

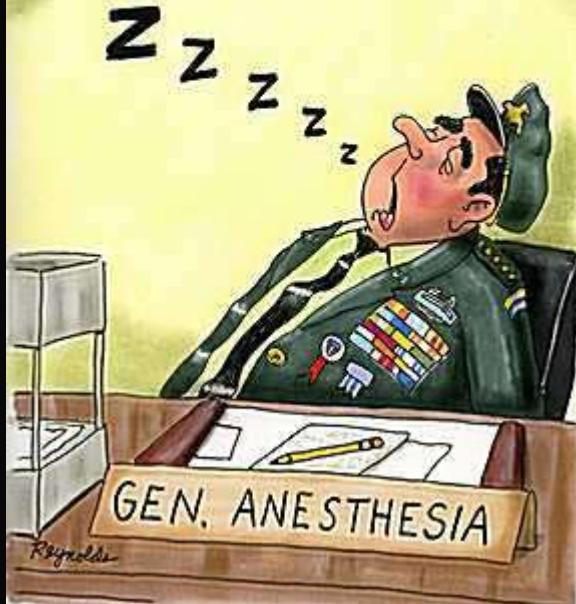


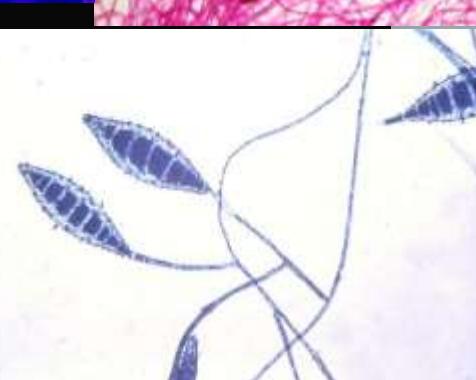
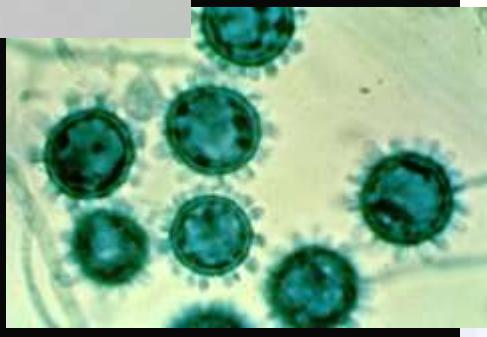
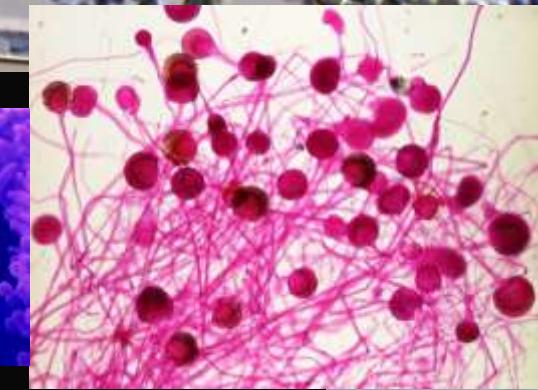
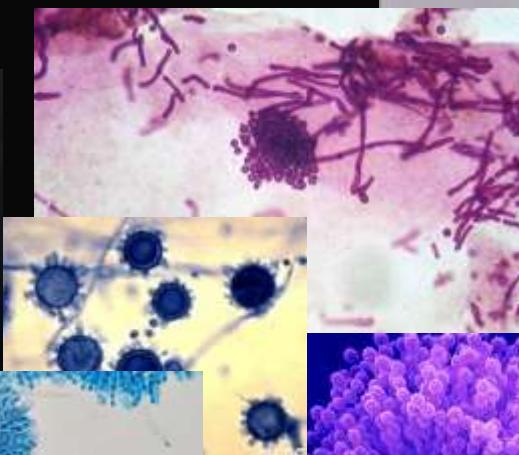
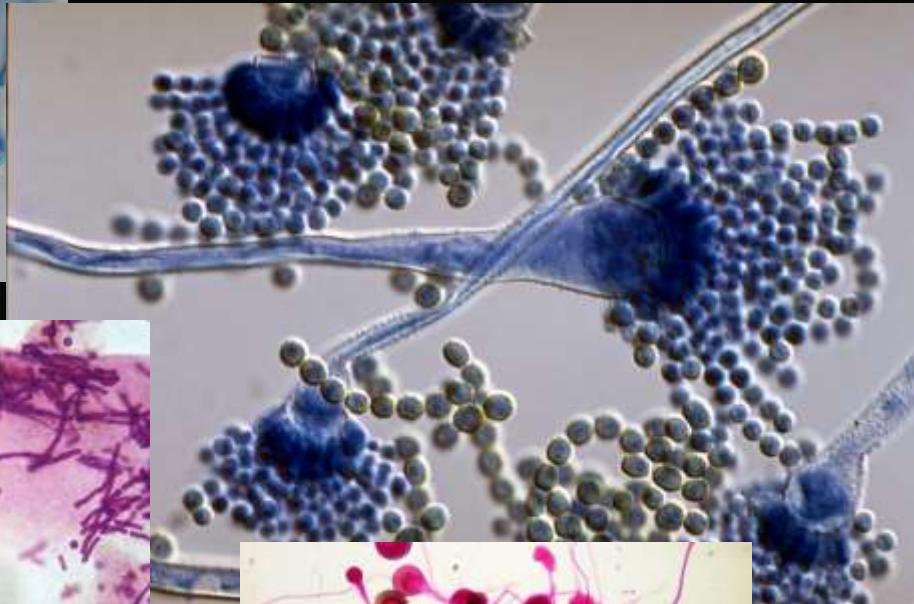
INFECȚII FUNGICE INVAZIVE

Cât de des ratăm ținta ?

Prof. Ioana Grigoras, MD, PhD
Universitatea de Medicină și Farmacie
Clinica Anestezie-Terapie Intensivă
Institutul Regional de Oncologie
Iasi, Romania

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MEETINGS
International Conference
on Antifungal Agents
and Mechanisms
of Action

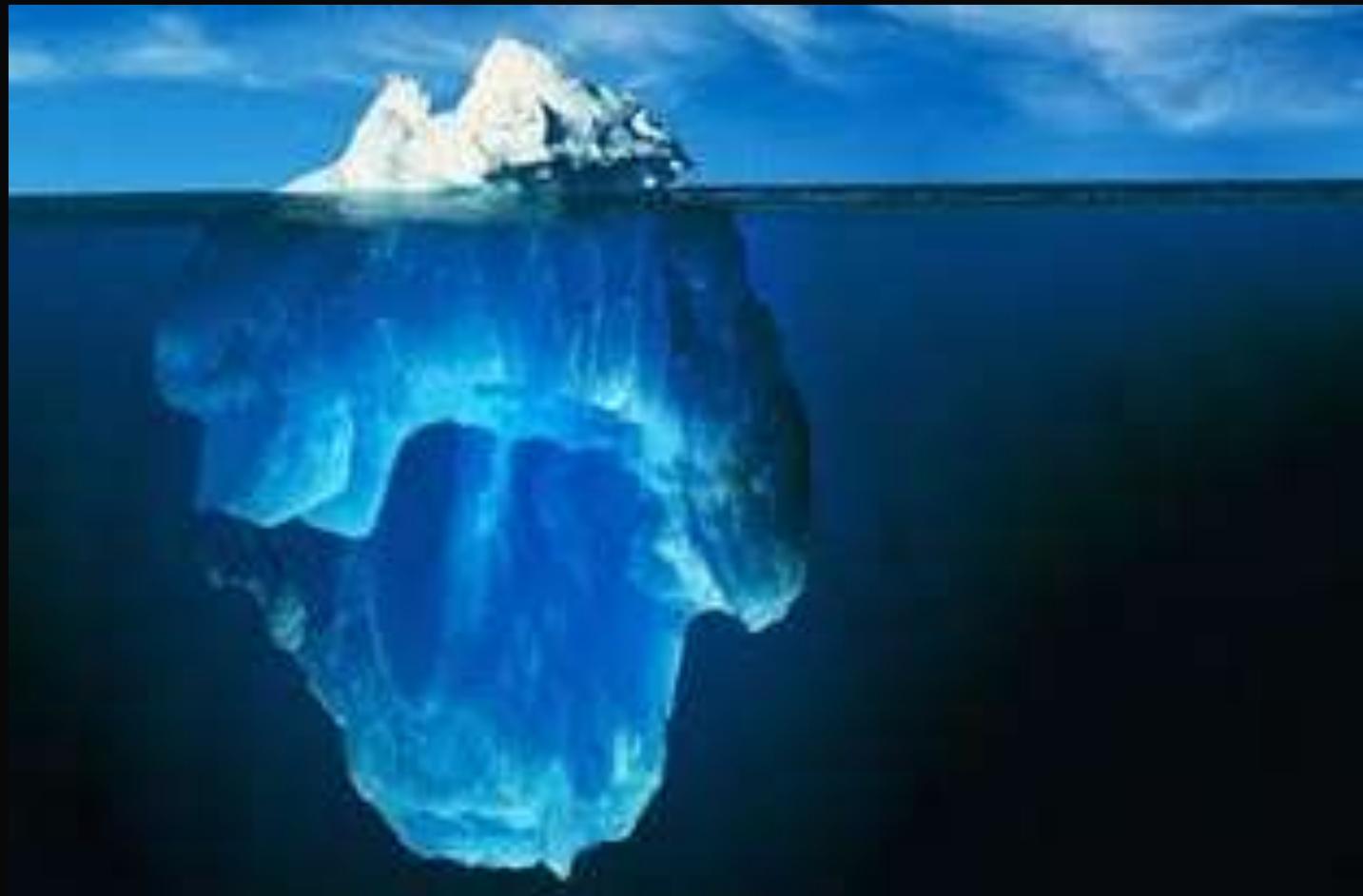
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of Amphibian
Chytridiomycosis



EPIDEMIOLOGIE

Incidența candidazei și aspergiliozei invazive în SUA 1996–2003

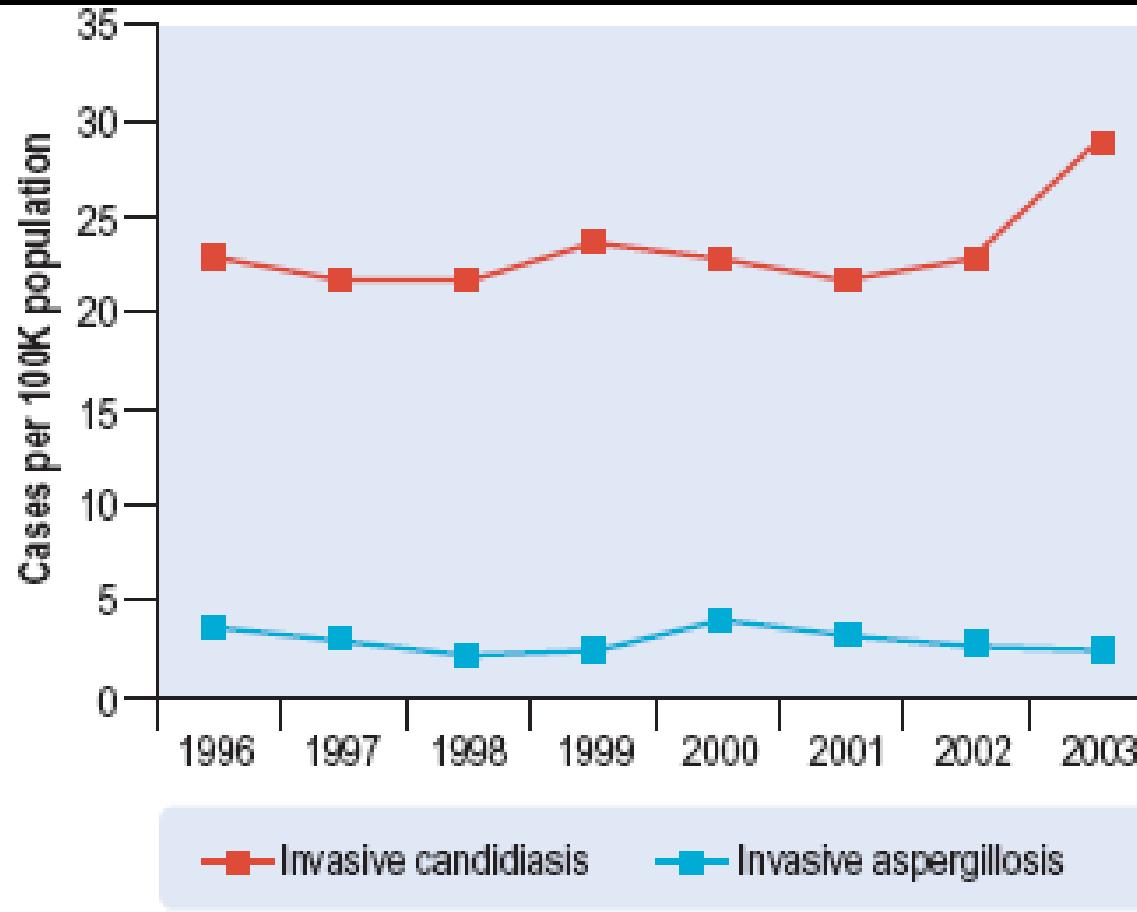


Table 2 Underlying conditions in patients with candidaemia

Underlying conditions ^{a,b}	No. (%) of patients
Surgery	933 (44.7)
Intensive care	839 (40.2)
Solid tumour	471 (22.5)
Haematological malignancy	257 (12.3)
Premature birth	125 (6.0)
Solid organ transplantation	74 (3.5)
HIV infection	63 (3.0)
Burns	29 (1.4)

^aSome patients had more than one underlying condition

^b364 (17.4%) were treated with steroids

MORTALITATE

Trends in BSI mortality

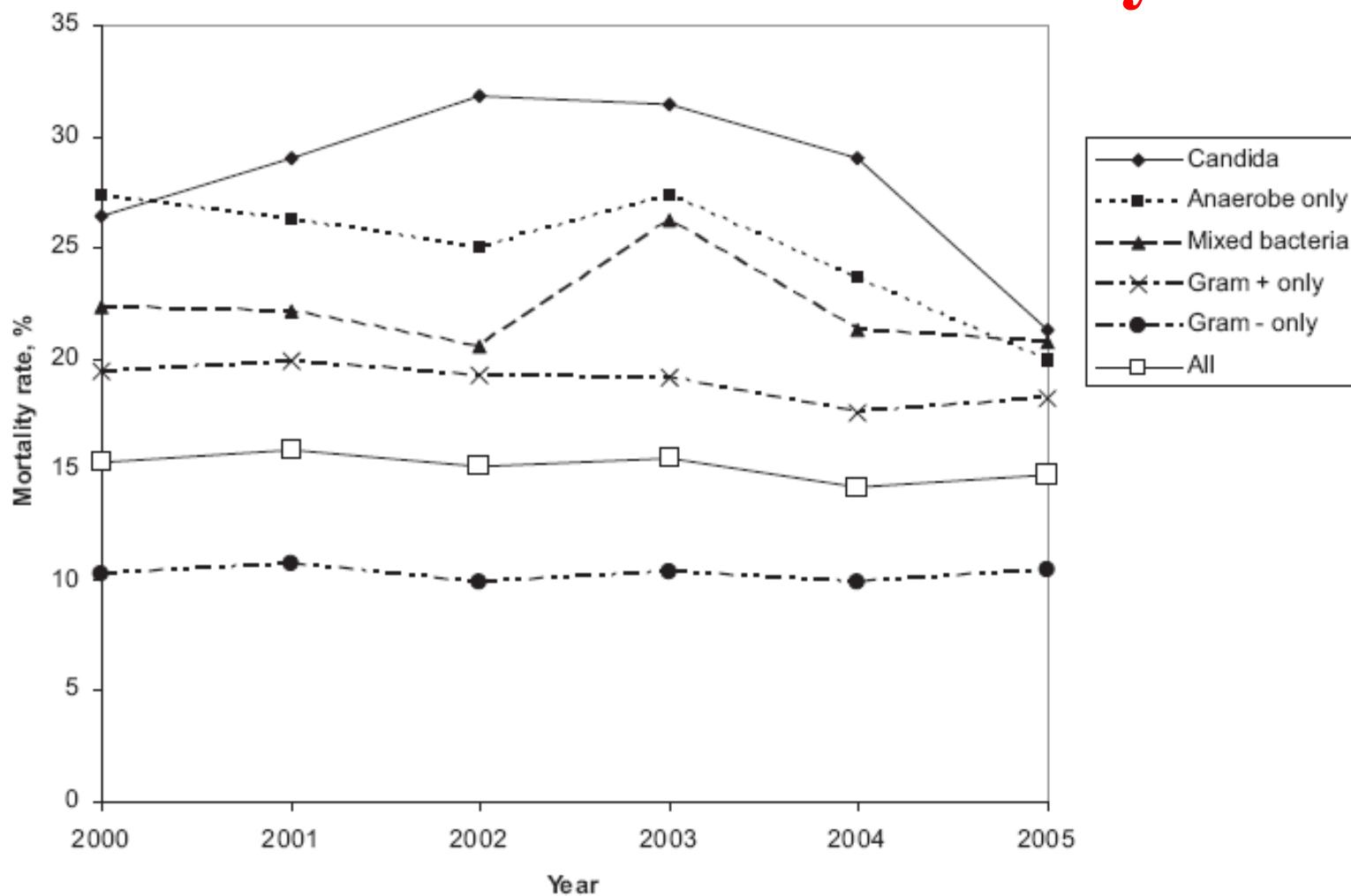
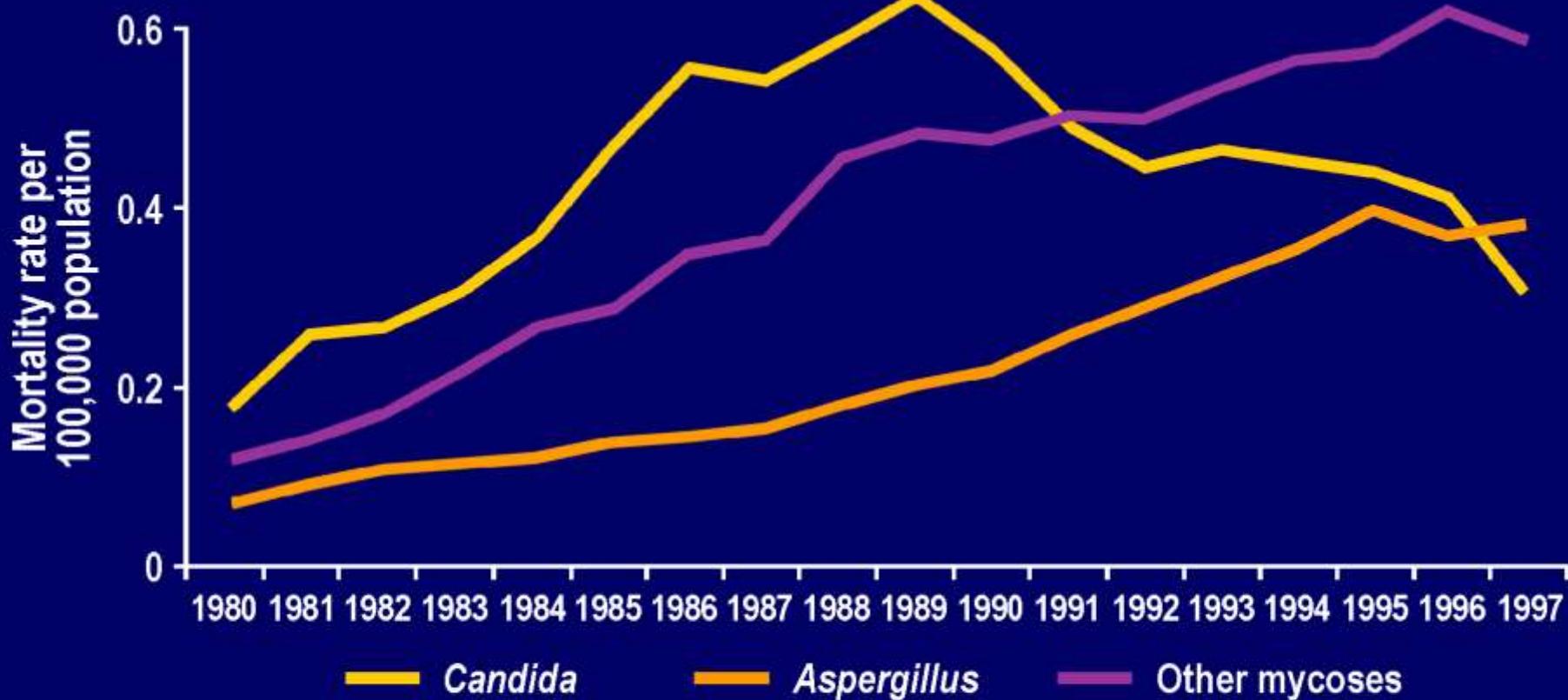


Figure 1. Trends in crude mortality by type of bloodstream infection.

Mortality Due to Invasive Mycoses



Adapted from McNeil MM et al. *Clin Infect Dis*. 2001;33:641-647.

Table 3. Outcomes associated with non-*albicans* *Candida* spp. and with *C. glabrata* or *C. krusei*

	Non- <i>albicans</i> <i>Candida</i> spp.		Potentially Fluconazole-resistant <i>Candida</i> spp.	
	Non- <i>albicans</i> <i>Candida</i> spp.	<i>C. albicans</i>	<i>C. glabrata</i> or <i>C. krusei</i>	All Other <i>Candida</i> spp.
Crude 30-day mortality				
Total, % (n)	53% (35/66)	41% (44/108)	54% (21/39)	43% (58/135)
Absolute difference, % (95% CI)	12% (-3% to 27%)		11% (-7% to 29%)	
Crude 5-day mortality				
Total, % (n)	27% (11/67)	22% (17/110)	13% (5/39)	19% (25/138)
Absolute difference, % (95% CI)	-1% (-12% to 10%)		-5% (-18% to 7%)	
Crude hospital length of stay ^a				
Total, median (IQR)	67.5 days (39–84)	59 days (34–102.5)	71 days (51–96)	59 days (34–99)
Absolute difference, median (95% CI)	2 days (-16 to 20)		-2 days (-24 to 18)	
Sepsis present at day 5	73% (35/48)	78% (62/79)	73% (22/30)	77% (75/97)
Ventilated at day 5	67% (38/57)	74% (70/95)	74% (25/34)	69% (83/120)
Candidemia relapse	13% (7/55)	17% (16/92)	16% (5/32)	15% (18/117)

^aAmong surviving patients. CI, confidence interval; IQR, interquartile range.

DIAGNOSTIC

GOLD STANDARD

Hemocultura

Cultura dintr-un situs steril - peritoneu, lcr, ...

Excepție: secreții bronhice și urina !!!!

Cultura din țesuturi profunde

**Numai 50-70% pozitive
Rezultate tardiv**

PCR

Multiplex polymerase chain reaction detection enhancement of bacteremia and fungemia*

Richard F. Louie, PhD; Zuping Tang, MD; Timothy E. Albertson, MD, PhD; Stuart Cohen, MD; Nam K. Tran, BS; Gerald J. Kost, MD, PhD

in ser

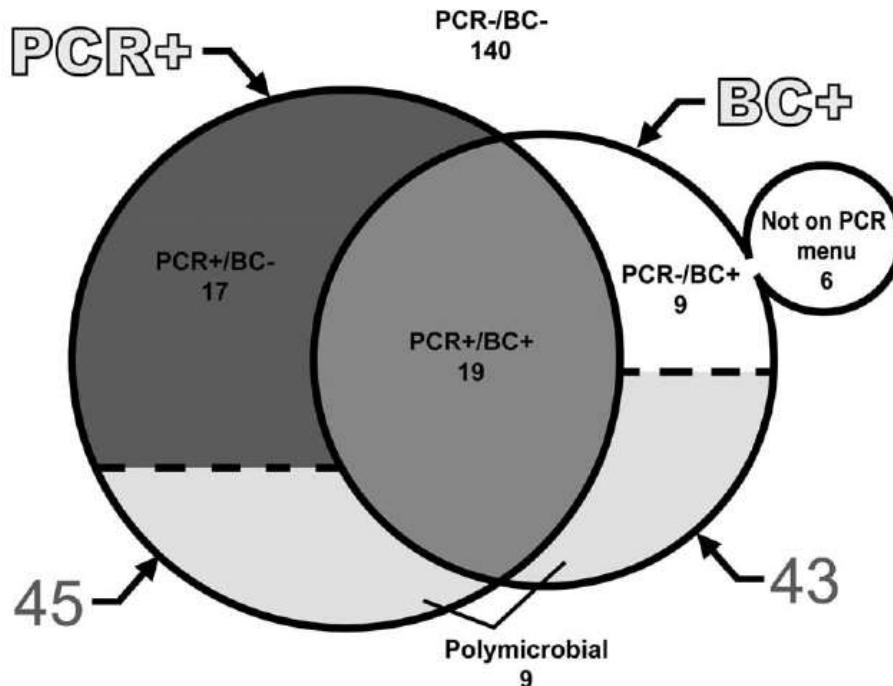


Figure 2. Comparison of polymerase chain reaction (PCR) and blood culture (BC) results. The Venn diagram shows the distribution of PCR- and BC-positive cases. The distribution of cases is based on comparison of PCR and BC results from samples collected at the same time.

Table 1. Organisms detected by the multiplex polymerase chain reaction system

Gram-Positive	Gram-Negative	Fungi
<i>S. aureus</i> <i>S. epidermidis</i> <i>S. viridans</i> <i>mecA</i> gene is tested with a separate modular test kit.	<i>Acinetobacter baumannii</i> <i>Enterobacter aerogenes/cloacae</i> <i>Escherichia coli</i> <i>Klebsiella pneumoniae/oxytoca</i> <i>Proteus mirabilis</i> <i>Pseudomonas aeruginosa</i> <i>Serratia marcescens</i> <i>Stenotrophomonas maltophilia</i>	<i>Aspergillus fumigatus</i> <i>Candida albicans</i> <i>Candida glabrata</i> <i>Candida krusei</i> <i>Candida parapsilosis</i> <i>Candida tropicalis</i>

S. aureus. ^a*S. epidermidis*, ^b*S. viridans*. ^c*mecA* gene is tested with a separate modular test kit.

Detectia **galactomanan**-ului în **BAL** și **ser** este utilă pentru diagnosticul aspergiliozei invazive la pacientul **imunocompromis**

Table 2

Detection of galactomannan in bronchoalveolar lavage using the Platelia *Aspergillus* enzyme immunoassay

Group	Sensitivity (%)	Specificity (%)	Reference
Hematologic patients (CO 1.0)	100 (N = 17)	100 (N = 18)	Becker (2003) ³¹
Hematopoietic stem cell transplantation (CO 0.5)	76 (N = 49)	94 (N = 50)	Musher(2004) ³²
Lung transplantation (CO 0.5)	67 (N = 6)	91 (N = 110)	Husain (2007) ³³
Solid organ transplantation (CO 0.5)	100 (N = 5)	84 (N = 76)	Clancy (2007) ³⁴
Nonimmunosuppressed (CO 0.5)	100 (N = 6)	78 (N = 67)	Nguyen (2007) ³⁵
Immunosuppressed ICU patients (CO 0.5)	88 (N = 26)	87 (N = 46)	Meerseman (2008) ³⁶

pacientul imunocompetent ????

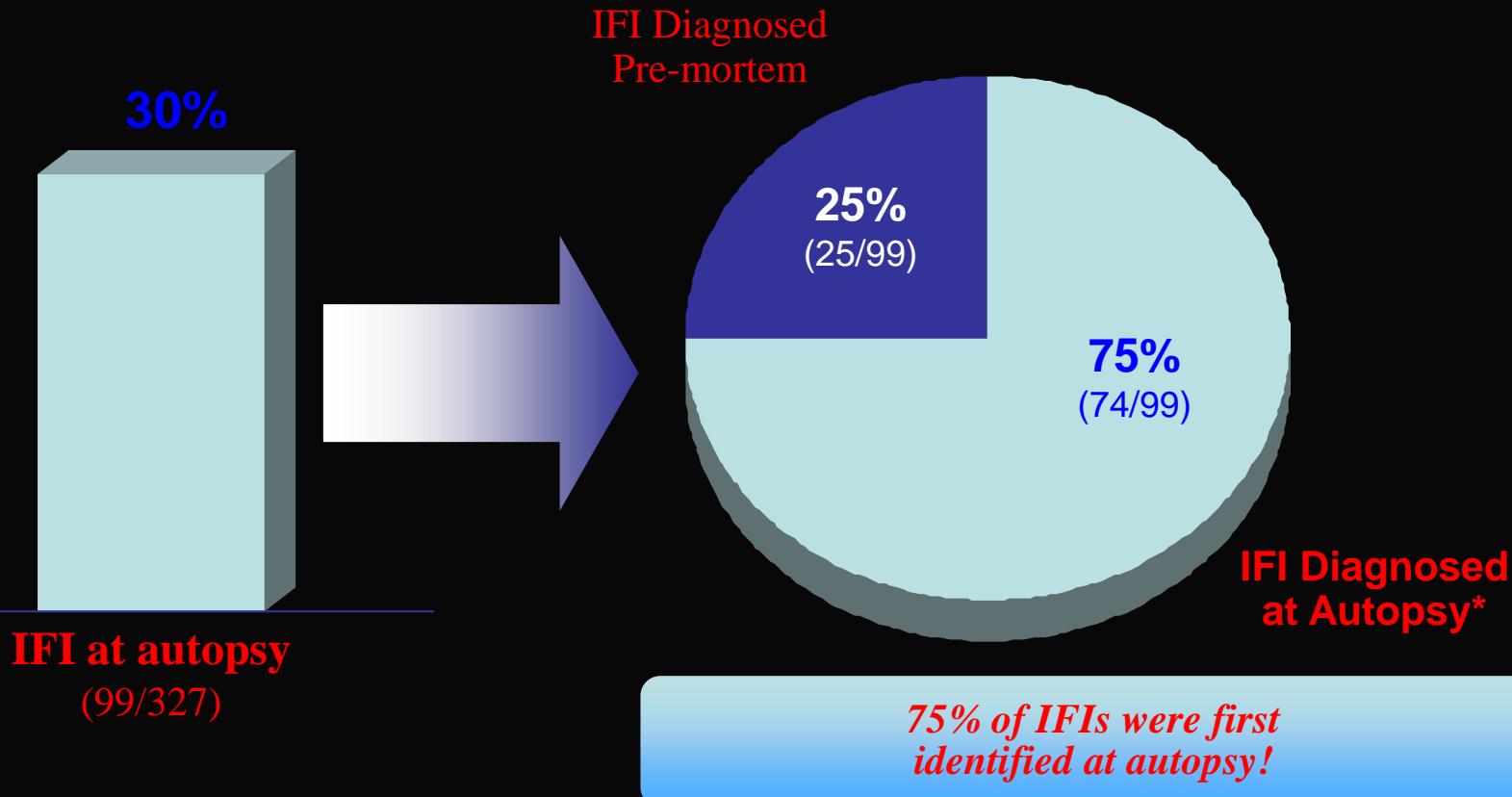
Table 3
Detection of (1 → 3)-β-D-glucan in patients who have invasive aspergillosis

Design	Sensitivity (%)	Specificity (%)	Reference
Once-weekly monitoring, hematology patients, CO 11 pg/mL (BG Wako test)	55 (N = 11)	98 (N = 125)	Kawazu (2004) ⁴⁸
Twice-weekly monitoring, neutropenia, CO 60 ng/mL (Fungitell®)	100 (N = 4)	90 (N = 230)	Odabasi (2004) ⁴⁸
Twice-weekly monitoring, neutropenia, CO 120 pg/mL (Fungitell)	100 (N = 8)	90 (N = 29)	Pazos (2005) ⁵⁰
Single specimen, CO 80 (Fungitell®)	100 (N = 10)	92 (N = 170) healthy subjects: outpatients and inpatients without IFI	Ostrosky-Zeichner (2005) ⁵¹
Liver transplantation, once-weekly monitoring, CO 40 pg/mL (Fungitec G test)	40 (N = 5)	83 (N = unknown)	Akamatsu (2007) ⁵²
Hematology or ICU, single test, CO 80 pg/mL (Fungitell)	68 (N = 70)	56 (N = 100)	Persat (2008) ⁵³

Table 4
Detection of (1 → 3)-β-D-glucan in patients who have candidiasis

Design	Sensitivity (%)	Specificity (%)	Reference
Candidemia, single specimen, CO 60 pg/mL	84 (N = 39)	88 (N = 40)	Mitsutake (1996) ⁶⁶
ICU patients, single specimen CO 100 pg/mL (Fungitell®)	57 (N = 7) candidemia	75 (N = 16) bacteremia	Digby (2003) ⁵⁴
Fungemia, single specimen, CO 60 pg/mL (Fungitell)	97 (N = 30) candidemia	93 (N = 30) healthy adults	Odabasi (2004) ⁴⁸
Fungemia, single specimen CO 80 pg/mL (Fungitell®)	87 (N = 15) candidemia	44 (N = 25) bacteremia	Pickering (2005) ⁵⁵
Fungemia, single specimen, CO 80 pg/mL (Fungitell)	78 (N = 92)	92 (N = 170) healthy subjects: outpatients, inpatients without IFI	Ostrosky-Zeichner (2005) ⁵¹
Liver transplantation, once-weekly monitoring, CO 40 pg/mL (Fungitec G test)	57 (N = 14)	83 (N = unknown)	Akamatsu (2007) ⁵²
Hematology or ICU, single test, CO 80 pg/mL (Fungitell)	85 (N = 27)	56% (N = 100)	Persat (2008) ⁵³

Adevărată incidentă a IFI în hematooncologie



FACTORI DE RISC

FACTORI DE RISC

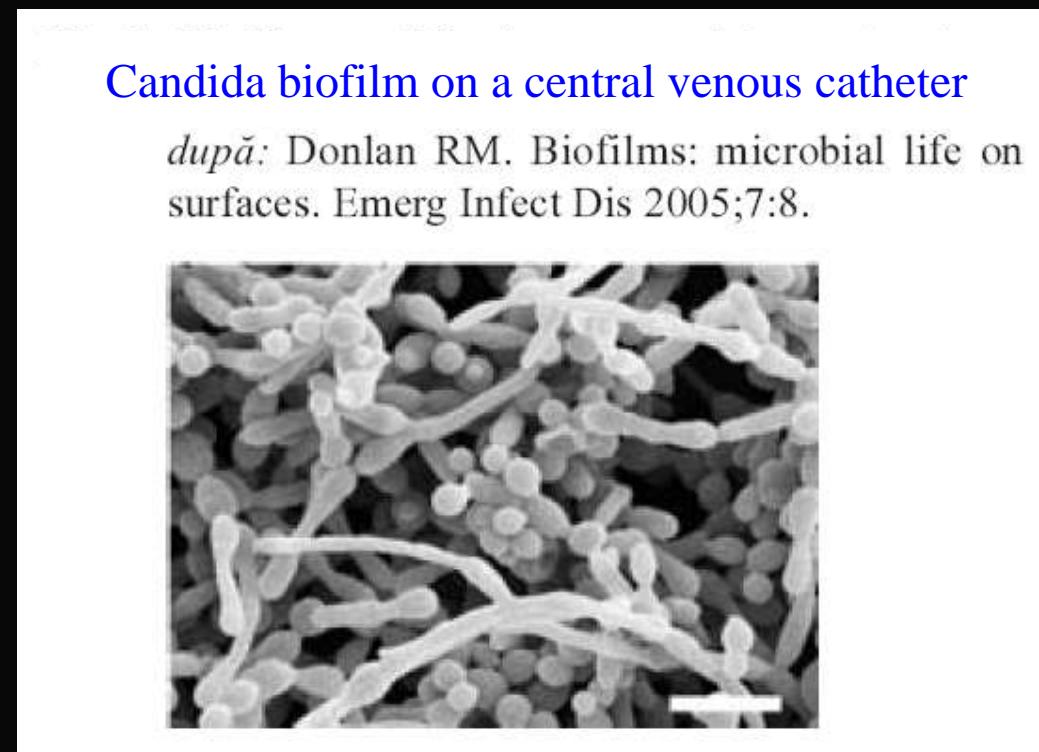
- **Întreruperea barierelor naturale de apărare**
 - Arsuri
 - Discontinuitatea tractului gastro-intestinal (perforații, fistule, etc.)
- **Statusul imunocompromis**
 - Boli hematologice (leucemii, aplazie medulară, etc.)
 - Agenti imunosupresori (cortizon, chimioterapice, imunosupresoare)
 - Pacienți transplantati
 - Diabetul zaharat, insuficiența renală cronică
- **Material străin implantat**
 - Catetere intravasculare, intraperitoneale
 - Proteze valvulare sau vasculare
 - Biofilm
- **Alterarea ecologiei bacteriene**
 - Terapia cu antibiotice
 - Colonizarea cu fungi

COLONIZAREA

- **Important factor de risc**
- **Colonizarea pe tegumente și mucoase**
- **Semne clinice de infecție (sepsis) + colonizare fungică = risc ↑ IFI**
- **Indexul de colonizare**
 - ✓ = numărul de situsuri colonizate (aceiași specie) / număr de situsuri cultivate
 - ✓ $\geq 0,5$ – valoare predictivă 66%
 - ✓ ↑ sensitivitatea prin culturi cantitative

BIOFILMUL

- Conține microorganisme care aderă la suprafete
- Scapă mecanismelor de apărare imună
- Biofilmul – generează și perpetuează infecția (rezervor)



LITERATURĂ

Factori de risc

Table 2. Predictive algorithms for IC in critically ill patients

Authors	Setting	n	Design	Risk Factors Utilized in Algorithm or Predictive Rule	Predictive Value (%)			
					Sensitivity (%)	Specificity (%)	Positive	Negative
Pitter et al (29)	SICU; neonatal ICU, patients with significant colonization for at least 2 d in the ICU	29	Prospective cohort study	Candidal colonization ^a Patients with a CCI ≥ 0.4	100	100	100	100
Michalopoulos et al (25)	Cardiothoracic ICU	150	Prospective case control single-center study followed by a prospective, 2 center validation study	Risk factors in final validation model included ongoing invasive mechanical ventilation ≥ 10 d, hospital-acquired bacteremia and/or bacteraemia, cardiopulmonary bypass duration >120 mins, and diabetes mellitus	57.9	100	100	99.6
DuPont et al (33)	SICU	221	Retrospective cohort study, with prospective validation, single center	Risk for isolation of yeast from peritoneal fluid. In patients with 3 of 4 independent risk factors (female gender, upper GI tract origin (above the transverse mesocolon), intraoperative cardiovascular failure, and antimicrobial therapy at least 48 hrs before onset of peritonitis)	84	50	87	72
Leon et al (24)	73 MICUs/SICUs in Spain, patients were admitted to ICU for ≥ 7 d	1699	Prospective cohort study, multicenter, observational	Risk factor score, TPN 0.908, surgery 0.997, multifocal colonization 1.112, severe sepsis 2.038, cutoff value: patients with a <i>Candida</i> score >2.5	81	74	16.1	98.5
Paphitou et al (26)	SICU, patients admitted to SICU for ≥ 4 d	327	Retrospective, single center	1) Any of the following: DM, TPN before ICU entry ^b ; or new onset hemodialysis 2) As with 1), OR BS ABX $D_{-7 \text{ to } 3}$ 3) As with 1), and BS ABX $D_{-7 \text{ to } 3}$	39.1	85.9	17.3	94.9
Ostrosky-Zeichner et al (30)	9 MICUs or SICUs in Brazil and United States, patients admitted to ICU for ≥ 4 d	2890	Retrospective, multicenter	Two major factors ^c Two major factors plus at least one minor factor One major factor plus at least two minor factor	89	38	4	99
					66	69	6	98
					34	90	9.9	97

ICU, intensive care unit; D_x to D_y day of therapy relative to admission to the ICU; D_0 , day of ICU admission; DM, diabetes mellitus; TPN, total parenteral nutrition; IC, invasive candidiasis; BS ABX, broad-spectrum antibiotics; CCI, corrected colonization index; CVC, central venous catheter; OR, odds ratio; SICU, surgical ICU; MICU, medical ICU; GI, gastrointestinal.

^aMycological surveillance cultures taken on admission and once weekly, including gastric aspirate, tracheal aspirate, urine, and oropharyngeal swabs. CCI: Refer to Table 1 for further information; ^ball patients required ICU stay ≥ 4 d and no antifungal therapy $D_{-7 \text{ to } 3}$; ^cclinical predictive criteria major factors = any systemic ABX use $D_{1 \text{ to } 5}$ CVC $D_{2 \text{ to } 3}$; minor factors = any surgery $D_{-7 \text{ to } 3}$ immunosuppression $D_{-2 \text{ to } 3}$ pancreatitis $D_{-7 \text{ to } 3}$ TPN $D_{1 \text{ to } 5}$; dialysis $D_{-7 \text{ to } 3}$; steroid use $D_{-7 \text{ to } 3}$.

Identificarea pacienților cu indicație de terapie empirică

Scorul Candida

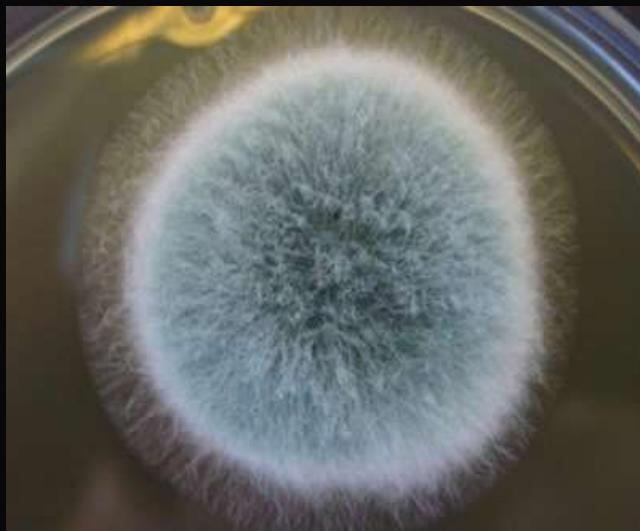
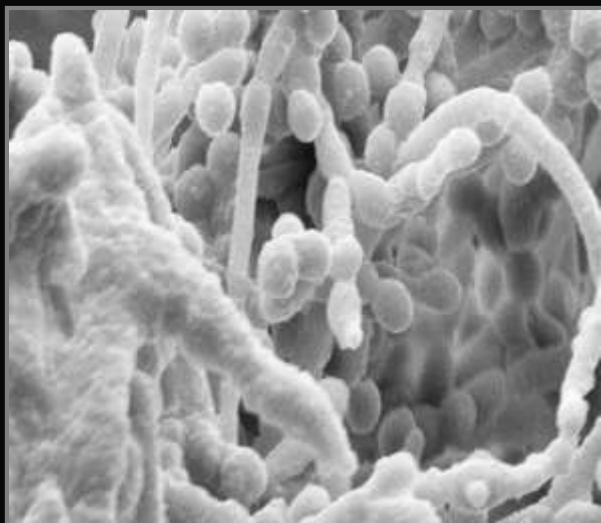
Factor predictiv	Rounded risk score
Chirurgie	1
Colonizare multifocală	1
Nutriție parenterală totală	1
Sepsis sever	2

Cut-off value: 2.5 (sensitivity 81%, specificitate 74%)

MICROBIOLOGIE

TOP TEN

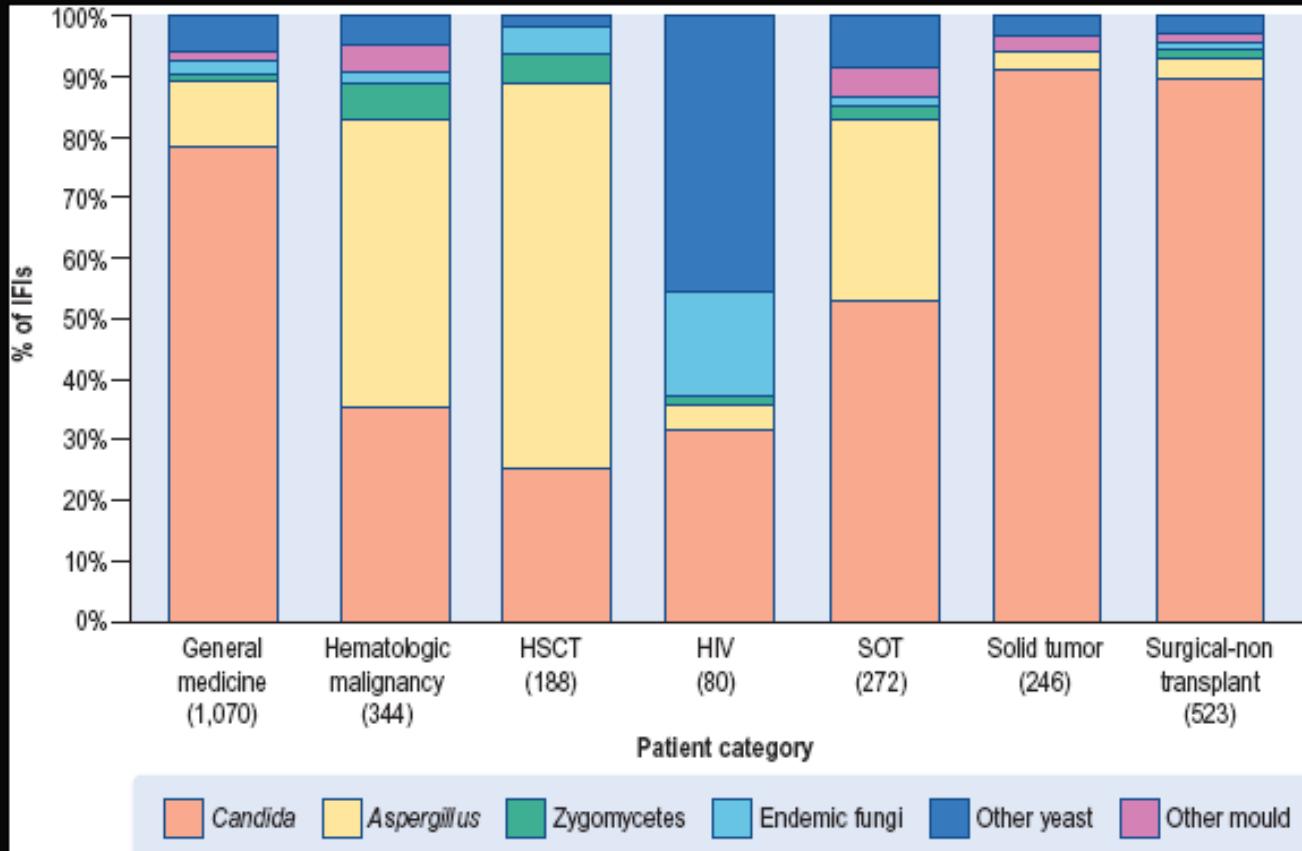
1. **Candida**
2. **Candida**
3. **Candida**
4. **Candida**
5. **Candida**
6. **Candida**
7. **Candida**
8. **Candida**
9. **Aspergillus**
10. **Others**



Candida as a Nosocomial Pathogen

Rank	Pathogen	BSI per 10,000 admissions	% BSI			% Crude Mortality		
			Total (n=20,978)	ICU (n=10,515)	Non-ICU (n=10,515)	Total	ICU	Non-ICU
1.	CoNS	15.8	31.3	35.9	26.6	20.7	25.7	13.8
2.	S aureus	10.3	20.2	16.8	23.7	25.4	34.4	18.9
3.	Enterococcus spp	4.8	9.4	9.8	9.0	33.9	43.0	24.0
4.	Candida spp	4.6	9.0	10.1	7.9	39.2	47.1	29.0
5.	E coli	2.8	5.6	3.7	7.6	22.4	33.9	16.9
6.	Klebsiella spp	2.4	4.8	4.0	5.5	27.6	37.4	20.3
7.	P aeruginosa	2.1	4.3	4.7	3.8	38.7	47.9	27.6
8.	Enterobacter spp	1.9	3.9	4.7	3.1	26.7	32.5	18.0
9.	Serratia spp	0.9	1.7	2.1	1.3	27.4	33.9	17.1
10.	A baumannii	0.6	1.3	1.6	0.9	34.0	43.4	16.3

Distribuția patogenilor IFI nosocomiale în funcție de patologia de bază



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HSCT, hematopoietic stem cell transplant; SOT, solid organ transplant

Susceptibilitatea la FLUCONAZOLE a Candida spp.

Exponerea anterioară la azoli

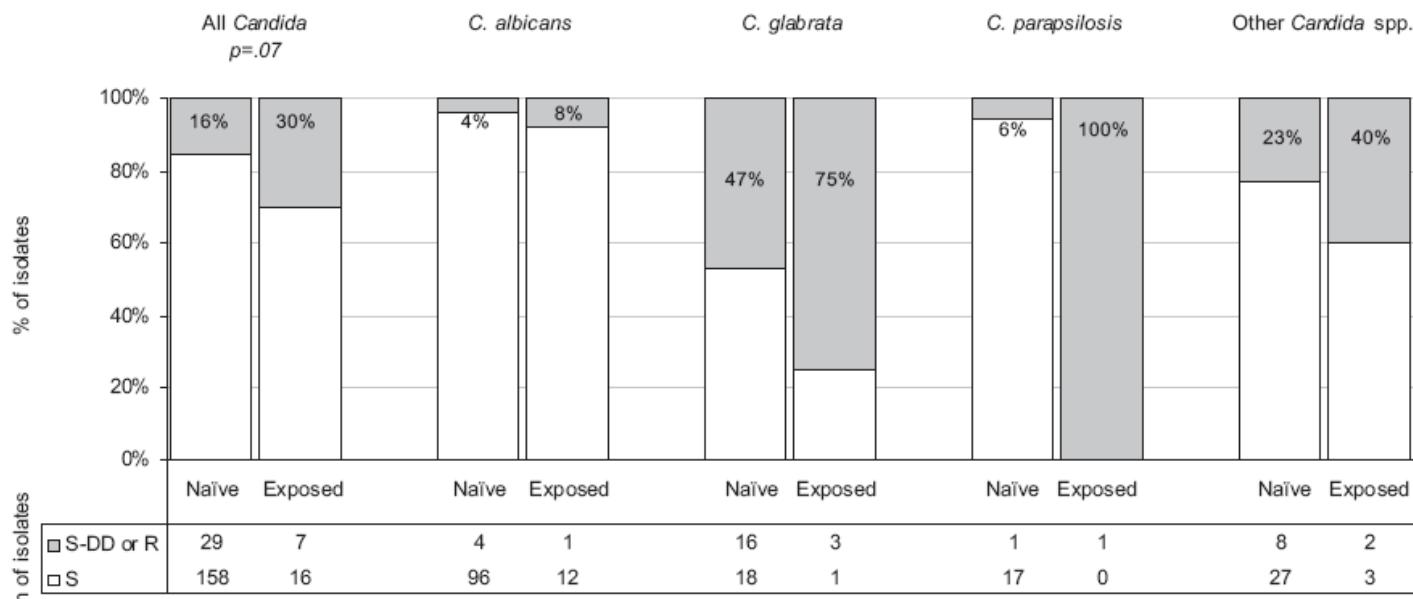


Figure 1. *In vitro* susceptibility to fluconazole of selected *Candida* species in patients naïve for azole agents and in patients previously exposed to azole agents. S, susceptible; S-DD, susceptible-dose dependent; R, resistant.

PACIENTUL CHIRURGICAL



Should we treat *Candida* isolates from the peritoneal fluid?



Heavy or increasing growth of *Candida* spp in specimens obtained from the peritoneal cavity is predictive of subsequent infections.^{148,151,152}

Reviews

Epidemiology of *Candida* species infections in critically ill non-immunosuppressed patients

Philippe Eggimann, Jorge Garbino, and Didier Pittet

Lancet Infect Dis 2003; 3: 685–702

There is no real consensus on diagnostic criteria for peritonitis. Some researchers judge that the presence of candida in any abdominal specimen justifies empirical antifungal treatment,¹¹² whereas others view it as a contaminant in most cases.

Candida spp were pathogenic in the presence of pancreatitis and in all patients with anastomotic leakage or recurrent perforation of the digestive tract.

Management of candidiasis

Management of *Candida* species infections in critically ill patients

Philippe Eggimann, Jorge Garbino, and Didier Pittet

Lancet Infect Dis 2003; 3: 772–85

FACTORI DE RISC

Candidemia la pacientul nonneutropenic

Continuing Medical Education Article

Candidemia in nonneutropenic critically ill patients: Risk factors for non-albicans *Candida* spp.

E. Geoffrey Playford, MBBS, MMed, FRACP, FRCPA; Deborah Marriott, MBBS, FRACP, FRCPA; Quoc Nguyen, BMedSci, MHA; Sharon Chen, PhD, FRACP, FRCPA; David Ellis, PhD; Monica Slavin, MD, FRACP; Tania C. Sorrell, MD, FRACP

Table 1. Risk factors for bloodstream infection with non-albicans *Candida* spp.

Multivariate analysis	Adjusted OR (95% CI) ^b	p
Recent systemic antifungal exposure	4.60 (1.36–15.53)	.01
Recent gastrointestinal surgery	2.87 (1.68–4.91)	<.001
Intravenous drug use	11.37 (1.17–110.19)	.04
Age (per each 10-yr increase)	1.19 (1.02–1.39)	.03

VIII. WHAT ANTIMICROBIAL REGIMENS SHOULD BE USED IN PATIENTS WITH HEALTH CARE-ASSOCIATED INTRA-ABDOMINAL INFECTION, PARTICULARLY WITH REGARD TO *CANDIDA*, *ENTEROCOCCUS*, AND *MRSA*?

Even when fungi are recovered, antifungal agents are unnecessary in adults unless the patient has recently received immunosuppressive therapy for neoplasm or has a perforation of a gastric ulcer on acid suppression or malignancy, transplantation, or inflammatory disease or has postoperative or recurrent intra-abdominal infection [104–106].

with the common use of fluconazole prophylaxis in the intensive care unit, suggests empiric use of echinocandins (caspofungin, anidulafungin, and micafungin) [110–114].

IDSA GUIDELINES

Diagnosis and Management of Complicated Intra-abdominal Infection in Adults and Children: Guidelines by the Surgical Infection Society and the Infectious Diseases Society of America

CATETERUL VENOS CENTRAL

TRATAMENT

ANTIFUNGICE

IFI – Medicamente antifungice

AZOLI

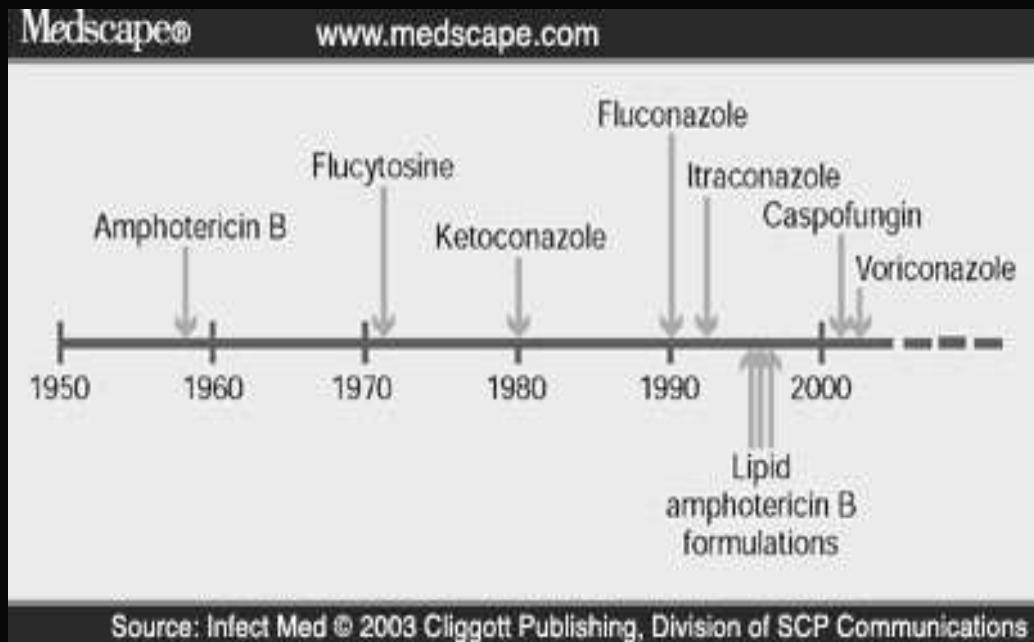
- Fluconazol
- Voriconazol
- Posaconazol

ECHINOCANDINE

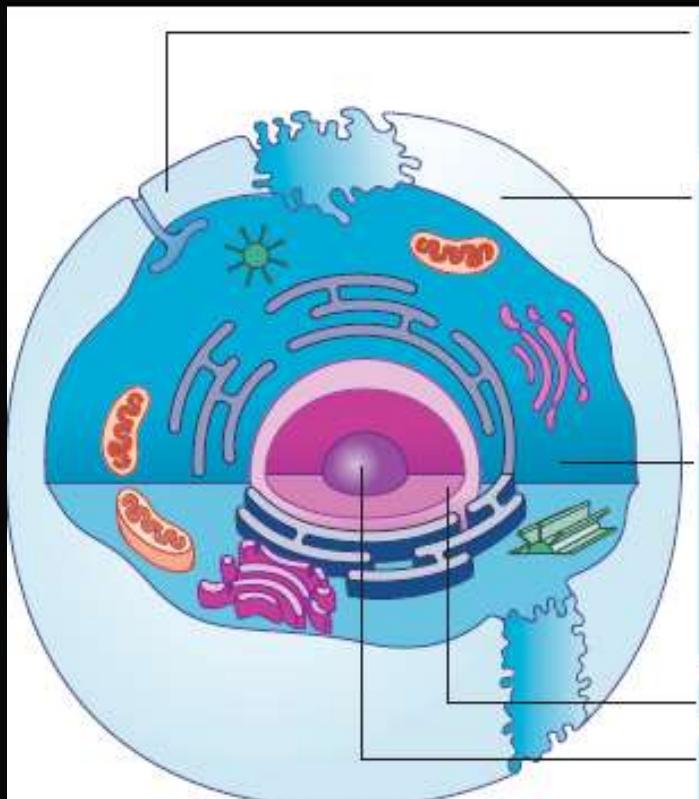
- Caspofungin
- Anidulafungin
- Micafungin

POLYENE

- Amphotericin B



ANTIFUNGICE – loc de acțiune

	<p>Cell wall synthesis *Echioncandins, pneumocandins and papulocandins; inhibit glucan synthase *Polyoxins and nikkomycins: inhibit chitin synthase</p> <p>Membrane function †Polyenes bind to ergosterol Antimicrobial peptides: defensins, the protegrins, gallinacini, cecropin A, thanatin and the dermaseptins †Pradimicins and benanomicins: bind to mannoprotein and cause a calcium-dependent alteration in membrane permeability</p> <p>Ergosterol synthesis ‡Azoles inhibit cytochrome P₄₅₀-dependent 14 -α-demethylase ‡Allylamines (naftifine and terbinafine) and thiocarbamates (tolnaftate): inhibit squalene epoxidase ‡Morpholine (amorolfine): inhibit Δ^{14} -reductase, Δ^7, Δ^8isomerase, oxido-squalene cyclase, and Δ^{24} methyltransferase</p> <p>Nuclear division ‡Griseofulvin</p> <p>Nuclear acid synthesis ‡5-Fluorocytosine, Sordarins: miscoding of RNA and inhibits thymidylate synthesis Cispentacin derivatives</p>
	<p>* Investigational</p> <p>† Potential target</p> <p>‡ Clinically available</p>

Candida spp.

Susceptibilitate nativă la antifungice

	AmfB	Fluco	Vor	Caspo	Anidula
C. Albicans	+	+	+	+	+
C. Glabrata	+	+/-	+/-	+	+
C. Krusei	+	-	+	+	+
C. Lusitaniae	-	+	+	+	+
C. Parapsilosis	+	+	+	+/-	+/-
C. tropicalis	+	+	+	+	+

ANTIFUNGICE

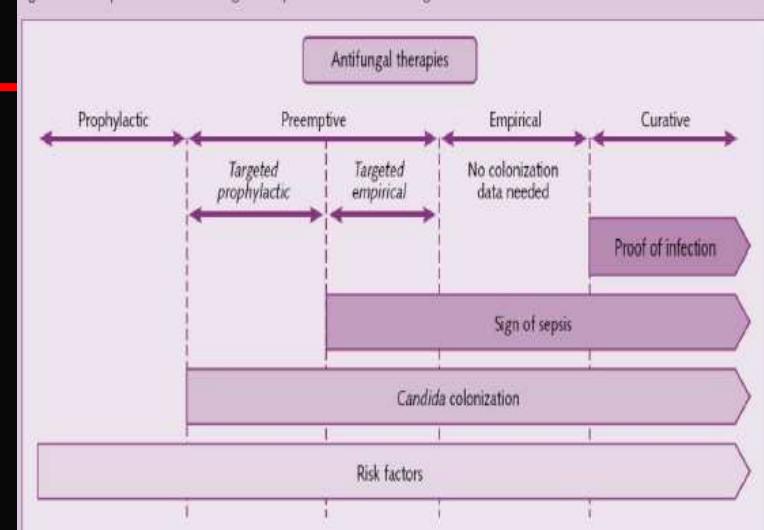
Și particularotățile pacientului

	Previous azole	Severe renal failure	Hepatic failure	Obese /anasarca	Shock
AB	NO	NO	NO	NO	NO
AB Lipidic form	++	NO	++	+	++
Fluconazole	NO	NO	NO	NO	NO
Voriconazol	++	+/-	+/-	++	+++
Caspofungin	+++	+++	+/-	+/++	+++
Anidulafungin	+++	+++	+++	+++	+++

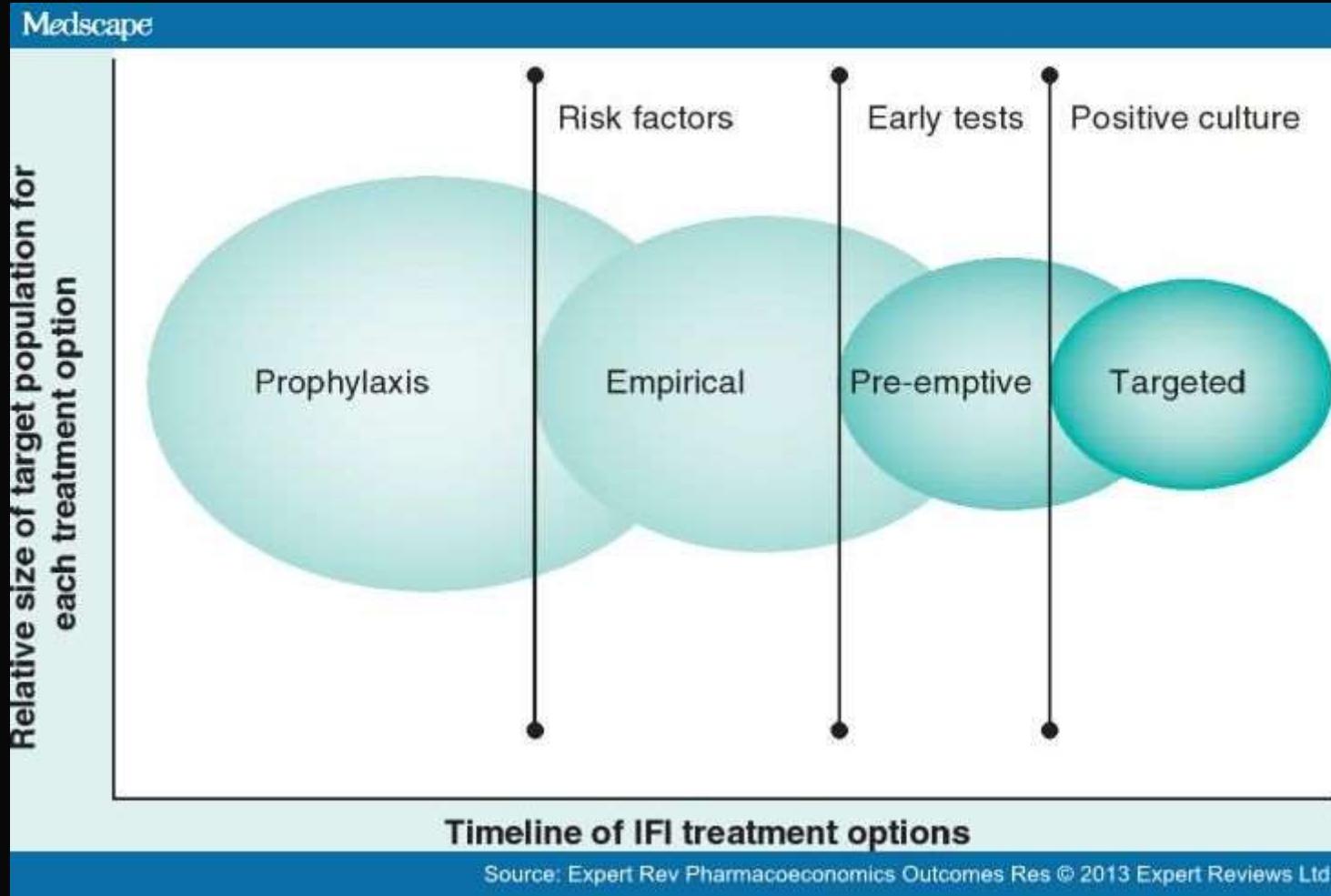
TERMINOLOGIE TERAPEUTICA

TERMINOLOGIE TERAPEUTICĂ – definiții

Figure 1. Conceptual basis of antifungal therapies in critical care settings



- ✓ Profilaxie
fără semne de boală (\pm factori de risc)
- ✓ Terapie empirică
boală, fără semne de infecție (multipli factori de risc)
- ✓ Terapie pre-emptivă
boală, semne de infecție (multipli factori de risc)
- ✓ Terapie țintită
cultură + identificare + testarea susceptibilității



GHIDURI TERAPEUTICE



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D

~~ASA GUIDELINES~~

American Thoracic Society Documents

An Official American Thoracic Society Statement: Treatment of Fungal Infections in Adult Pulmonary and Critical Care Patients

Andrew H. Limper, Kenneth S. Knox, George A. Sarosi, Neil M. Ampel, John E. Bennett, Antonino Catanzaro, Scott F. Davies, William E. Dismukes, Chadi A. Hage, Kieren A. Marr, Christopher H. Mody, John R. Perfect, and David A. Stevens, on behalf of the American Thoracic Society Fungal Working Group

Alison G. Freifeld,¹ Eric J. Bow,⁹ Kent A. Sepkowitz,² Michael J. Boeckh,⁴ James I. Ito,⁵ Craig A. Mullen,³ Issam I. Raad,⁶ Kenneth V. Rolston,⁶ Jo-Anne H. Young,⁷ and John R. Wingard⁸

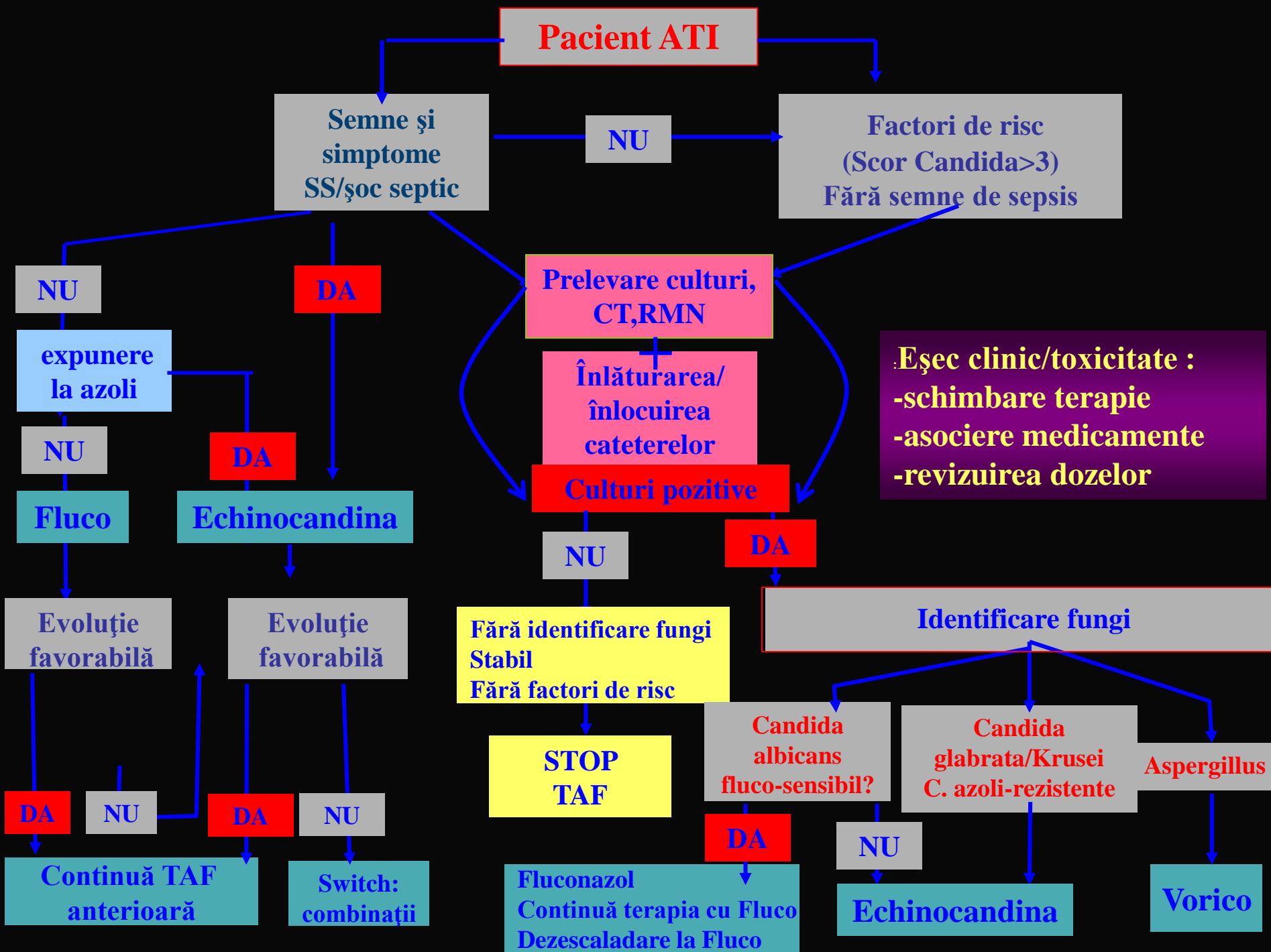
Stefan Reuter • Gerda Silling • Thomas Südhoff •
Andrew J. Ullmann • Georg Maschmeyer

GHIDURI TERAPEUTICE

pentru subpopulații specifice

- pacient neutropenic/non-neutropenic
- pacient imunocompromis
- pacient cu cancer
- pacient hemato-oncologic/transplant medular
- pacient critic
- ...

ABORD TERAPEUTIC



FARCUIS®

David Waisglass and Gordon Coulthart

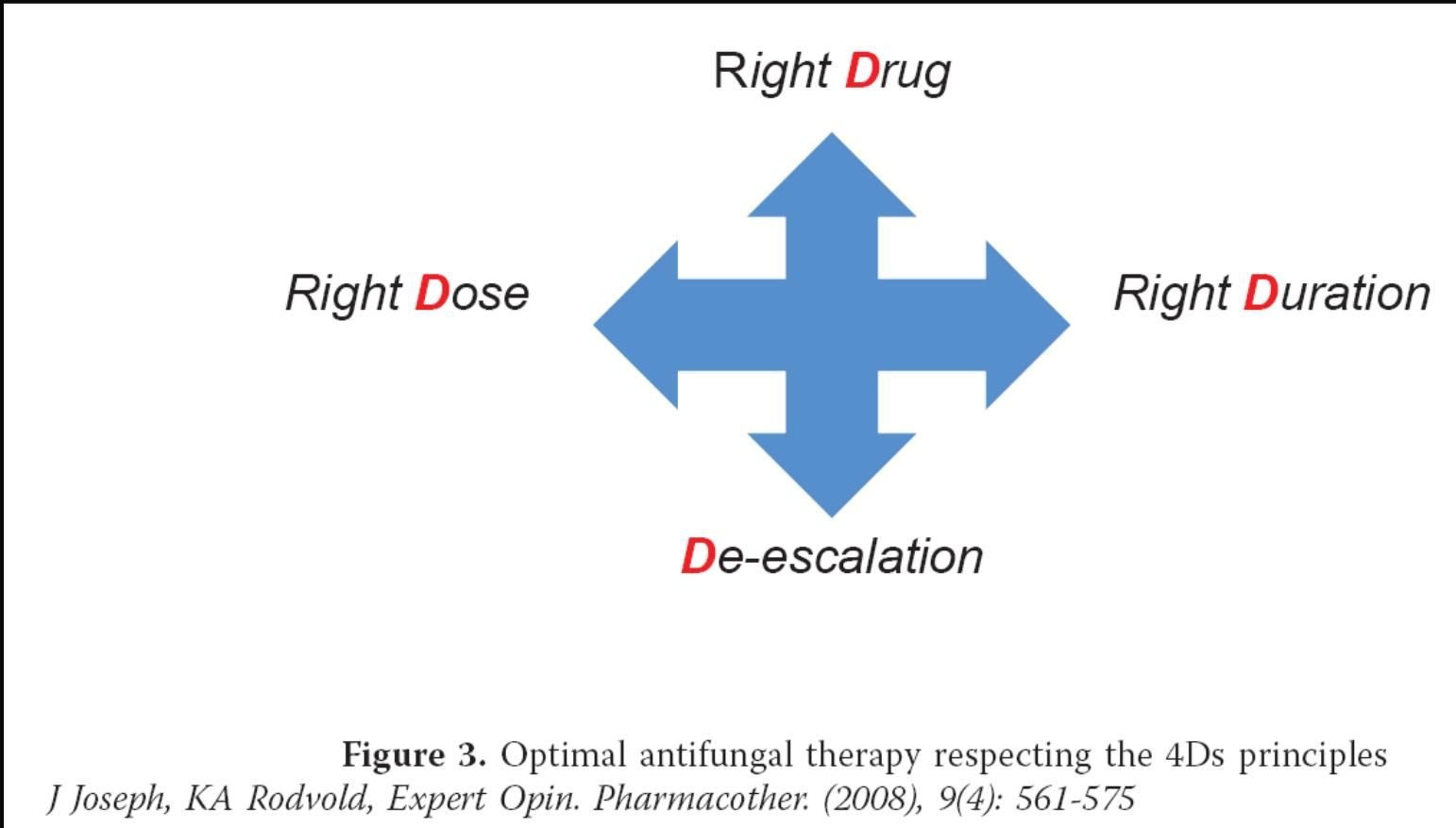


SAY PLEASE

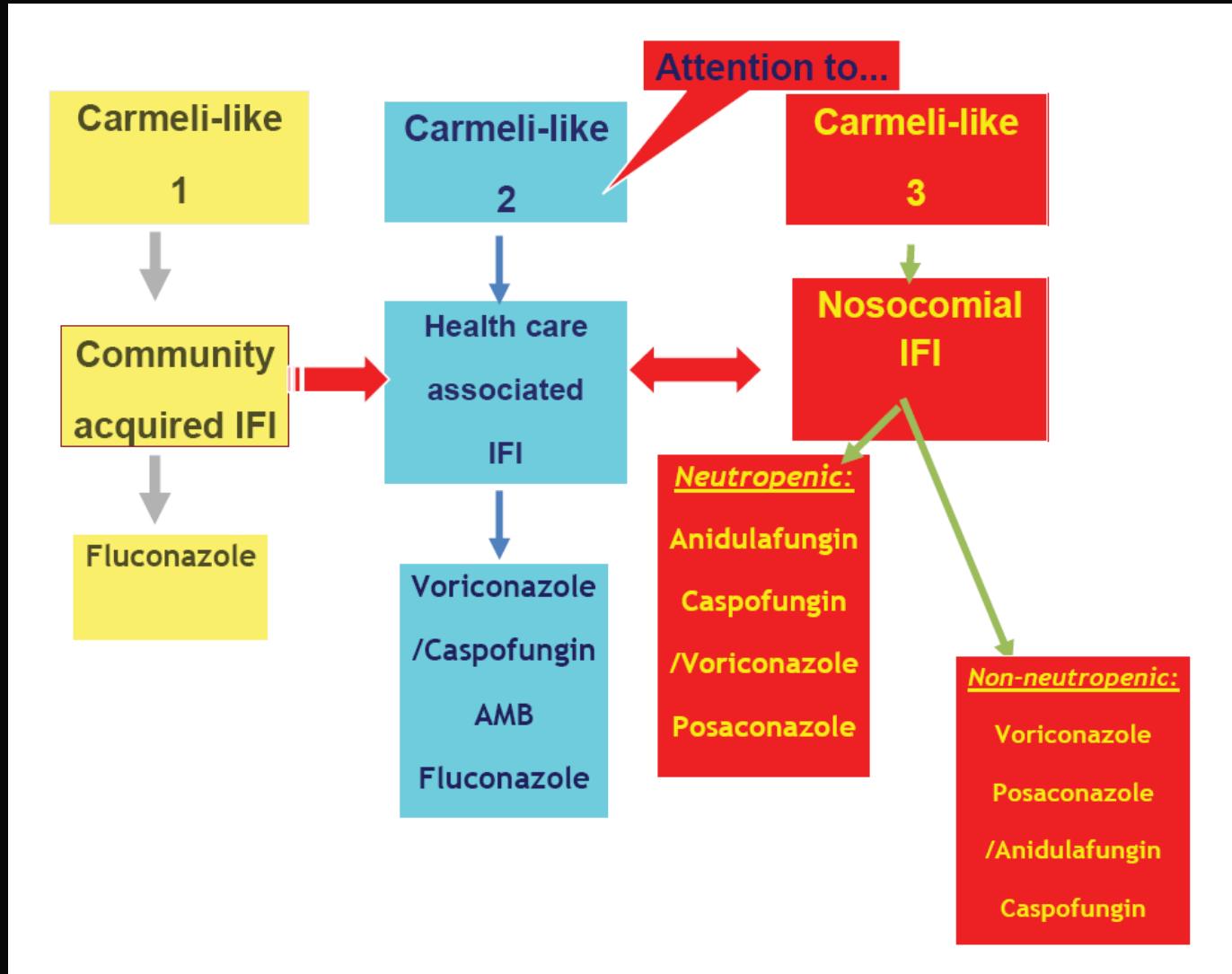
<http://www.fun4u.dk>

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MAKE IT SIMPLE!!!

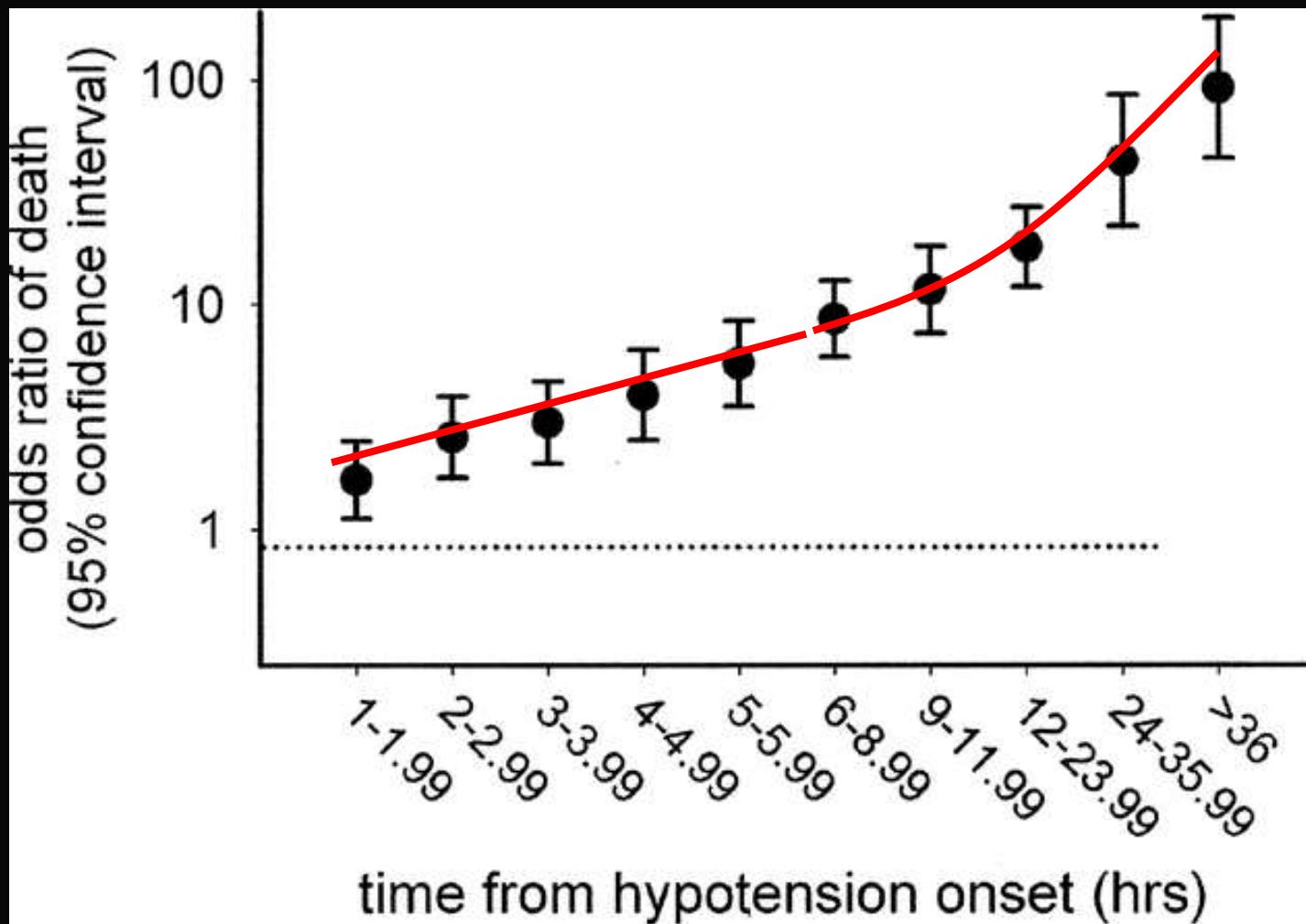


Joseph, Exper Opin Pharmacother, 2008, 9(4):561

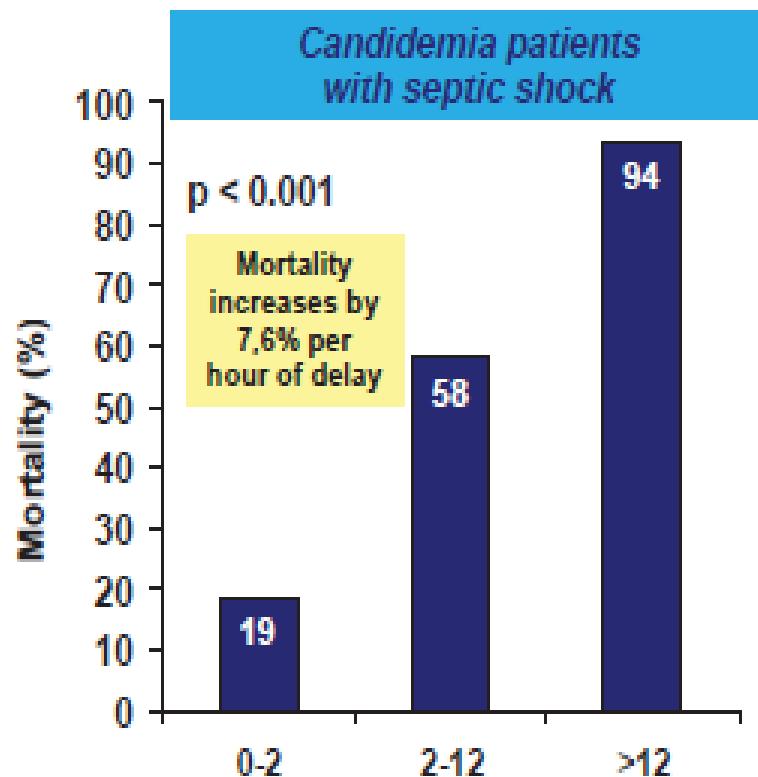


TIMINGUL TRATAMENTULUI

Mortality risk with increasing delays in initiation of effective antimicrobial therapy



Inițierea rapidă a tratamentului antifungic adecvat este crucială pentru scăderea mortalității



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

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W. W. Ho

A. J. Ullm:

TABLE 4. Recommendations on fever-driven and diagnosis-driven therapy of candidaemia and invasive candidiasis

Population	Intention	Intervention	SoR	QoE	References
Adult ICU patients with fever despite broad-spectrum antibiotics and APACHE II >16	To resolve fever	Fluconazole 800 mg/day	D	I	[30]
ICU patients persistently febrile, but without microbiological evidence	To reduce overall mortality	Fluconazole or echinocandin	C	II _u	[28] [163] [164] [7] [27]
ICU patients with candida isolated from respiratory secretions	To cure invasive candidiasis or candidaemia early	Any antifungal	D	II _u	[42]
ICU patients with positive (1,3)- β -D-glucan test ^a	To cure invasive candidiasis or candidaemia early	Any antifungal	C	II _u	[39] [31] [37] [35] [32] [36] [34]
Any patient with <i>Candida</i> isolated from a blood culture	To cure invasive candidiasis	Antifungal treatment	A	II	[46] [47] [48] [49]

APACHE, acute physiology and chronic health evaluation.

^aThe (1,3)- β -D-glucan tests have low specificity and sensitivity with false-positive results in the presence of haemodialysis, other fungal or bacterial infection, wound gauze, albumin or immunoglobulin infusion.

Empiric treatment – the non-neutropenic patient

ESCMID* guideline for the diagnosis and management of *Candida* diseases 2012: adults with haematological malignancies and after haematopoietic stem cell transplantation (HCT)

A. J. Ullmann^{1†}, M. Akova^{2†}, R. Herbrecht^{3†}, C. Viscoli^{4†}, M. C. Arendrup⁵, S. Arikan-Akdagli⁶, M. Bassetti⁷, J. Bille⁸, T. Calandra⁸, E. Castagnola⁹, O. A. Cornely¹⁰, J. P. Donnelly¹¹, J. Gorbino¹², A. H. Groll¹³, W. W. Hope¹⁴, H. E. Jensen¹⁵, B. J. Kullberg¹¹, C. Lass-Flörl¹⁶, O. Lortholary^{17,18}, W. Meersseman¹⁹, G. Petrikos²⁰, M. D. Richardson²¹, E. Roilides²², P. E. Verweij¹¹ and M. Cuenca-Estrella²³ for the ESCMID Fungal Infection Study Group (EFISG)

Empiric treatment – the neutropenic patient

TABLE 4. Empiric therapy to treat possible *Candida* disease: All situations causing severe and prolonged neutropenia

Intention	Intervention	Allogeneic HCT included	SoR	QoE	References
Morbidity reduction	Liposomal amphotericin B (3 mg/kg/day)	Yes	A	I	[44,45,47,55]
	Caspofungin (70 mg on day 1 then 50 mg)	Yes	A	I	[46,47]
	Amphotericin B colloidal dispersion (4 mg/kg/day)	Yes	C	I	[54]
	Amphotericin B lipid complex (5 mg/kg/day)	Yes	B	I	[55]
	Itraconazole (200 mg iv q12h on day 1 & 2 then 200 mg iv/day)	ND	B	I	[56,57]
	Voriconazole (2 × 6 mg/kg on day 1 then 2 × 3 mg/kg/day) [§]	Yes	B	I	[48]
	Fluconazole (400 mg/day)	ND	C*	II _E	[52,53]
	Amphotericin B deoxycholate (0.5–1.0 mg/kg/day)	Yes	D	II _E	[44,54,56,57]
	Micafungin (100 mg)	Yes	B	II	[49,50]
	Anidulafungin	ND	NR		No data

*Limited use since fluconazole has no mould activity. Application requires appropriate work-up to rule out mould disease.

NR, no recommendation; ND, no data available; [§], dosis according to trial [48].

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

TABLE 5. Recommendations on initial targeted treatment of candidaemia and invasive candidiasis in adult patients

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M. C. Ar
W. W. H
A. J. Ulln

Intervention	SoR	QoE	References	Comment
Anidulafungin 200/100 mg	A	I	[64]	Consider local epidemiology (<i>Candida parapsilosis</i> , <i>Candida krusei</i>), less drug–drug interactions than caspofungin
Caspofungin 70/50 mg	A	I	[67] [55] [63]	Consider local epidemiology (<i>C. parapsilosis</i>)
Micafungin 100 mg	A	I	[61] [63]	Consider local epidemiology (<i>C. parapsilosis</i>), less drug–drug interactions than caspofungin, consider EMA warning label
Amphotericin B liposomal 3 mg/kg	B	I	[61] [62]	Similar efficacy as micafungin, higher renal toxicity than micafungin
Voriconazole 6/3 mg/kg/day ^{a,b}	B	I	[43] [78] [77]	Limited spectrum compared to echinocandins, drug–drug interactions, limitation of IV formulation in renal impairment, consider therapeutic drug monitoring
Fluconazole 400–800 mg ^a	C	I	[165] [53] [74] [54] [64] [74] [75] [73] [72]	Limited spectrum, inferiority to anidulafungin (especially in the subgroup with high APACHE scores), may be better than echinocandins against <i>C. parapsilosis</i>
Amphotericin B lipid complex 5 mg/kg	C	II _a	[57] [58]	
Amphotericin B deoxycholate 0.7–1.0 mg/kg	D	I	[50] [51] [165] [53] [54] [55]	Substantial renal and infusion-related toxicity
Amphotericin B deoxycholate plus fluconazole	D	I	[74]	Efficacious, but increased risk of toxicity in ICU patients No survival benefit
Amphotericin B deoxycholate plus 5-fluorocytosine	D	II	[75]	
Efugumab plus lipid-associated amphotericin B	D	II	[166]	
Amphotericin B colloidal dispersion	D	II _a	[60]	
Itraconazole	D	II _a	[76]	
Posaconazole	D	III	No reference found	

EMA European Medicine Agency

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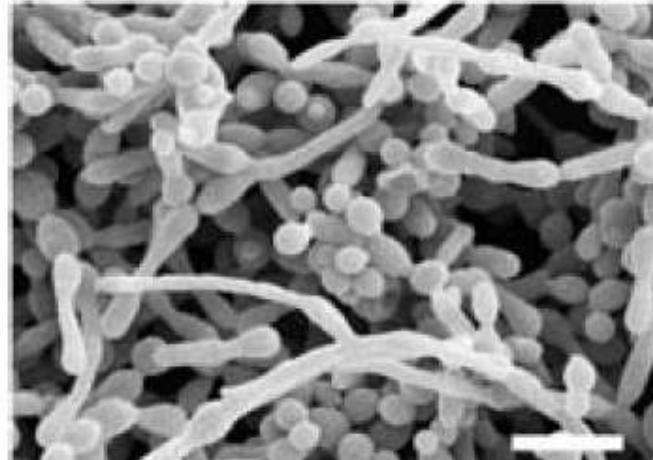
Targeted treatment – the non-neutropenic patient

The BIOFILM

- **Surface-associated microorganisms**
 - Feature of unicellular organisms to adhere to surfaces
- **Escape the host immune defence**
- **Infections are generated/perpetuated by biofilms**

Candida biofilm on a central venous catheter

după: Donlan RM. Biofilms: microbial life on surfaces. Emerg Infect Dis 2005;7:8.



60

The Clinical and Prognostic Importance of Positive Blood Cultures in Adults

Brian C. Pien, MD,^{a,b} Punidha Sundaram, MD,^c Natalia Raoof, MD,^c Sylvia F. Costa, MD,^{a,d} Stanley Mirrett, MS,^a Christopher W. Woods, MD,^{b,d,e} L. Barth Reller, MD,^{a,d,e} Melvin P. Weinstein, MD^{c,f}

CLINICAL SIGNIFICANCE

- More than three quarters (81%) of bacteremias and fungemias are now acquired in the hospital (46%) or other health care settings (35%).
- Intravenous catheters are now the single most common sources of bacteremia and fungemia (23% of episodes).

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

O. A. Cornely^{1†}, M. Bassetti^{2†}, T. Calandra^{3†}, J. Garbino^{4†}, B. J. Kullberg^{5†}, O. Lortholary^{6,7†}, W. Meersseman^{8†}, M. Akova⁹, M. C. Arendrup¹⁰, S. Arikan-Akdagli¹¹, J. Bille³, E. Castagnola¹², M. Cuenca-Estrella¹³, J. P. Donnelly⁵, A. H. Groll⁴, R. Herbrecht¹⁵, W. W. Hope¹⁶, H. E. Jensen¹⁷, C. Lass-Flörl¹⁸, G. Petrikos¹⁹, M. D. Richardson²⁰, E. Roilides²¹, P. E. Verweij⁵, C. Viscoli²² and A. J. Ullmann²³ for the ESCMID Fungal Infection Study Group (EFISG)

Catheter-related Candidemia

TABLE 7. Recommendations on catheter management in candidaemia

Population	Intervention	SoR	QoE	References
Central venous catheter can be removed	Remove indwelling lines (not over a guidewire)	A	II _r	[98]
Central venous catheter cannot be removed	Echinocandin, liposomal amphotericin B or amphotericin B lipid complex	B	II _r	[98] [90] [89] [91] [93] [92]
	Azole or amphotericin B deoxycholate	D	II _r	[95] [98] [73] [97] [96] [94]

Interventions are intended to clear candidaemia and to improve survival.

Caspofungin at Catheter Lock Concentrations Eradicates Mature Biofilms of *Candida lusitaniae* and *Candida guilliermondii*

Maria Simitopoulou,^a Daniela Kyripiti,^a Aristea Velegraki,^b Thomas J. Walsh,^c Emmanuel Rollides^a

Laboratory of Infectious Diseases, 3rd Department of Pediatrics, Faculty of Medicine, Aristotle University School of Health Sciences, Hippokration Hospital, Thessaloniki, Greece^a; Mycology Research Laboratory, Microbiology Department, Medical School, National & Kapodistrian University of Athens, Athens, Greece^b; Transplantation-Oncology Infectious Diseases Program and Departments of Medicine, Pediatrics, and Microbiology & Immunology, Weill Cornell Medical Center, New York, New York, USA^c

experimental study
 biofilm with *C. lusitaniae/C. guilliermondii*
 incubation
 2 different high concentration LF solutions
 % of biofilm damage

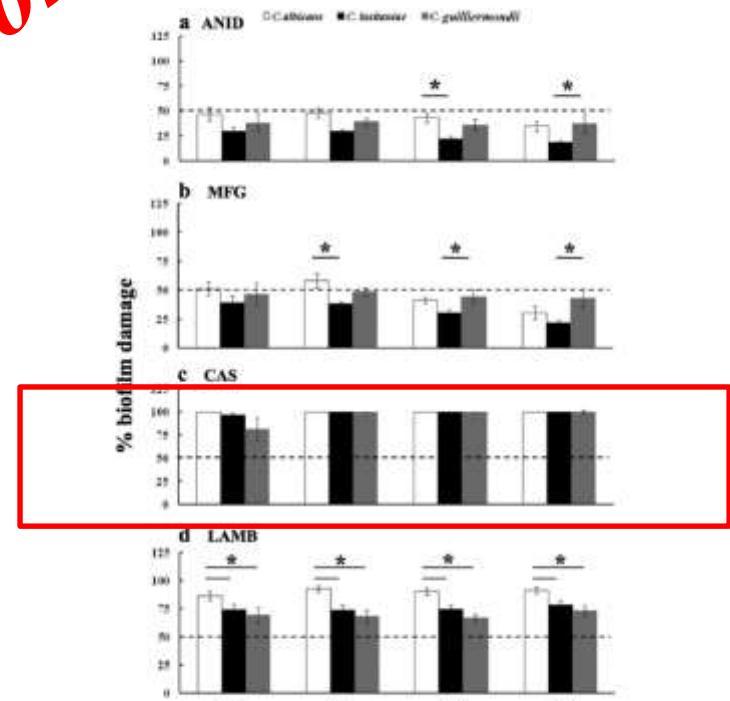
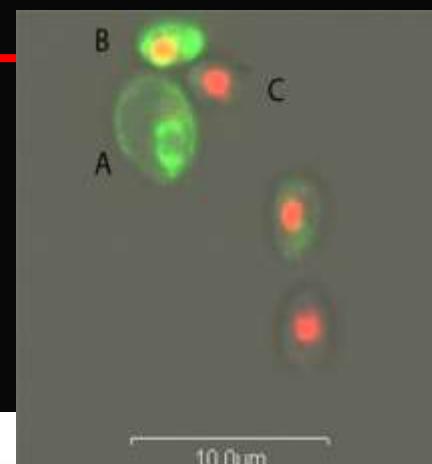
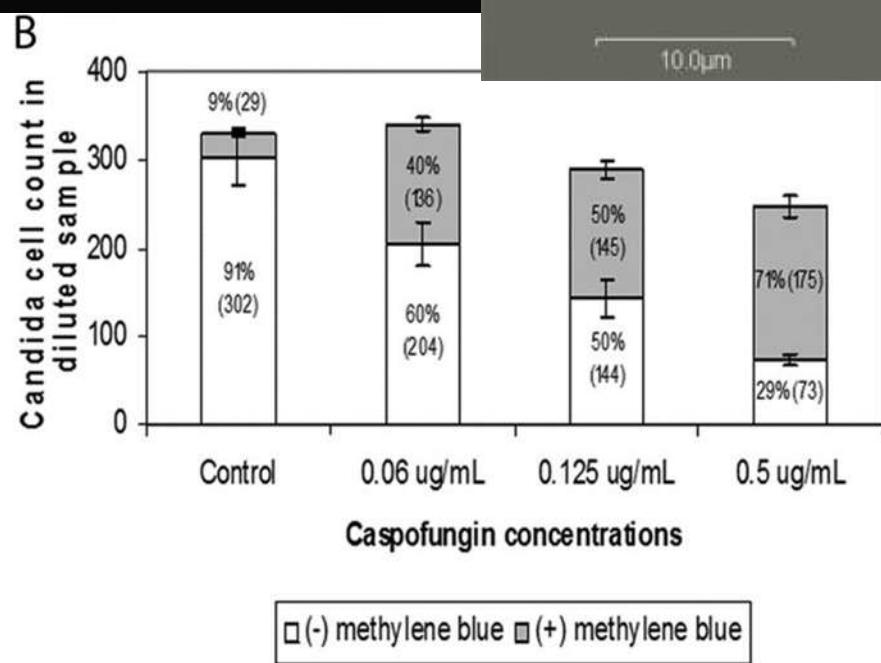
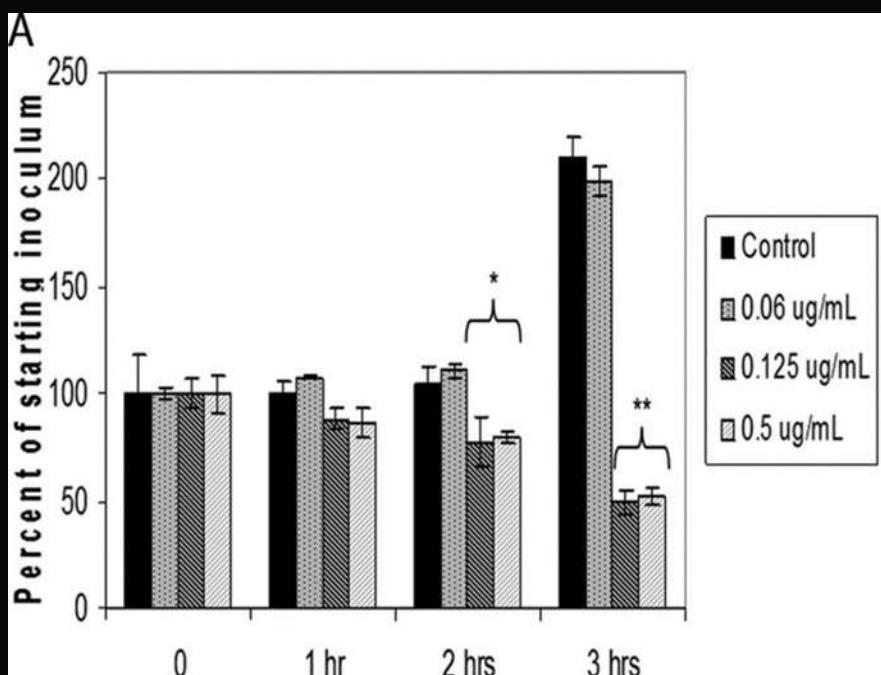


FIG 1 Fungal damage of biofilms of *C. albicans*, *MGI*, *C. lusitaniae*, and *C. guilliermondii* bloodstream isolates caused by different lock concentrations of ANID, MFG, CAS, and LAMB. Fungal damage was assessed by XTT assay. Results are means \pm standard errors (SE) of percentages of biofilm damage of *C. albicans* MGI (open bars), *C. lusitaniae* (black bars), and *C. guilliermondii* (gray bars) isolates for each drug. Asterisks show significant differences between biofilms of organisms for the concentrations indicated by horizontal lines ($P < 0.05$). The discontinuous line denotes 50% MIC.

Effects of caspofungin on *C. albicans* viability

Apoptosis (programmed cell death) and necrosis



CONCLUZII

- ✓ IFI – frecvențe și severe
- ✓ fecvent – DIAGNOSTIC RATAT !!!
- ✓ mortalitate mare
- ✓ culturi pozitive – rar și târziu
- ✓ diagnostic:
semne și simptome de sepsis sever/șoc septic
+ teste rapide
+ FACTORI de RISC!!!
- ✓ tratmentul precoce ameliorează prognosticul
- ✓ echinocandine – prima alegere

NEVER GIVE UP

