant granulocyte–macrophage colony-stimulating factor; rIFN-γ, recombinant interferon-γ; SIRS, systemic inflammatory response syndrome; Th, T-helper lymphocyte.

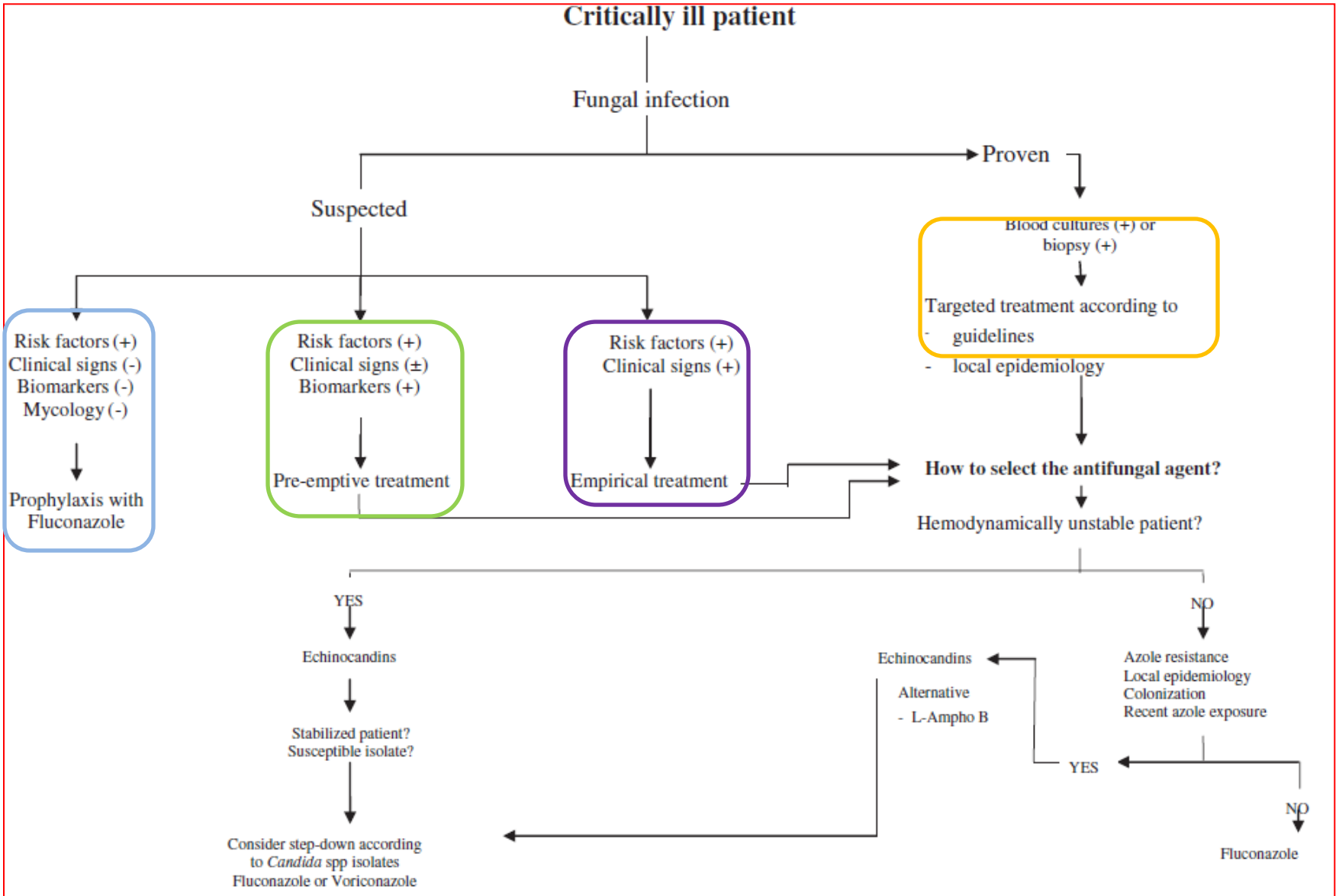


Fig. 1 Suggested algorithm for the management of candidiasis in the ICU patient.

Dimopoulos, et al. J Crit Care 2013

IDSA GUIDELINE

Infectious Diseases Society of America hiv medicine association OXFORD

Clinical Practice Guideline for the Management of Candidiasis: 2016 Update by the Infectious Diseases Society of America

Peter G. Pappas,[1] Carol A. Kauffman,[2] David R. Andes,[3] Cornelius J. Clancy,[4] Kieren A. Marr,[5] Luis Ostrosky-Zeichner,[6] Annette C. Reboli,[7] Mindy G. Schuster,[8] Jose A. Vazquez,[9] Thomas J. Walsh,[10] Theoklis E. Zaoutis,[11] and Jack D. Sobel[12]

What is new?

- Increasing role of echinocandins in initial therapy
- Increasing role of Susceptibility tests
- Switch: Step-down from echinocandins to fluconazole
- Emphasis
  - Risk factors
  - Fundoscopic exam
  - Cathether removal
  - Duration of therapy

IDSA 2016: Non-neutropenic patients

- Initial therapy should be an echinocandin
  - For selected patients who are not critically ill and are unlikely to have fluconazole-resistant *Candida* species, an acceptable alternative to an echinocandin as initial therapy is fluconazole

- Azole and echinocandin susceptibility in patients previously treated with an echinocandin or infected with *C glabrata* or *C parapsilosis*

- Clinically stable, susceptible to fluconazole; switch an echinocandin to fluconazole, usually within 5 to 7 days or from amphotericin B to fluconazole after 5 to 7 days

- For *C glabrata* infection, transition to higher-dose fluconazole 800 mg (12 mg/kg) daily or voriconazole 200 to 300 (3-4 mg/kg) twice daily should only be considered.

IDSA 2016: Neutropenic Patients

- Initial therapy should be an echinocandin
  - Less attractive alternative: amphotericin B (lipid)
  - Fluconazole is an alternative for patients who are not critically ill and have had no previous azole exposure

- *C krusei:* echinocandin, amphotericin B (lipid), or voriconazole

- Without metastatic complications, recommended minimum duration of therapy is 2 weeks after documented clearance

- Dilated funduscopic examinations should be performed within the first week after recovery from neutropenia.

- Catheter removal should be considered on an individual basis

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

TABLE 3. Recommendations on antifungal prophylaxis in ICU patients

Population	Intention	Intervention	SoR	QoE	References	Comment
Recent abdominal surgery AND recurrent gastrointestinal perforations or anastomotic leakages	To prevent intraabdominal *Candida* infection	Fluconazole 400 mg/day	B	I	[8]	Placebo *N* = 43
		Caspofungin 70/50 mg/day	C	II_u	[9]	Single arm *N* = 19
Critically ill surgical patients with an expected length of ICU stay ≥3 day	To delay the time to fungal infection	Fluconazole 400 mg/day	C	I	[10]	Placebo *N* = 260
Ventilated for 48 h and expected to be ventilated for another ≥72 h	To prevent invasive candidiasis/candidaemia	Fluconazole 100 mg/day	C	I	[162]	Placebo *N* = 204 SDD used
Ventilated, hospitalized for ≥3 day, received antibiotics, CVC, and ≥1 of: parenteral nutrition, dialysis, major surgery, pancreatitis, systemic steroids, immunosuppression	To prevent invasive candidiasis/candidaemia	Caspofungin 50 mg/day	C	II_a	[5]	Placebo *N* = 186 EORTC/MSG criteria used
Surgical ICU patients	To prevent invasive candidiasis/candidaemia	Ketoconazole 200 mg/day	D	I	[22]	Placebo *N* = 57
Critically ill patients with risk factors for invasive candidiasis/candidaemia	To prevent invasive candidiasis/candidaemia	Itraconazole 400 mg/day	D	I	[21]	Open *N* = 147
Surgical ICU with catabolism	To prevent invasive candidiasis/candidaemia	Nystatin 4 Mio IU/day	D	I	[20]	Placebo *N* = 46

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

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

When to Start?

Empirical Therapy

Risk factors (Candida colonization) AND fever

Tailored Therapy

ANY candidal growth from blood, tissue or sterile body fluids

Urinary candidal growth along with urinary tract infection symptoms

Histopathological diagnosis of Candida in tissue samples

Azap O, Ergonul O, AFS, 2017

How to follow up?

All patients

Blood cultures should be drawn everyday OR every other day

Transesophageal or at least transthoracic echocardiography

For non-neutropenic patients

Catheter should be removed because the source is probably the catheter

Fundoscopic examination within one week of antifungal therapy

For neutropenic patients

Catheter removal should be considered because the source may also be the endogenous flora of the patient

Fundoscopic examination within the first week after neutrophill recovery

Azap O, Ergonul O, AFS, 2017

When to stop?

For candidemia WİTHOUT distant foci

14 days after the last negative blood culture

For candidemia WİTH distant foci

Endophtahlmitis: 6 weeks

Endocarditis: Valve replacement if posible and at least 6 weeks after surgery

Azap O, Ergonul O, AFS, 2017

Differences in Stewardship

Antibiotic

- Diagnosis
  - CRP
  - Procalcitonin
  - Culture: earlier
- Resistance reports
  - Set
- Switch
- Consensus in treatment better

Antifungal

- Diagnosis
  - BDG
  - GM/CT
  - Culture: not very early
    - Difficult if seated deeply
- Resistance reports
  - Improving
- Switch: not well developed
- Consensus in treatments needs to be improved

Essentials of Antifungal Stewardship

1. Adequate diagnosis
2. Appropriate antifungal drugs
3. Appropriate duration
4. Removal of iv catheters
5. Ophtalmologic examination
6. Hepatic/renal dose adjustment
7. Drug interactions

J Antimicrob Chemother 2014; **69**: 1993–1999
doi:10.1093/jac/dku053 Advance Access publication 21 March 2014

Journal of Antimicrobial Chemotherapy

Evaluation of antifungal use in a tertiary care institution: antifungal stewardship urgently needed

Maricela Valerio[1,2], Carmen Guadalupe Rodriguez-Gonzalez[2,3], Patricia Muñoz[1,2,4]*, Betsabe Caliz[2,3], Maria Sanjurjo[2,3] and Emilio Bouza[1,2,4] on behalf of the COMIC Study Group (Collaborative Group on Mycoses)†

[1]Clinical Microbiology and Infectious Diseases Department, Hospital General Universitario Gregorio Marañón, Madrid, Spain; [2]Instituto de Investigación Sanitaria del Hospital Gregorio Marañón, Madrid, Spain; [3]Pharmacy Department, Hospital General Universitario Gregorio Marañón, Madrid, Spain; [4]Medicine Department, School of Medicine, Universidad Complutense de Madrid, Madrid, Spain

Table 1. Score for evaluating antifungal adequacy

Feature	Question	Answer	Points
Indication	Did the patient need an antifungal?	Yes	2
		No	0
Selection	Did the antifungal cover the suspected fungi and was it the first option recommended by guidelines?	It covered the suspected fungi and was the first option	2
		It covered the suspected fungi but was the alternative option	1
		It did not cover the suspected fungi	0
Dosage[a]	Was the dosage correct according to the body weight, the liver and renal function and potential interaction with other drugs?	Yes	1
		No	0
Microbiological adjustment	Was the antifungal adjusted after microbiological results (microorganism identification, antifungal susceptibility tests and indirect tests) were available?	Yes	2
		No	0
Administration route	Was intravenous switched to oral when possible?	Yes	1
		No	0
Duration	Was the duration of therapy correct according to the guidelines?[b]	Yes	2
		No	0
Total score			0–10

Table 3. Initial antifungal drug used for different indications

	Prophylaxis (n=15)	Empirical (n=42)	Pre-emptive (n=20)	Tailored (n=20)
Antifungal drug, *n* (%)				
fluconazole	3 (20.0)	33 (78.6)	14 (70.0)	13 (65.0)
echinocandins	6 (40.1)	8 (19.1)	6 (30.0)	2 (10.0)
caspofungin	1 (6.7)	7 (16.7)	5 (25.0)	—
micafungin	4 (26.7)	1 (2.4)	1 (5.0)	2 (10.0)
anidulafungin	1 (6.7)	—	—	—
posaconazole	4 (26.7)	—	—	—
liposomal amphotericin B	—	—	—	3 (15.0)
voriconazole	1 (6.7)	1[a] (2.4)	—	1 (5.0)
ketoconazole	—	—	—	1 (5.0)
itraconazole	1 (6.7)	—	—	—
Global therapy duration (days), median (IQR)	15.0 (9.0–28.0)	11.0 (7.0–18.0)	10.0 (8.0–15.3)	11.0 (3.3–21.5)

Valerio M, et al. JAC 2014

J Antimicrob Chemother 2016; **71**: 2498–2501
doi:10.1093/jac/dkw162 Advance Access publication 4 May 2016

Journal of Antimicrobial Chemotherapy

Comparison of the antifungal activity of micafungin and amphotericin B against *Candida tropicalis* biofilms

Laura Judith Marcos-Zambrano[1,2], Pilar Escribano[1–3], Emilio Bouza[1–4] and Jesús Guinea[1–4]*

[1]*Clinical Microbiology and Infectious Diseases, Hospital General Universitario Gregorio Marañón, Madrid, Spain;* [2]*Instituto de Investigación Sanitaria Gregorio Marañón, Madrid, Spain;* [3]*CIBER Enfermedades Respiratorias-CIBERES (CB06/06/0058), Madrid, Spain;* [4]*Medicine Department, School of Medicine, Universidad Complutense de Madrid, Madrid, Spain*

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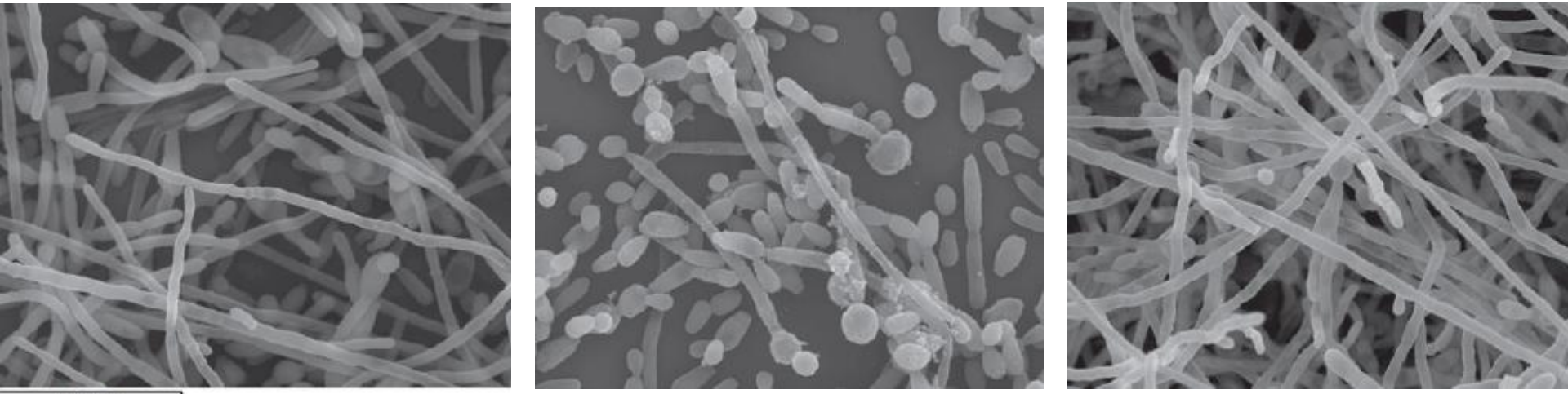
Untreated control

Micafungin

Amphotericin B



Evaluation of antifungal use in a tertiary care institution: antifungal stewardship urgently needed

Maricela Valerio[1,2], Carmen Guadalupe Rodriguez-Gonzalez[2,3], Patricia Muñoz[1,2,4]*, Betsabe Caliz[2,3], Maria Sanjurjo[2,3] and Emilio Bouza[1,2,4] on behalf of the COMIC Study Group (Collaborative Group on Mycoses)†

Table 4. Adequacy of antifungal therapy for different indications

	Prophylaxis ($n=15$)	Empirical ($n=42$)	Pre-emptive ($n=20$)	Tailored ($n=20$)	Overall ($n=100$)
Score, mean ± SD	9.1 ± 1.3	6.6 ± 2.7	8.3 ± 2.2	9.5 ± 1.9	7.7 ± 2.6
Inappropriate prescription, *n* (%)	6 (40)	33 (78.6)	10 (50)	5 (25)	57 (57)
Reason for inappropriate prescription, *n* (%)					
no microbiological adjustment	1 (6.7)	21 (50.0)	7 (35.0)	3 (15.0)	35 (35.0)
inappropriate antifungal selection	1 (6.7)	20 (47.6)	3 (15.0)	4 (20.0)	31 (31.0)
inappropriate duration	2 (13.3)	18 (42.9)	4 (20.0)	2 (10.0)	27 (27.0)
inappropriate administration route	1 (6.7)	12 (28.6)	4 (20.0)	3 (15.0)	20 (20.0)
unnecessary prescription (incorrect indication)	1 (6.7)	9 (21.4)	2 (10.0)	1 (5.0)	16 (16.0)
inappropriate dosage	2 (13.3)	9 (21.4)	2 (10.0)	1 (5.0)	16 (16.0)

Valerio M, et al. JAC 2014

Antifungal stewardship in a tertiary-care institution: a bedside intervention

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- Decrease in antifungal use 50%

TABLE 4. Impact of the antifungal stewardship on clinical and demographical characteristics

	Pre-AFS	During AFS			
	2010	2011	2012	2013	p
Candidaemia incidence/1000 admissions	1.49	1.76	1.44	1.14	0.08
Candidaemia albicans	0.87	0.83	0.67	0.48	**0.01**
Candidaemia parapsilosis	0.27	0.53	0.38	0.35	0.75
Candidaemia tropicalis	0.09	0.13	0.24	0.12	0.35
Candidaemia glabrata	0.16	0.19	0.16	0.08	0.29
Non-albicans *Candida*	0.62	0.93	0.77	0.66	0.97
Non-albicans *Candida* (%)	41.5	52.7	53.5	58.2	**0.05**
Fluconazole resistance in candidaemia (%)	6.1	4.3	4.2	3.6	0.53
Candidaemia-related mortality (%)	28.0	23.7	22.5	16.4	0.12

Significative p values are in bold.

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CLINICAL AND EPIDEMIOLOGICAL STUDY

A 6-year antifungal stewardship programme in a teaching hospital

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Table 2 Local therapeutic guidelines (2008) regarding antifungal treatment of candidaemia and invasive aspergillosis

Invasive fungal infection	Clinical situation	Recommended antifungal treatment
Candidaemia	Absence of all the following criteria:	Fluconazole
Treatment based on a blood culture positive for yeast (before identification and susceptibility testing)	Neutropaenia	
	Severe sepsis or septic shock	
	Recent azole exposure	
	Presence of at least one of the criteria mentioned above	Caspofungin
		Or liposomal amphotericin B
Suspected invasive aspergillosis	First-line treatment	Voriconazole
		Alternative (particularly if current prophylaxis using voriconazole): liposomal amphotericin B
	Salvage therapy (unfavourable outcome after at least 7 days of therapy)	Caspofungin
		Or posaconazole
		Or antifungal combination, after approval

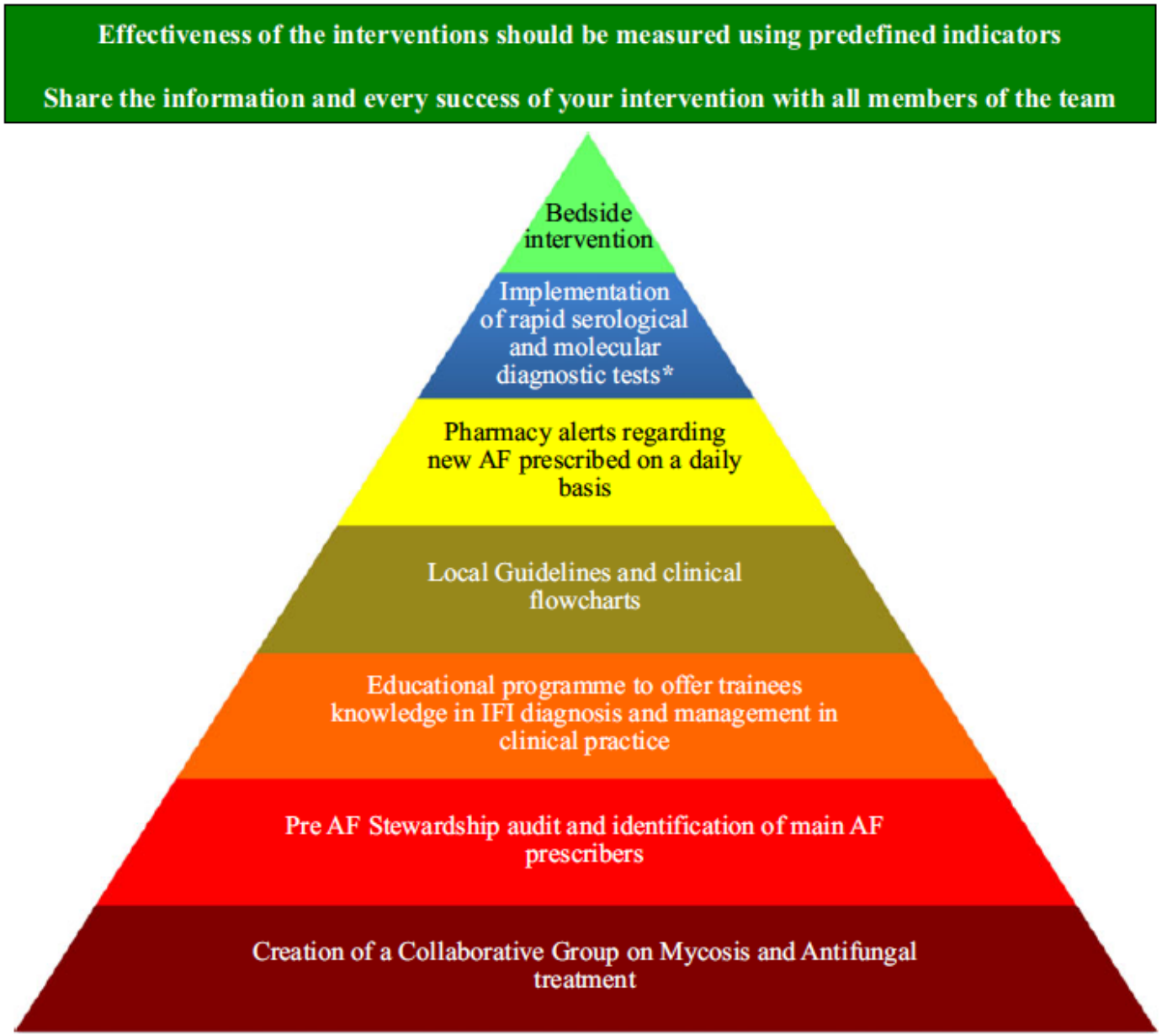
Candidemia

Table 4 Process of care measures regarding the management of candidaemia ($N = 60$) from 2007 to 2010

Process measures	2007 $N = 9$ *n* (%)	2008 $N = 14$ *n* (%)	2009 $N = 18$ *n* (%)	2010 $N = 19$ *n* (%)	*p* Value[a]
Antifungal therapy					
Started within 24 h after a positive blood culture	9 (100)	14 (100)	18 (100)	19 (100)	
Recommended first-line therapy	6 (67)	14 (100)	18 (100)	19 (100)	**0.0025**
Antifungal combination therapy	0 (0)	0 (0)	0 (0)	0 (0)	
Appropriate duration of therapy	8 (89)	13 (93)	17 (94)	19 (100)	0.46
Associated measures					
Removal of intravascular catheter[b]	5/5 (100)	4/5 (80)	6/9 (67)	7/7 (100)	0.27
Echocardiography performed	4 (44)	4 (29)	7 (39)	12 (63)	0.24
Follow-up blood cultures performed	5 (56)	10 (71)	14 (78)	14 (73)	0.70
Outcome					
Favourable outcome regarding candidaemia	7 (78)	11 (79)	16 (89)	18 (95)	0.41

Mondain, et al. Infection 2013

Antifungal Stewardship: Step by Step



Munoz, et al. Mycosis 2015.

Multifaceted Aspects of Antifungal Stewardship Programs

Intervention	Comment	References
Educational	Evaluation of gaps in knowledge of antifungal prescribers in order to tailor AFS programmes	Standiford *et al.* [5] Valerio *et al.* [11] Valerio *et al.* [35]
Restrictive prescription	ID consultant imposed the implementation of practice guidelines, provided approval of prescribed drugs or new diagnostic and therapeutic approaches for prescribing antifungal treatment	Cook *et al.* [4] Swobada *et al.* [27] Aguilar-Guisado *et al.* [30]
Bedside ID advice	Recommendations to change from IV to oral, change to fluconazole, cease antifungal treatment	Lopez-Medrano *et al.* [7]
Bundle of care	Antifungal order forms, educational and unit-specific feedback activities, expert infectious diseases bedside interventions; preauthorisation of treatment by antifungal team	Mondain *et al.* [3] Apisarnthanarak *et al.* [6] Antworth *et al.* [26] Guarascio *et al.* [28]
Pharmaceutic advice	Recommendations from pharmacist to change or stop the controlled antimicrobial agents based on microbiological data and institutional criteria for antimicrobial use	Cook *et al.* [4] Cappelletty *et al.* [25]
New diagnostic strategy	Application of PCR testing and serological markers for diagnosis of invasive fungal infection Use of molecular analysis for characterisation of clinical isolates	Guinea *et al.* [36] Escribano *et al.* [37] Marcos-Zambrano *et al.* [38] Escribano *et al.* [37] Martinez-Jimenez *et al.* [40] Barnes *et al.* [32]

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Conclusion

- Awareness about Candidemia among physicians
- Need for better serological diagnosis
  - biomarkers
- Keep updated
  - IDSA
  - + European guidelines
- A new common tool for evaluation?