

Complicacions infeccioses en el malalt neutropènic

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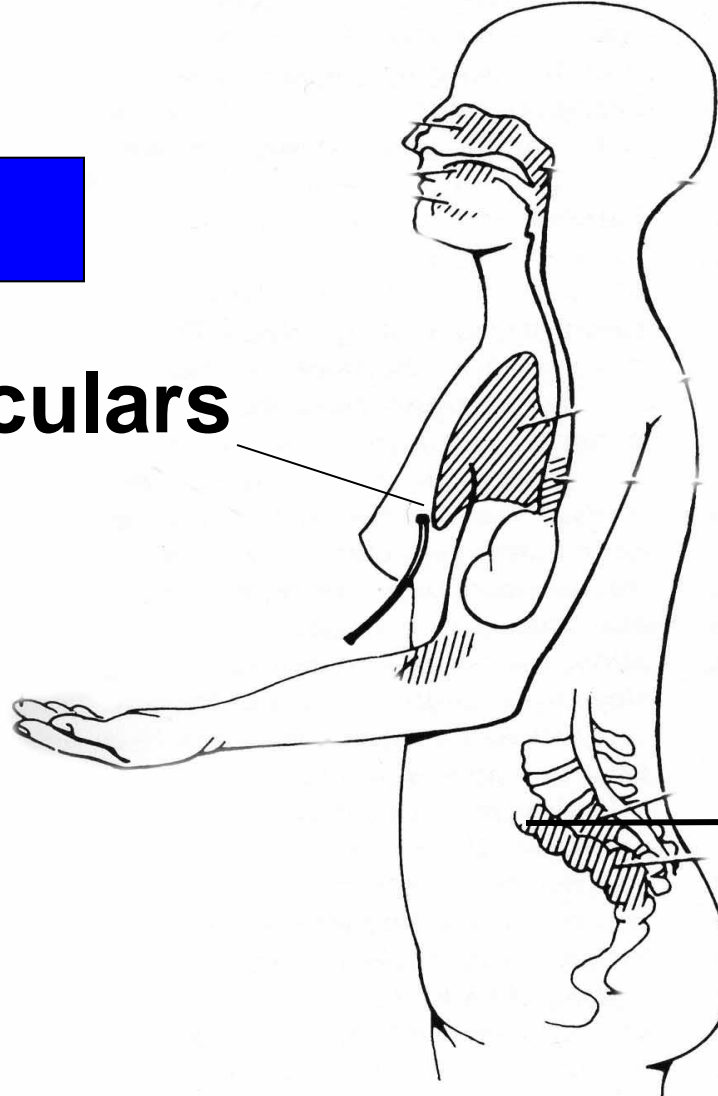
Barcelona, 27 de gener 2011

VI Conferència d'experts de la SOCMIC

Origen principal de les infeccions en el malalt neutropènic

Gram (+)

accessos vasculars



tracte gastro-intestinal

Gram (-)

Conseqüències de la quimioteràpia

**Cytostatic
chemotherapy**

mucosa

bone marrow

decreased cell renewal

epithelial thinning

mucositis

discomfort
pain
dry mouth
burning sensation
loss of taste
erythema
ulceration

Micro-organisms

infection

myelosuppression

neutropenia
thrombocytopenia

**infectious
disease**

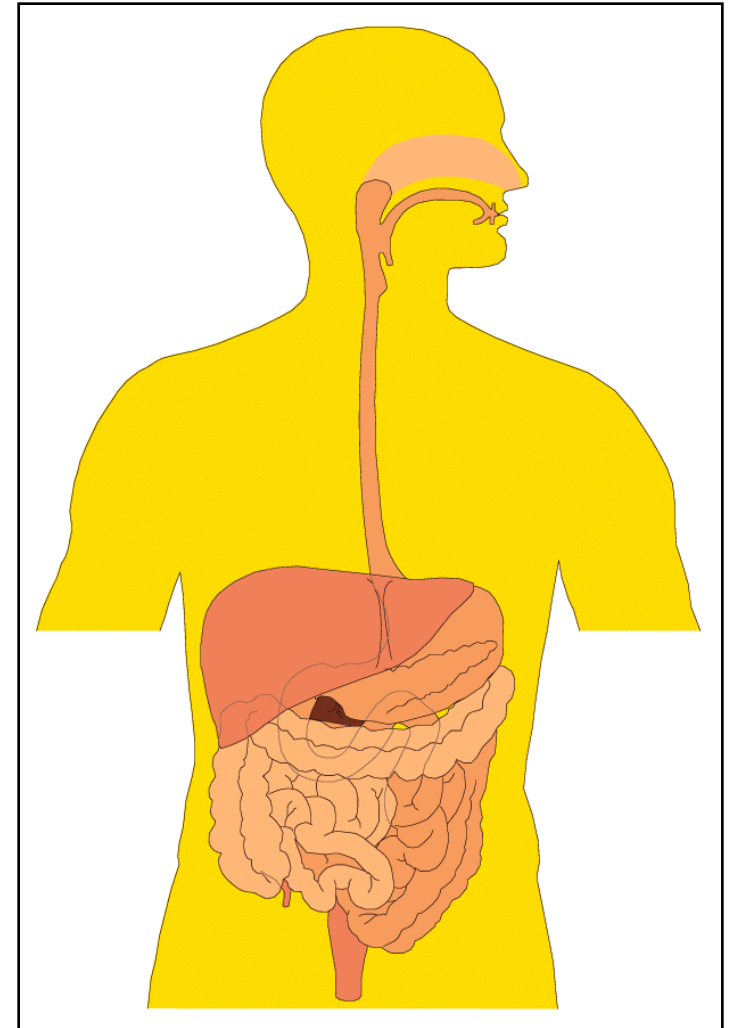
Clinical Practice Guidelines for the Diagnosis and Management of Intravascular Catheter-Related Infection: 2009 Update by the Infectious Diseases Society of America

Leonard A. Mermel,¹ Michael Allon,² Emilio Bouza,⁹ Donald E. Craven,³ Patricia Flynn,⁴ Naomi P. O'Grady,⁵ Issam I. Raad,⁶ Bart J. A. Rijnders,¹⁰ Robert J. Sherertz,⁷ and David K. Warren⁸

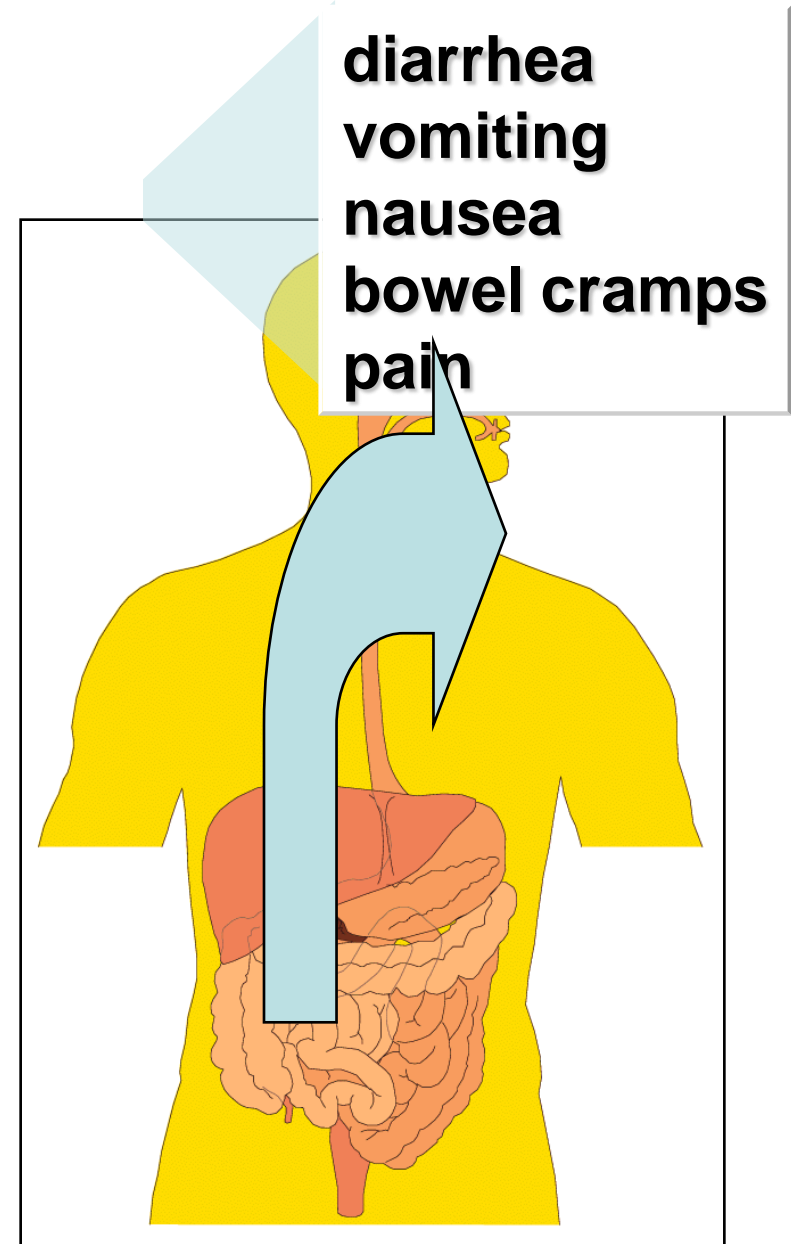
Clinical Infectious Diseases 2009: 49: 1 – 44.



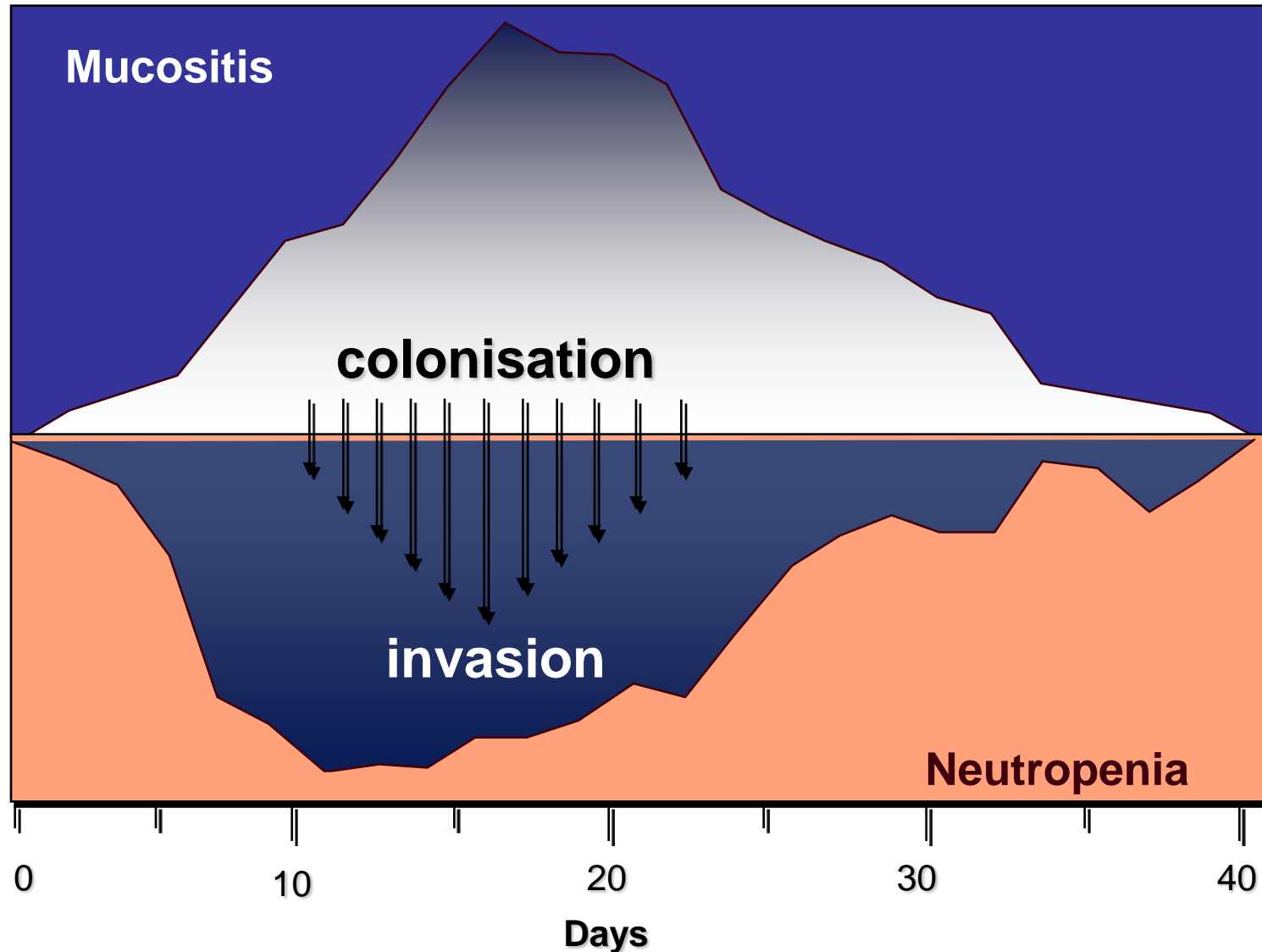
Mucositis:



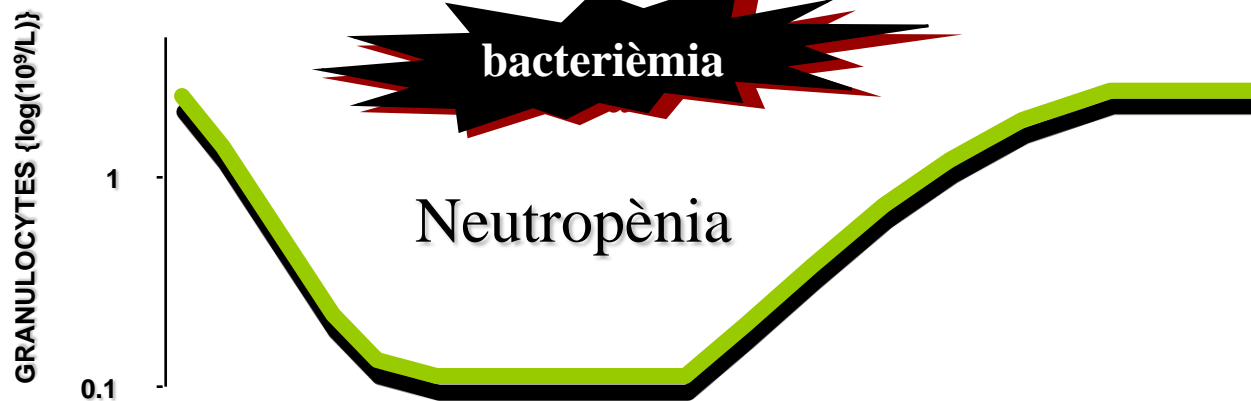
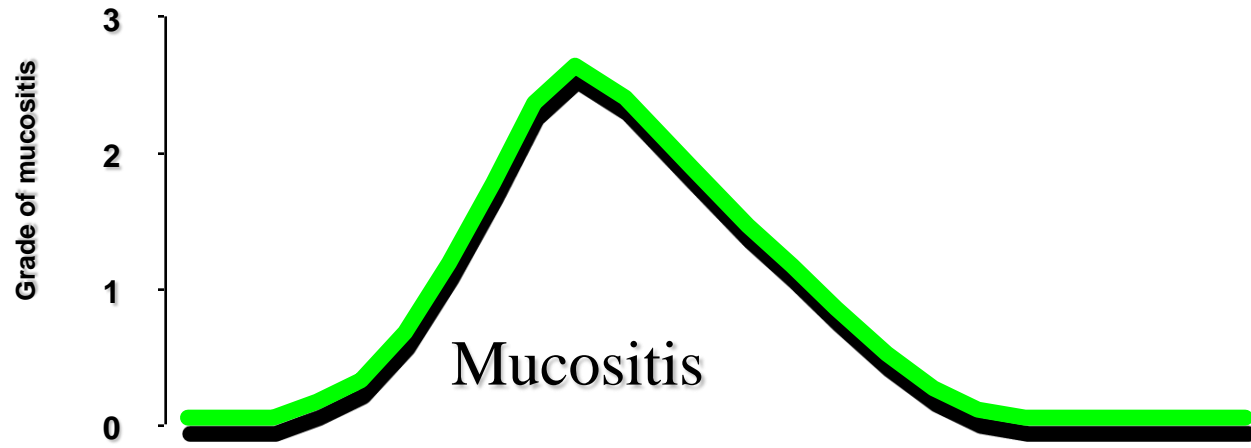
Mucositis:



Risc infeccióis durant neutropènia i mucositis

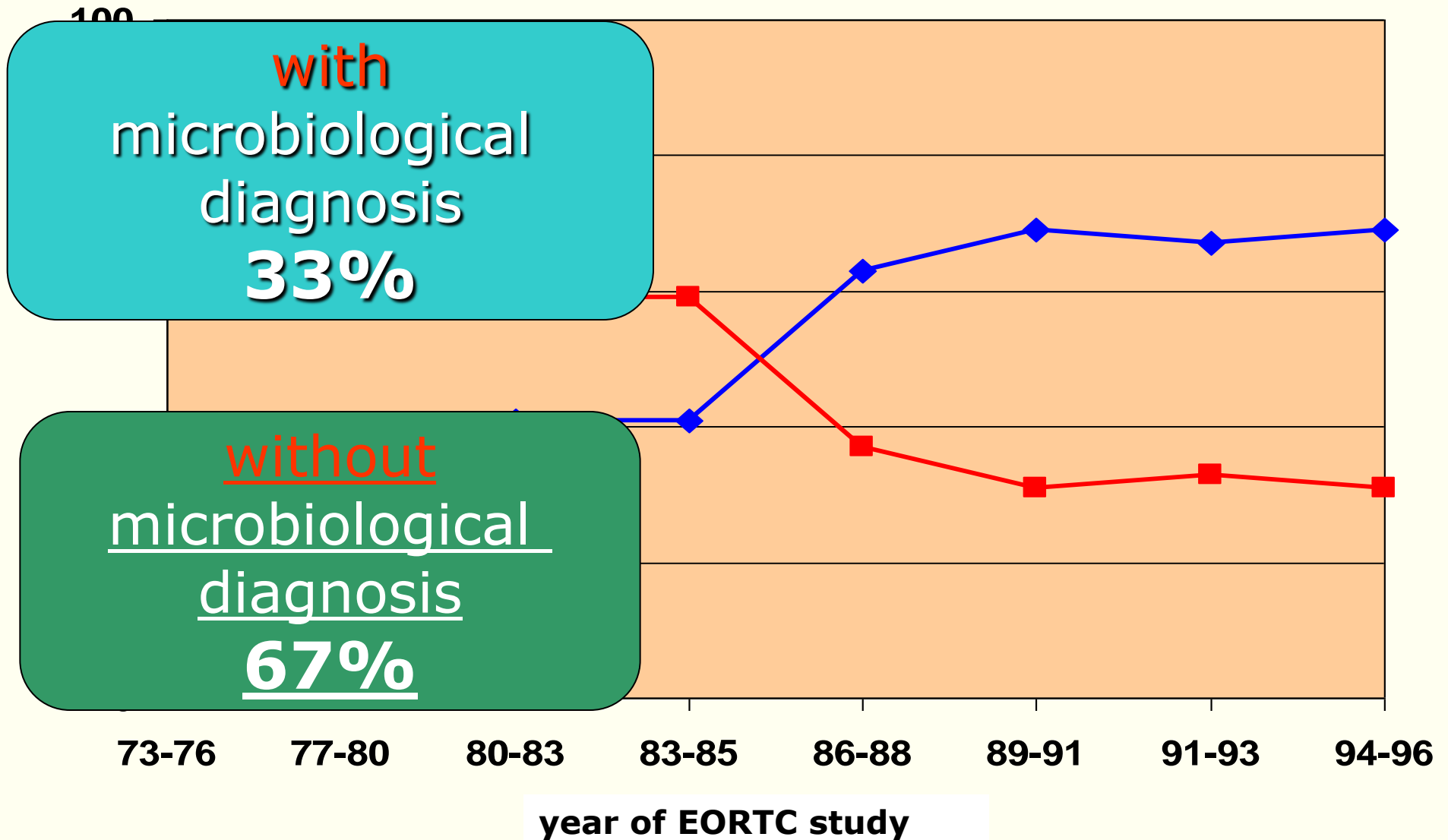


Mucositis i neutropènia després quimioteràpia

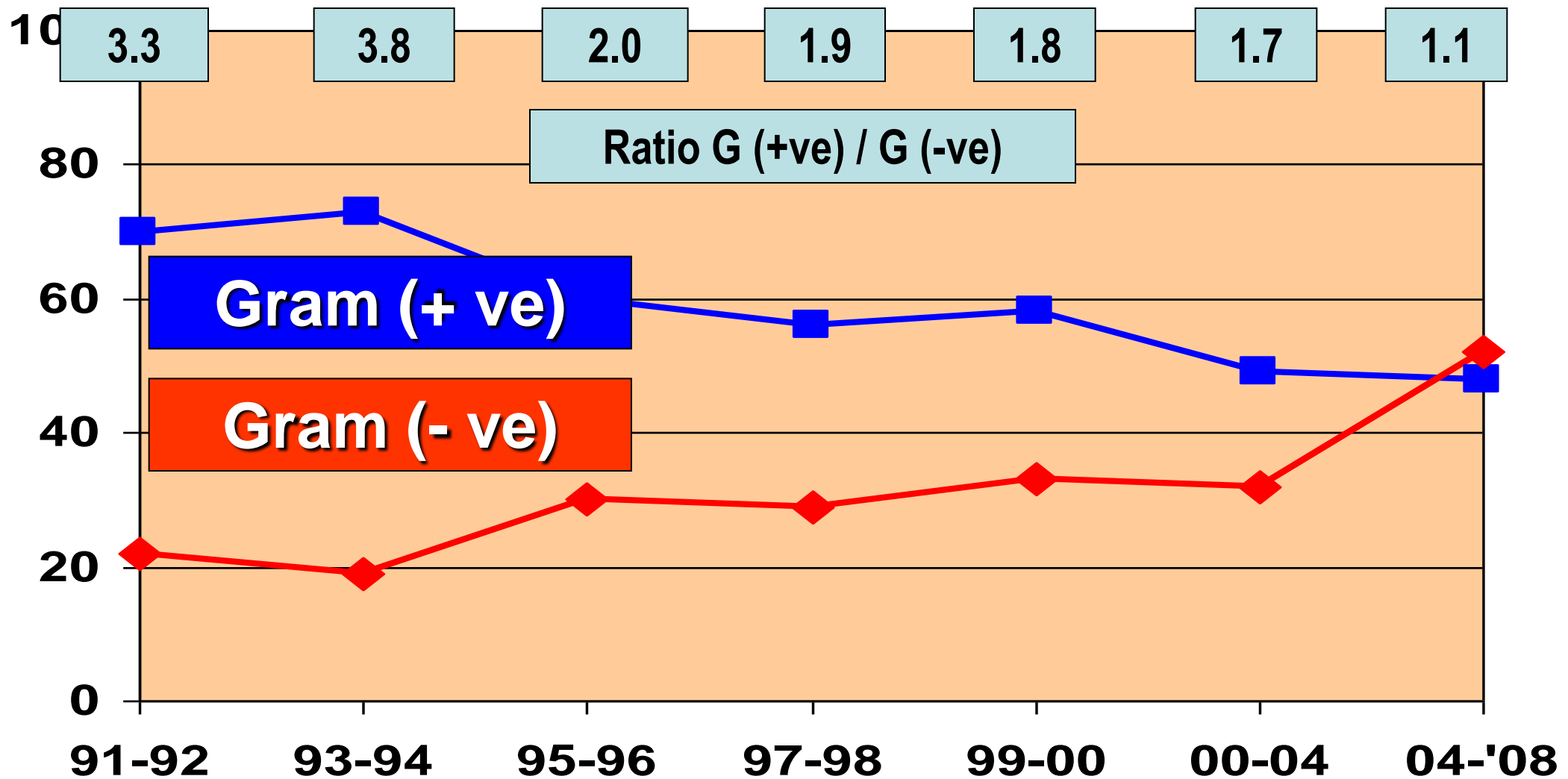


Infeccions bacterianes

Febrile episodes in neutropenic patients – EORTC trials–



Febrile episodes in neutropenic patients *



* Hospital Clínic. Barcelona 1991-2008

Distribution of 275 micro-organisms isolated in 835 neutropenic patients (PETHEMA study)

Gram positive	n° (%)	Gram negative	n° (%)
SPCN	W/O microbiological diagnosis 67%	<i>E. coli</i>	62 (23)
<i>Streptococcus</i>		<i>Pseudomonas aeruginosa</i>	16 (6)
<i>Corynebacterium</i>		<i>Pseudomonas</i> spp	15 (5)
<i>S. aureus</i>	11 (4)	<i>Enterobacter</i> spp	7 (3)
<i>Enterococcus</i>	7 (2,5)	<i>Acinetobacter</i> spp	6 (3)
<i>Neumococcus</i>	3 (1)	others	11 (4)
otros	10 (4)		

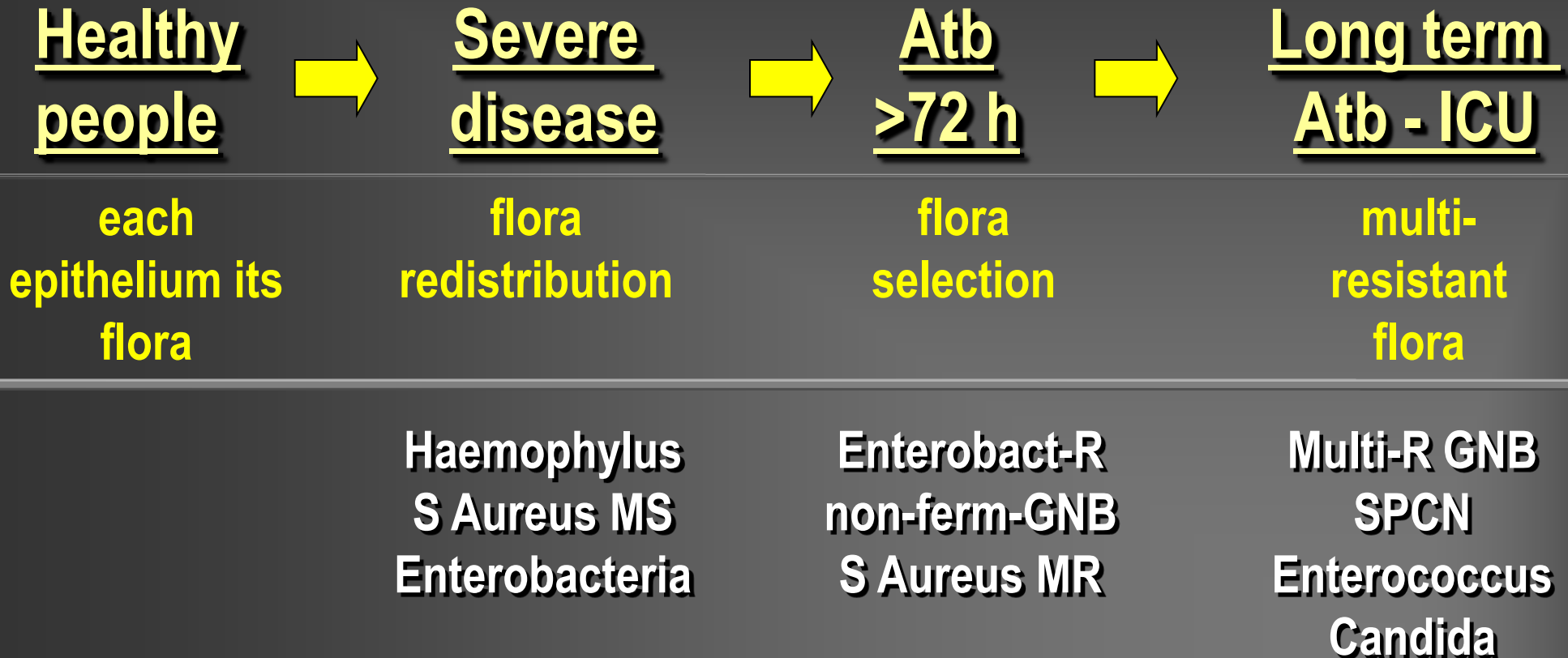
Distribution of 275 micro-organisms isolated in 835 neutropenic patients (PETHEMA study)

Gram positive	n° (%)	Gram negative	n° (%)
SPCN	86 (31)	<i>E. coli</i>	62 (23)
<i>Strept. viridans</i>	26 (10)	<i>P. aeruginosa</i>	16 (6)
<i>Corynebacterium</i>	15 (5)	<i>Klebsiella spp</i>	15 (5)
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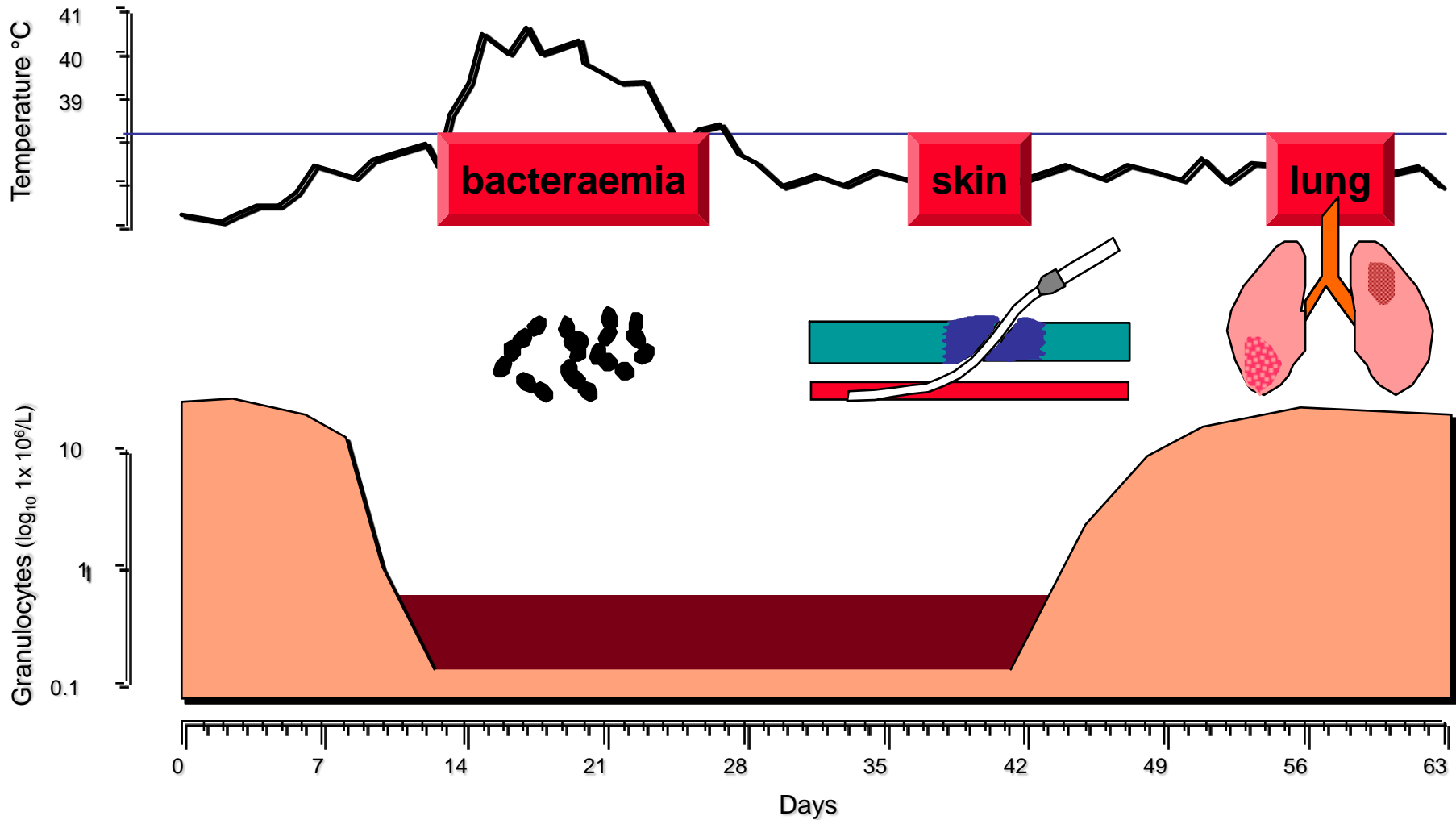
1491 episodes of bacteriemia in neutropenic patients (<500/mL) *

Agent	Isolates (%)	Mortality (%)
Staph. coagulase (-ve).	476 (32)	25 (5)
<i>E. coli</i>	283 (19)	54 (19)
<i>P. aeruginosa</i>	133 (9)	28 (21)
<i>Streptococcus viridans</i>	96 (6)	9 (9)

Flora changes during severe disease evolution

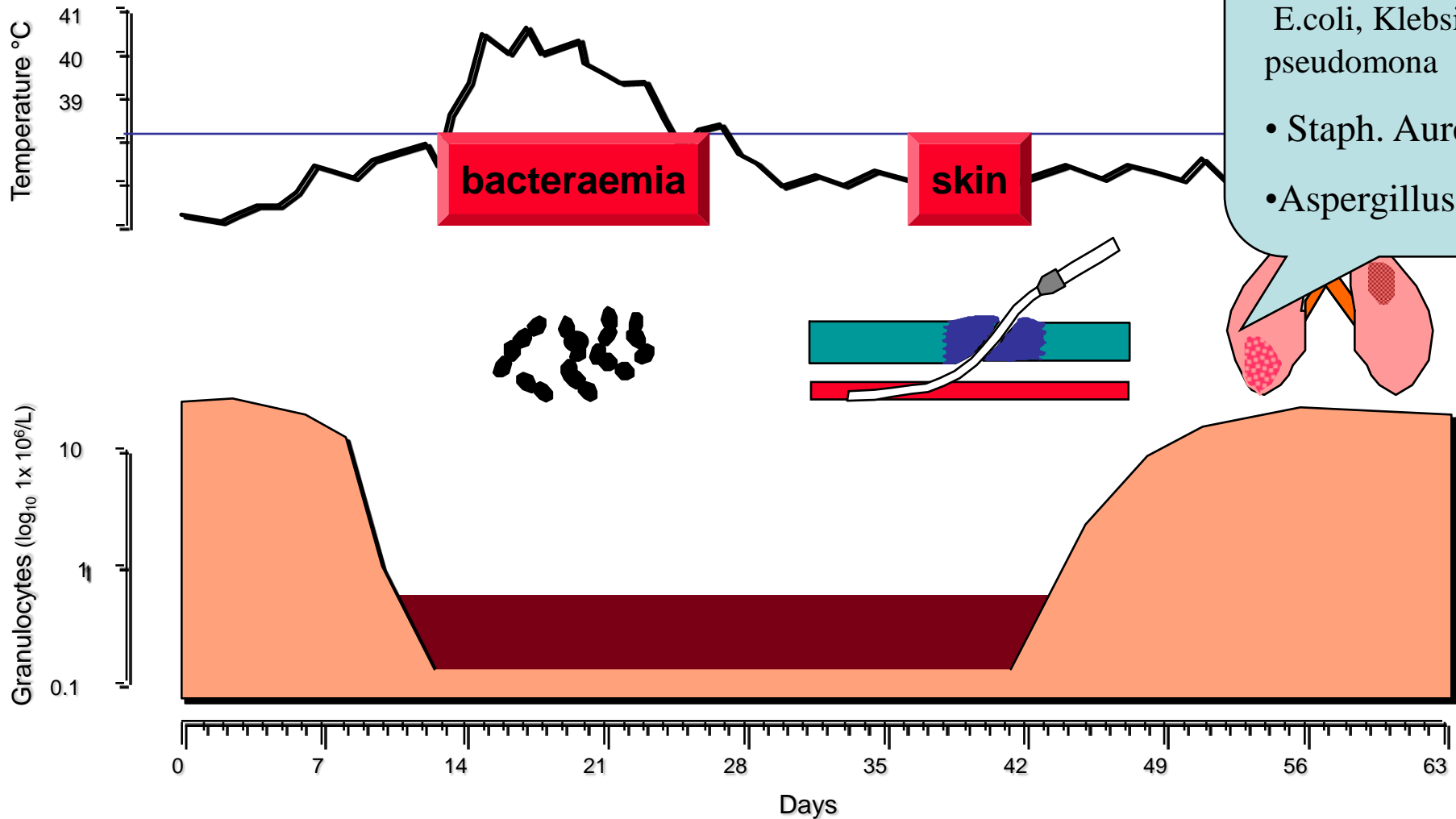


Infeccions comuns durant neutropènia



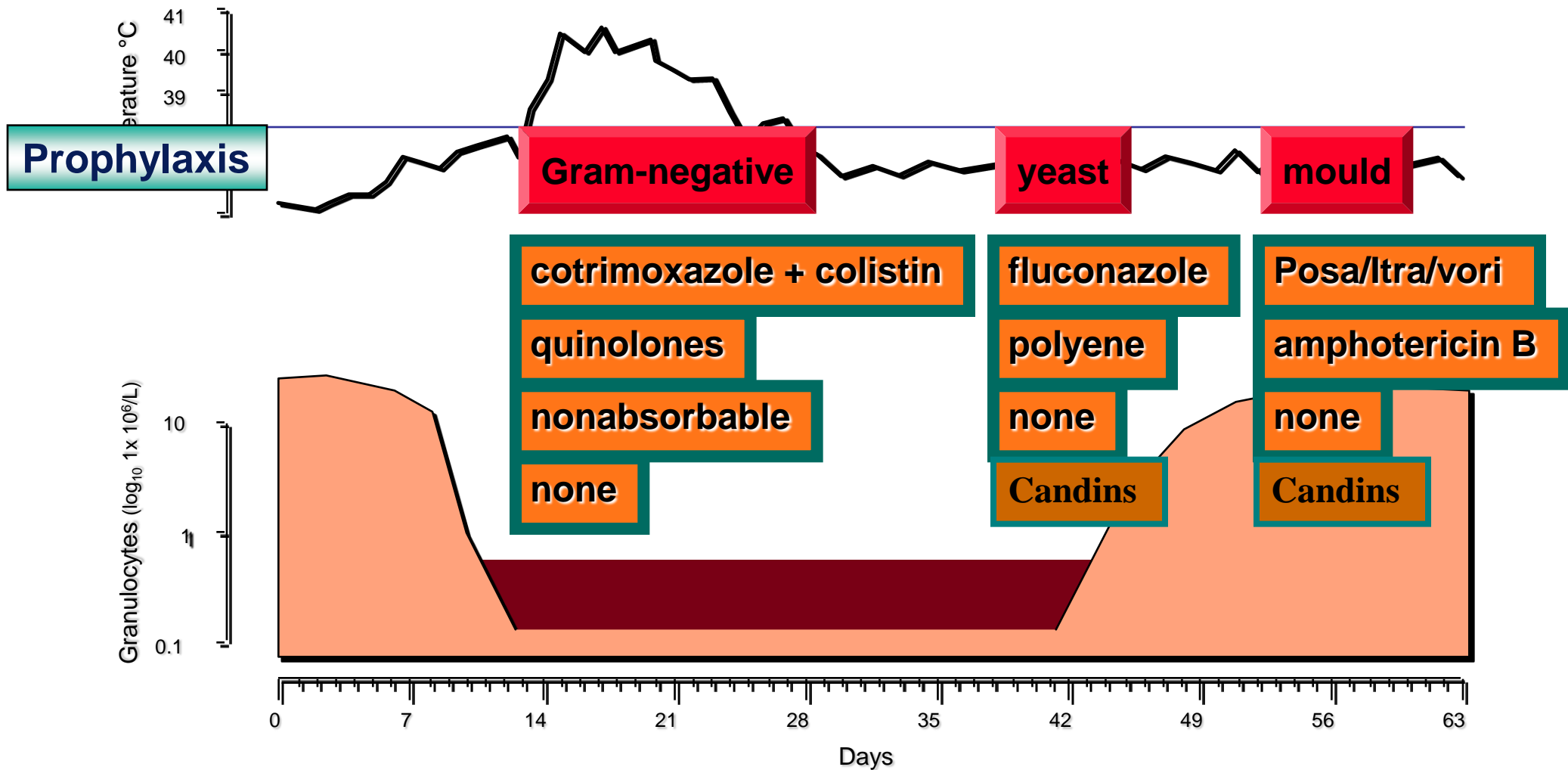
Infeccions comuns durant neutropènia

- Bact gram(-):
E.coli, Klebsiella.,
pseudomona
- Staph. Aureus
- Aspergillus, mucor

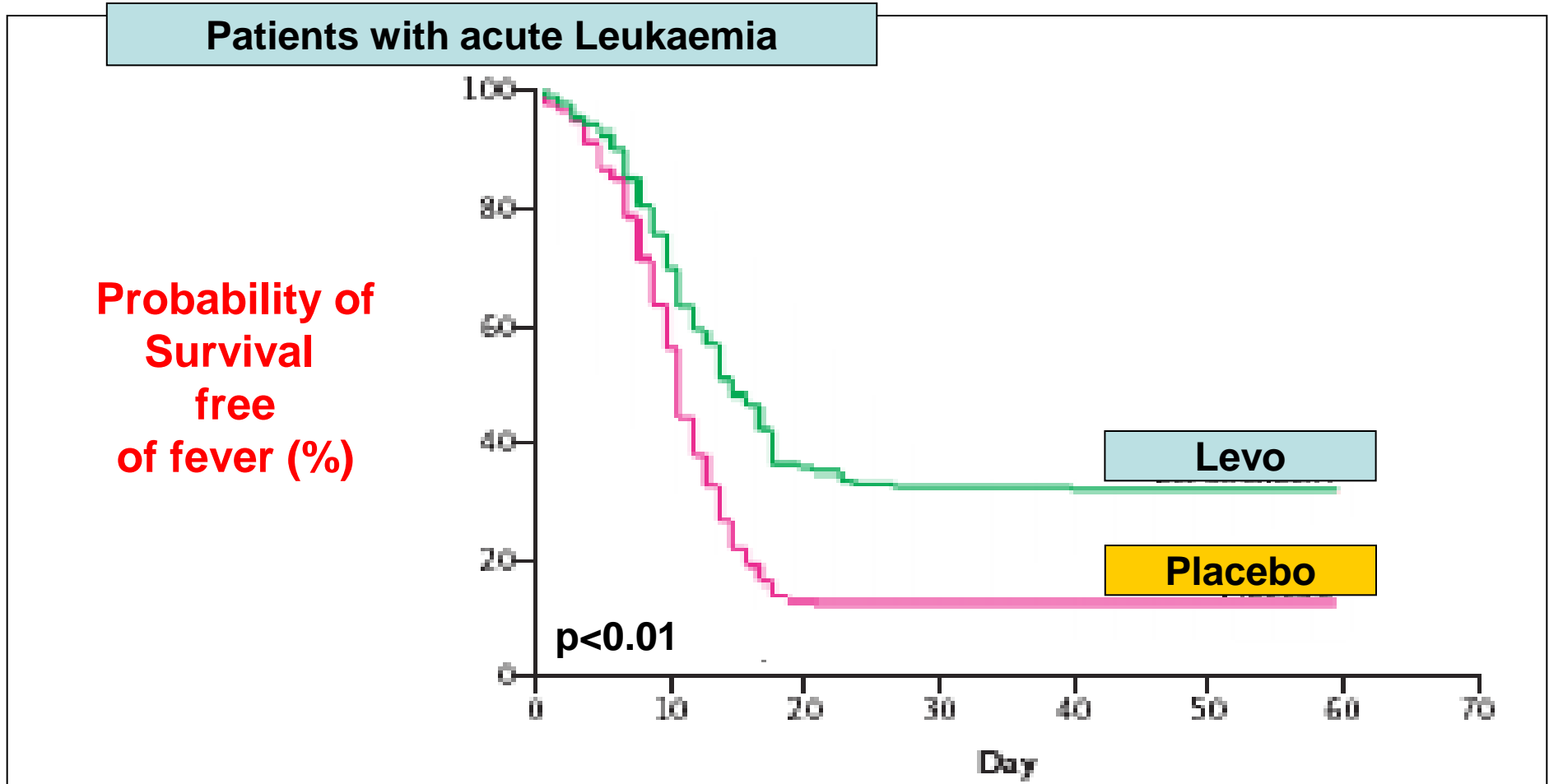


Profilaxis

Profilaxis

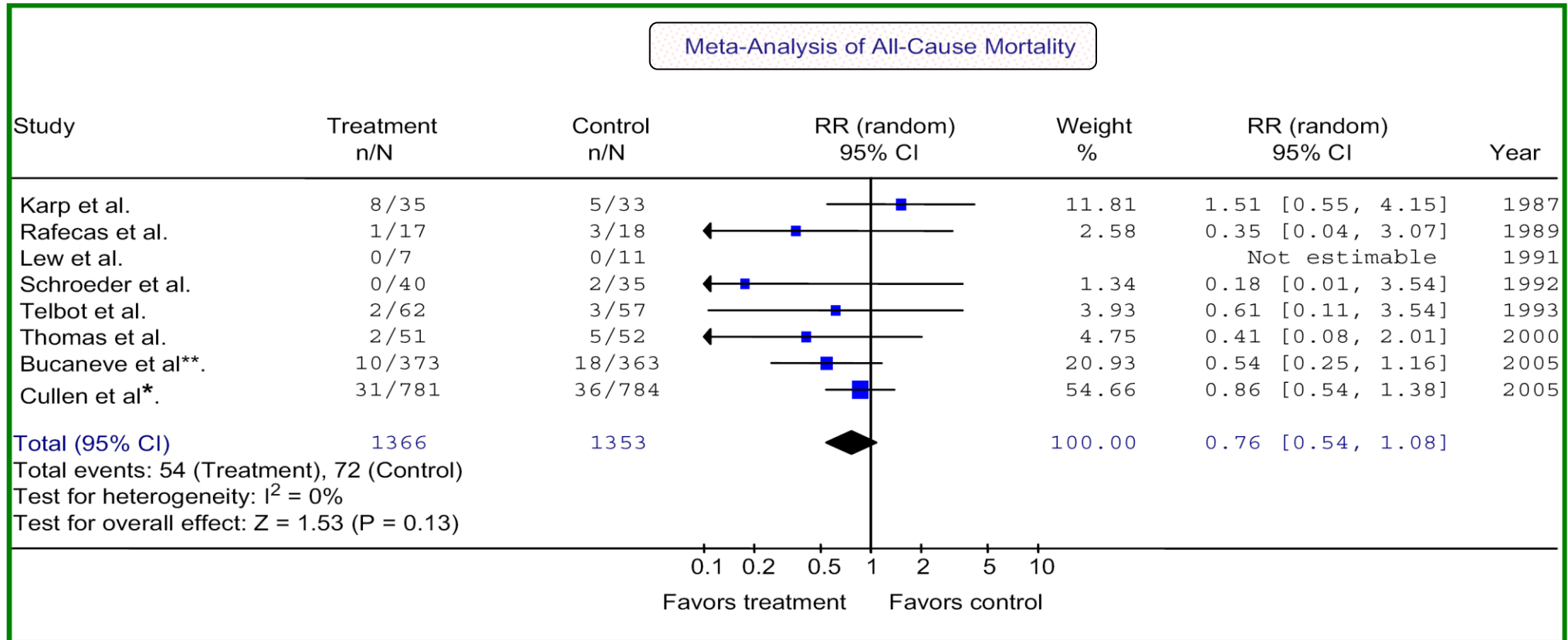


GID with levofloxacin



GID with quinolones

Meta-analysis randomized studies (2719 patients)



1st European Conference on Infections in Leukemia (ECIL)

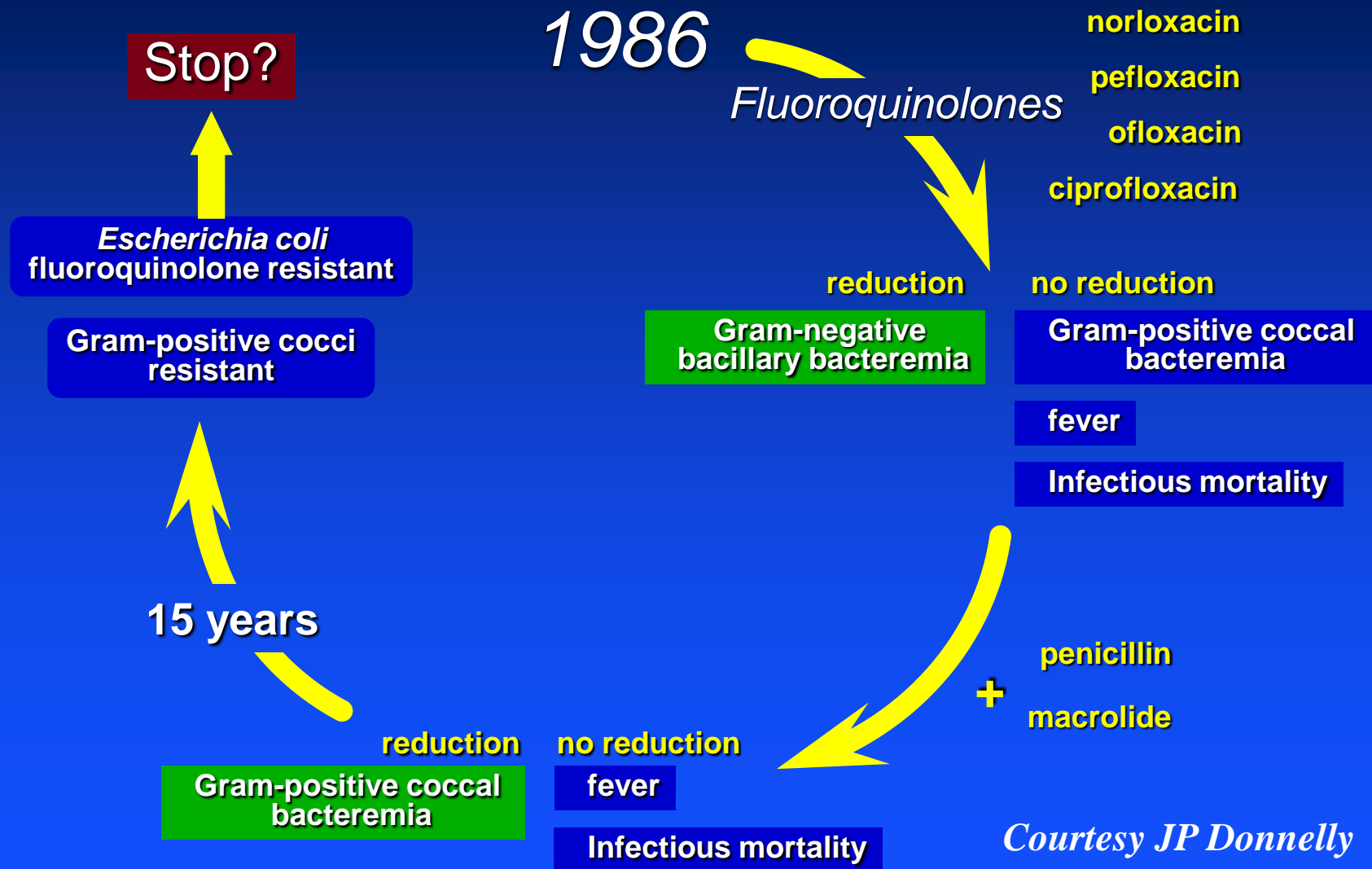


Does fluoroquinolone prophylaxis prevent infections in patients with acute leukemia or in recipients of hematopoietic stem cell transplantation?

YES

Drug of Choice	Strength of Recommendation and level of evidence
Levofloxacin (500 mg once daily):	AI
Ciprofloxacin (500 mg bid):	AI
Ofloxacin (200 - 400 mg bid):	BI
Norfloxacin (400 mg bid):	BI

The life cycle of fluoroquinolone prophylaxis



Courtesy JP Donnelly

Infeccions bacterianes

Tractament

A, B, C of treatment of febrile neutropenia

- **It must be:**
- Started immediately after onset of fever
- Based in an empirical approach
- Adapted to the flora usually observed in each centre ①
- Adapted to the type of patient ②
- Adapted to the clinical situation ③

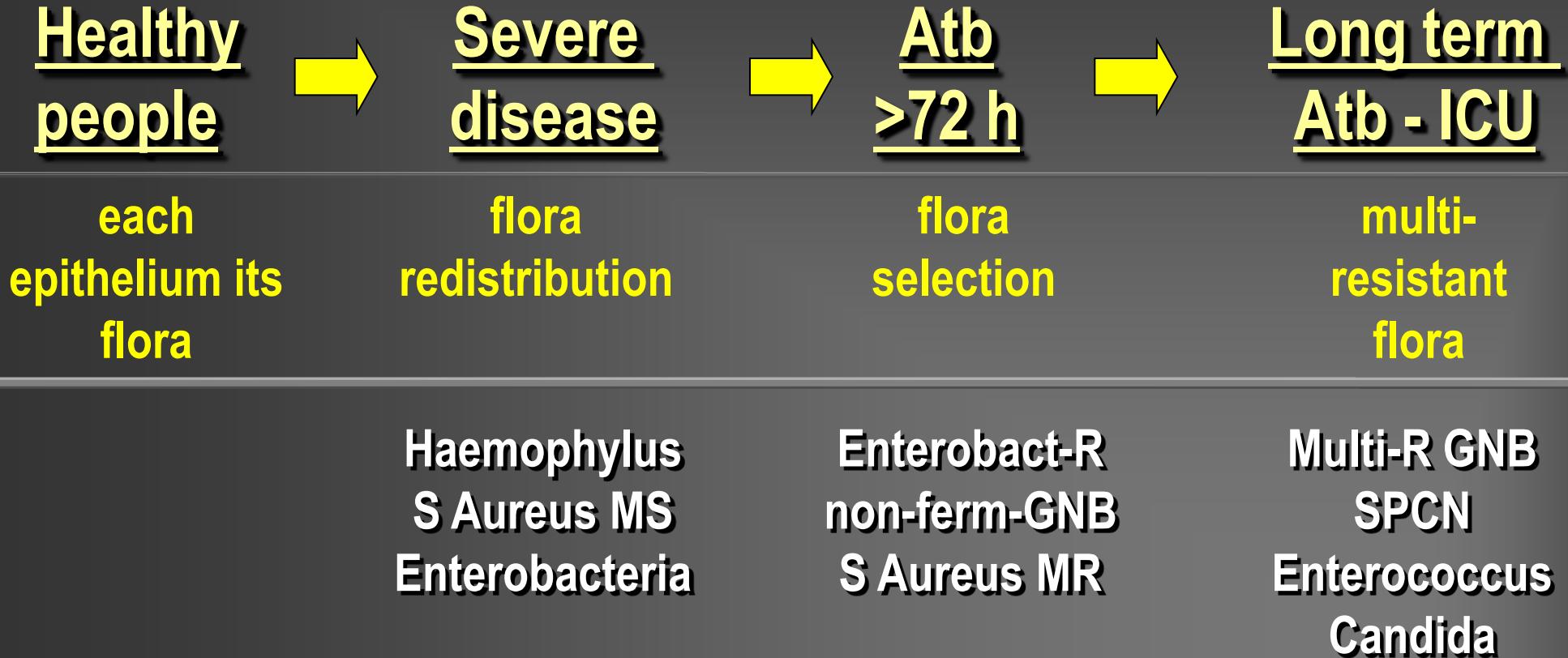
1

Distribution of 275 micro-organisms isolated in 835 neutropenic patients (PETHEMA study)

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Flora changes during severe disease evolution

2



Level of bacterial burden

3

Adapted to clinical situation

low $\leq 10^5$ UFC/mL

(urinary infection)
primary bacteraemia
catheter infection

B-lactamic

high $\geq 10^7$ UFC/mL

pneumonia
meningitis
empiema
septic arthritis
endocarditis
osteomyelitis
peritonitis, abscess

B-lactamic + aminoglycoside

Summary: Initial empirical antibiotic therapy in neutropenic patients with fever

clinical situation

- fever without clinical focality
- possible catheter infection
- severe mucositis
- colonization by MRSA

All

BIII

All

antibiotic

- meropenem (All)
- imipenem (All)
- piperac.-tazo (All)
- cefepime (All)

+

- vancomycin

Initial empirical antibiotherapy in neutropenic patients with fever

clinical situation

- fever without clinical focality
- focality (tiphlytis, pneumonia,..)
- previous Atb treatment (>5-7d)
- colonization with resistant G(-ve)
- high incidence of ESBL

antibiotic

- meropenem (AI)
- imipenem (All)
- piperac.-tazo (All)
- cefepime (All)

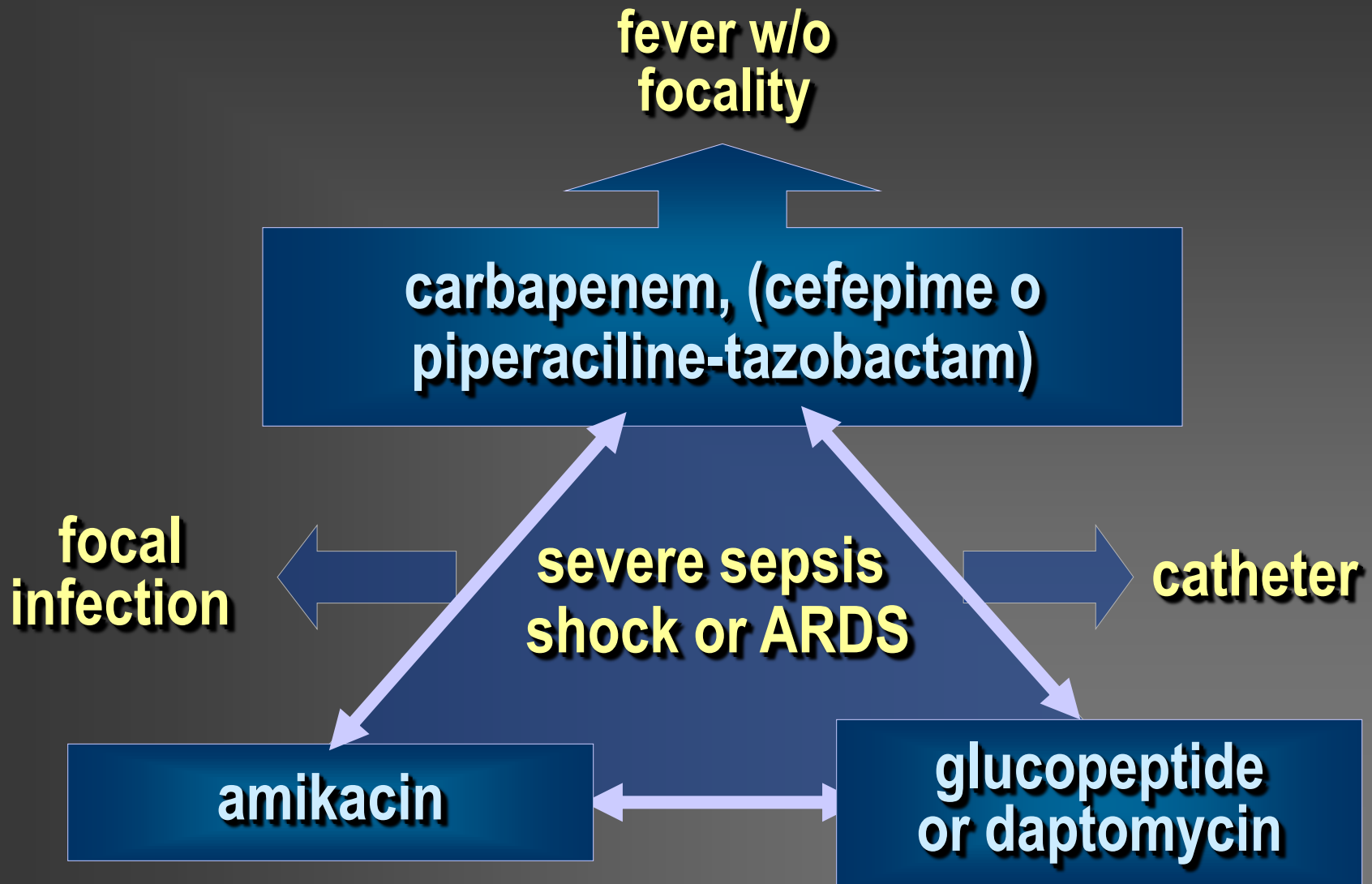
+

All

BIII

BIII

- aminoglycoside



Elting L, et al

Time to clinical response: An outcome of antibiotic therapy of febrile neutropenia with implications for quality and cost of care

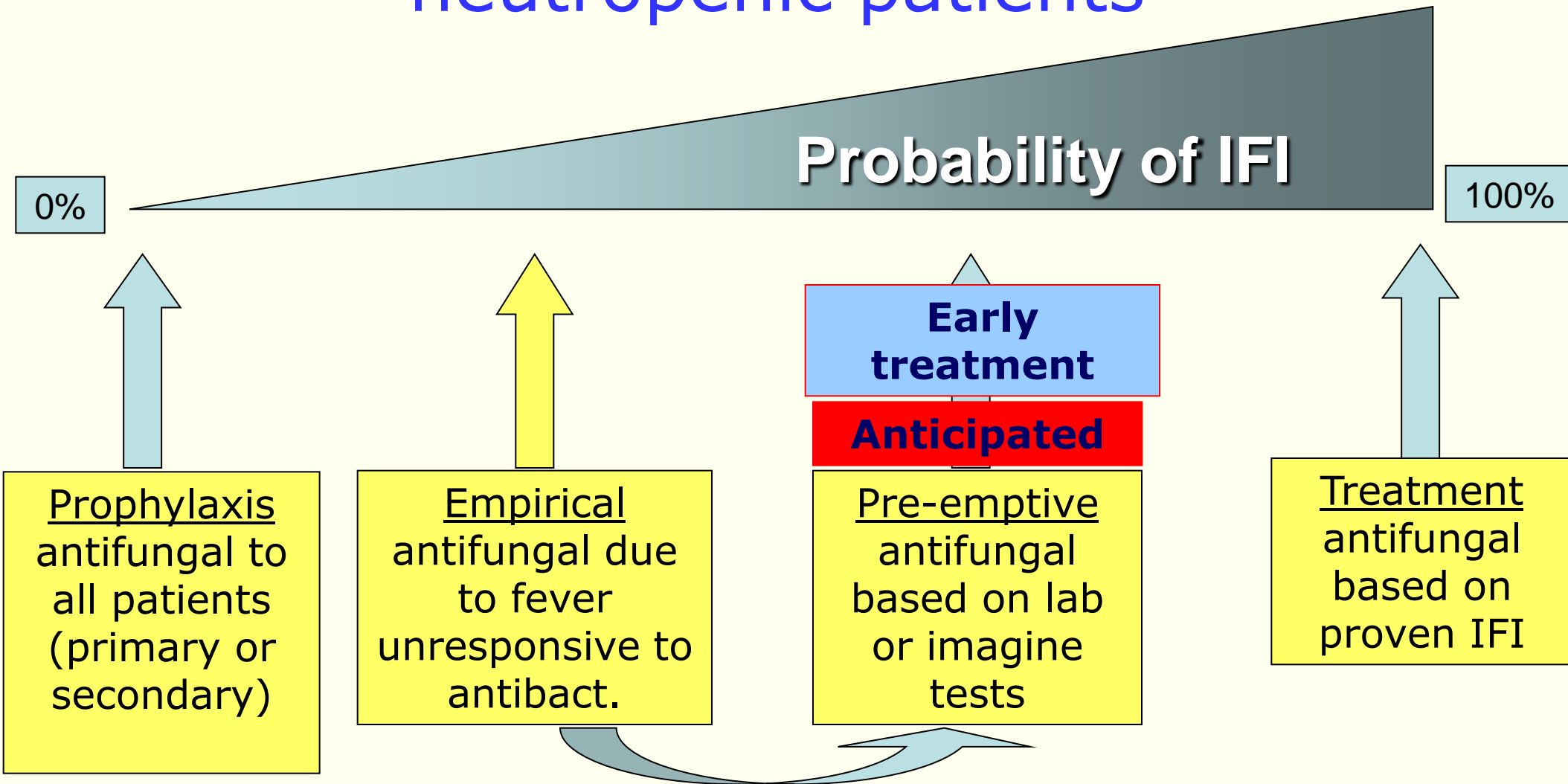
J Clin Oncol 2000; 21: 3699-3706

	imip. 112	cefta. 112	P	imip.+ vanco. 166	cefta.+ vanco. 98	P
• time clinical resp.*	5	7	.003	5	6	.09
• response at 72 h	33%	18%	.01	29%	16%	.03
• days w Atb.	7	9	.04	8	9	.05
• days hospital.	9	12	.04	9	13	.02

*** 24 h w/o fever and clinical improvement**

Infeccions fúngiques

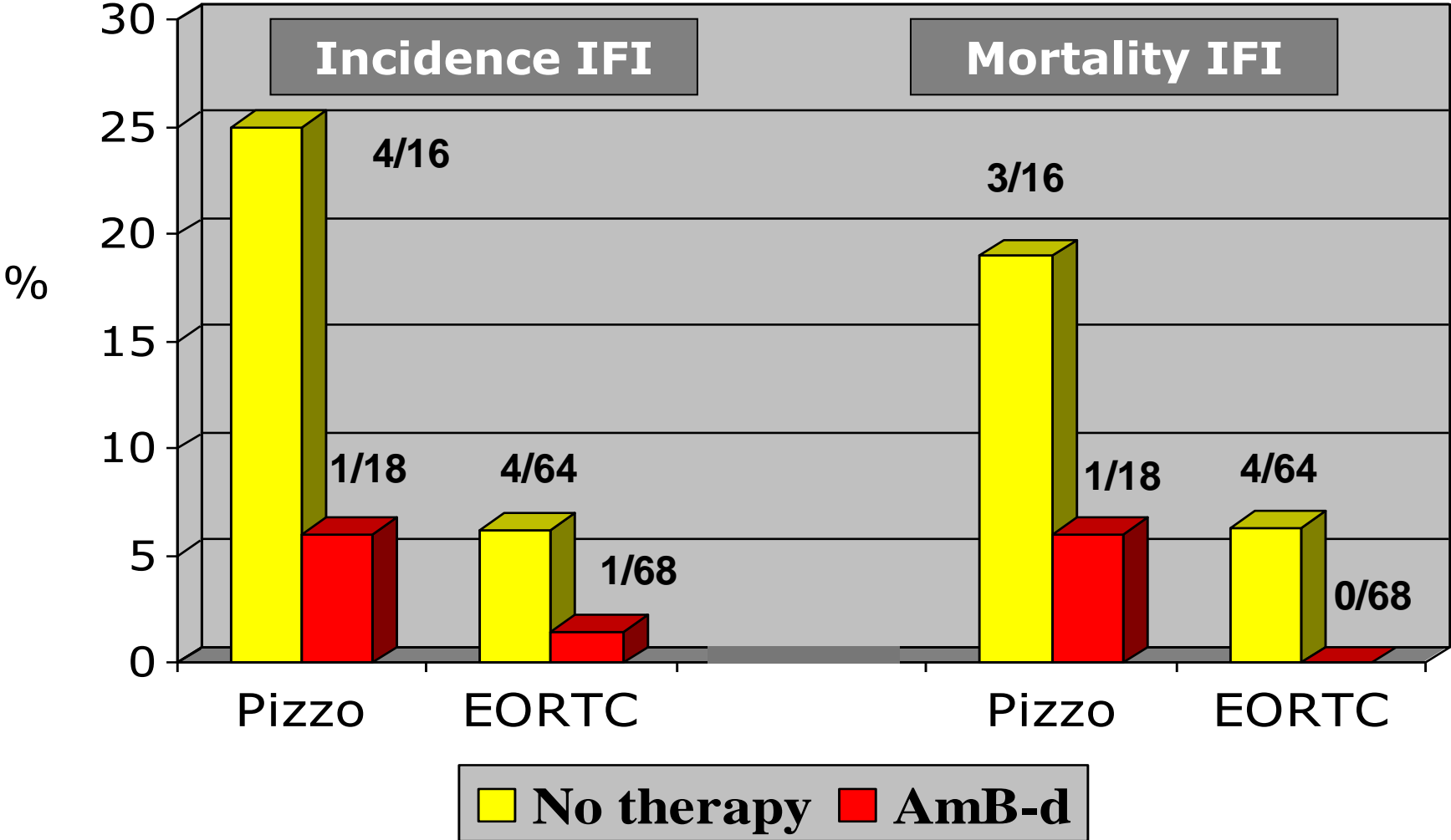
Therapeutic approaches to IFI in neutropenic patients



~ 80% unnecessary treat. (IFI incidence <20%)

Empirical Ampho-d vs no therapy

Pizzo et al, Am J Med 1982 / EORTC, Am J Med 1989



Empirical antifungal therapy

Double-blind clinical trials

Author, year	Drugs compared	Composite Endpoint	Outcome baseline IFI	Break-trough IFI	Nephro-toxicity
White 1998	ABCD vs AmB-d	NS	NS	NS	Less
Walsh, 1999	Lipo-AmB vs. AmB-d	NS	NS	Less	Less
Wingard, 2000	ABCD vs. Lipo-AmB	NS	NS	NS	More
Walsh, 2002*	Vori vs. Lipo-AmB	NS	NS	Less	NS
Walsh, 2004	Caspo vs. Lipo-AmB	NS	Better	NS	Less

* open trial

2009 UPDATE : Antifungal Drugs for Empirical Therapy

Antifungal agent	Daily dose	CDC Grading			
		Level of Recommendation	Evidence for		
			Efficacy	Safety	
Liposomal AmB	3 mg/kg	A ₋ *	I	I	
Caspofungin	50 mg	A ₋ * ¹	I	I	
ABCD	4 mg/kg	B ²	I	I	
ABLCL	5 mg/kg	B ²	I	I	
Itraconazole	200 mg iv	B ^{1,4}	I	I	
Voriconazole	2x 3 mg/kg iv	B ^{1,3,4}	I	I	
<u>NEW: Micafungin</u>	<u>100 mg</u>	<u>B</u>	<u>II</u>	<u>II</u>	
AmB deoxycholate	0.5-1 mg/kg	B ² / D ⁵	I	I	
Fluconazole	400 mg iv	C ^{1,4,6}	I	I	

* A double-blind, randomized trial comparing caspofungin 50 mg/m² (n=56) with liposomal amphotericin B 3 mg/kg/d (n=25) (published in abstract form) suggests a provisional grading BII for children : the constitution of a pediatric group specifically addressing antifungal prophylaxis and therapy in children will be considered for 2011 update of ECIL guidelines

¹ No activity against mucorales

² Infusion-related toxicity (fever, chills, hypoxia)

³ Failed the 10% non-inferiority cut-off when compared with liposomal AmB (and thus not approved by the FDA for this indication), but first-line for aspergillosis, effective therapy for candidiasis, and efficacious for prevention of breakthrough IFI.

⁴ Activity of azoles empirical therapy for persistent fever may be limited in patients receiving prophylaxis with an agent of the same class.

⁵ B in absence of / D in presence of risk factors for renal toxicity (e.g. impaired renal function at baseline, nephrotoxic co-medication including cyclosporin or tacrolimus in allogeneic HSCT recipients, aminoglycoside antibiotics, history of previous toxicity).

⁶ No activity against *Aspergillus* and other moulds. Not approved by the FDA for this indication.

Empirical antifungal therapy in persistent febrile neutropenic patients

ECIL recommendations



BII

Most patients do not have an IFI
Adverse effects
Development of resistances
Costs
Better lab + imaging techniques

Early therapy

Neutropenia - bridging the gap with supportive care



Courtesy JP Donnelly

No tots els pacients hematològics a risc d'infeccions estàn neutropènics!!!!

	Neutropènia / Disf. Neutr.	Inmunodef. Cel.lular	Inmunodef. Humoral
Leucèmies agudes	+++ / +	+ / -	-
Mielodisplasies	++ / +++	+ / -	-
Linfoma – LLC- Mieloma múltiple	+ / -	++	++
Trasplant autòleg	++ / -	++	+
Trasplant al.logènic	+++ / -	+++	+++

Impaired T-cell function: responsible agents

Bacteria

Listeria

Mycobacteria

Legionella

Nocardia

Brucella

Salmonella

Fungi

Pneumocystis j.

Cryptococcus

Histoplasma

Candida

Aspergillus

Blastomyces

Zygomycosis

Virus

Herpes

Respiratory virus

JC, EBV

Parasites

Toxoplasma

Giardia

Impaired B-cell function: responsible agents

- **Capsulated bacteria**

Streptococcus pneumoniae

Haemophilus influenzae

Neisseria meningitidis

- **Parasites**

Babesiosis

Agraïments:

- Dr E. Carreras
- Dr J. Mensa
- Dr JP. Donnelly

Moltes gràcies per la seva atenció!!!!

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