Antimicrobial prophylaxis in haematological patients

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Antimicrobial prophylaxis in haematological patients

Infectious complications during neutropenia

From SDD to SOAP

Antibacterial prophylaxis

Antifungal prophylaxis

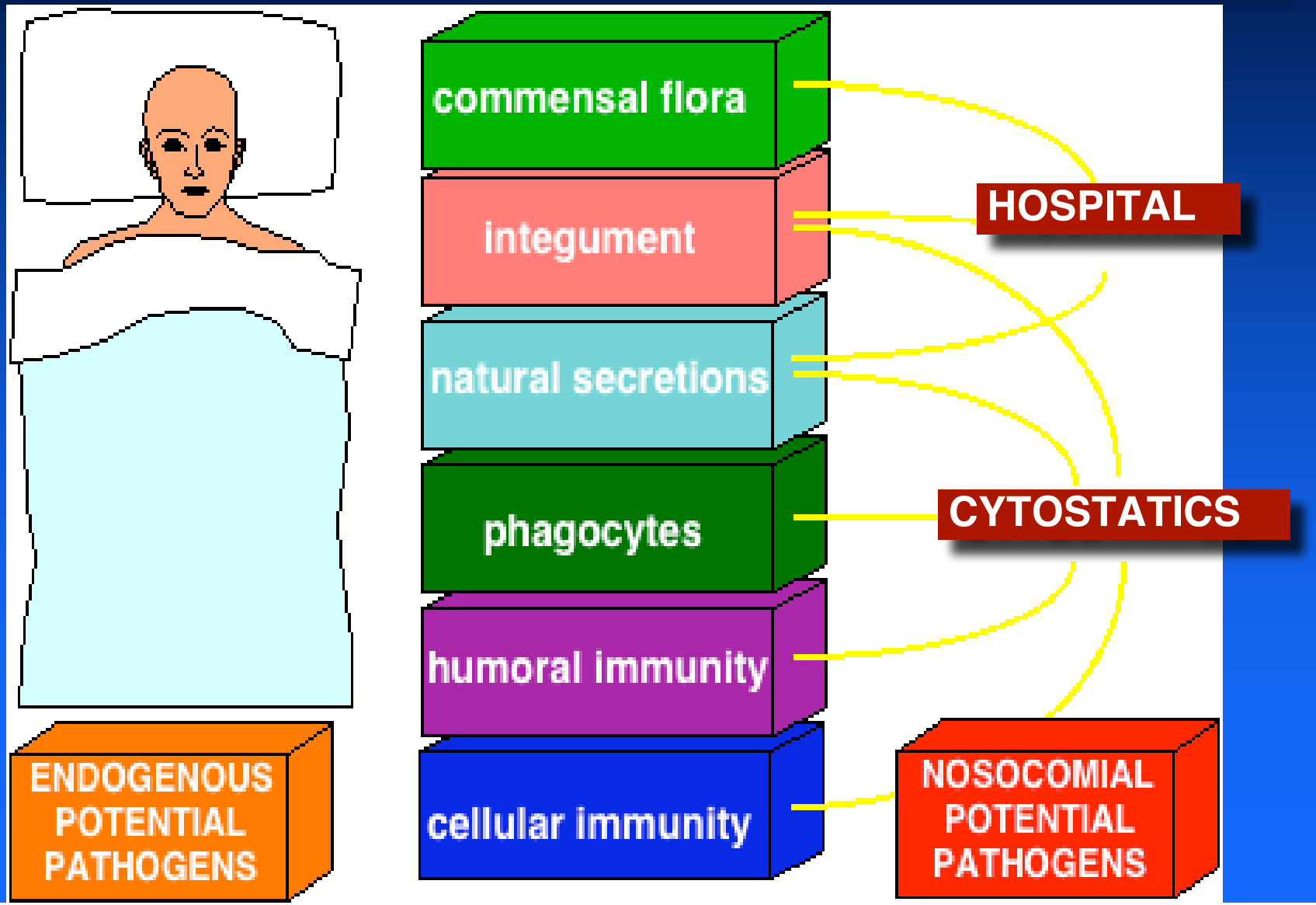
What do the experts say?

Should we use prophylaxis?

Do we use prophylaxis?

Infectious complications during neutropenia

Host defences



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Body surfaces and their resident microbial flora

NASAL SECRETIONS 10^5 organisms/mL

DENTAL PLAQUE 10^{11} organisms/g

SALIVA 10^8 organisms/mL

LUNGS sterile

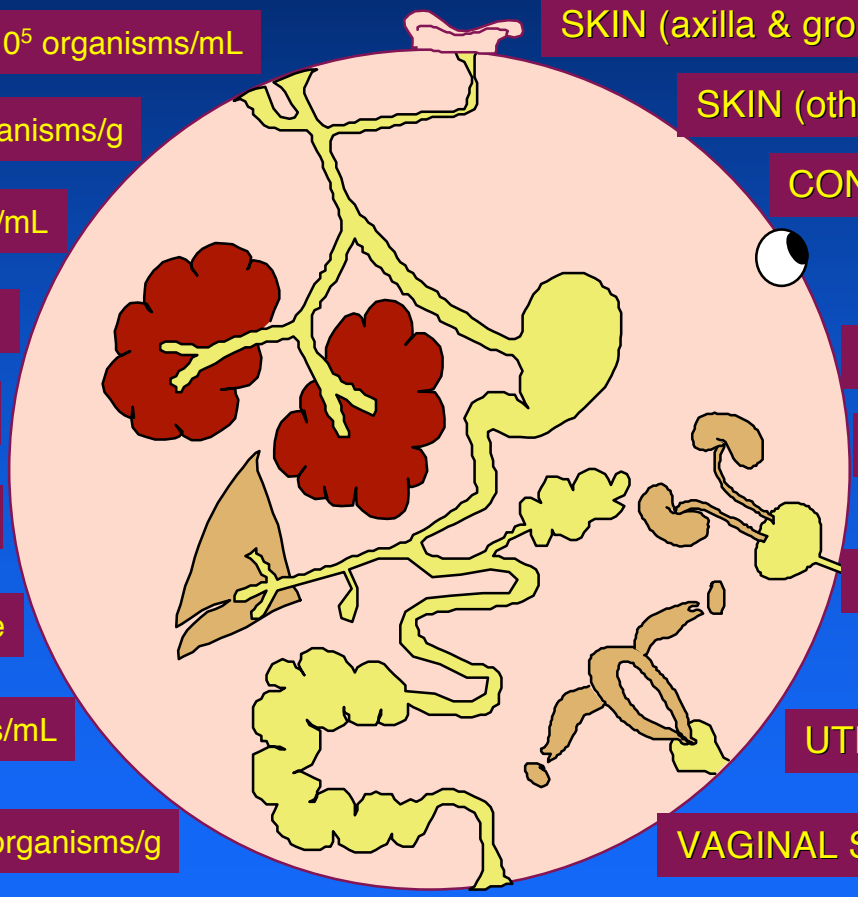
STOMACH 10^3 organisms/mL

LIVER sterile

BILE sterile

SMALL INTESTINE 10^4 organisms/mL

LARGE INTESTINE 10^{11} organisms/g



SKIN (axilla & groin) 10^6 organisms/cm^2

SKIN (other sites) 10^3 organisms/cm^2

CONJUNCTIVA <10 organisms/mL

PANCREAS sterile

KIDNEYS sterile

BLADDER $<10^3$ organisms/mL

UTERUS sterile

VAGINAL SECRETIONS 10^9 organisms/g

De Pauw & Donnelly, 1999, Principles & practice in Infectious Diseases

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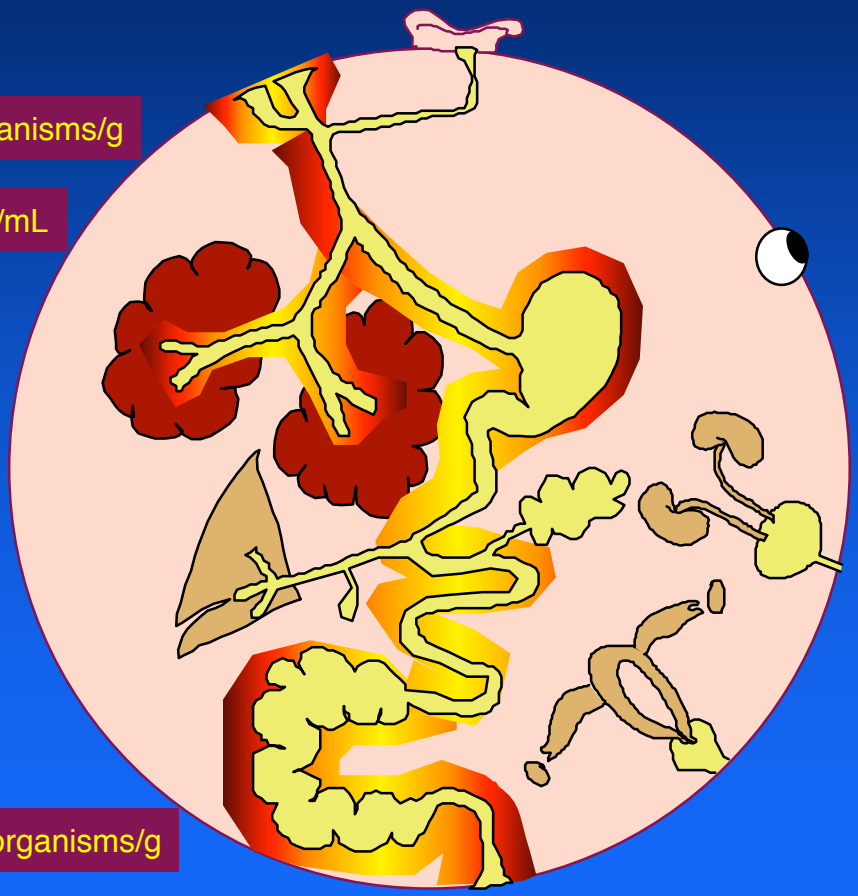
Mucosal barrier injury and the resident microbial flora

DENTAL PLAQUE 10^{11} organisms/g

SALIVA 10^{8} organisms/mL



LARGE INTESTINE 10^{11} organisms/g

Common causes of infection in neutropenia

Bacteria

- Enterobacteriaciae *eg. Escherichia coli*
- Other Gram-negative bacilli *eg. Pseudomonas aeruginosa*
- Staphylococci *eg. S. aureus, S. epidermidiis*
- Viridans streptococci *eg. S. mitis*

Fungi

- Yeast *eg. Candida albicans*
- Moulds *eg. Aspergillus fumigatus*

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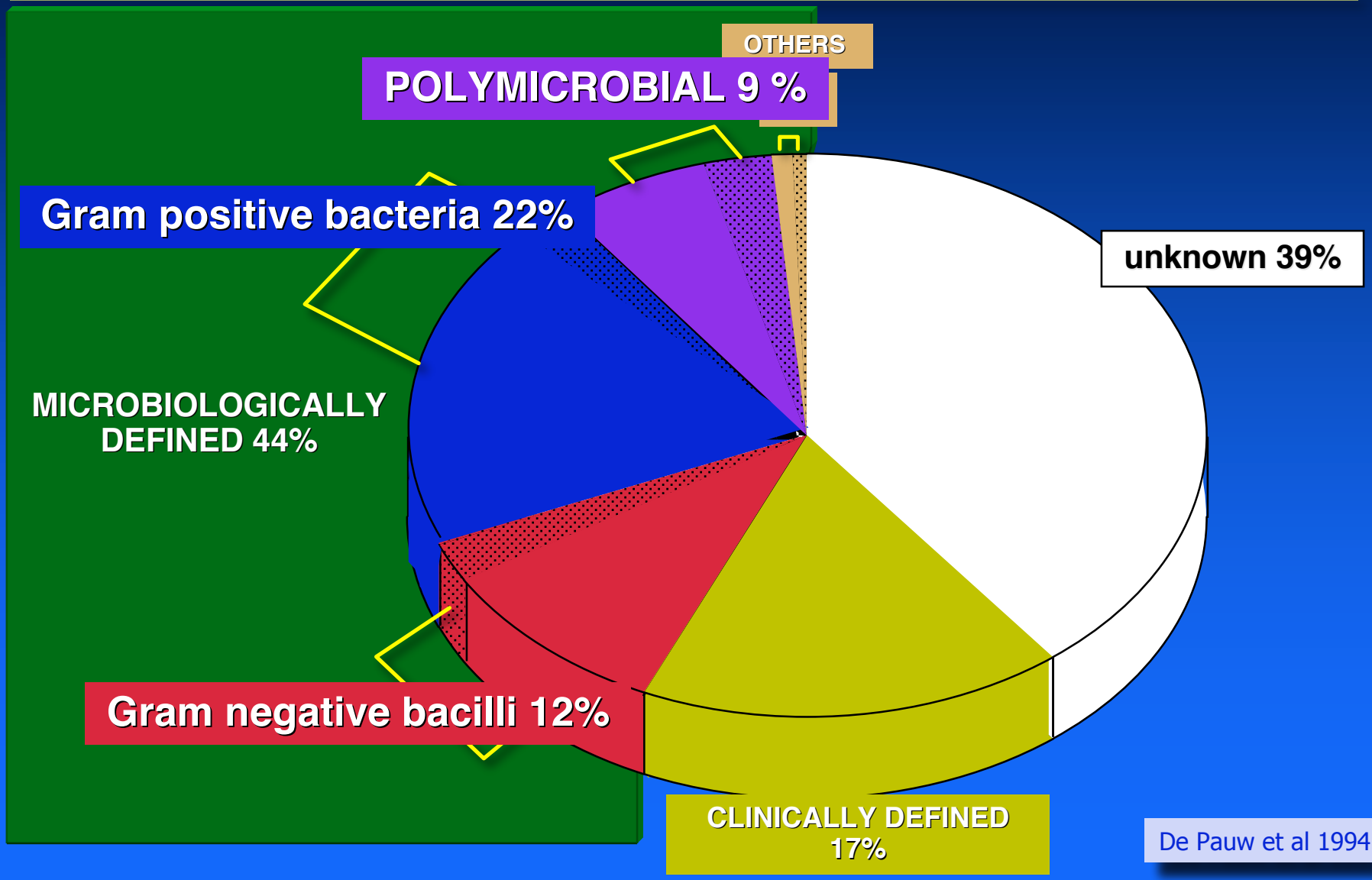
Causes of 968 episodes of fever during neutropenia



De Pauw et al 1994

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Neutropenia

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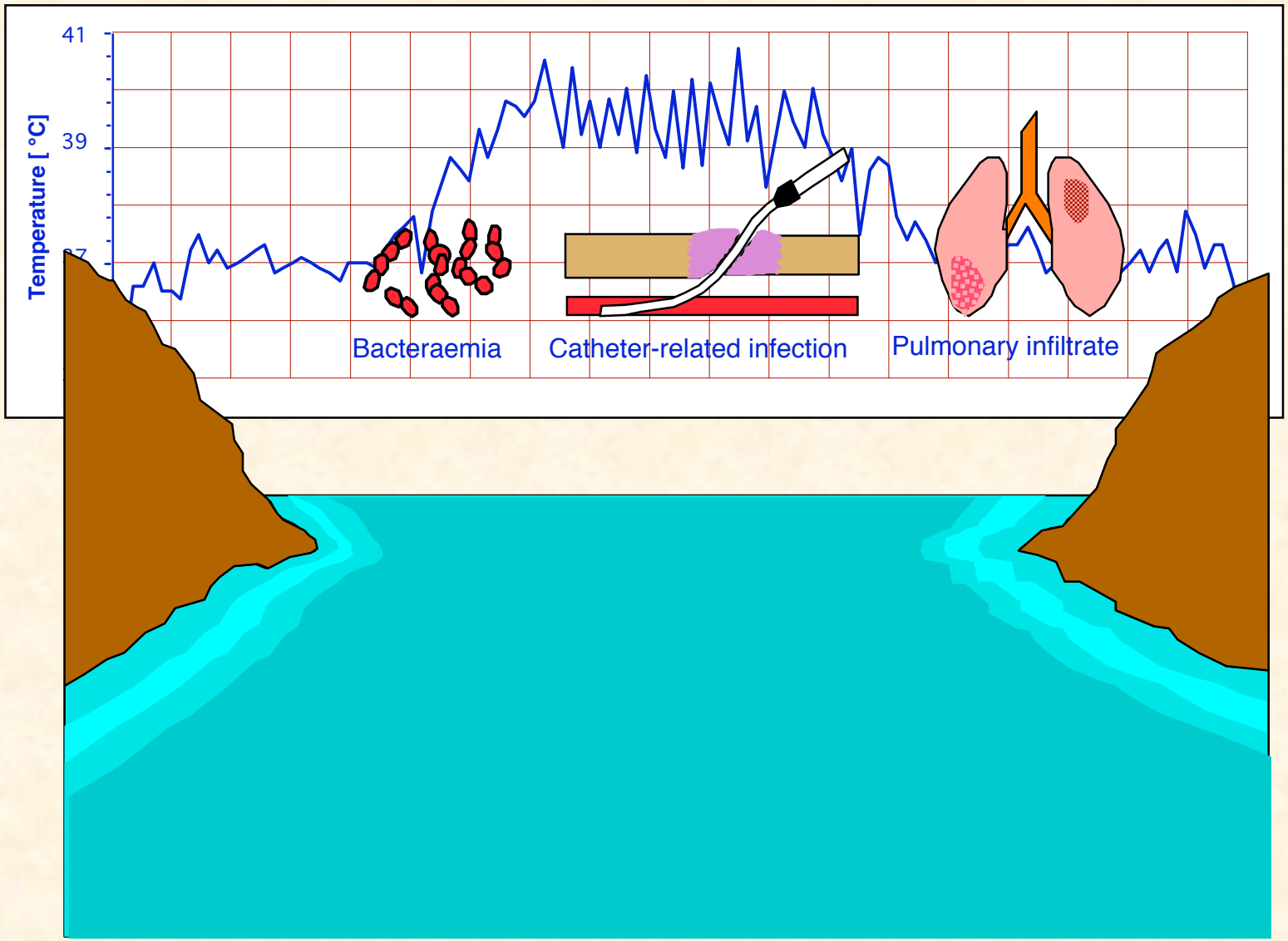
Neutropenia - infectious complications



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Neutropenia - bridging the gap with supportive care

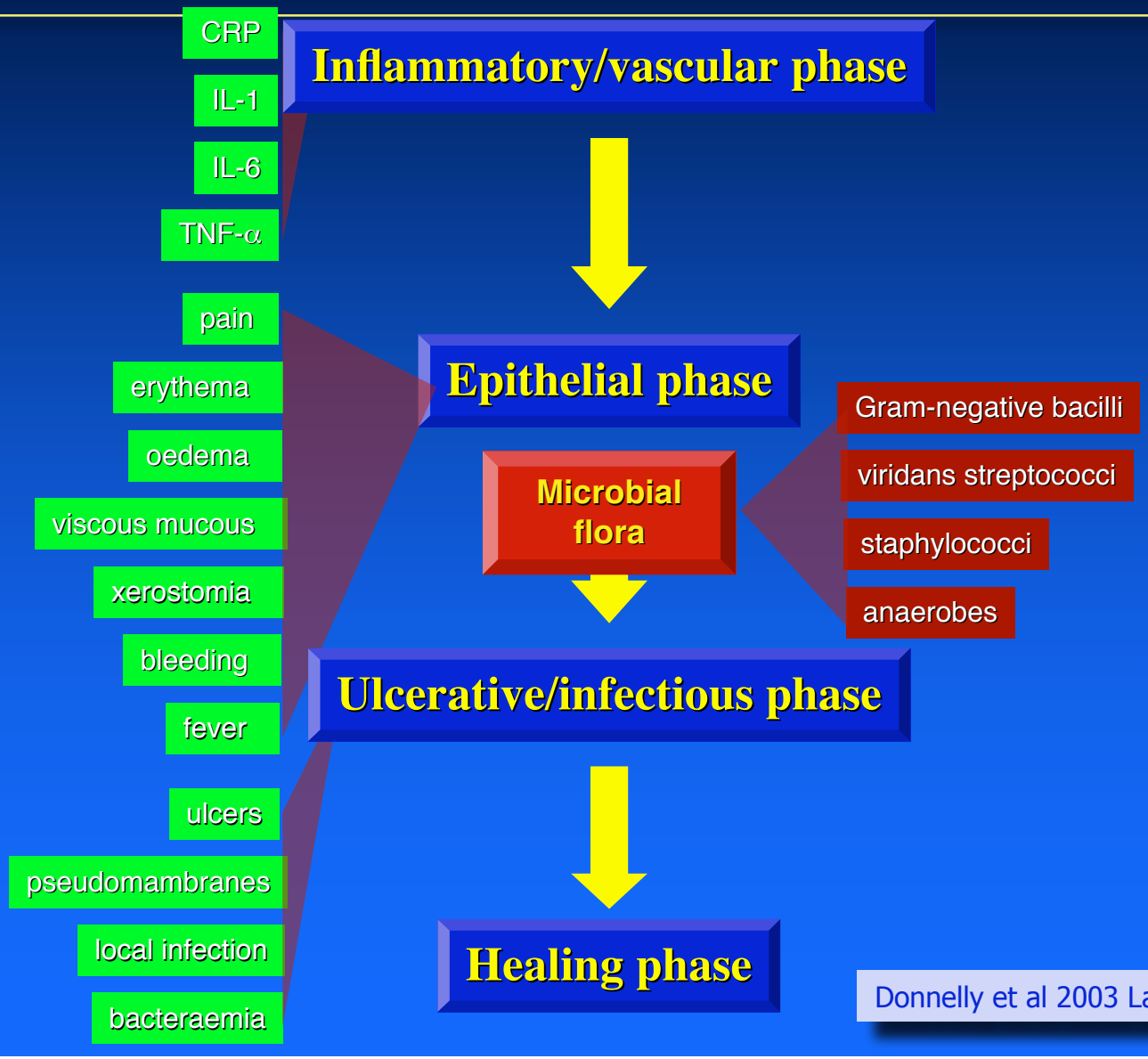
From SDD to SOAP

Gram-negative bacilli should be covered

because infection can:-

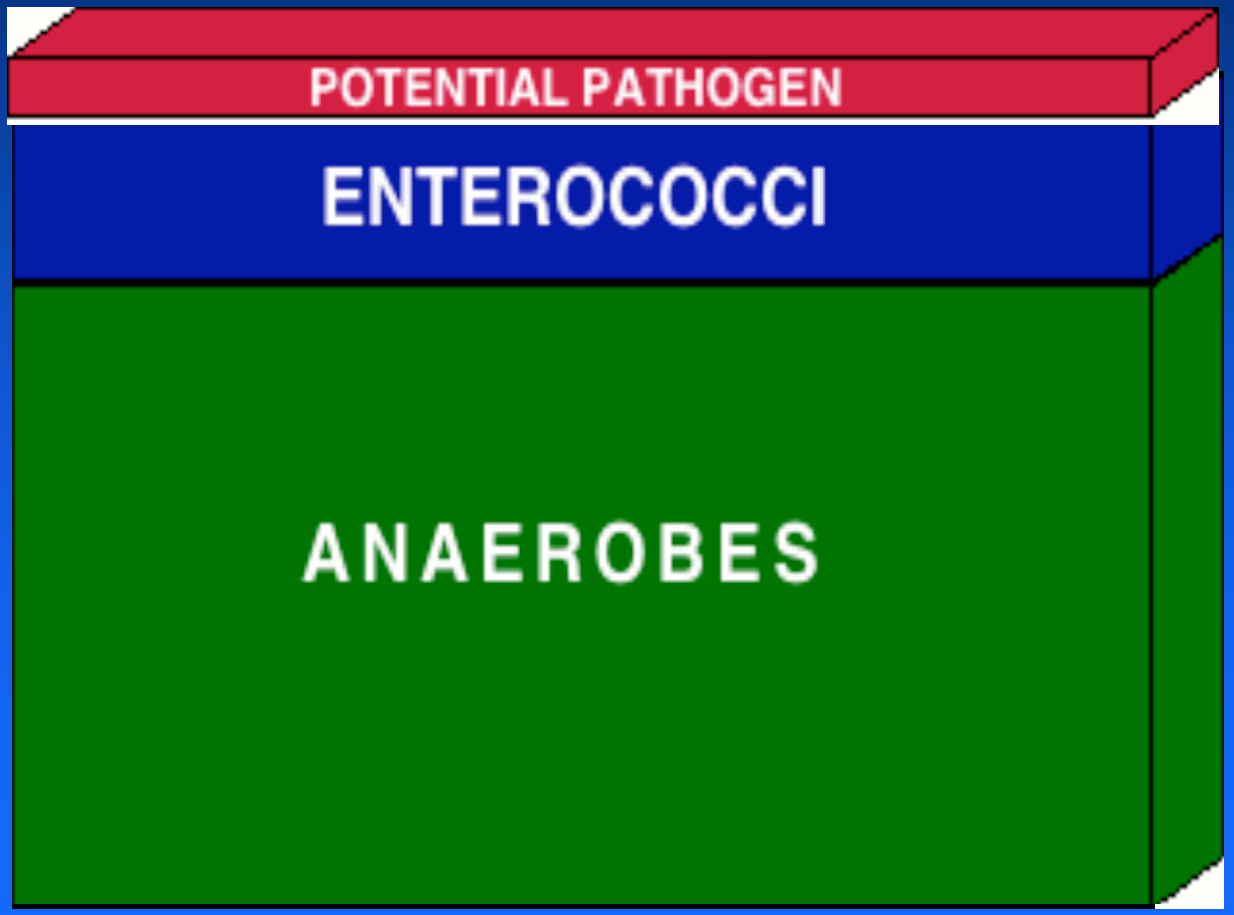
- **develop from colonisation**
- **progress rapidly**
- **lead to shock**
- **fulminate**

Evolution of mucositis



Donnelly et al 2003 Lancet ID; 3: 405–12

Elements of the gut flora



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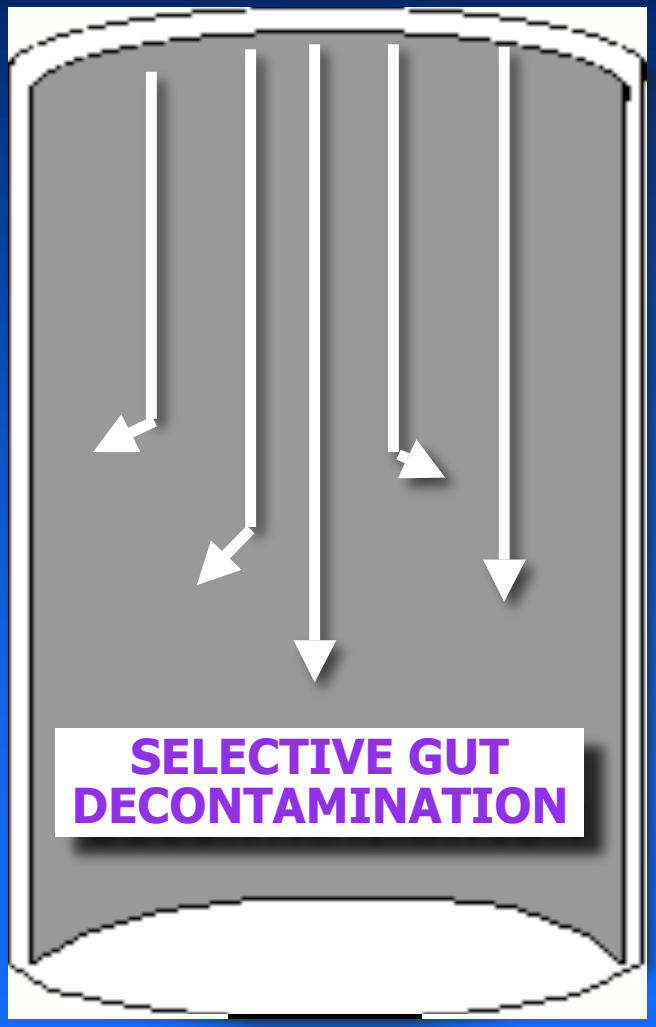
Selective Gut Decontamination



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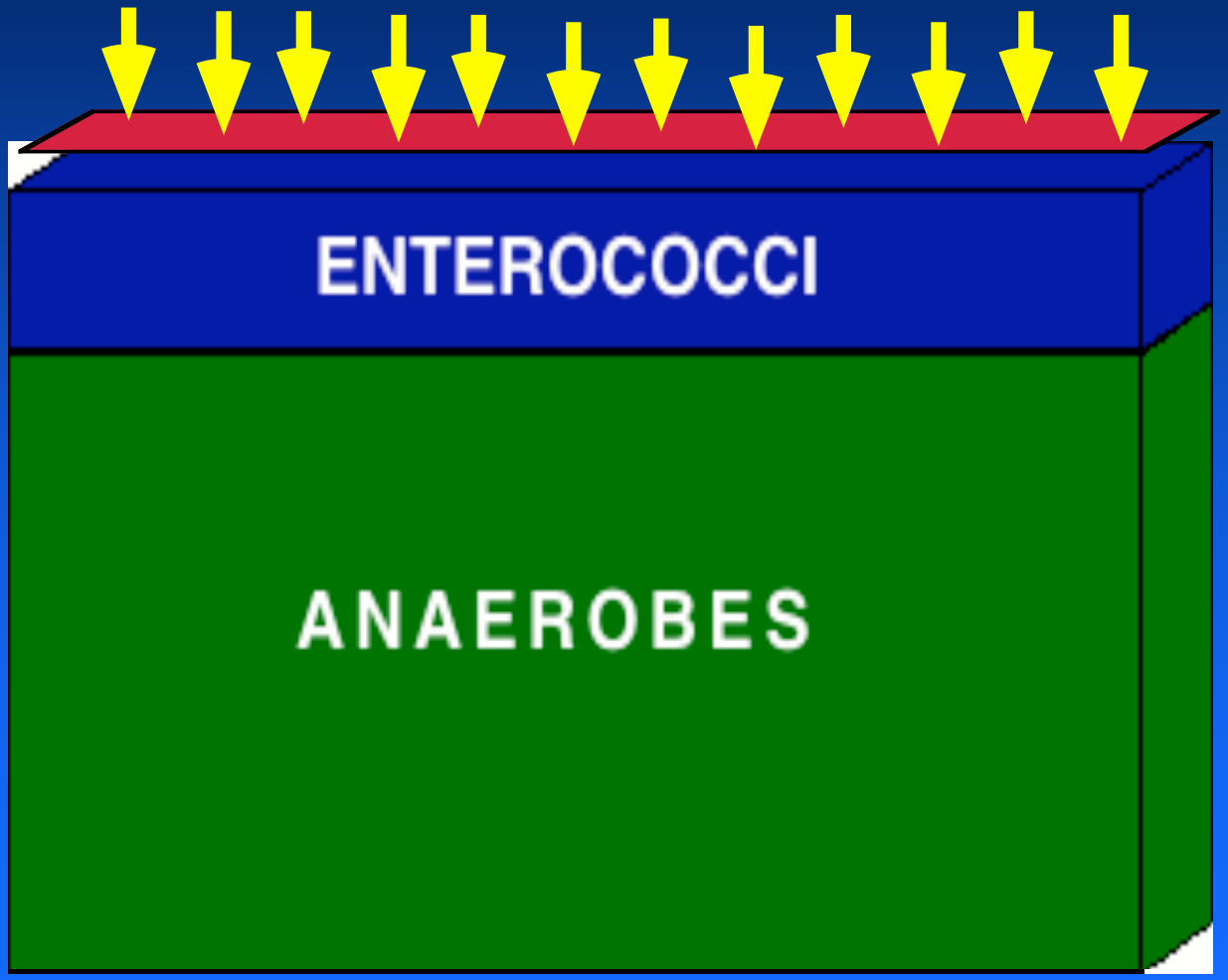
Elements of the gut flora



Terminology -

Selective Oral Antimicrobial Prophylaxis

" the oral administration of antimicrobials in order to eliminate potential pathogens while preserving the microbial ecology of the alimentary tract"

AKA

- Partial Antimicrobial Decontamination (PAD)
- Selectieve Darm Decontaminatie (SDD)
- Selective Decontamination of the Digestive Tract (SDD)
- Selective Gut Decontamination (SGD)
- Selective Antimicrobial Modulation (SAM)
- Selective Decontamination of the Intestines (SDI)

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Impairment of colonization resistance by various antibiotics

Impairment	antibiotics
high	rifampicin, penicillin V, cloxacillin, clindamycin, erythromycin, bacitracin
moderate	ampicillin, piperacillin, azlocillin, cefoperazone, (po) gentamicin, (po) amikacin, (po) vancomycin
low	cefuroxime, cefotaxime, moxalactam, cefoxitin aztreonam, imipenem, neomycin, doxycycline
no effect	cotrimoxazole, polymyxins, quinolones, ceftazidime, meropenem

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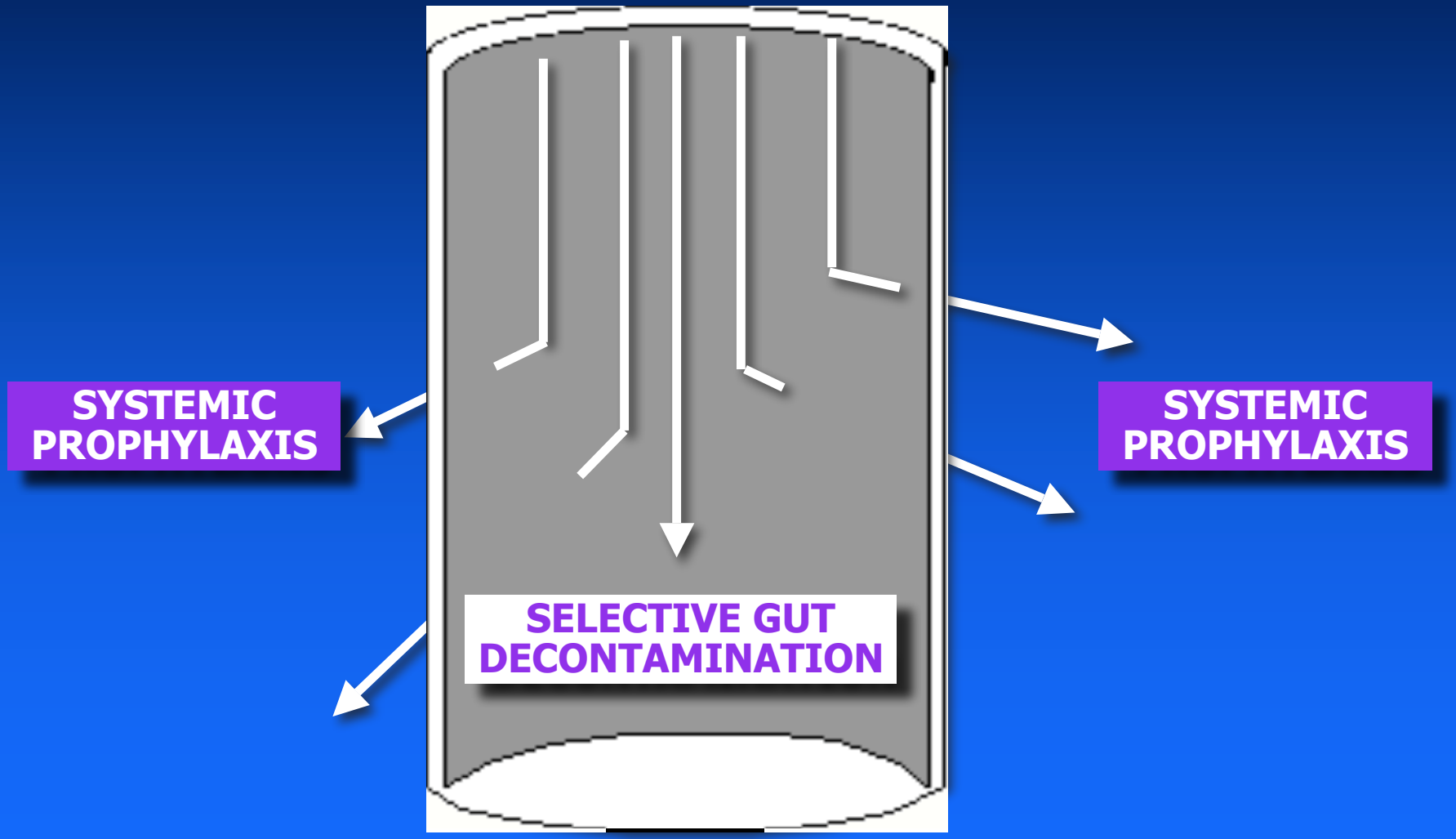
Selective oral antimicrobial prophylaxis



Antibacterial prophylaxis

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Question

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

- **Yes**
- **No**
- **Don’t know**

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Question

Which regimen do you use for antibacterial prophylaxis to prevent infections in patients with acute leukemia or in recipients of hematopoietic stem cell transplantation?

- co-trimoxazole/colistin
- ciprofloxacin
- levofloxacin
- none of the above
- don't know

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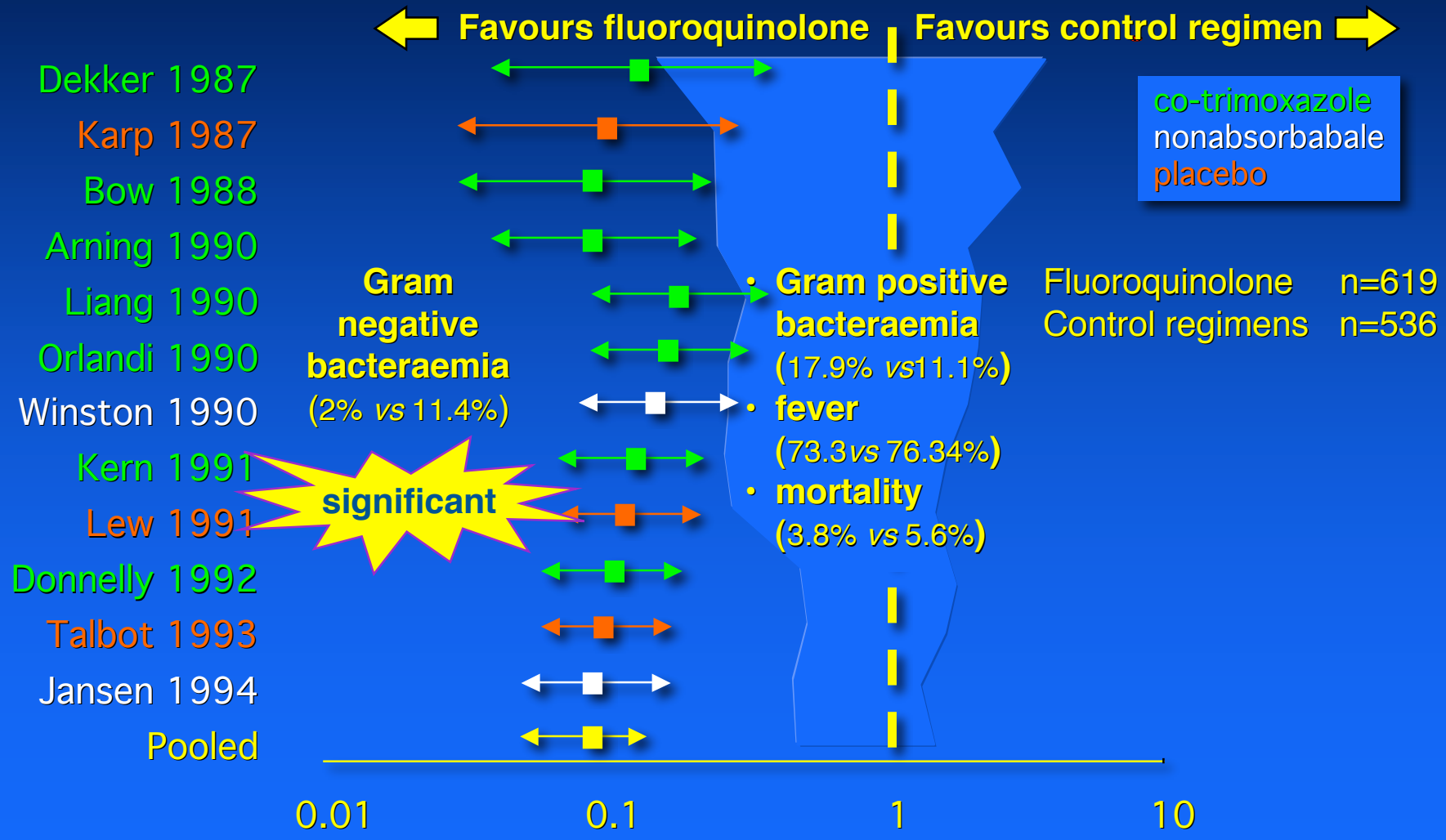
Comparison of fluoroquinolone with control regimens



Cruciani et al 1996Clin Infect Dis 23;795

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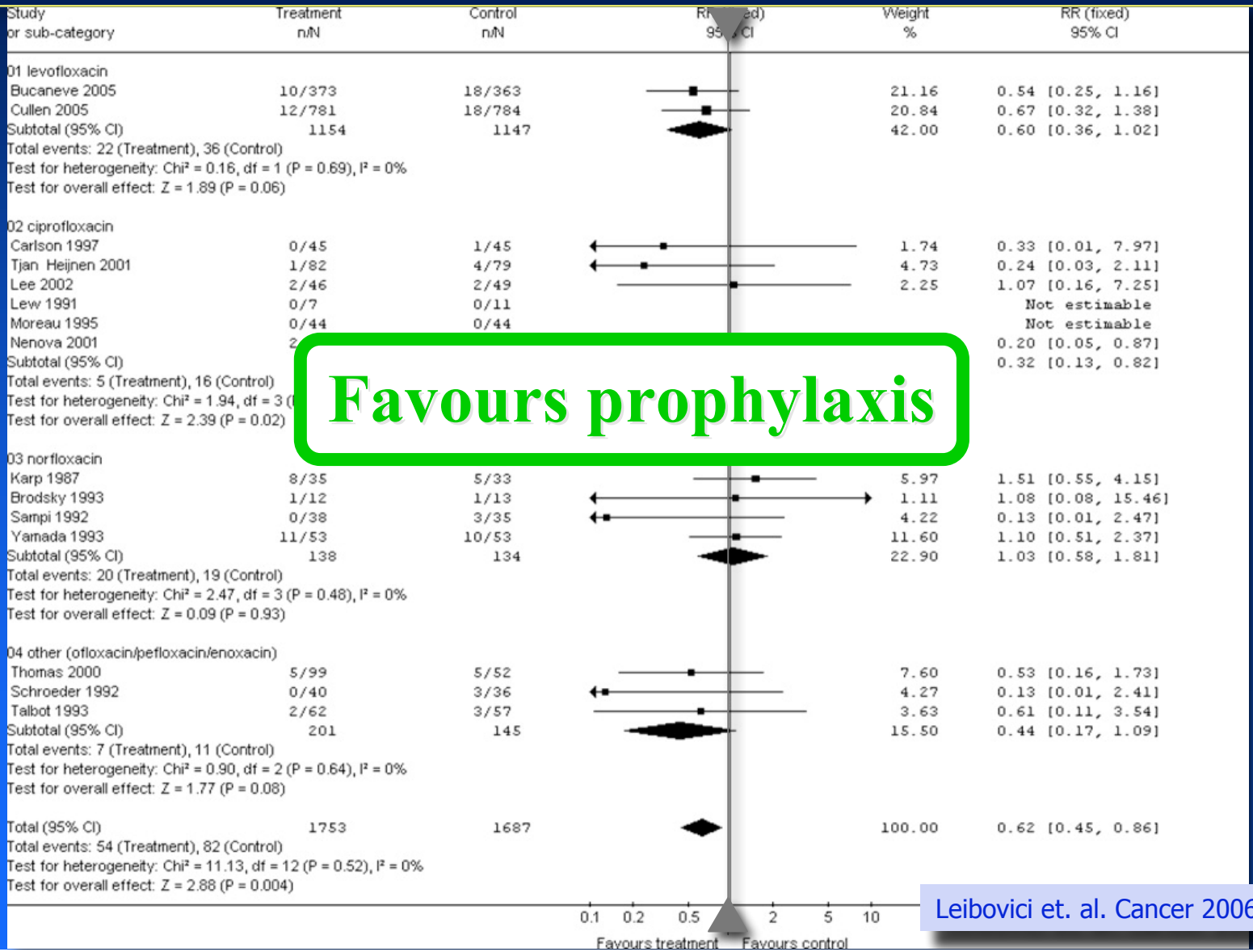
Fluoroquinolones vs placebo/no treatment

- febrile episode



Leibovici et. al. Cancer 2006;107:1743

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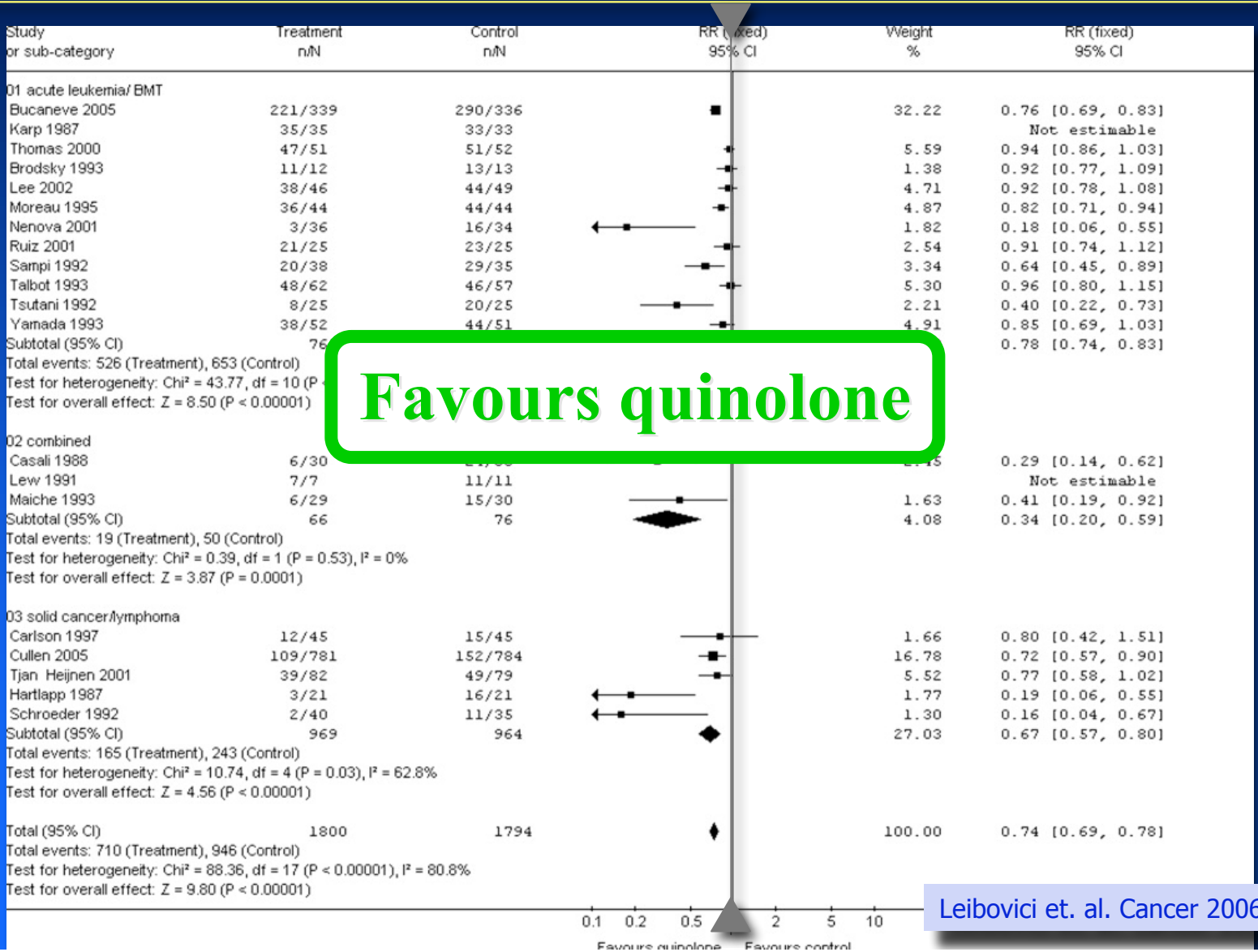
Fluoroquinolones vs placebo/no treatment

- infection due to Gram-positive pathogen(s)



Study or sub-category	Treatment n/N	Control n/N	RR (fixed) 95% CI	Weight %	RR (fixed) 95% CI
01 acute leukemia/ BMT					
Bucaneve 2005	221/339	290/336		32.22	0.76 [0.69, 0.83]
Karp 1987	35/35	33/33			Not estimable
Thomas 2000	47/51	51/52		5.59	0.94 [0.86, 1.03]
Brodsky 1993	11/12	13/13		1.38	0.92 [0.77, 1.09]
Lee 2002	38/46	44/49		4.71	0.92 [0.78, 1.08]
Moreau 1995	36/44	44/44		4.87	0.82 [0.71, 0.94]
Nenova 2001	3/36	16/34		1.82	0.18 [0.06, 0.55]
Ruiz 2001	21/25	23/25		2.54	0.91 [0.74, 1.12]
Sampi 1992	20/38	29/35		3.34	0.64 [0.45, 0.89]
Talbot 1993	48/62	46/57		5.30	0.96 [0.80, 1.15]
Tsutani 1992	8/25	20/25		2.21	0.40 [0.22, 0.73]
Yamada 1993	38/52	44/51		4.91	0.85 [0.69, 1.03]
Subtotal (95% CI)	76				0.78 [0.74, 0.83]
Total events: 526 (Treatment), 653 (Control)					
Test for heterogeneity: Chi² = 43.77, df = 10 (P					
Test for overall effect: Z = 8.50 (P < 0.00001)					
02 combined					
Casali 1988	6/30				0.29 [0.14, 0.62]
Lew 1991	7/7	11/11			Not estimable
Maiche 1993	6/29	15/30		1.63	0.41 [0.19, 0.92]
Subtotal (95% CI)	66	76		4.08	0.34 [0.20, 0.59]
Total events: 19 (Treatment), 50 (Control)					
Test for heterogeneity: Chi² = 0.39, df = 1 (P = 0.53), I² = 0%					
Test for overall effect: Z = 3.87 (P = 0.0001)					
03 solid cancer/lymphoma					
Carlson 1997	12/45	15/45		1.66	0.80 [0.42, 1.51]
Cullen 2005	109/781	152/784		16.78	0.72 [0.57, 0.90]
Tjan Heijnen 2001	39/82	49/79		5.52	0.77 [0.58, 1.02]
Hartlapp 1987	3/21	16/21		1.77	0.19 [0.06, 0.55]
Schroeder 1992	2/40	11/35		1.30	0.16 [0.04, 0.67]
Subtotal (95% CI)	969	964		27.03	0.67 [0.57, 0.80]
Total events: 165 (Treatment), 243 (Control)					
Test for heterogeneity: Chi² = 10.74, df = 4 (P = 0.03), I² = 62.8%					
Test for overall effect: Z = 4.56 (P < 0.00001)					
Total (95% CI)	1800	1794		100.00	0.74 [0.69, 0.78]
Total events: 710 (Treatment), 946 (Control)					
Test for heterogeneity: Chi² = 88.36, df = 17 (P < 0.00001), I² = 80.8%					
Test for overall effect: Z = 9.80 (P < 0.00001)					

Leibovici et. al. Cancer 2006;107:1743

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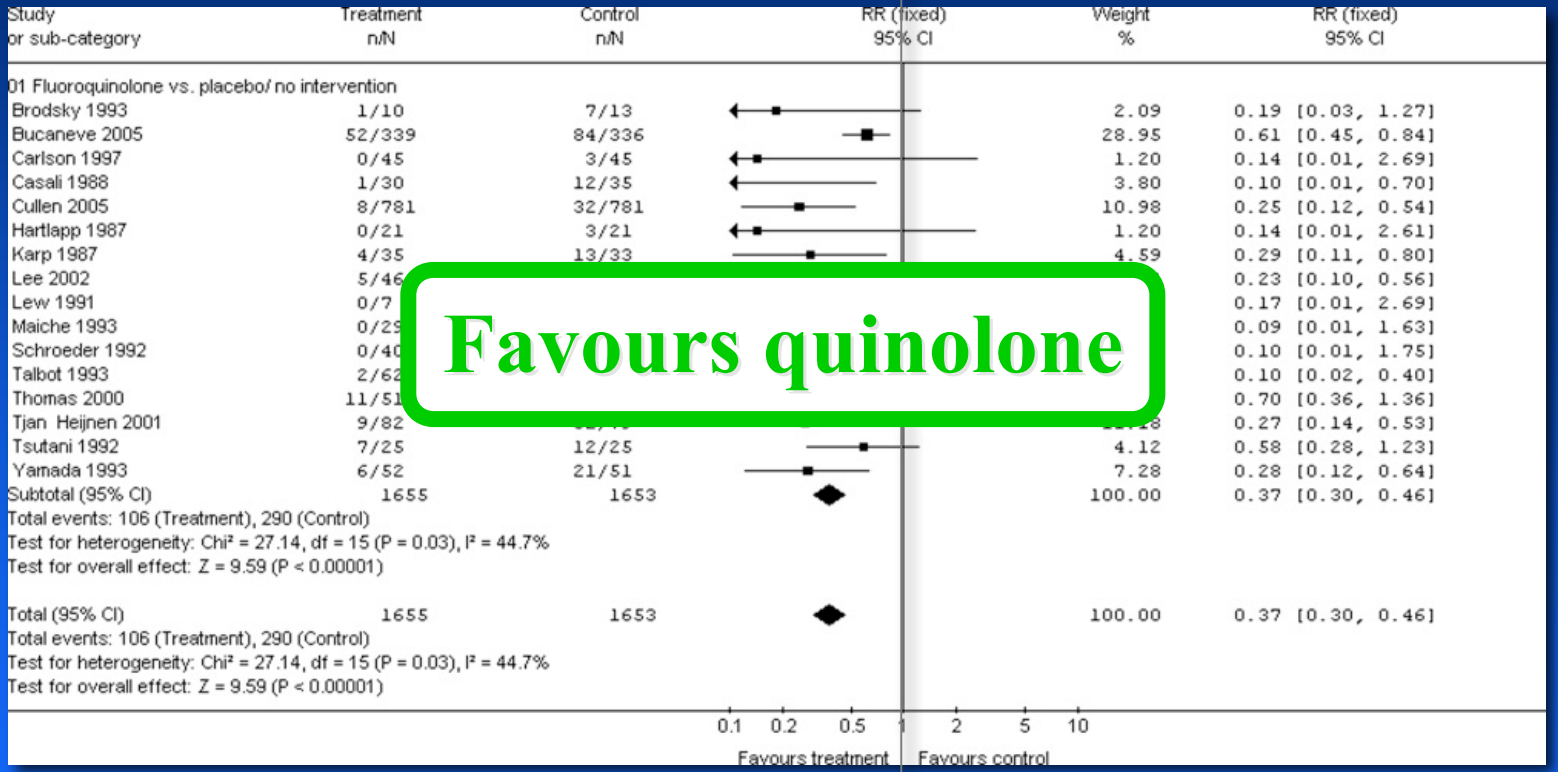
Fluoroquinolones vs placebo/no treatment

- survival



Study or sub-category	Treatment n/N	Control n/N	RR (fixed) 95% CI	Weight %	RR (fixed) 95% CI
01 Fluoroquinolone vs. placebo/ no intervention					
Brodsky 1993	1/10	7/13		2.09	0.19 [0.03, 1.27]
Bucaneve 2005	52/339	84/336		28.95	0.61 [0.45, 0.84]
Carlson 1997	0/45	3/45		1.20	0.14 [0.01, 2.69]
Casali 1988	1/30	12/35		3.80	0.10 [0.01, 0.70]
Cullen 2005	8/781	32/781		10.98	0.25 [0.12, 0.54]
Hartlapp 1987	0/21	3/21		1.20	0.14 [0.01, 2.61]
Karp 1987	4/35	13/33		4.59	0.29 [0.11, 0.80]
Lee 2002	5/46				0.23 [0.10, 0.56]
Lew 1991	0/7				0.17 [0.01, 2.69]
Maiche 1993	0/29				0.09 [0.01, 1.63]
Schroeder 1992	0/40				0.10 [0.01, 1.75]
Talbot 1993	2/62				0.10 [0.02, 0.40]
Thomas 2000	11/51				0.70 [0.36, 1.36]
Tjan Heijnen 2001	9/82				0.27 [0.14, 0.53]
Tsutani 1992	7/25	12/25		4.12	0.58 [0.28, 1.23]
Yamada 1993	6/52	21/51		7.28	0.28 [0.12, 0.64]
Subtotal (95% CI)	1655	1653		100.00	0.37 [0.30, 0.46]
Total events: 106 (Treatment), 290 (Control)					
Test for heterogeneity: Chi² = 27.14, df = 15 (P = 0.03), I² = 44.7%					
Test for overall effect: Z = 9.59 (P < 0.00001)					
Total (95% CI)	1655	1653		100.00	0.37 [0.30, 0.46]
Total events: 106 (Treatment), 290 (Control)					
Test for heterogeneity: Chi² = 27.14, df = 15 (P = 0.03), I² = 44.7%					
Test for overall effect: Z = 9.59 (P < 0.00001)					

0.1 0.2 0.5 1 2 5 10

Favours treatment Favours control

Leibovici et. al. Cancer 2006;107:1743

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Number needed to treat

Table 1. Prophylaxis with Fluoroquinolones in Neutropenic Patients*

Neutropenia 7 days

Patients (Study				**reated needed to 1 event**
All patients (Gafter-Gvili et al., 2005[11])				
Death from any cause				24
Febrile episode				4
Bacterial infection	0.50	0.35-0.70	45	5
Patients with expected prolong… transplantation (Bucaneve et al				**kemia and stem cell**
Death from any cause				43
Febrile episode				5
Bacterial infection				6
Patients with solid tumors and lymphomas. No stem cell transplantation (Cullen et al., 2005[3])				
Death from any cause	0.67	0.32-1.38	2.3	132
Febrile episode§	0.71	0.55-0.92	15	23
Bacterial infection§	0.82	0.73-0.94	42	13

bacteraemia NNT 6

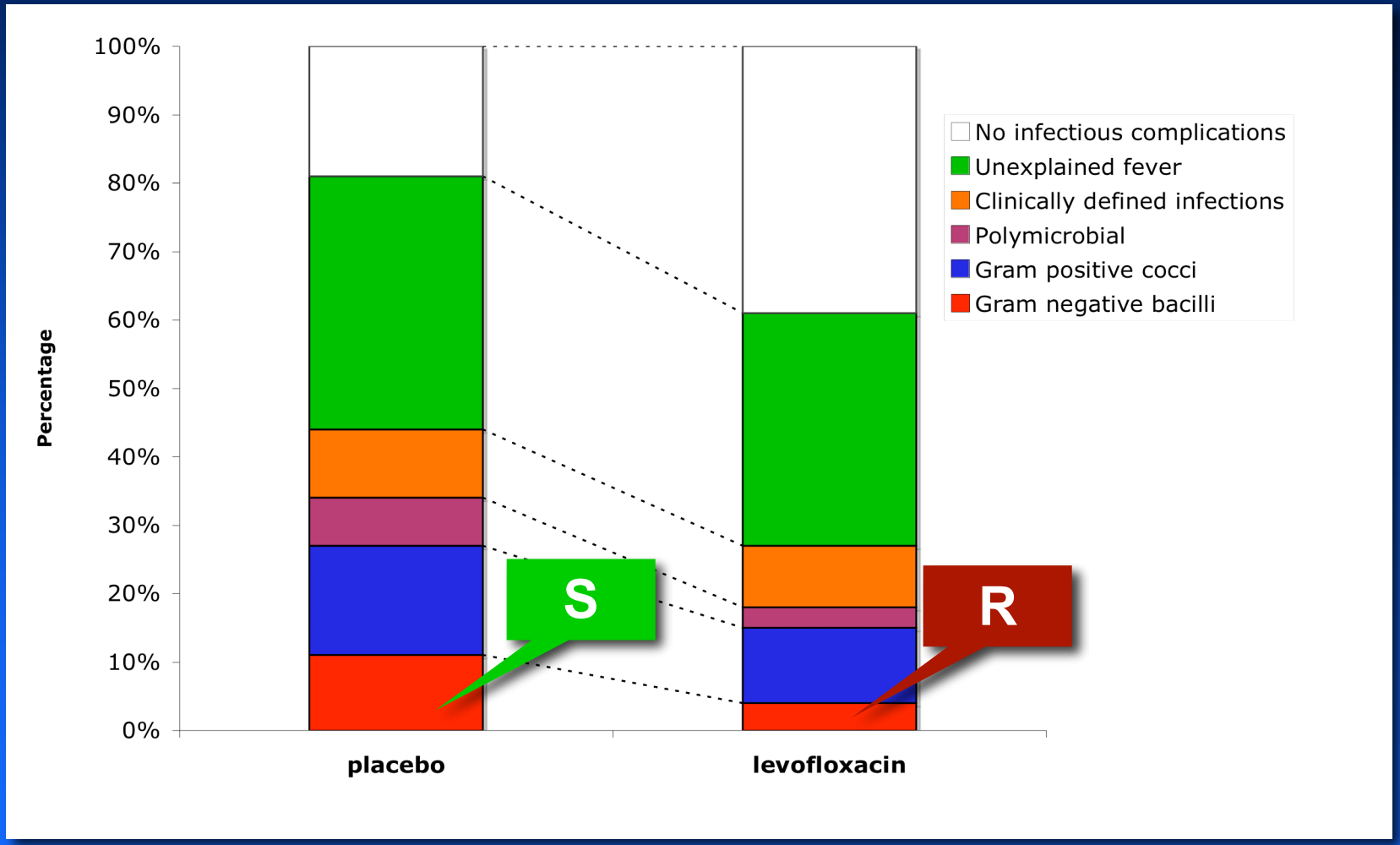
fever NNT 5

mortality NNT 43

Leibovici et. al. Cancer 2006;107:1743

Downside

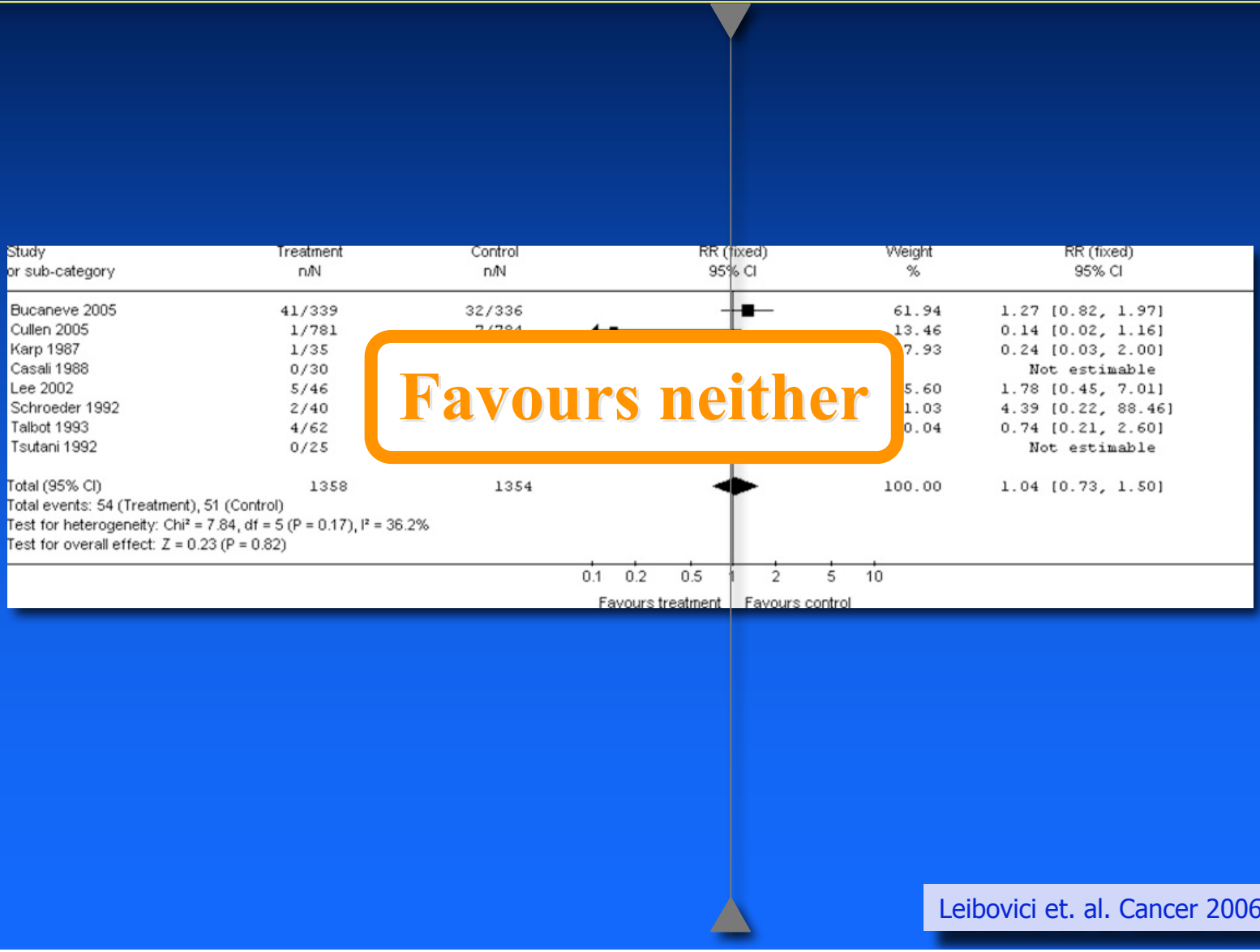
Levofloxacin versus placebo



Bucaneve et al 2005 NEJM 353:977-87

Fluoroquinolones vs placebo/no treatment

- infection due to fluoroquinolone resistant pathogen(s)



Leibovici et. al. Cancer 2006;107:1743

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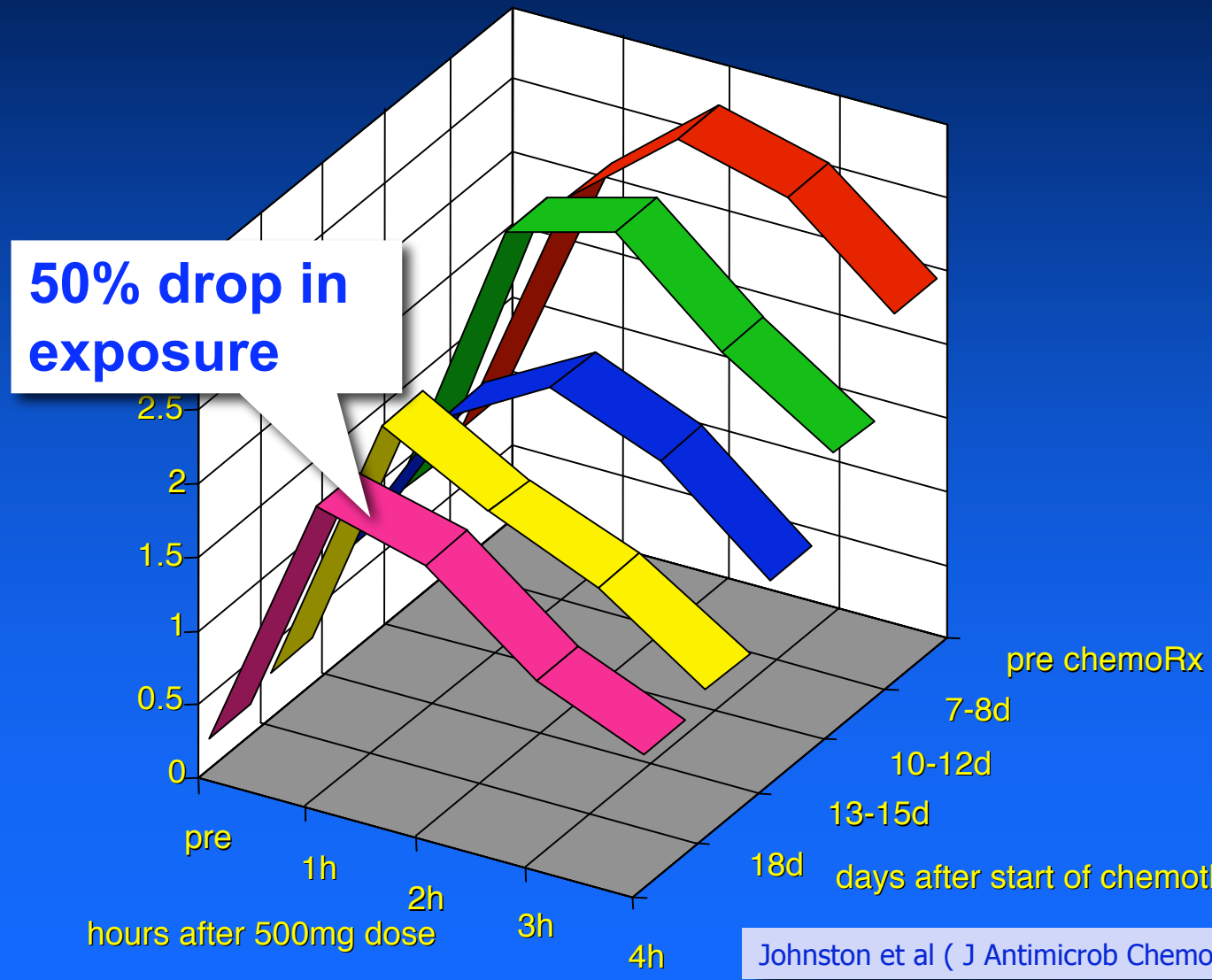
Absorption of ciprofloxacin after chemotherapy



Johnston et al (J Antimicrob Chemother 1990:25, 837-842)

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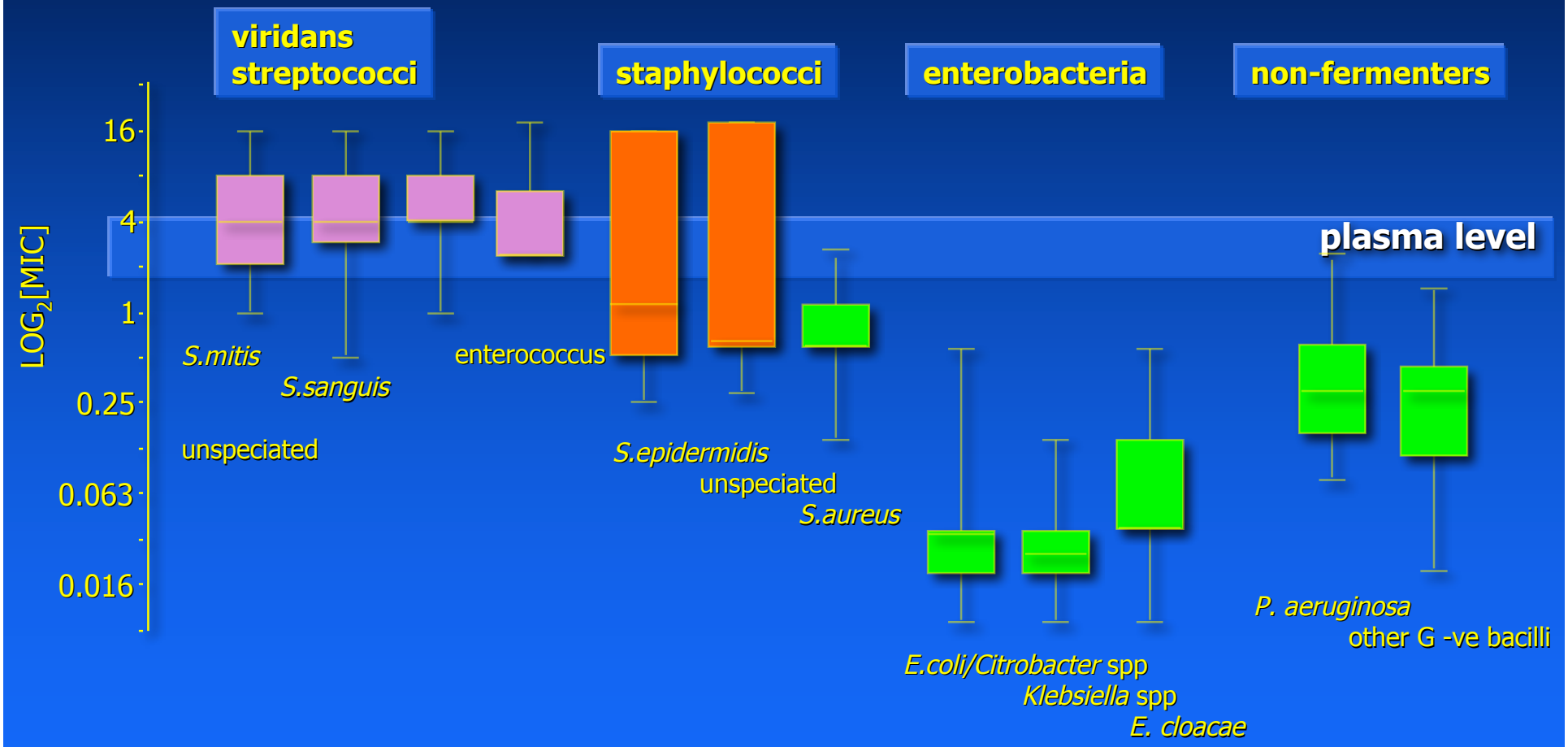
Plasma levels and MICs of ciprofloxacin



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Ciprofloxacin comes out in the sweat and rapidly selects resistant Staphylococcus epidermidis

	Ciprofloxacin MIC (mg/L)	Resistance
Pre-study	0.13 - 0.38	none
Post-study	4-12	MET
	>32	MET-ERY-SUL-TRI-GEN

6 volunteers took 750 mg bd ciprofloxacin for 7 days

Høiby et al, Lancet 1997, 349;167

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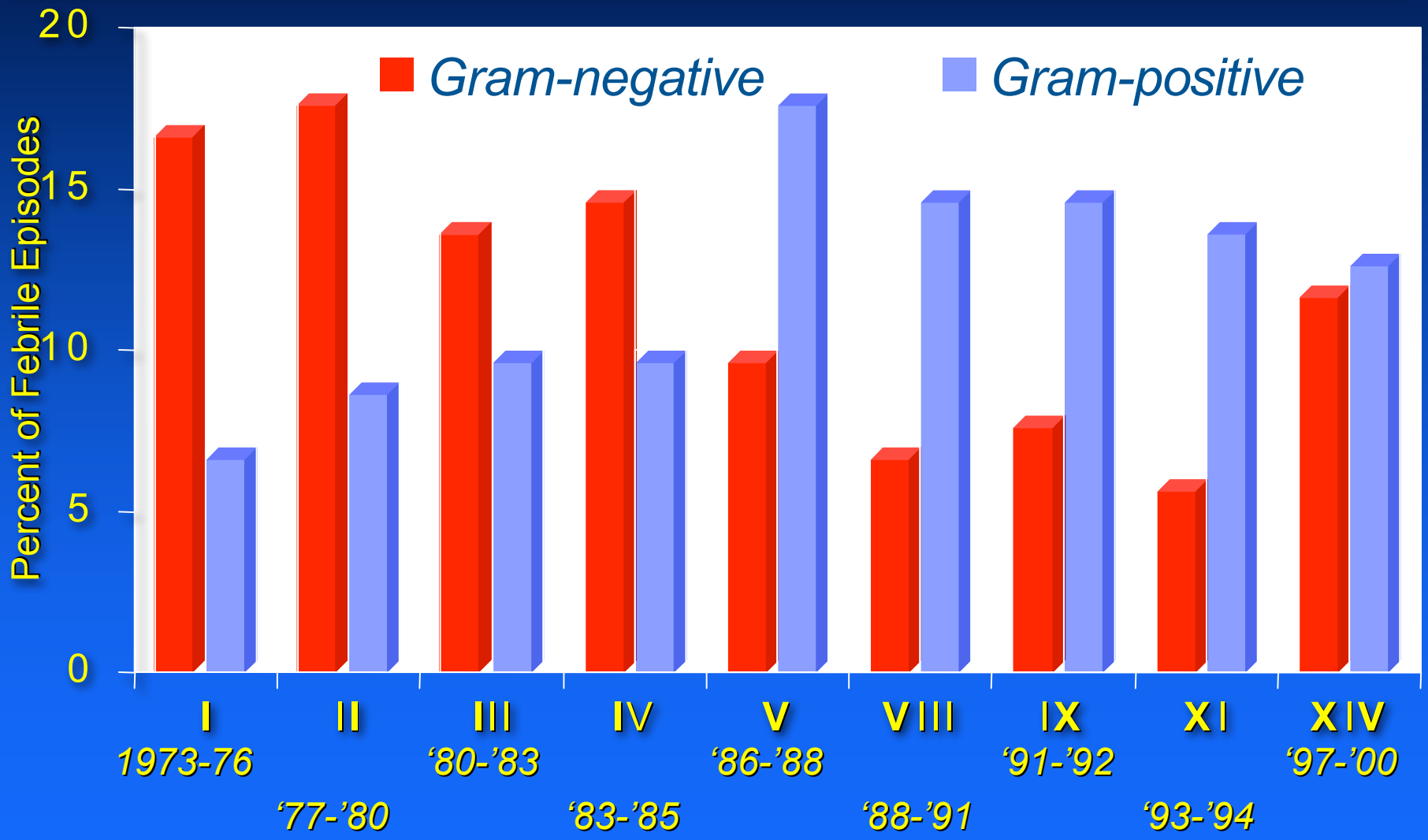
Single-Organisms Bacteraemias
EORTC-IATG Trials



Calandra 2002

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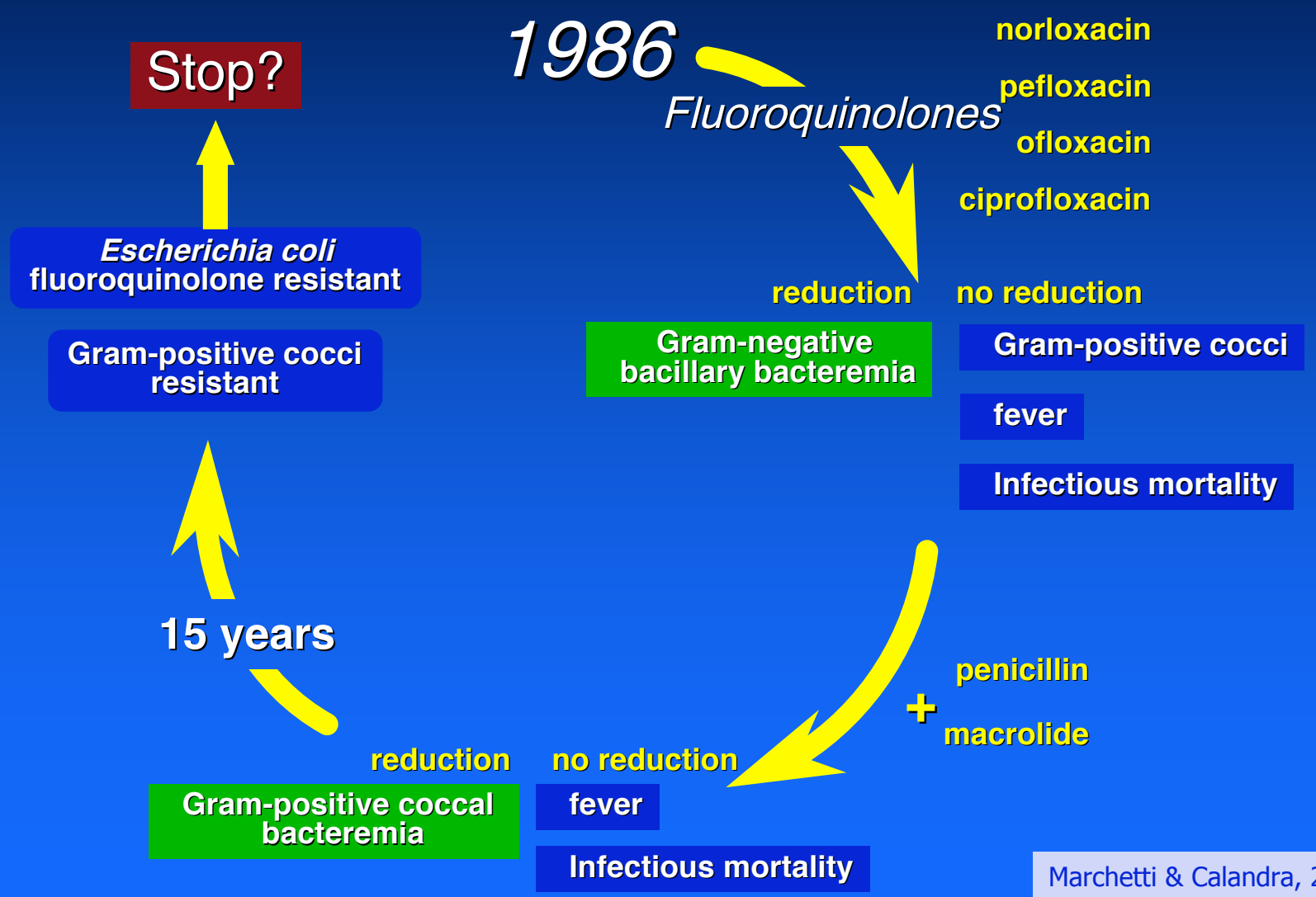
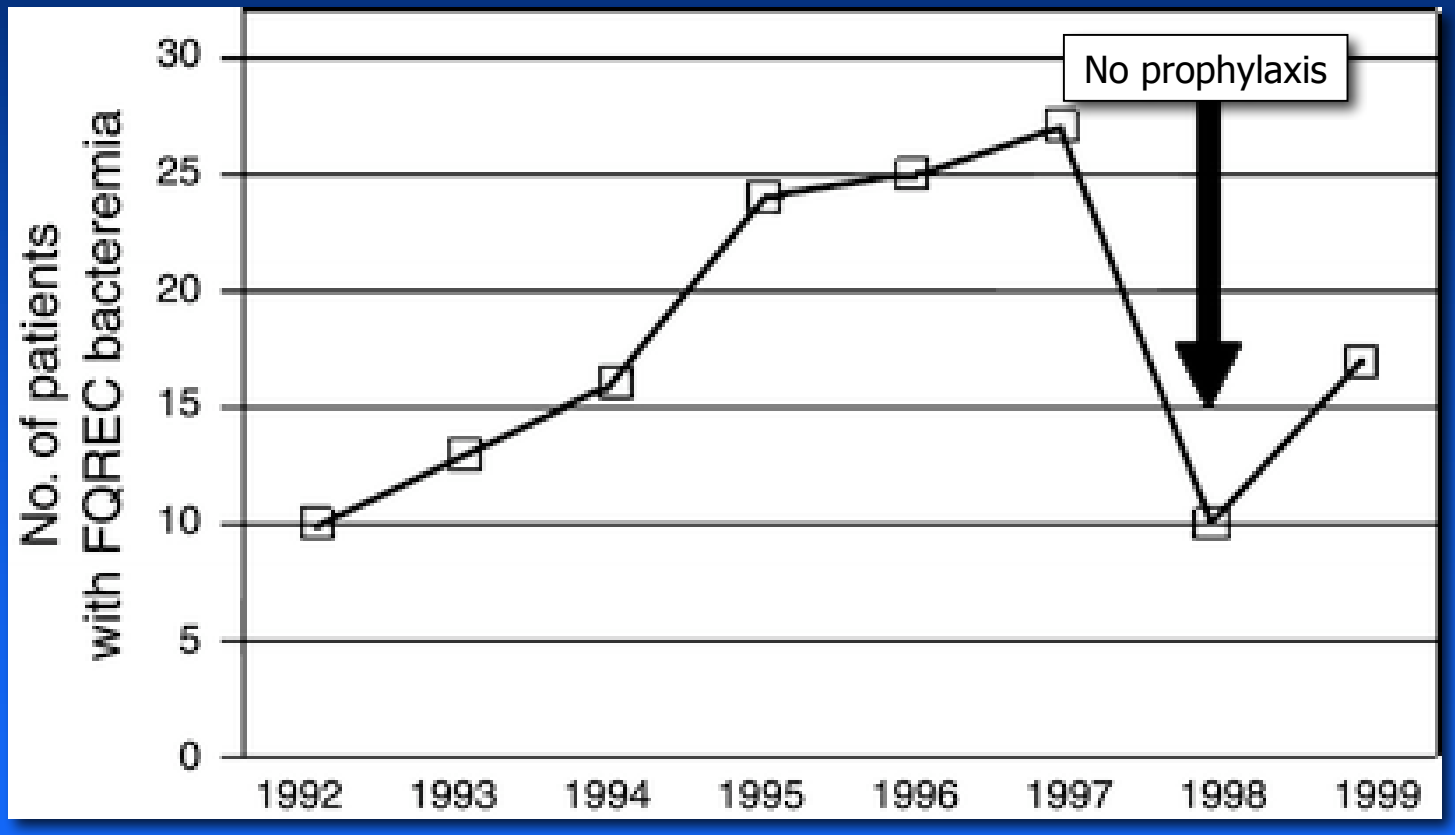
The life cycle of fluoroquinolone prophylaxis



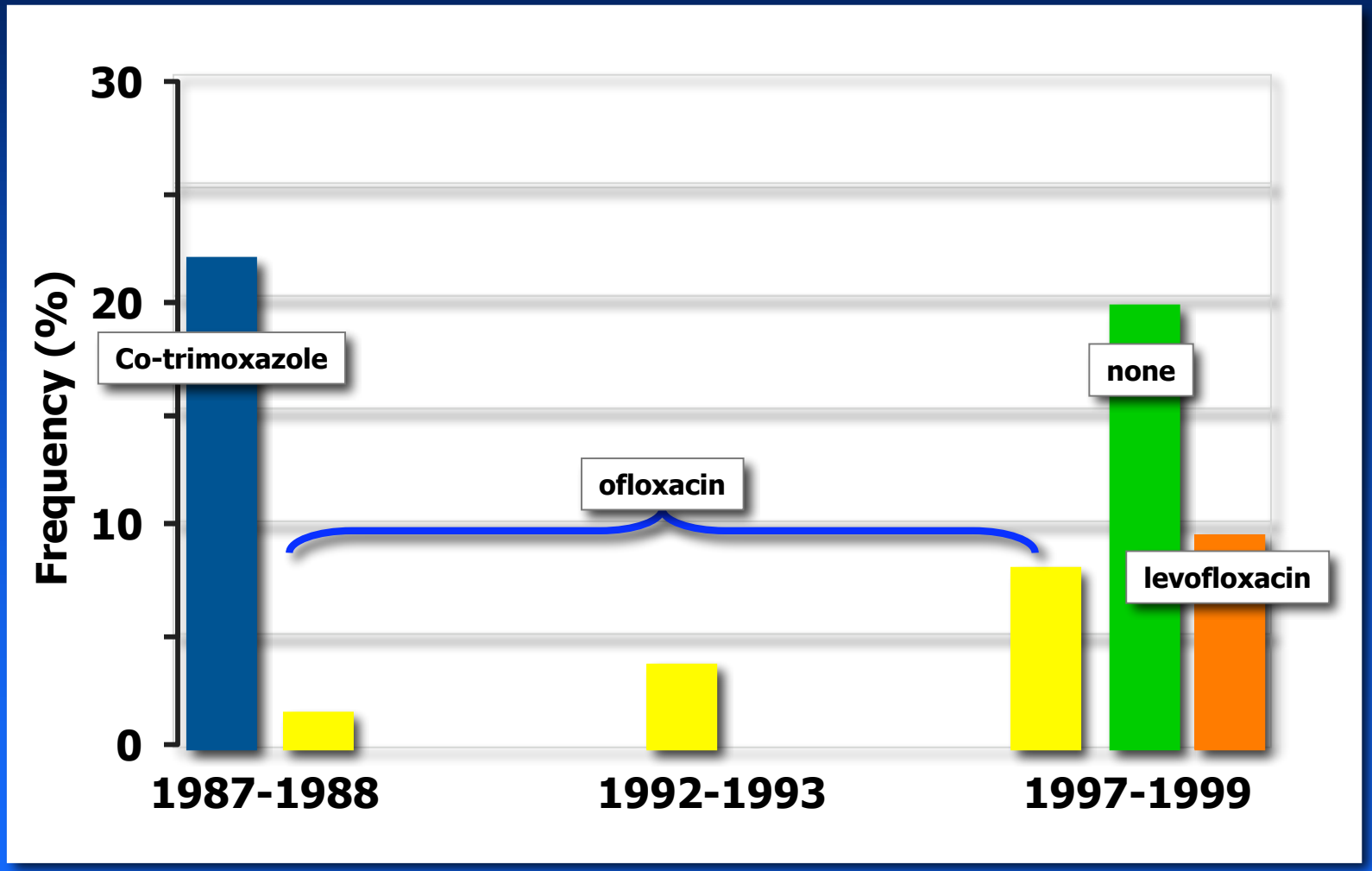
Marchetti & Calandra, 2002

Incidence of ofloxacin resistant E.coli in Ulm



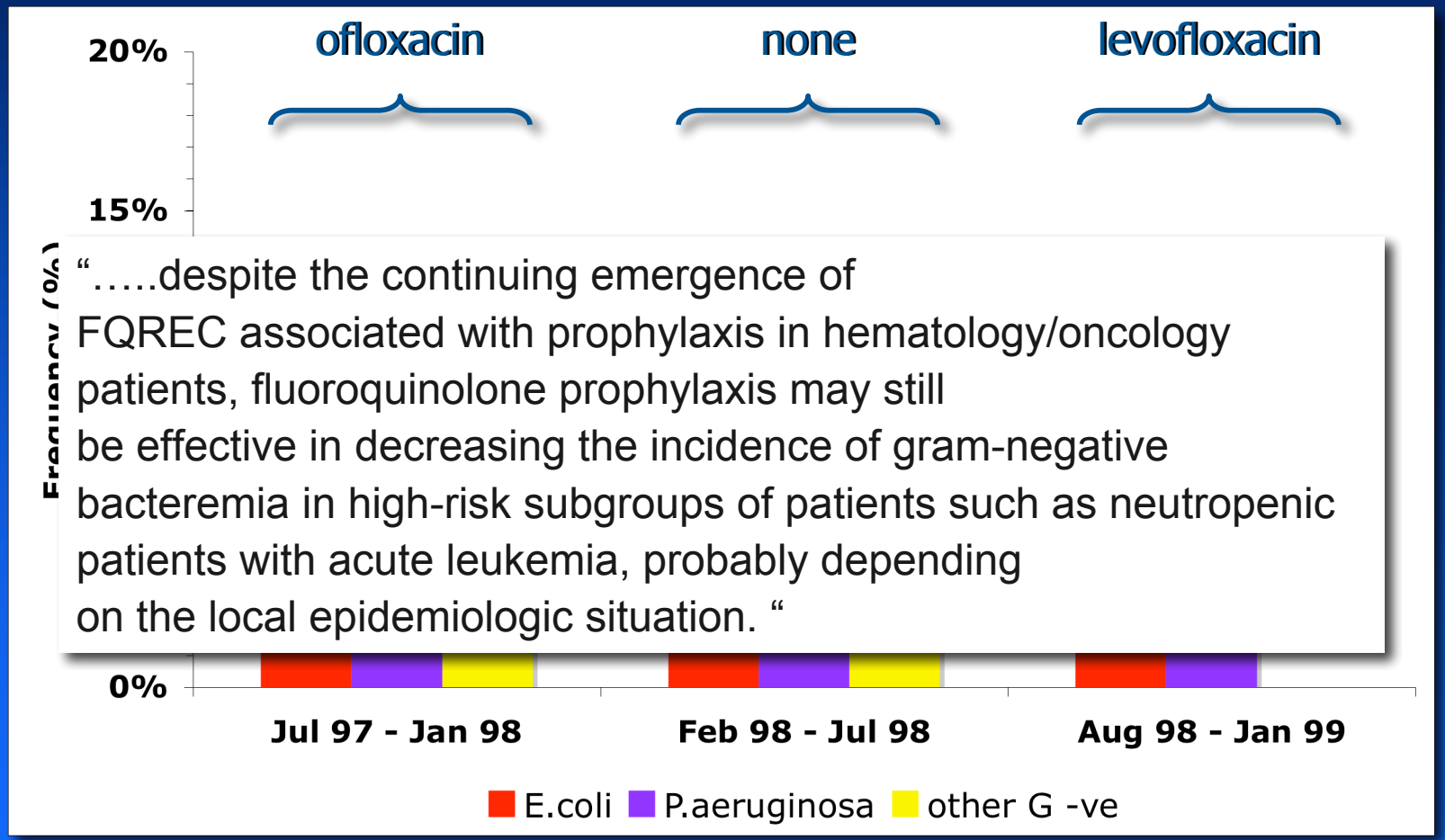
Kern et al 2005 Eur J Clin Microbiol Infect Dis 24;111

Bacteraemia due to Gram-negative bacilli



Kern et al 2005 Eur J Clin Microbiol Infect Dis 24;111

Impact of prophylaxis

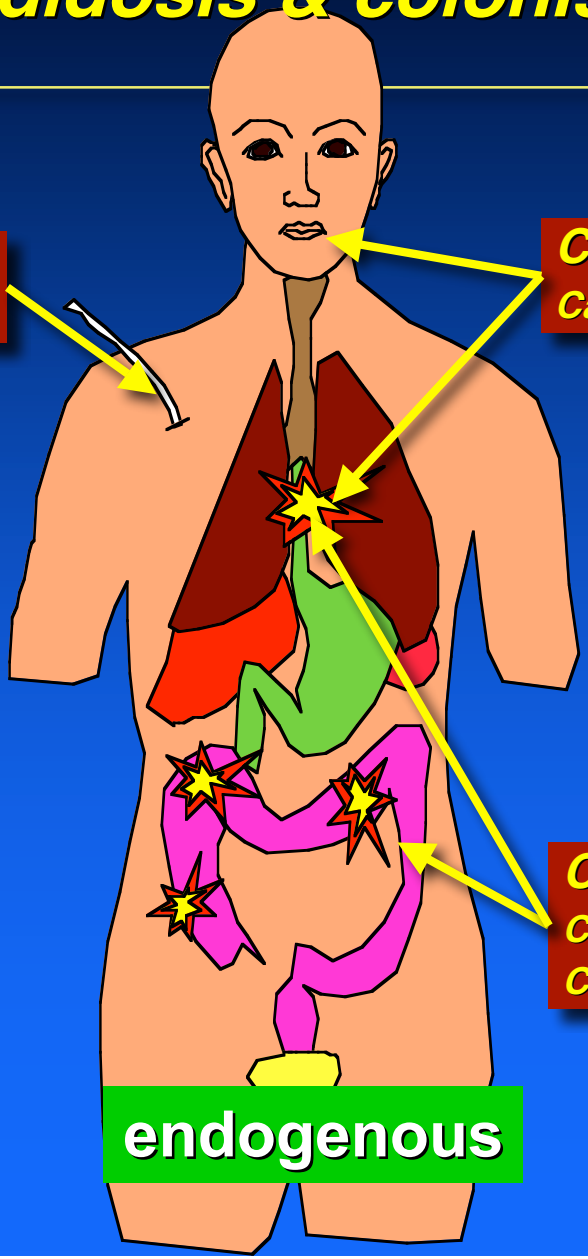


"…..despite the continuing emergence of FQREC associated with prophylaxis in hematology/oncology patients, fluoroquinolone prophylaxis may still be effective in decreasing the incidence of gram-negative bacteremia in high-risk subgroups of patients such as neutropenic patients with acute leukemia, probably depending on the local epidemiologic situation. "

Kern et al 2005 Eur J Clin Microbiol Infect Dis 24;111

Antifungal prophylaxis

Candidosis & colonisation



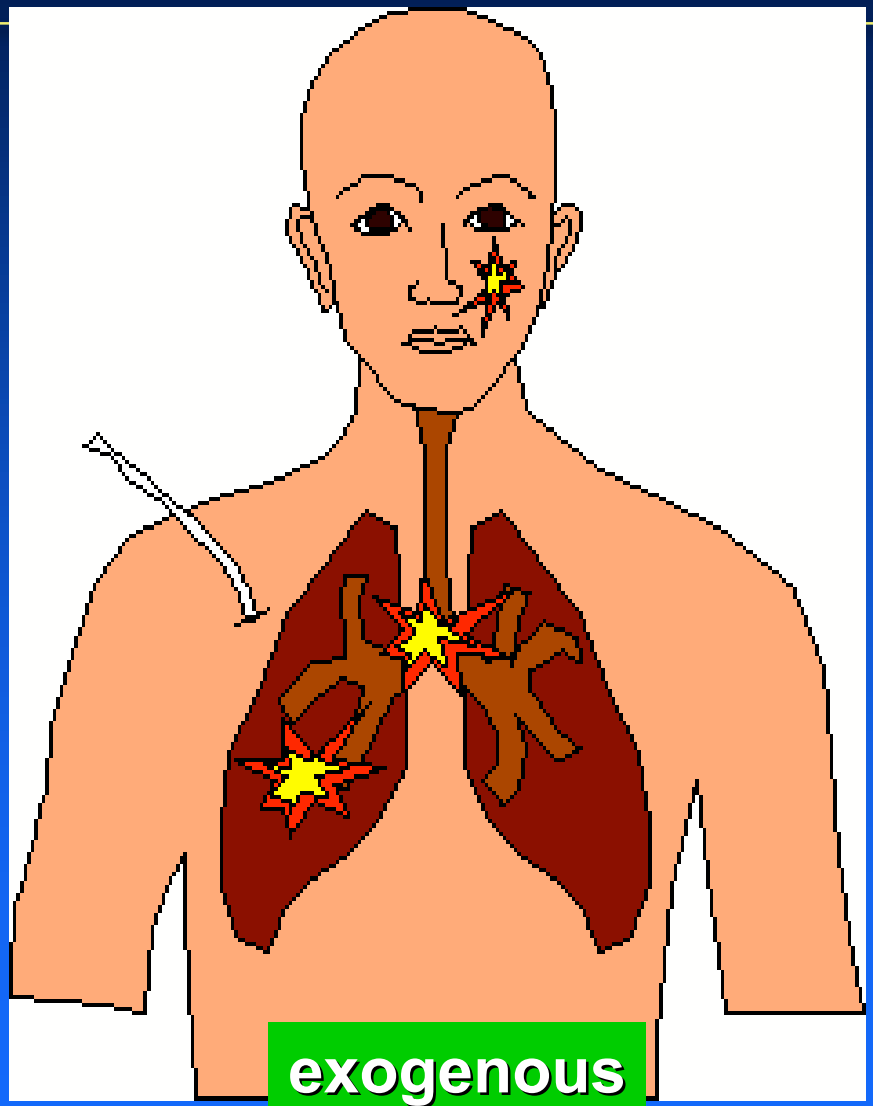
Candida parapsilosis
Candida albicans

Candida albicans
Candida tropicalis

Candida albicans
Candida glabrata
Candida krusei

endogenous

Aspergillosis



exogenous

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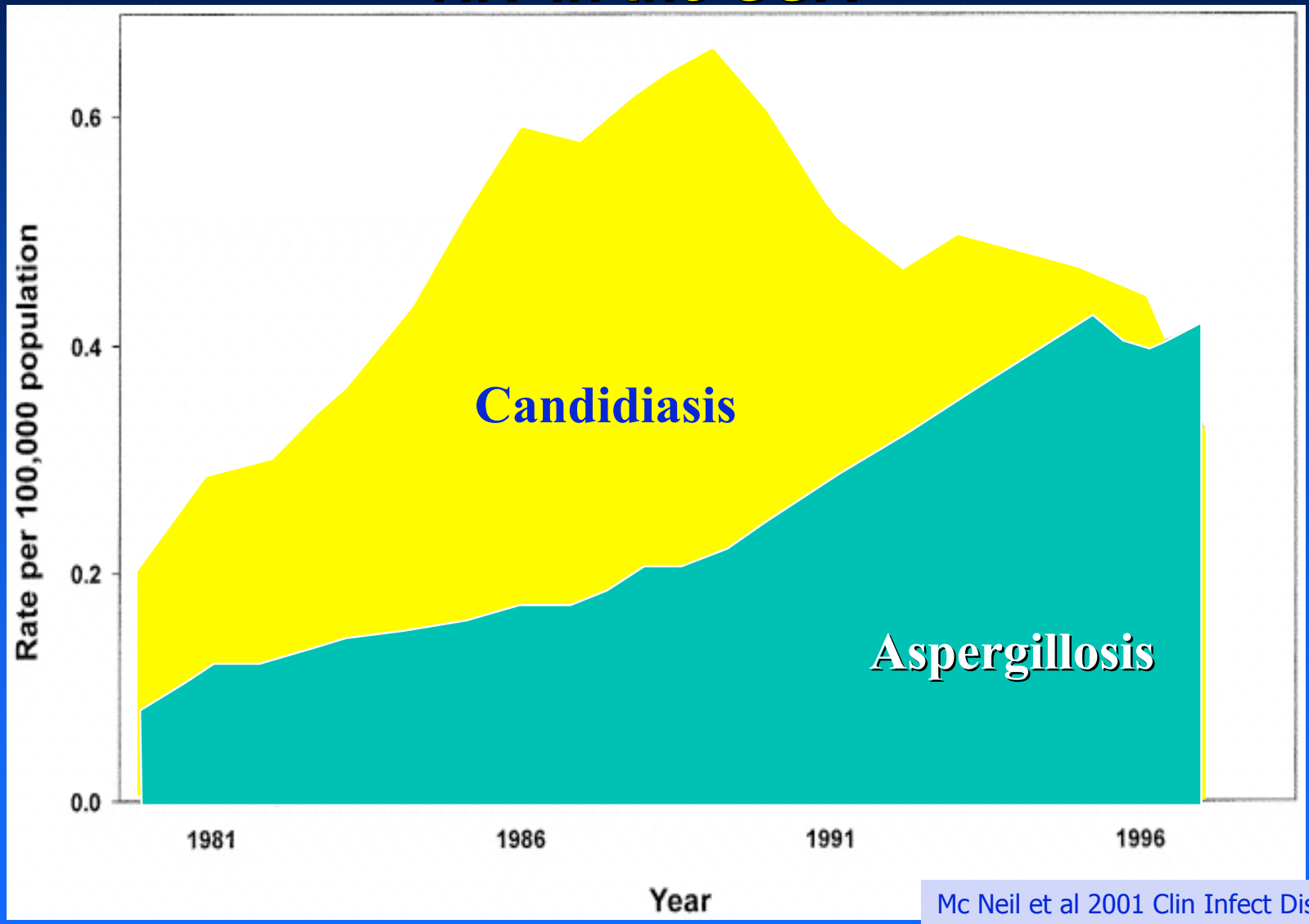
Invasive aspergillosis and underlying disease

Condition	range (%)
Chronic granulomatous disease	25-40
Lung ± heart transplant	19-26
Liver transplant	1.5-10
Heart & renal transplant	0.5-10
AIDS	0-12
SCID	3.5
Burns	1-7
SLE	1
Acute leukaemia	5-24
Allogeneic HSCT	4-9
Autologous HSCT (no growth factors)	0.5-6
Autologous HSCT (with growth factors)	<1

Denning Clin Infect Dis 2001 26 pp781-805

Incidence of fatal fungal infections amongst patients other than those with HIV in the USA



Mc Neil et al 2001 Clin Infect Dis 33;641

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Question

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

- **Yes**
- **No**
- **Don’t know**

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Question

Which regimen do you use for antifungal prophylaxis to prevent infections in patients with acute leukemia?

- **fluconazole**
- **itraconazole**
- **posaconazole**
- **none of the above**
- **don’t know**

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Question

Which regimen do you use for antifungal prophylaxis to prevent infections in HSCT recipients?

- fluconazole
- itraconazole
- posaconazole
- none of the above
- don’t know

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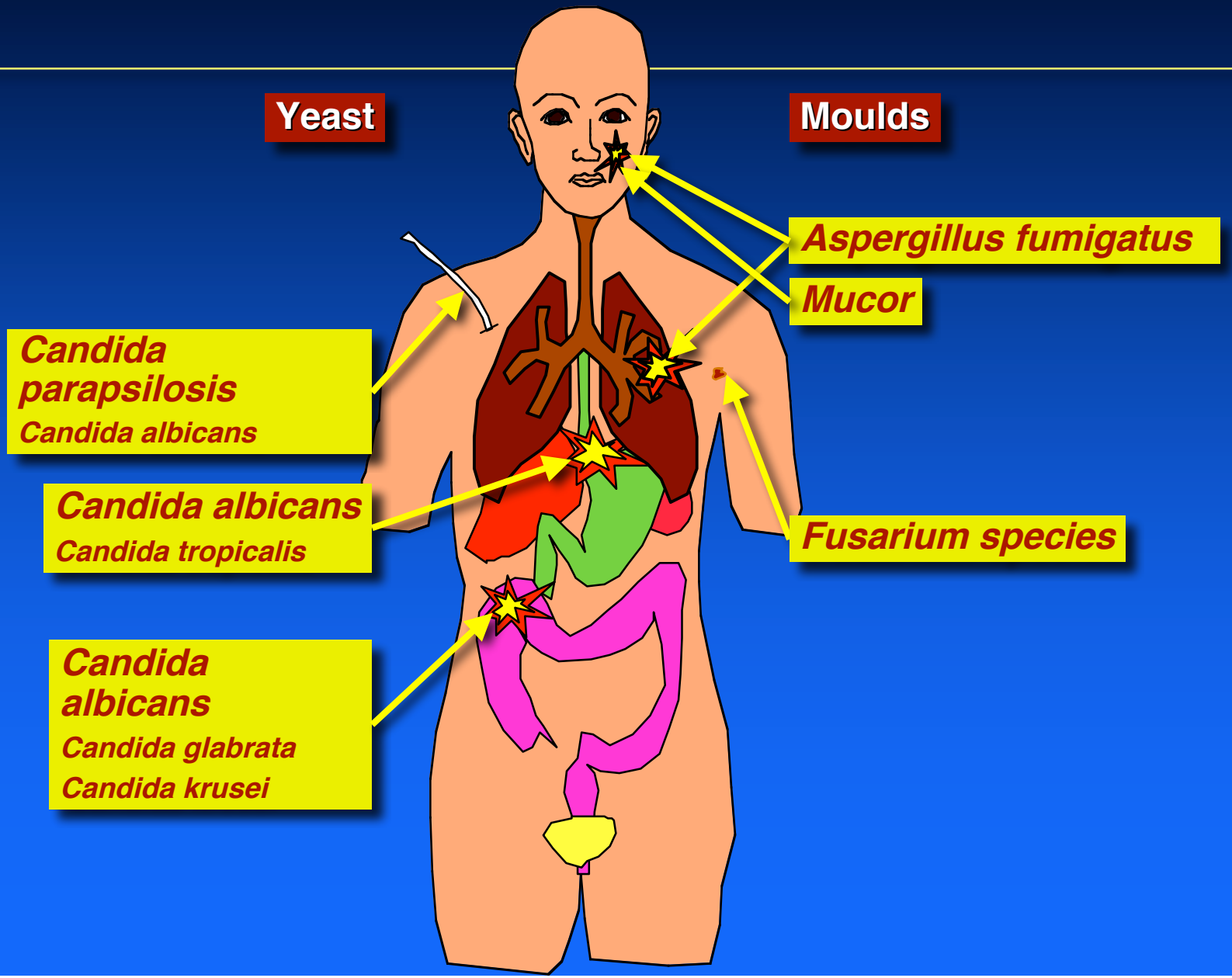
Sites of infection



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Prophylaxis - candidosis

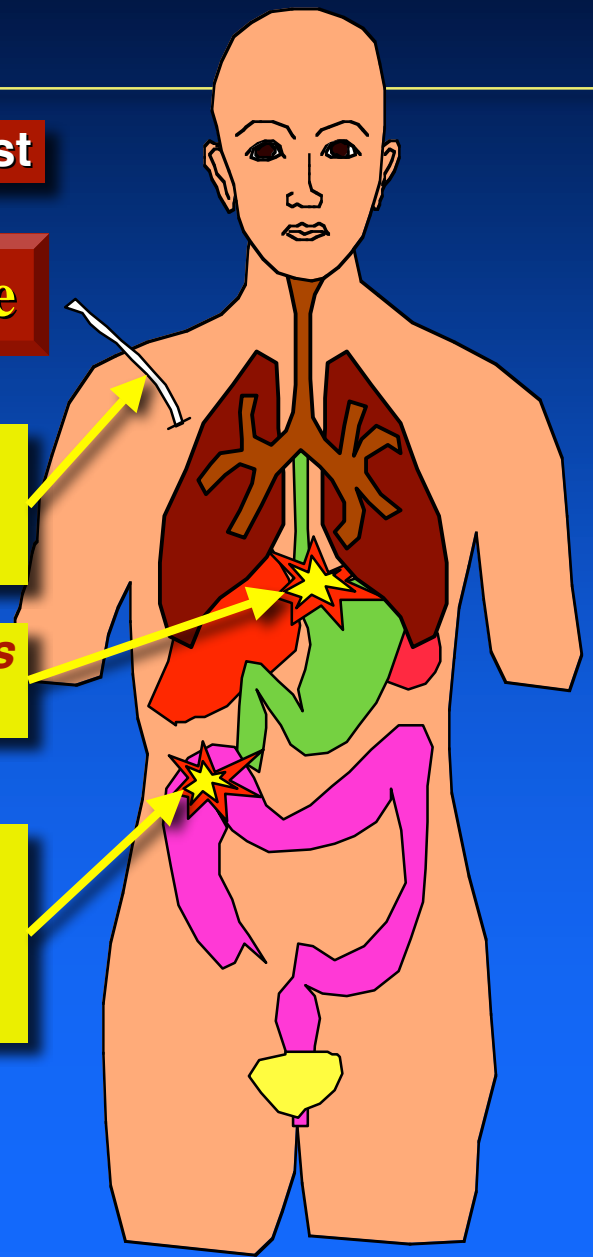
Yeast

Fluconazole

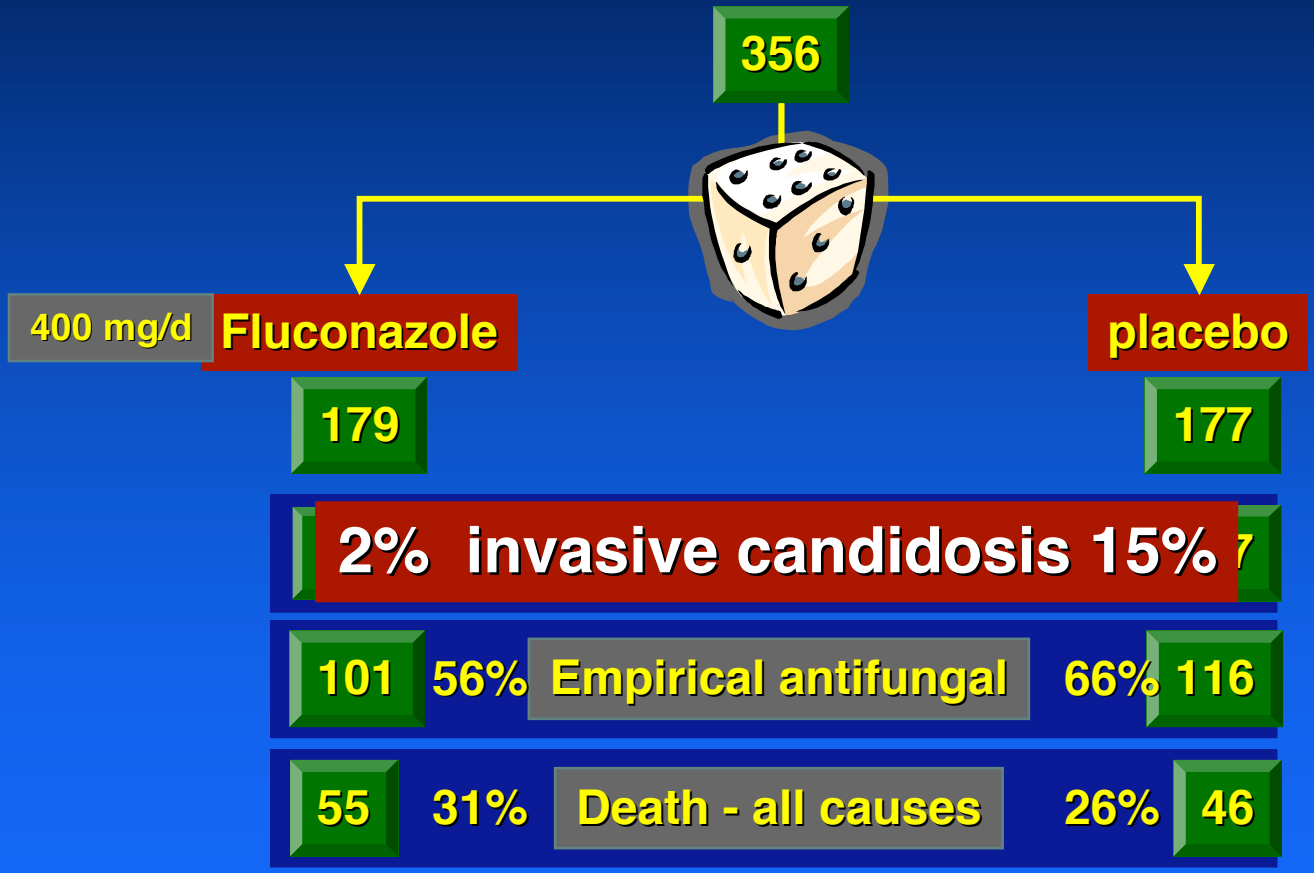
Candida parapsilosis
Candida albicans

Candida albicans
Candida tropicalis

Candida albicans
Candida glabrata
Candida krusei

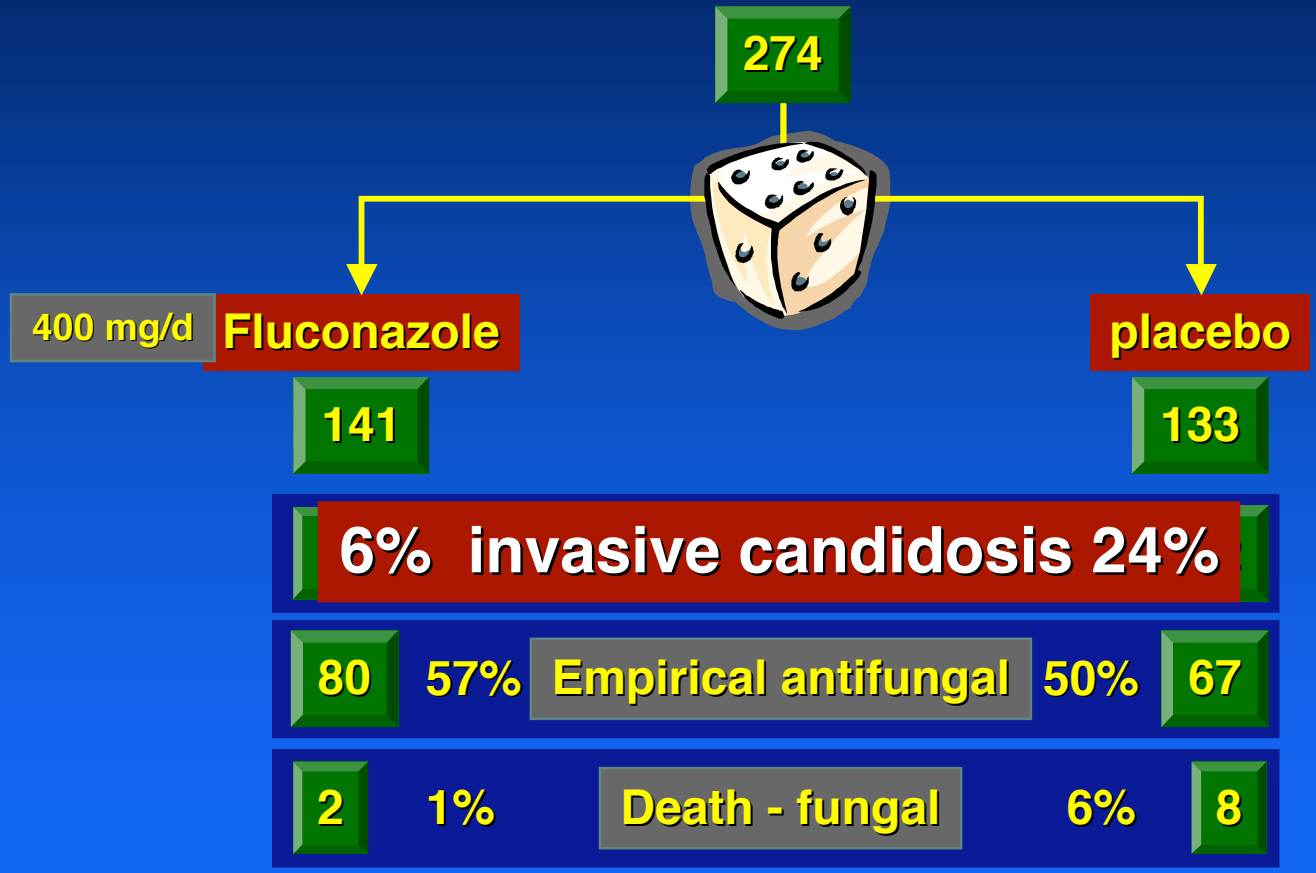


Fluconazole for HSC transplantation



Goodman et al. N Eng J Med. 1992 326 845

Fluconazole - neutropenic patients



Rotstein et al 1999 Clin Infect Dis 28 331

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Prophylaxis - candidosis

Yeast

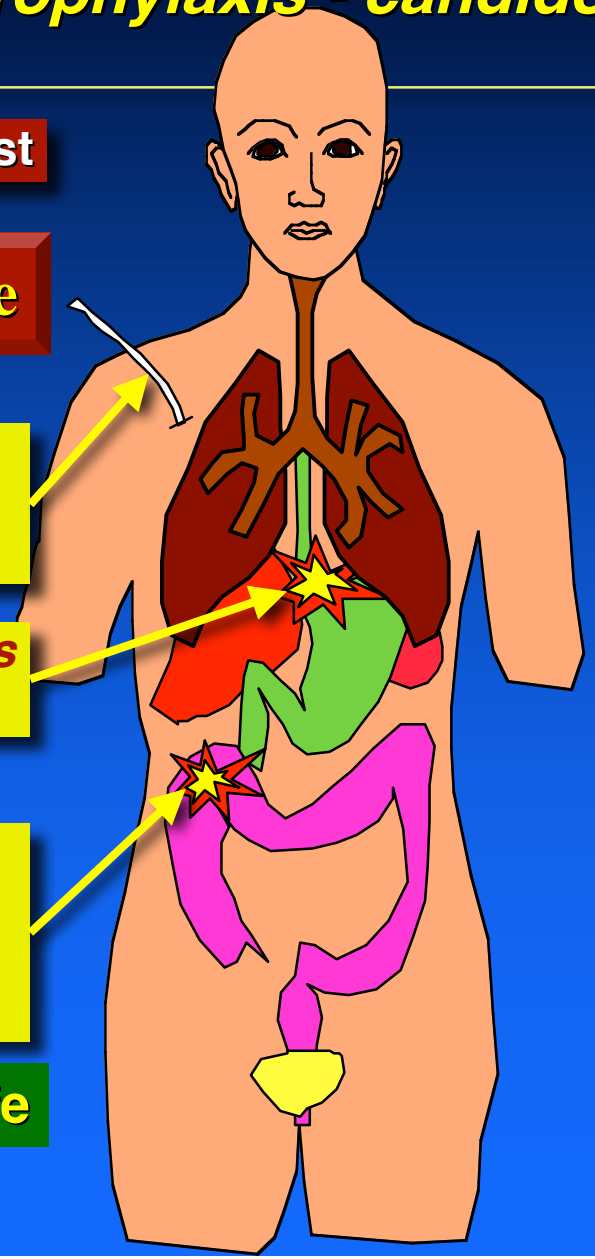
Fluconazole

Candida parapsilosis
Candida albicans

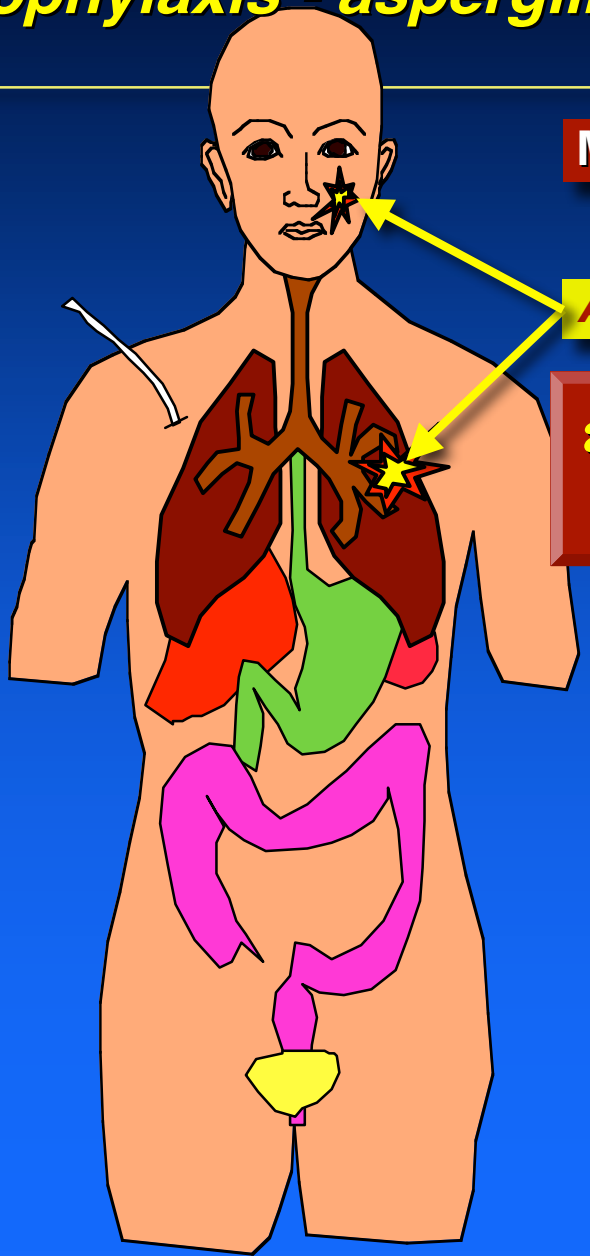
Candida albicans
Candida tropicalis

Candida albicans
Candida glabrata
Candida krusei

Effective & safe



Prophylaxis - aspergillosis

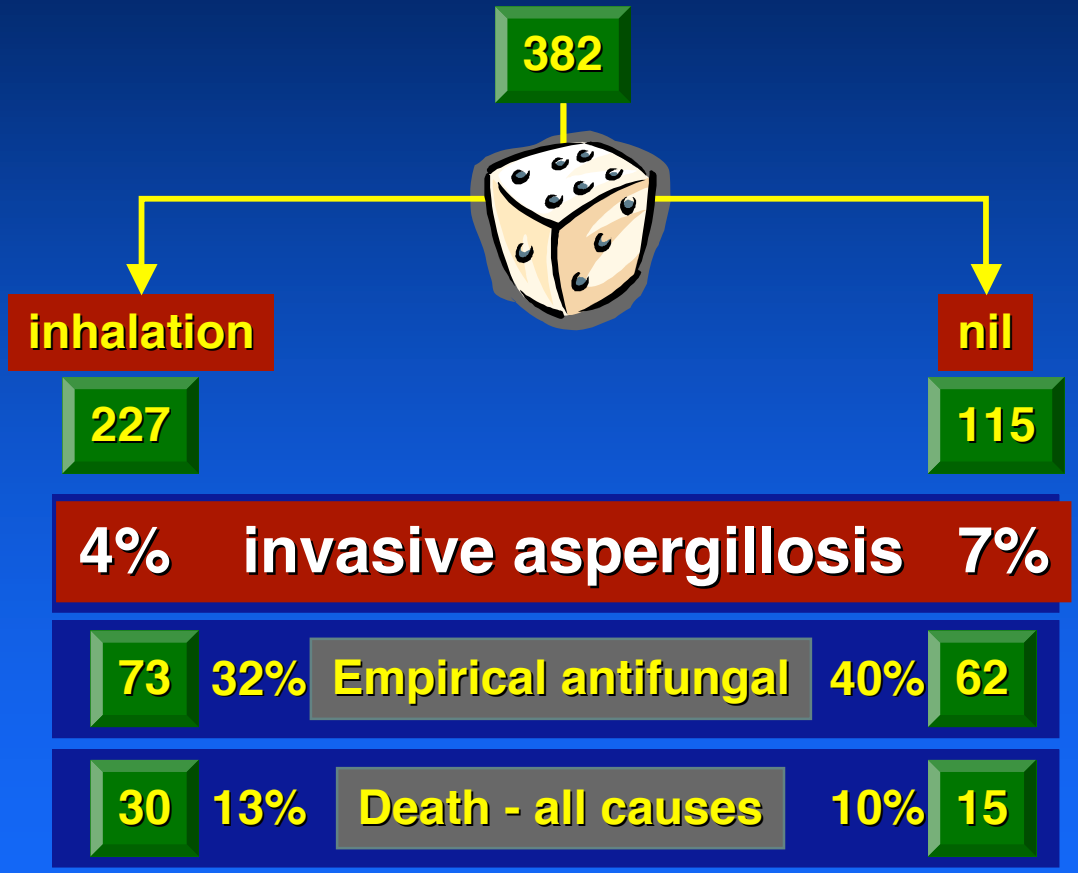


Moulds

Aspergillus fumigatus

amphotericin B inhalation

Amphotericin B inhalation study of prophylaxis



Schwartz et al. Blood. 93, 1999 pp. 3654-3661

Abstracts
47th Interscience Conference on
Antimicrobial Agents and Chemotherapy

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Aerosolised liposomal amphotericin B

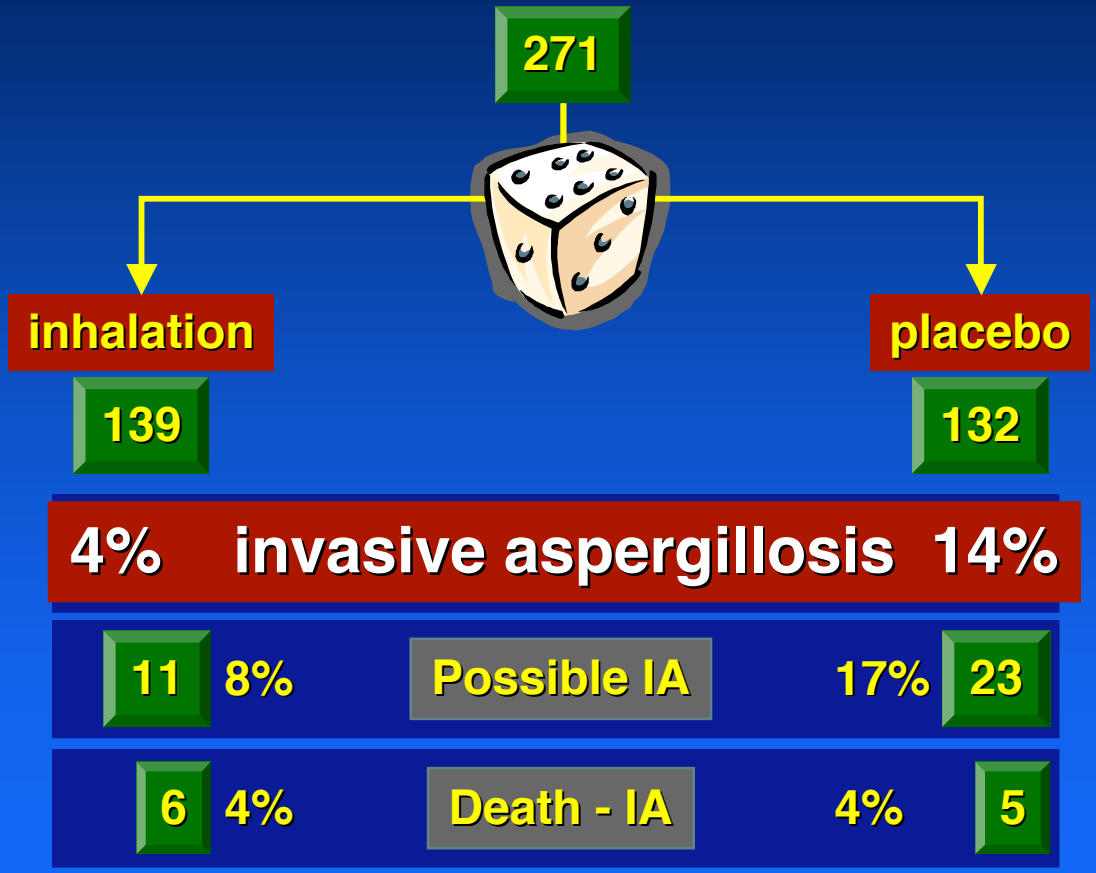
AMERICAN SOCIETY FOR MICROBIOLOGY

M-1308c
Aerosolised Liposomal AmphoB (lipoAmB) To Prevent Invasive Aspergillosis (IA) During Prolonged Neutropenia. Randomized Placebo Controlled Trial.

B. J. RIJNDERS, L. SLOBBE, For The Prof Study Investigators;
Erasmus MC, Rotterdam, The Netherlands.

Background: Inhalation of aspergillus conidia is the first step in the pathogenesis of IA. Inhalation of AmB may prevent IA without the toxicity of I.V. AmB. Inhalation of lipoAmB (Ambisome®) may be better tolerated as, in contrast to AmB deoxycholate, it does not interfere with lung surfactant. Methods: RCT in 3 hemato units at Erasmus MC. Pts with therapy induced expected PMN<300/mm3 for ≥10d were randomized to 12mg lipoAmB / placebo inhalation with Adaptive Aerosol Delivery system (30 min/d 2d/wk) until PMN>300/mm3. Pr. Endp: EORTCMSG defin. of proven/probable IA. Sec. Endp: (1) Modif. EORTCMSG prov/prob IA (nodule with halo is also prob IA) (2) IA-related mortality. FU was until PMN>300/mm3 +28d. ITT (all pts with ≥1 inhalation) and OT analysis (neutropenic episodes during which inhalations were never discontinued) was done. Time to IA was compared with log rank test. Results: 271 pts (406 neutropenic episodes) were randomized. 18/132 with placebo had EORTC-MSG prov/prob IA vs 6/139 with lipoAmB (ITT p=.003 / OT 13/97 vs 2/91 p=.004). 11 had modif. EORTC-MSG prov/prob IA with lipoAmB vs 23 with placebo (ITT p=.007 / OT 3/91 vs 17/97 p=.001). IA-related mortality was 6 (placebo) vs 5 (lipoAmB) but study was not powered for mortality (p=.8). Discontinuation of lipoAmB was as frequent as placebo (p=.2). Conclusion: LipoAmB inhalation dramatically reduced incidence of IA from 14 to 4

Aerosolised liposomal inhalation study of prophylaxis



Rijnders et al. ICAAC 2006

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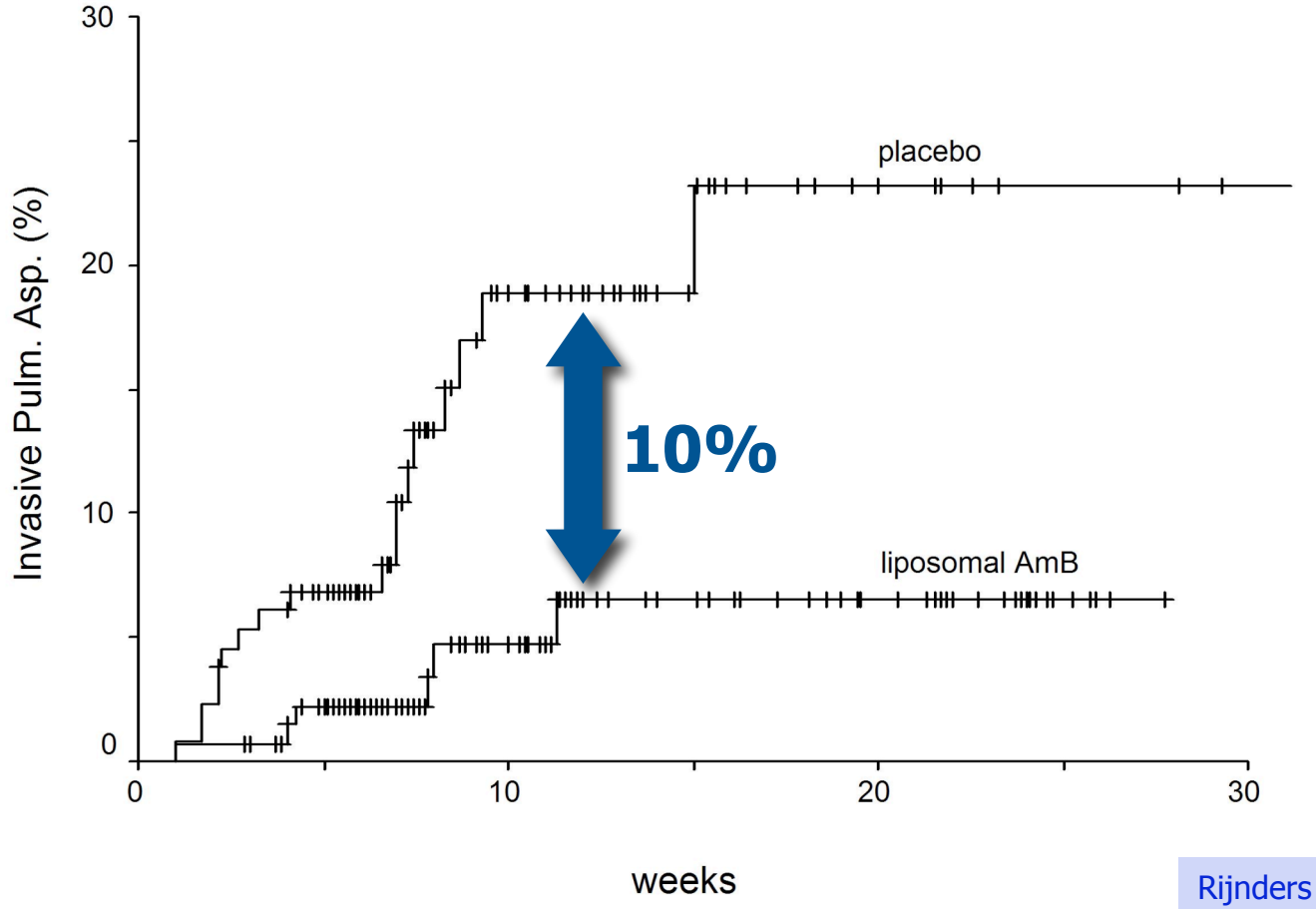
Abstracts
47th Interscience Conference on
Antimicrobial Agents and Chemotherapy

Aerosolised liposomal amphotericin B

AMERICAN SOCIETY FOR MICROBIOLOGY

M-1308c

Fig. Kaplan-Meier curves of the time to Proven/Probable Invasive Pulmonary Aspergillosis According to the EORTC-MSG definitions. Intention to treat analysis. P=0.003.



Rijnders et al. ICAAC 2006

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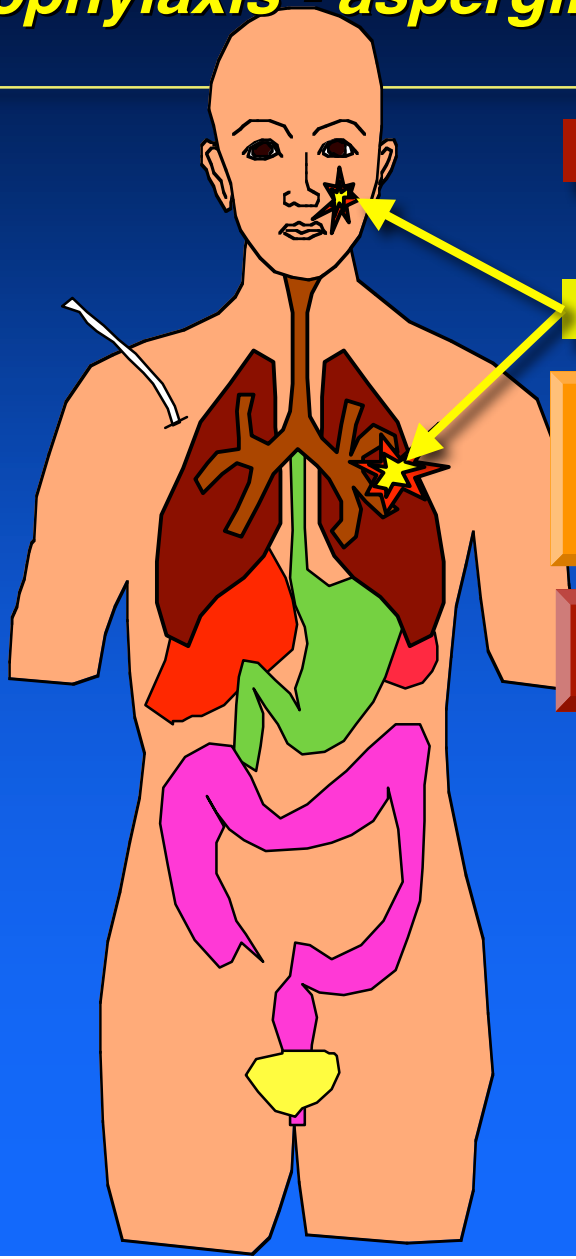
Prophylaxis - aspergillosis



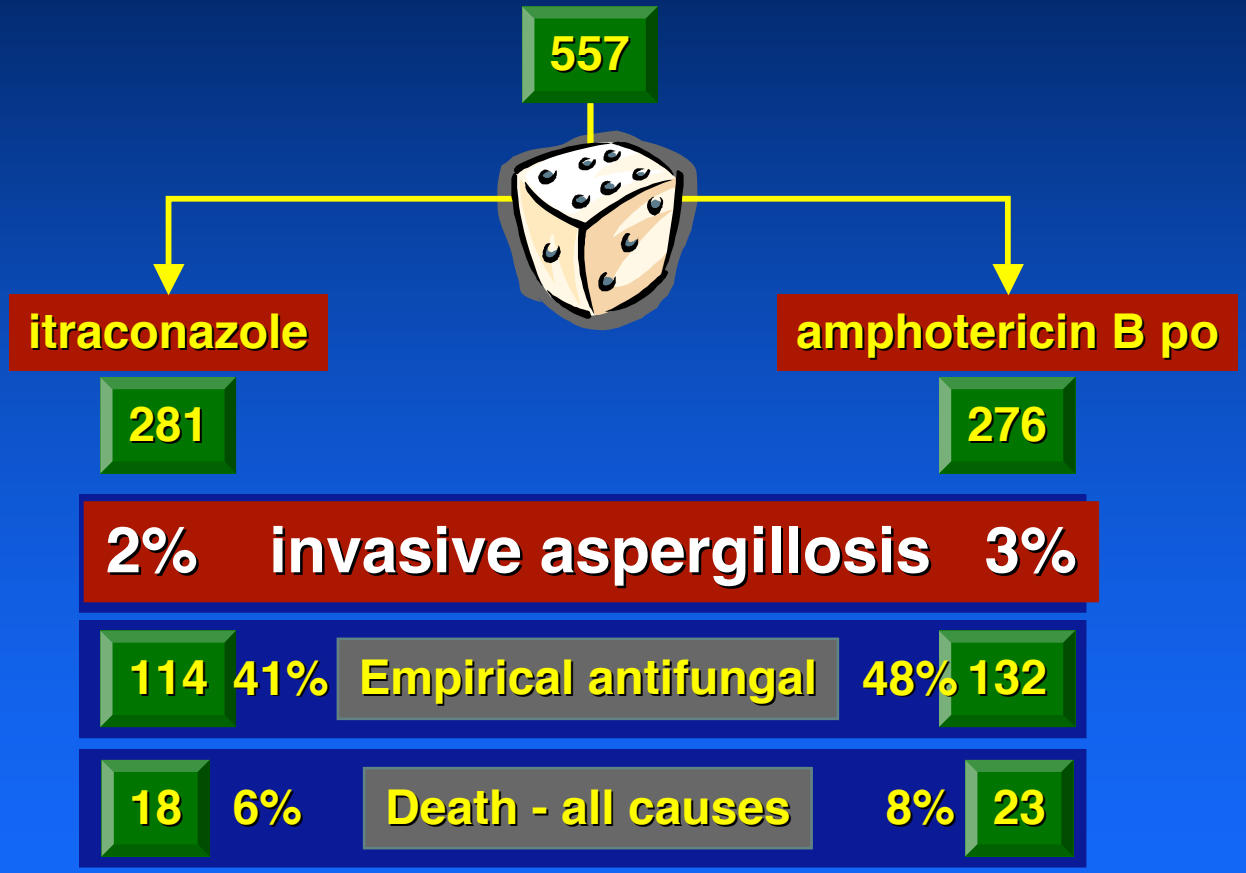
Moulds

Aspergillus fumigatus

amphotericin B inhalation

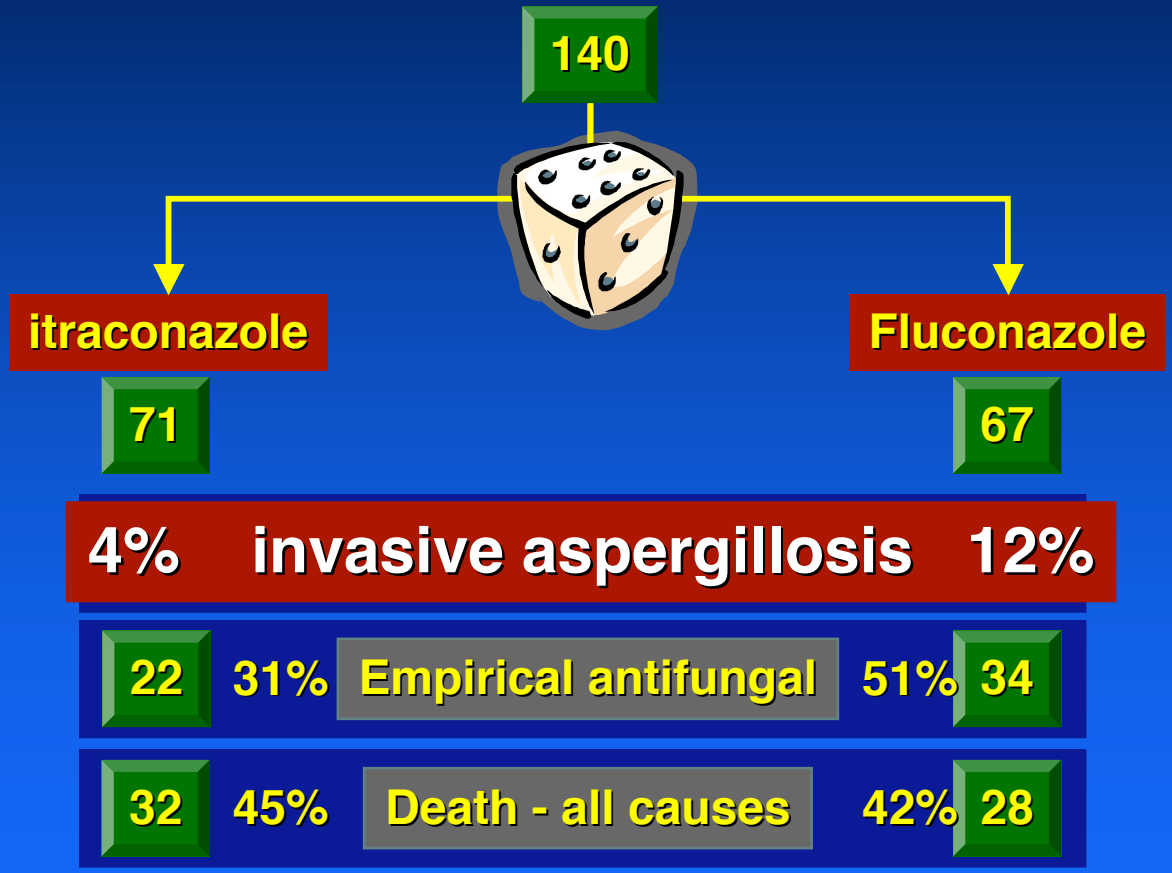
itraconazole

Itraconazole study of prophylaxis



Harrassou et al. Antimicrob Ag Chemother. 44, 2000 1887

Itraconazole study of prophylaxis



Winston et al. Ann Intern Med 2003. 138 705

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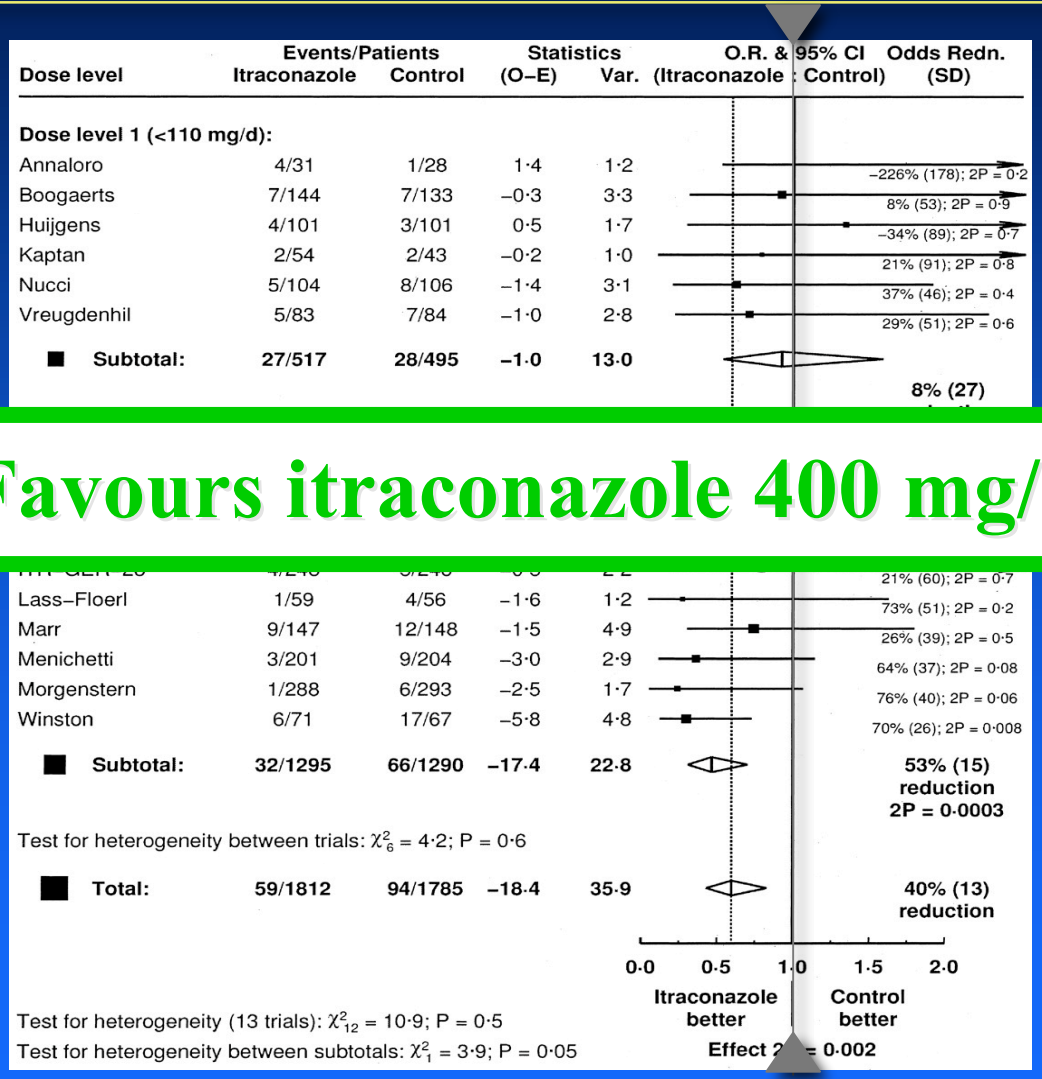
Itraconazole dose response:
proven invasive fungal disease



Dose level	Events/Patients Itraconazole	Control	Statistics (O–E)	Var.	O.R. & 95% CI (Itraconazole : Control)	Odds Redn. (SD)
Dose level 1 (<110 mg/d):						
Annaloro	4/31	1/28	1·4	1·2		–226% (178); 2P = 0·2
Boogaerts	7/144	7/133	–0·3	3·3		8% (53); 2P = 0·9
Huijgens	4/101	3/101	0·5	1·7		–34% (89); 2P = 0·7
Kaptan	2/54	2/43	–0·2	1·0		21% (91); 2P = 0·8
Nucci	5/104	8/106	–1·4	3·1		37% (46); 2P = 0·4
Vreugdenhil	5/83	7/84	–1·0	2·8		29% (51); 2P = 0·6
Subtotal:	**27/517**	**28/495**	**–1·0**	**13·0**		**8% (27)**
Lass–Floerl	1/59	4/56	–1·6	1·2		73% (51); 2P = 0·2
Marr	9/147	12/148	–1·5	4·9		26% (39); 2P = 0·5
Menichetti	3/201	9/204	–3·0	2·9		64% (37); 2P = 0·08
Morgenstern	1/288	6/293	–2·5	1·7		76% (40); 2P = 0·06
Winston	6/71	17/67	–5·8	4·8		70% (26); 2P = 0·008
Subtotal:	**32/1295**	**66/1290**	**–17·4**	**22·8**		**53% (15) reduction 2P = 0·0003**
Total:	**59/1812**	**94/1785**	**–18·4**	**35·9**		**40% (13) reduction**

Test for heterogeneity between trials: $\chi^2_6 = 4{\cdot}2$; P = 0·6

Test for heterogeneity (13 trials): $\chi^2_{12} = 10{\cdot}9$; P = 0·5

Test for heterogeneity between subtotals: $\chi^2_1 = 3{\cdot}9$; P = 0·05

0·0 0·5 1·0 1·5 2·0

Itraconazole better | Control better

Effect 2 = 0·002

Favours itraconazole 400 mg/d

Glasmacher, A. et al. J Clin Oncol; 21:4615-4626 2003

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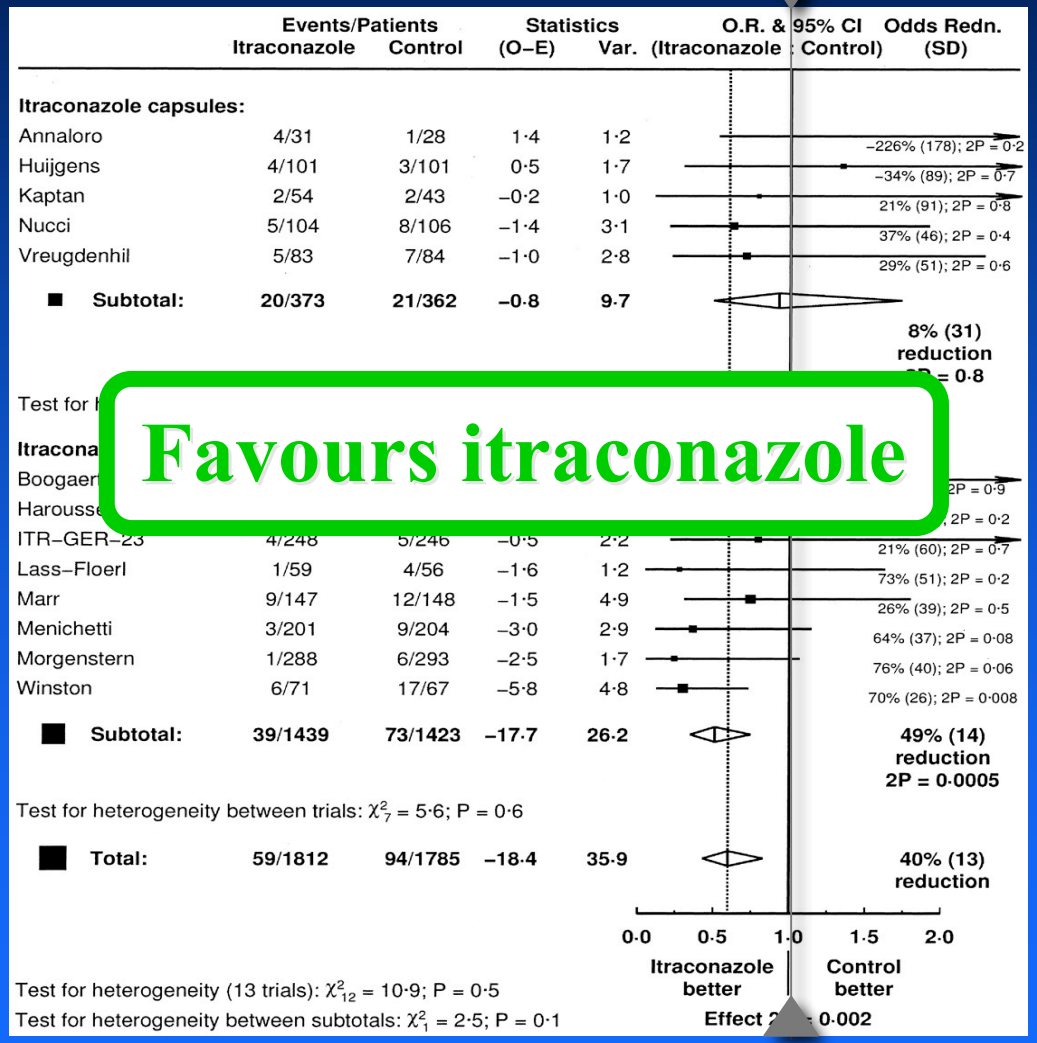
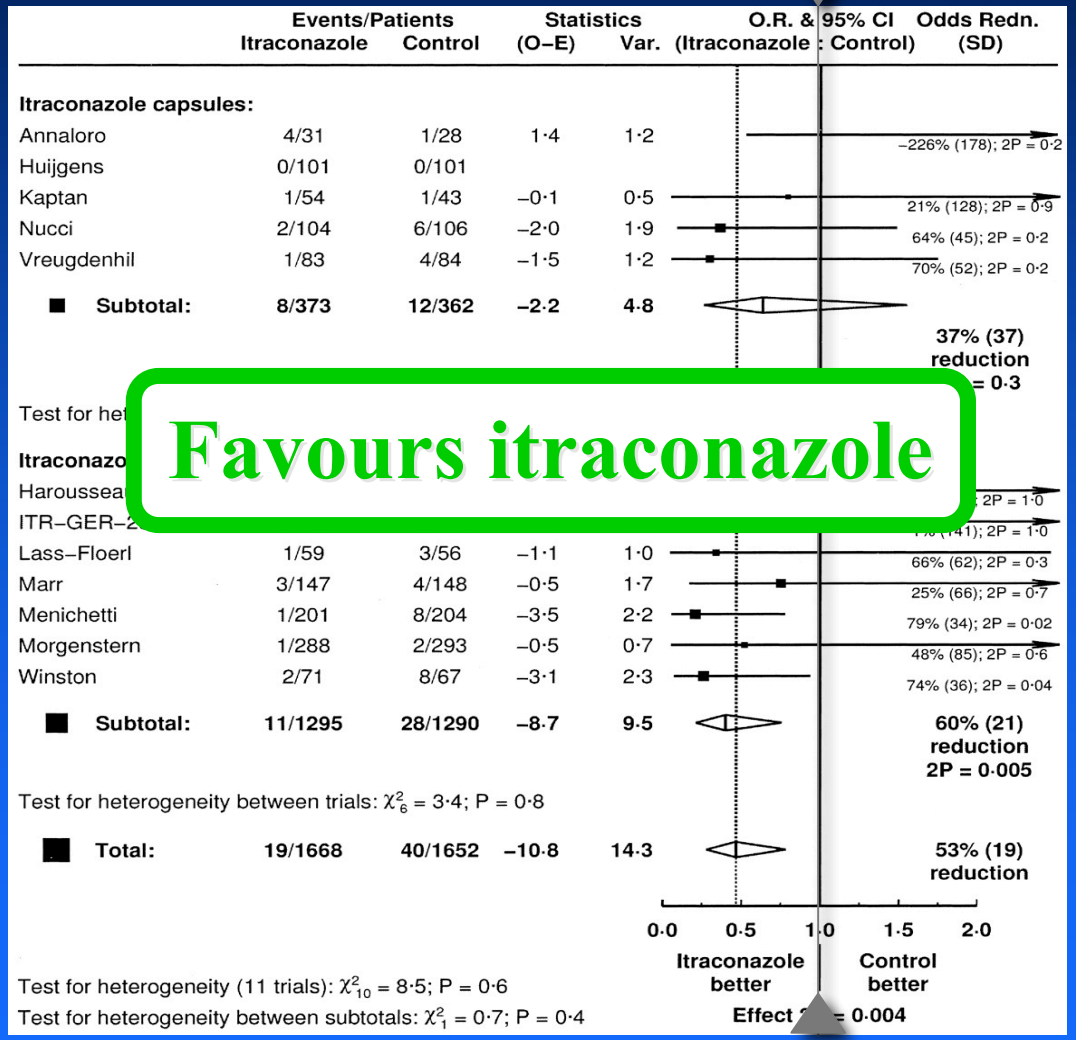
Itraconazole solution:
proven invasive fungal disease



Glasmacher, A. et al. J Clin Oncol; 21:4615-4626 2003

UMC St Radboud

Itraconazole solution:
proven invasive candidosis



Glasmacher, A. et al. J Clin Oncol; 21:4615-4626 2003

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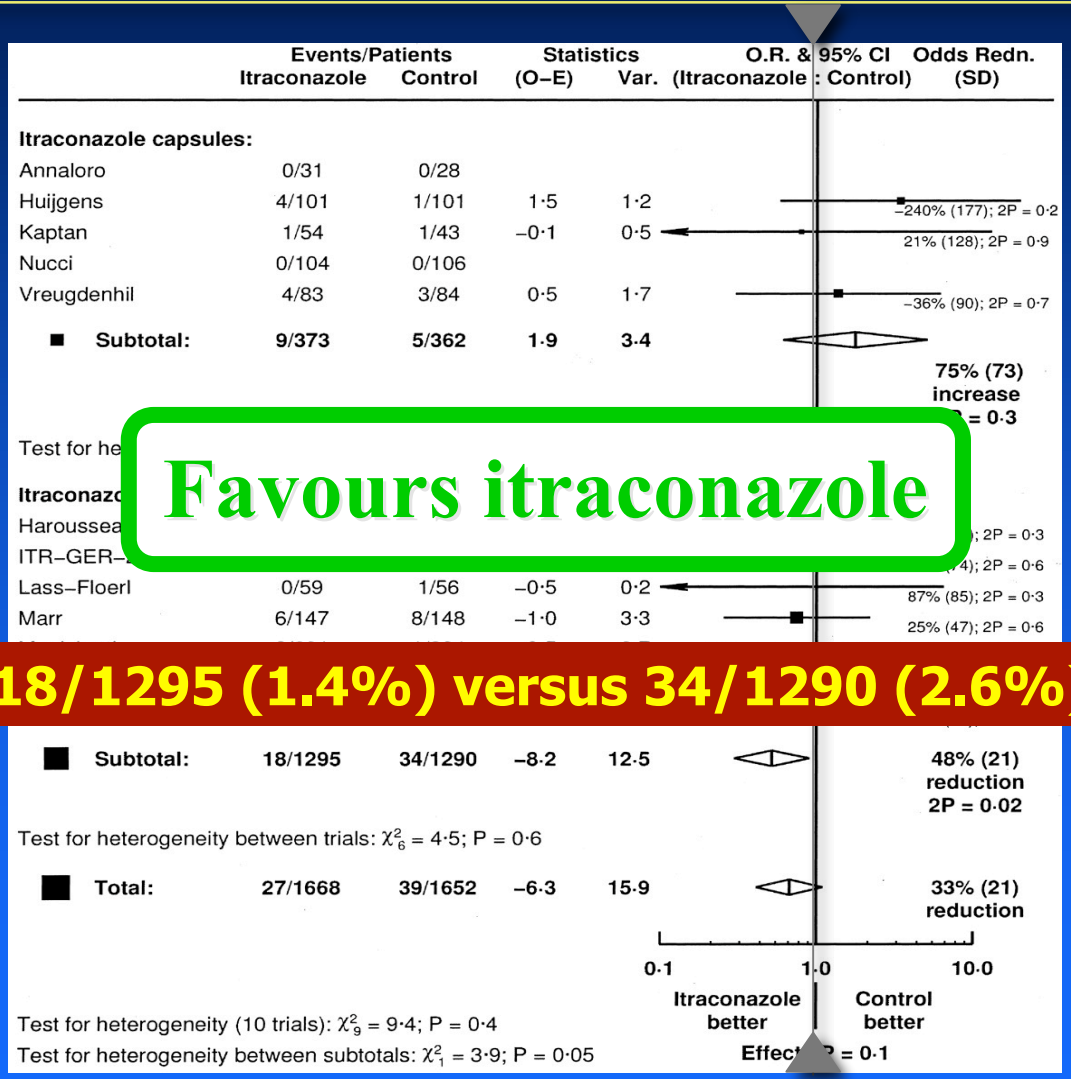
Itraconazole solution:
proven invasive aspergillosis



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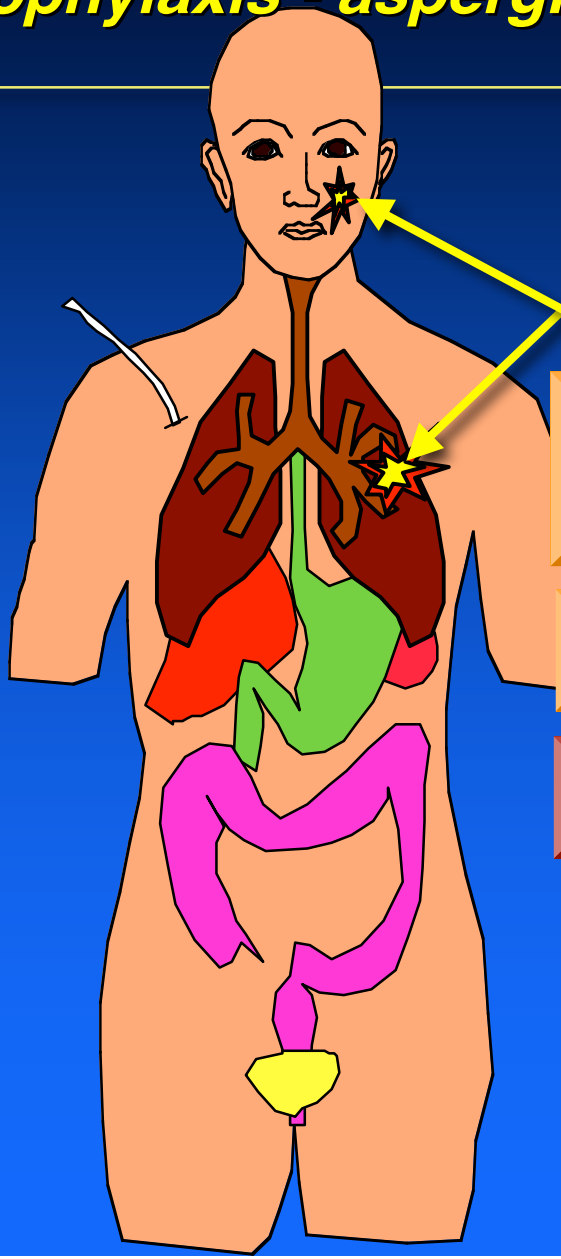
Prophylaxis - aspergillosis



Moulds

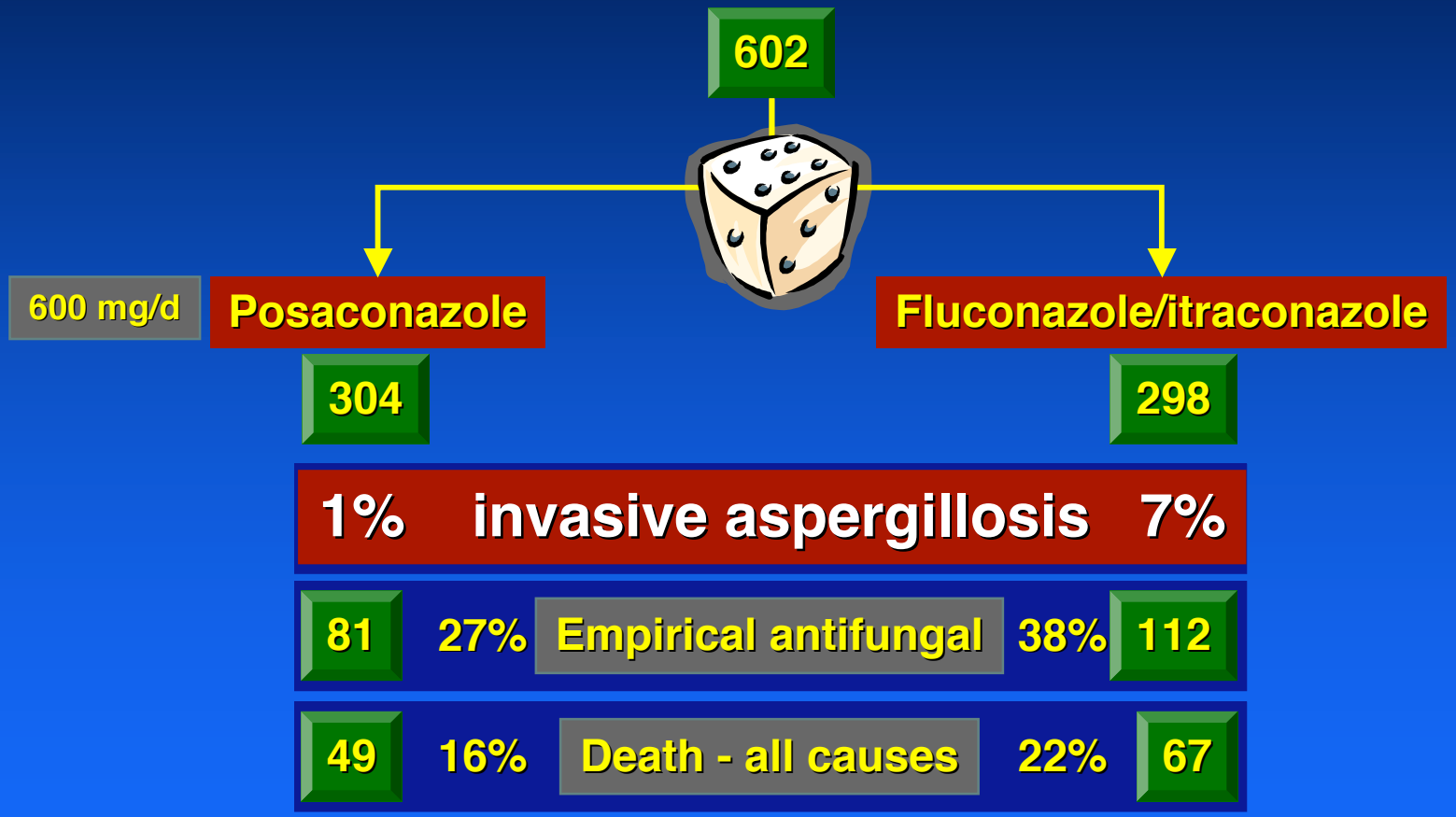
Aspergillus fumigatus

amphotericin B inhalation

itraconazole

posaconazole

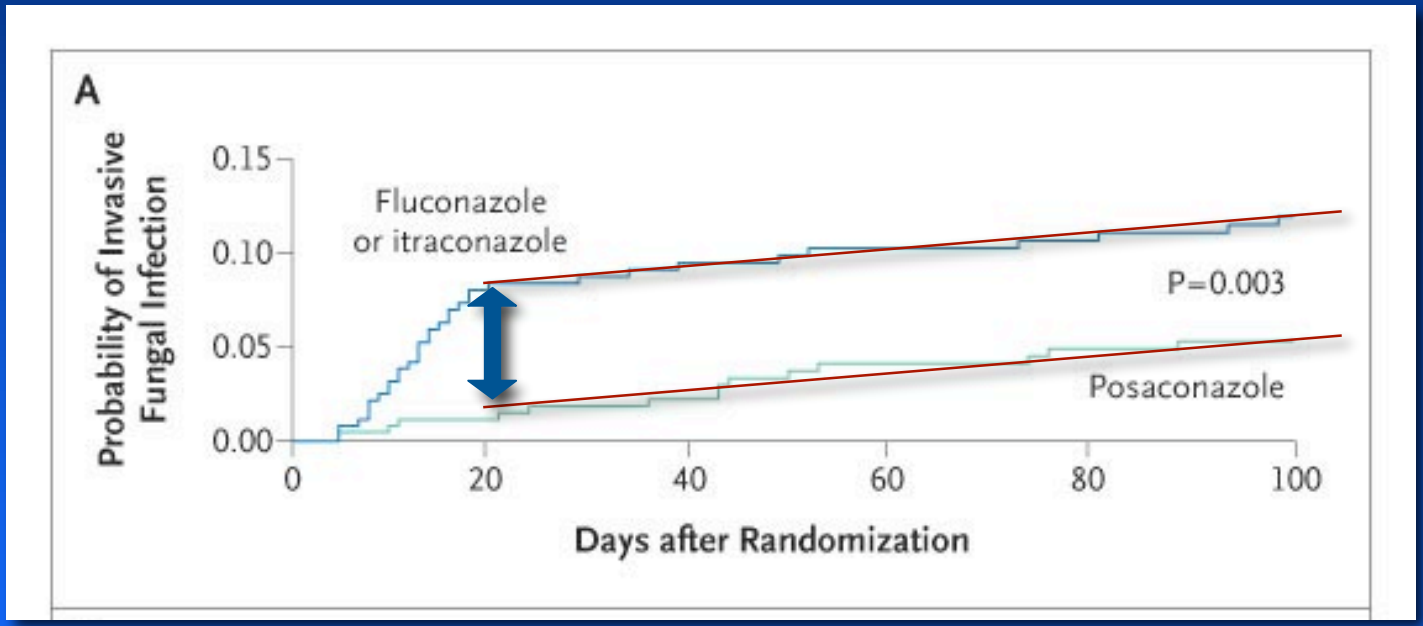
Posaconazole study of prophylaxis



Cornely et al. N Eng J Med 2007 356:348

Posaconazole study of prophylaxis

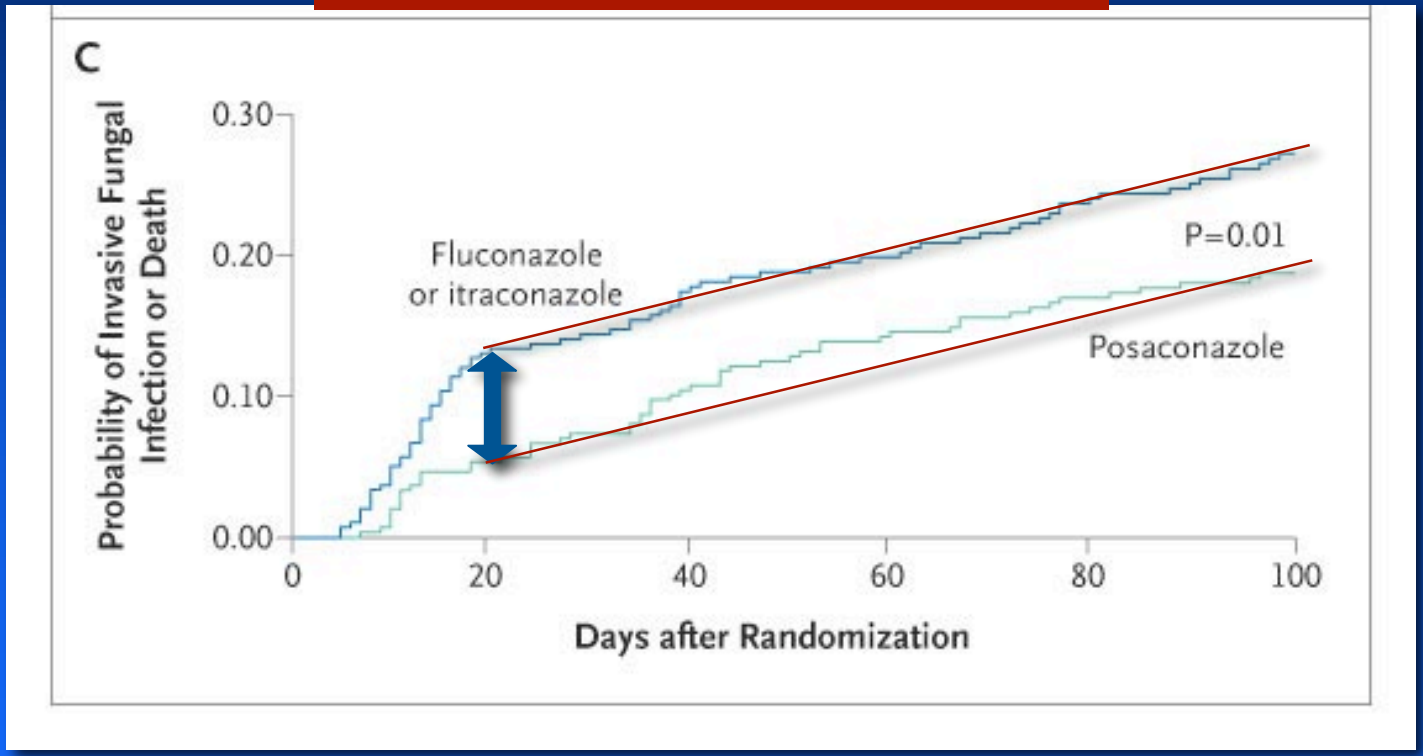
Invasive fungal disease



Cornely et al. N Eng J Med 2007 356:348

Posaconazole study of prophylaxis

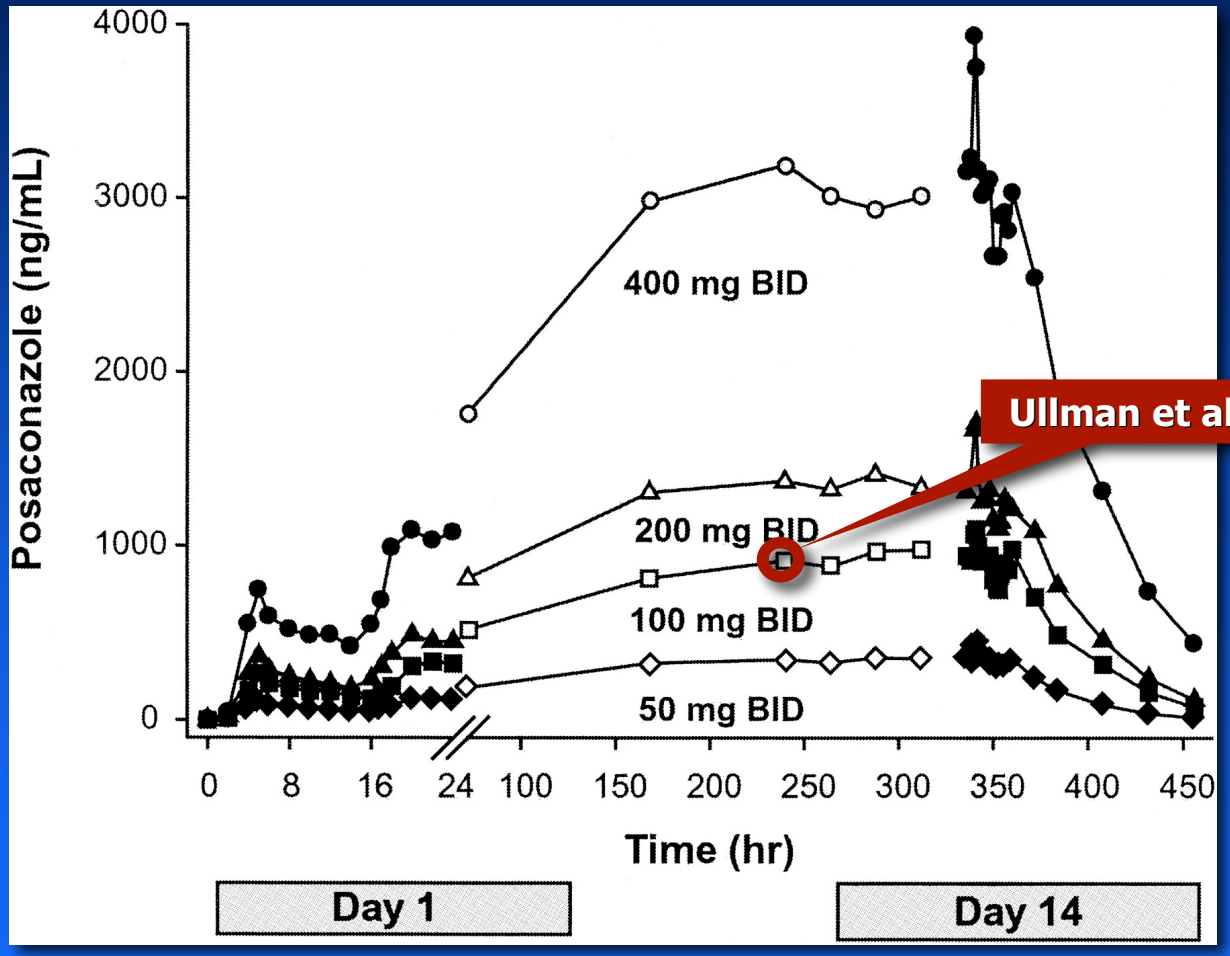
Death attributed to IFD



Cornely et al. N Eng J Med 2007 356:348

Downside

Low levels of posaconazole ?



Courtney et al. Antimicrob Ag Chemother 2003 47:2788

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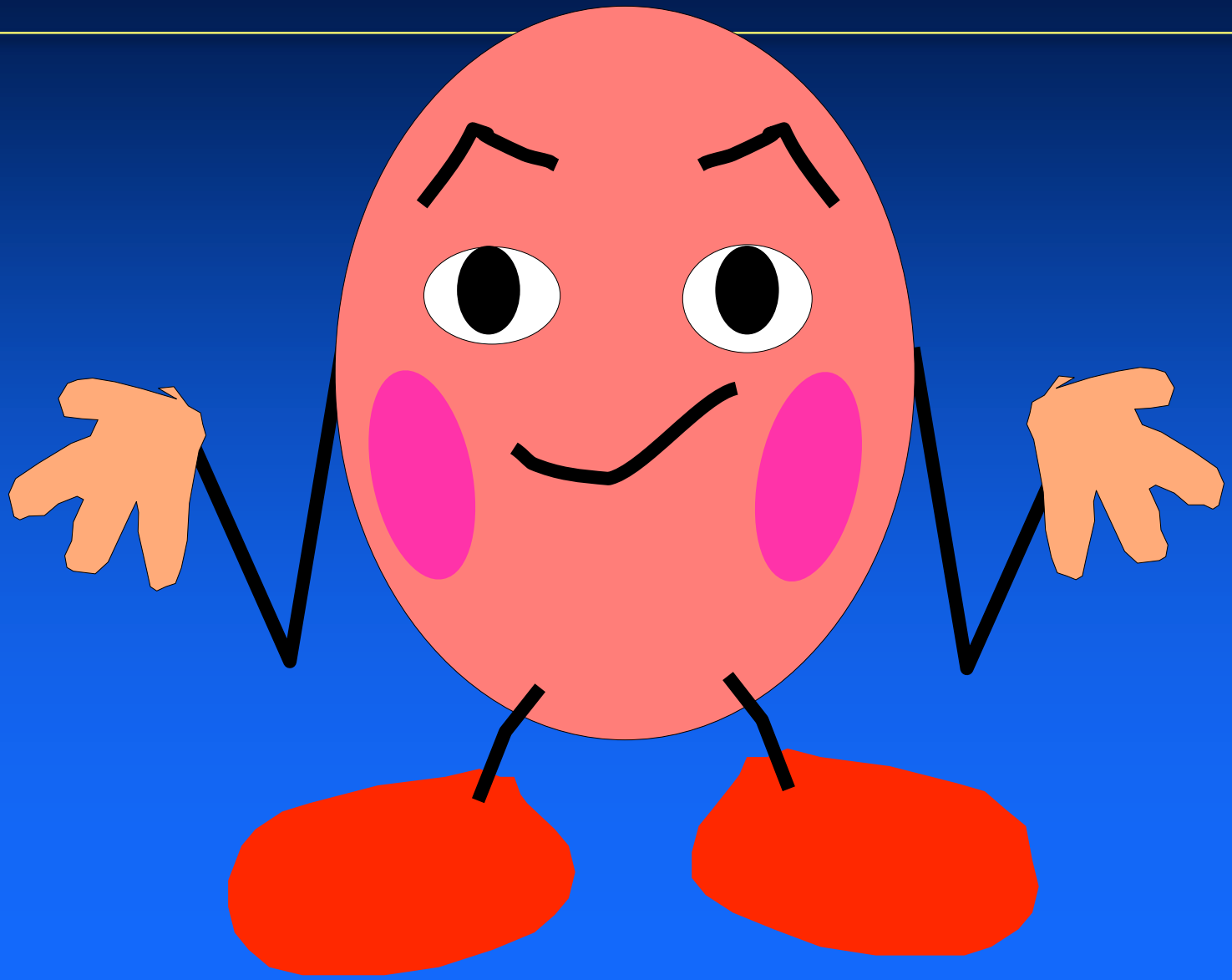
What do you do when posaconazole fails….



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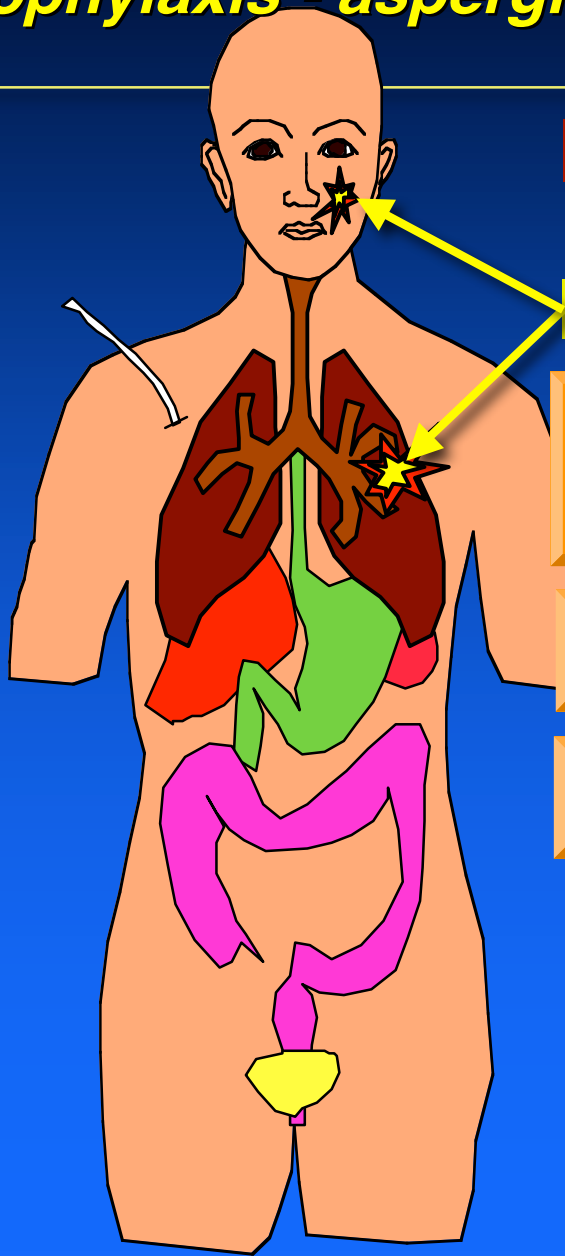
Prophylaxis - aspergillosis



Moulds

Aspergillus fumigatus

amphotericin B inhalation

itraconazole

posaconazole

Efficacy in reducing systemic IFD

Author	drugs	N	ARR	NNT
Morgenstern	FCZ vs. ICZ	445	2.2	46
Harrouseau	AMB-po vs. ICZ	557	1.9	54
Menichetti	NIL vs. ICZ	405	1.9	52
Nucci	NIL vs. ICZ	210	3.7	27
Goodman	NIL vs. FCZ	356	10.8	9
Rotstein	NIL vs. FCZ	304	12.0	8
Cornely	FCZ/ICZ vs PCZ	602	6.0	17

What do the experts say?

1st European Conference on Infection in Leukemia

Sept. 30th / Oct. 1st 2005 Juan-les-Pins - France

ELN European LeukemiaNet

EBMT

EORTC European Organisation for Research and Treatment of Cancer

ICHS International Society for Compromised Host

1st European Conference on Infection in Leukemia

Antibacterial prophylaxis

Sept. 30th / Oct. 1st 2005 Juan-les-Pins - France

European LeukemiaNet

EBMT

EORTC European Organisation for Research and Treatment of Cancer

ICHS International Immunocompromised Host Society

Recommendations

QUALITY OF EVIDENCE

High risk patients
(expected duration of neutropenia > 7 days)

Acute Leukemia and Autologous HSCT

Antibacterial prophylaxis with fluoroquinolones showed to be effective in reducing each of the following (quality of evidence I) :

- Mortality
- Febrile episodes
- Bacterial infections and bacteremias
- Gram-negative infections and bacteremias
- Gram-positive infections but not bacteremias
- The use of empirical antibiotics

Allogeneic HSCT

Considered at high risk if likely to be neutropenic > 7 days

Data on efficacy of quinolone prophylaxis are not available for all types of allogeneic HSCT recipients.

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

When should fluoroquinolone prophylaxis be started and how long should it be continued?

AII Start with chemotherapy and continue until resolution of neutropenia or initiation of empirical antibacterial therapy for febrile neutropenia

As a note of caution, antibacterial prophylaxis with fluoroquinolones should be started 24-48 hours after the end of high dose cyclophosphamide therapy (AIII).

The prophylactic administration of ciprofloxacin during cyclophosphamide conditioning was a risk factor for relapse of haematological malignancy in patients undergoing allogeneic bone marrow transplantation (Carlens S, *Clin Transplant* 1998) and the same quinolone administration prior to cyclophosphamide has resulted in significantly lower exposure of patients with non-Hodgkin lymphoma to 4-hydroxy-cyclophosphamide, the active metabolite of cyclophosphamide (Afsharian P *Eur J Haematol* 2005).

"Caveat"

- Periodic monitoring for any marked increase in (AIII):
  - Use of empirical antibacterial therapy
  - Fluoroquinolone resistance among gram-negative
  - Mortality

1st European Conference on Infection in Leukemia

Antifungal prophylaxis

Sept. 30th / Oct. 1st 2005 Juan-les-Pins - France

European LeukemiaNet

EBMT

EORTC
European Organisation for Research and Treatment of Cancer

ICHS
International Immunocompromised Host Society

Antifungal prophylaxis in leukemia patients

- **Induction chemotherapy of acute leukemia**

AI Posaconazole 200 mg tid oral: AI[2]

CI Fluconazole 50-400 mg qd iv/oral: CI

CI[1] Itraconazole oral solution 2.5 mg/kg bid:

CI Polyene[2] iv: CI-CII

Candins iv: no data

[1] May be limited by drug interactions or patient tolerability

[2] Includes low doses of AmB deoxycholate and lipid formulations

Antifungal prophylaxis in leukemia patients

- **Allogeneic HSCT**

AI Fluconazole 400 mg qd iv/oral

AI Posaconazole 200 mg tid oral

BI[1] Itraconazole 200 mg IV followed by oral solution 200 mg bid

CI Micafungin 50 mg qd iv

CI Polyene[2] iv: CI

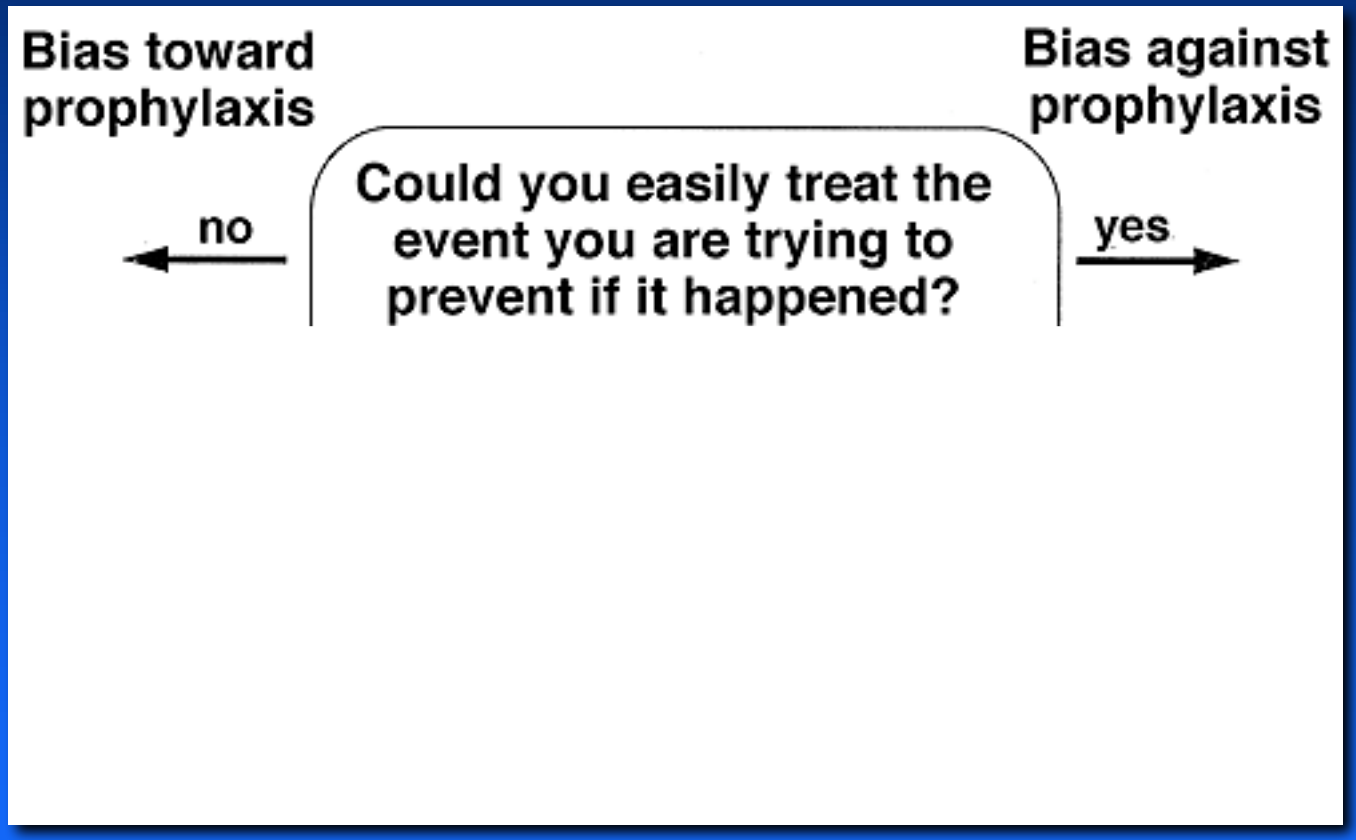
DI Polyene aerosol

[1] May be limited by drug interactions or patient tolerability

[2] Includes low doses of AmB deoxycholate and lipid formulations

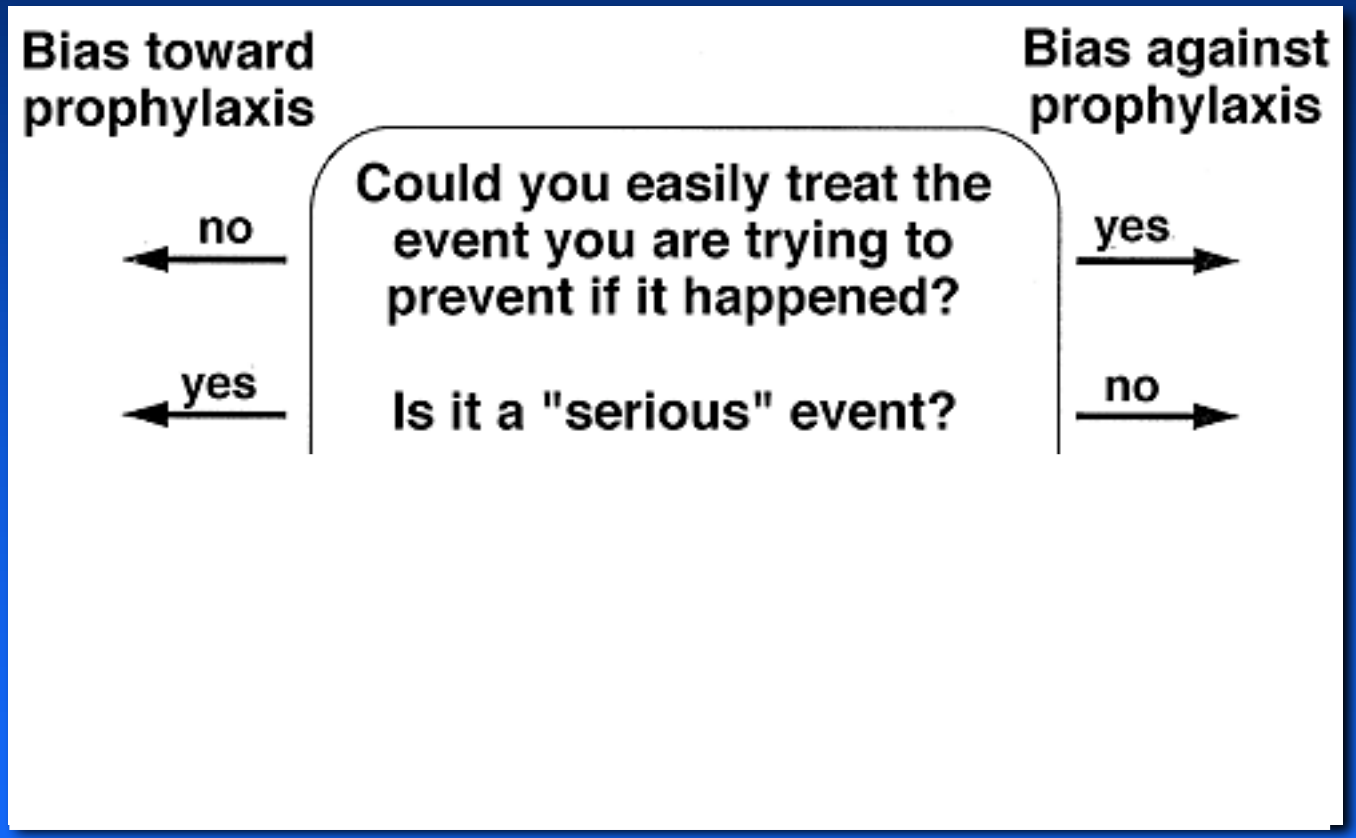
Should we use prophylaxis?

Prophylaxis: for or against?



McQuay & Moore, 1997 Ann Intern Med 126:712-720.

Prophylaxis: for or against?



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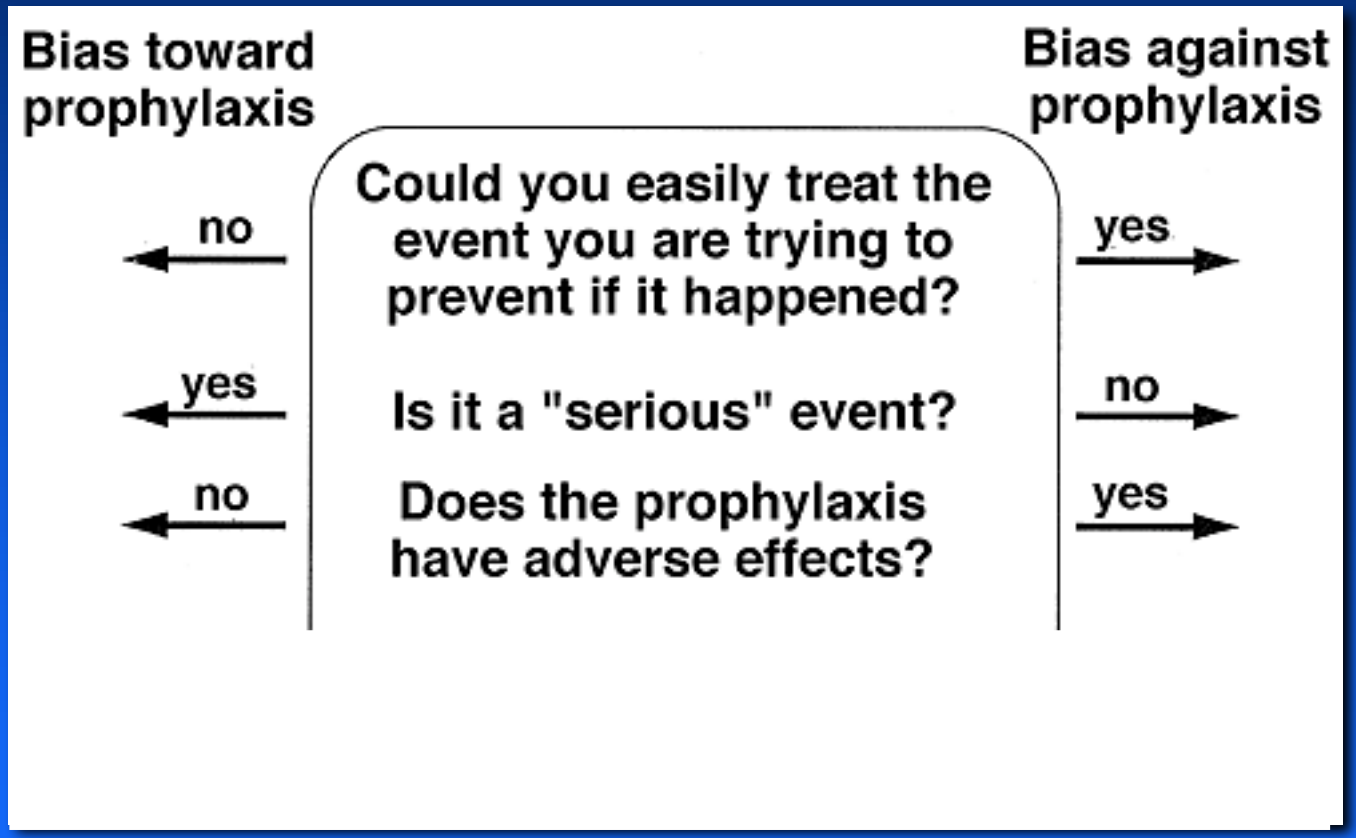

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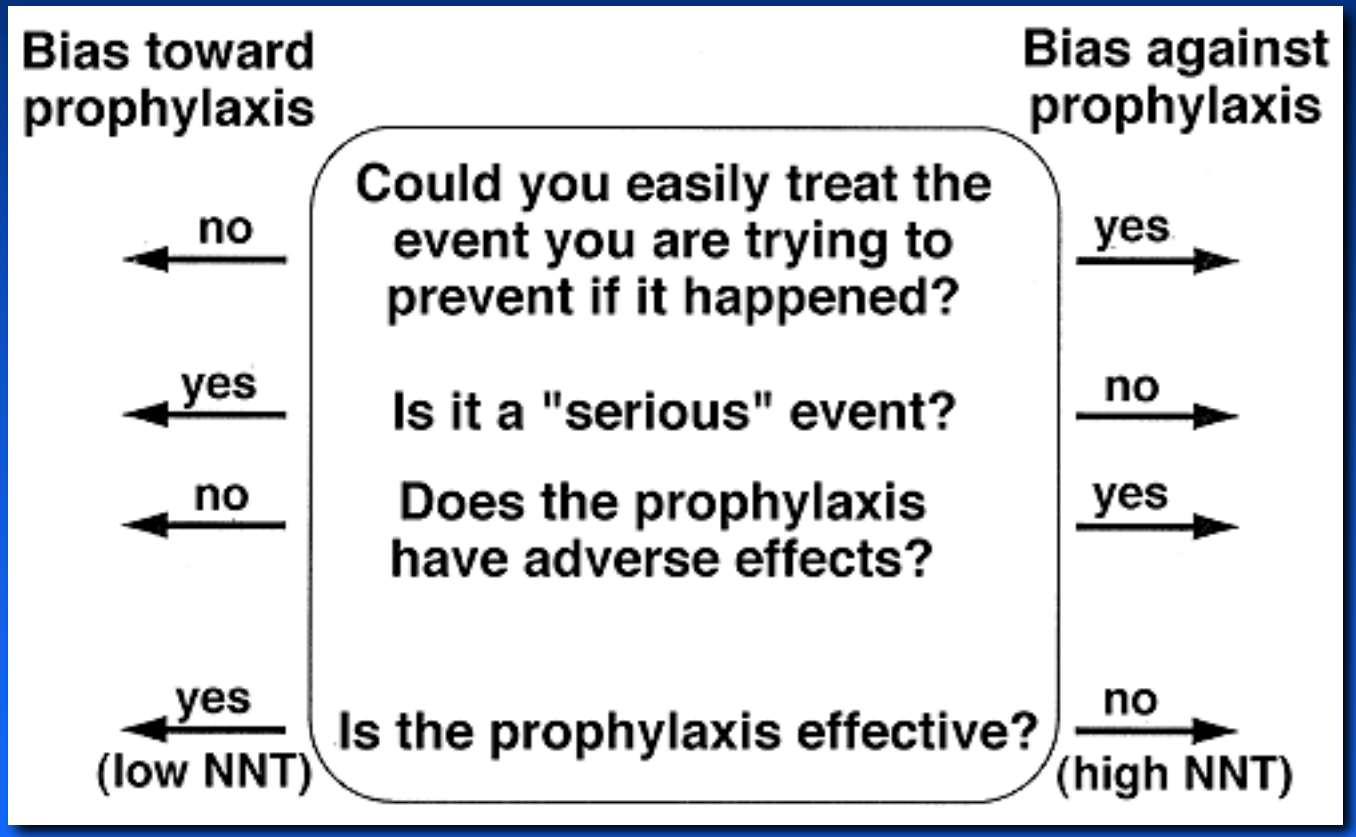

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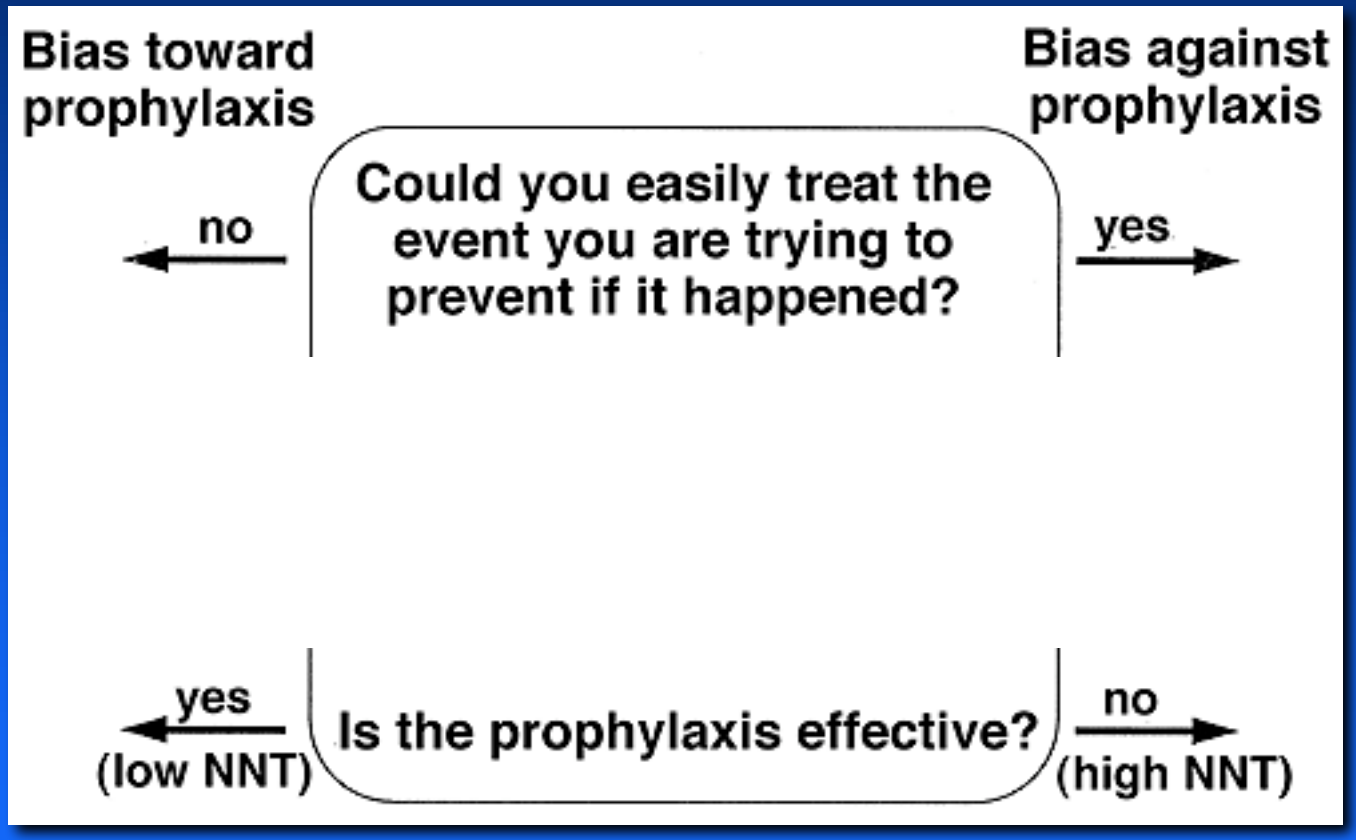

McQuay & Moore, 1997 Ann Intern Med 126:712-720.

Risk assessment

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Risk assessment

How would you describe an event rate of 5%?

Very common

Common

Occasional

Uncommon

Rare

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Risk assessment

How would you describe an event rate of 1 in 20?

Very common

Common

Occasional

Uncommon

Rare

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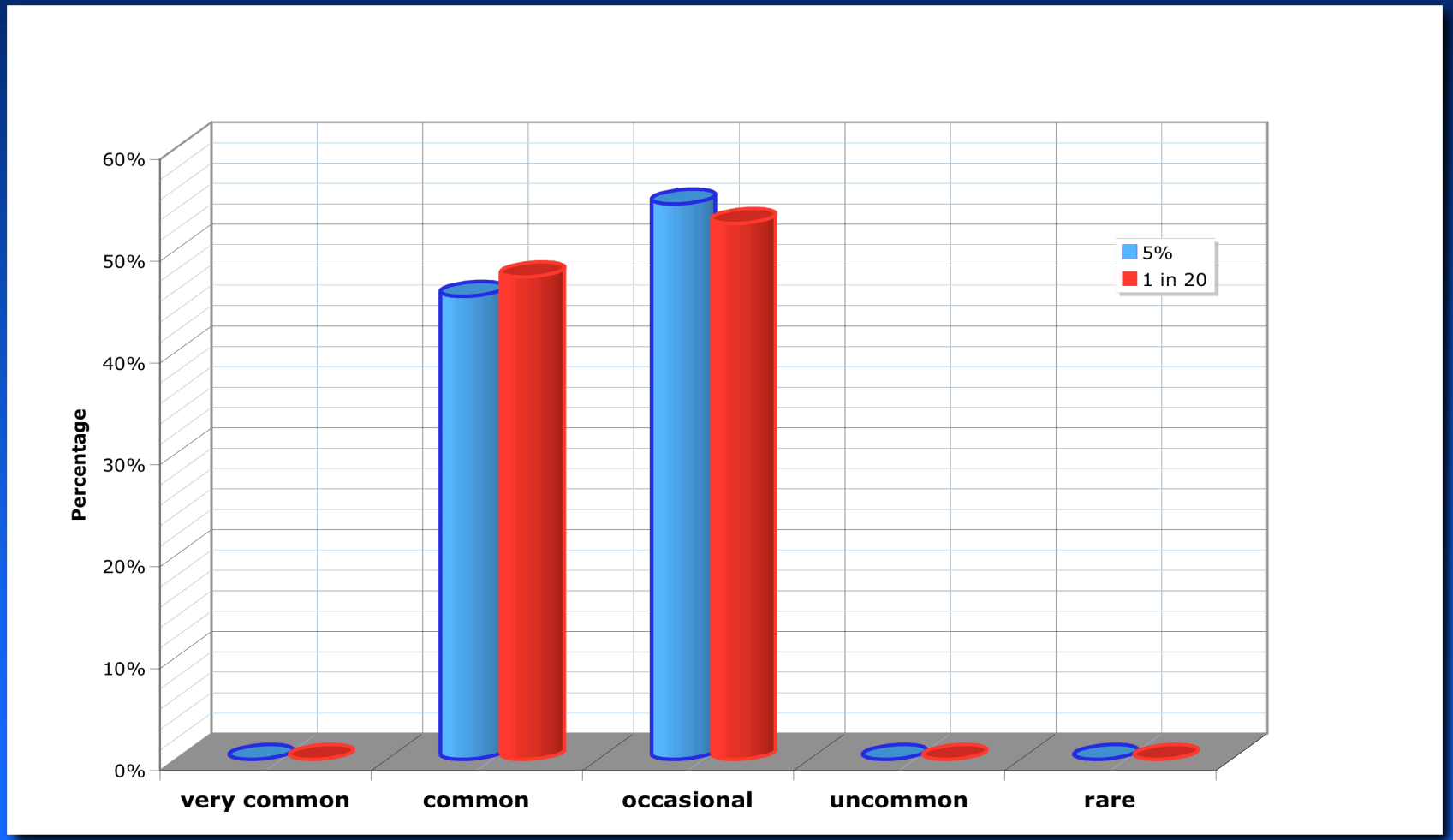
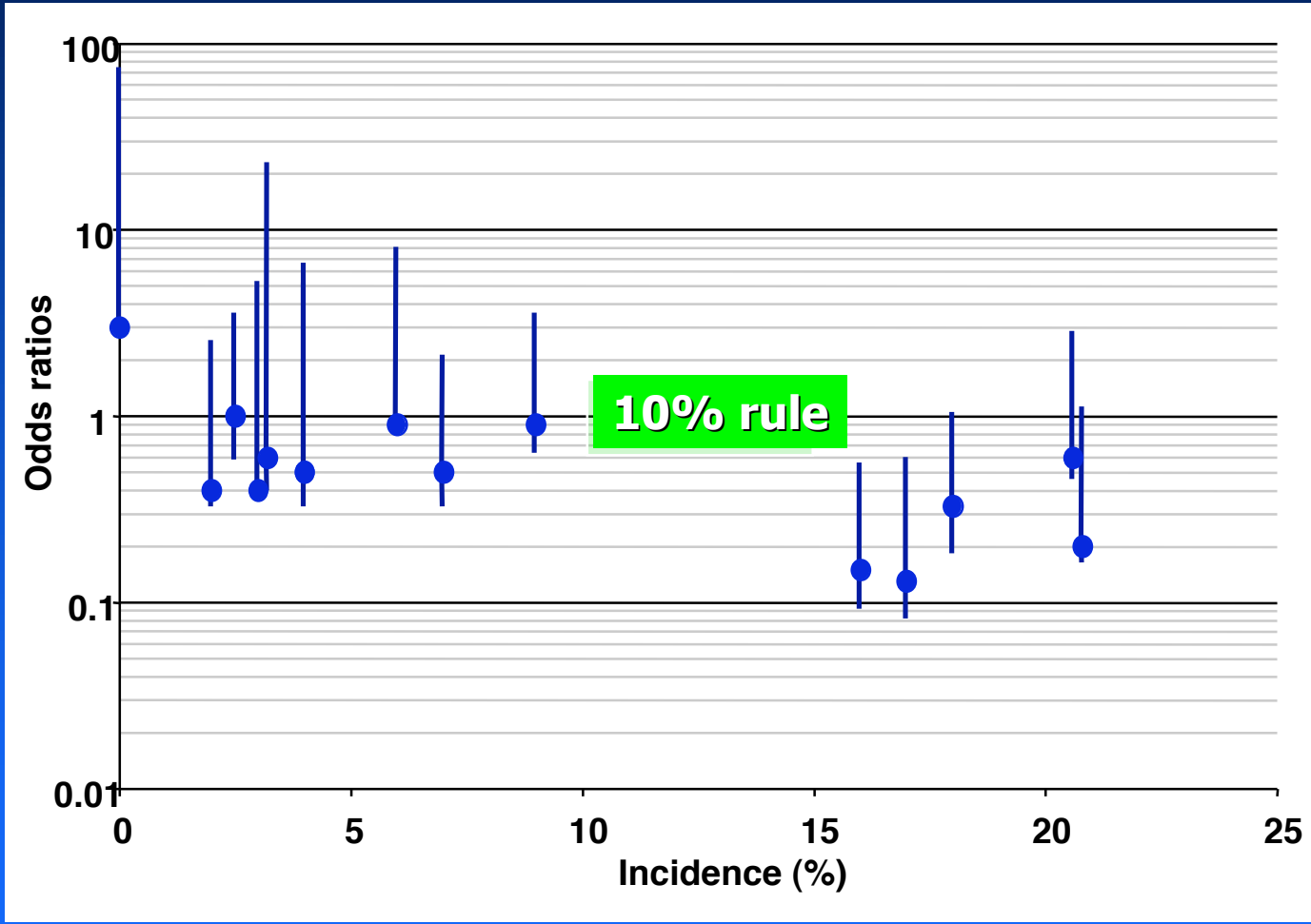
Risk assessment



Playing the odds

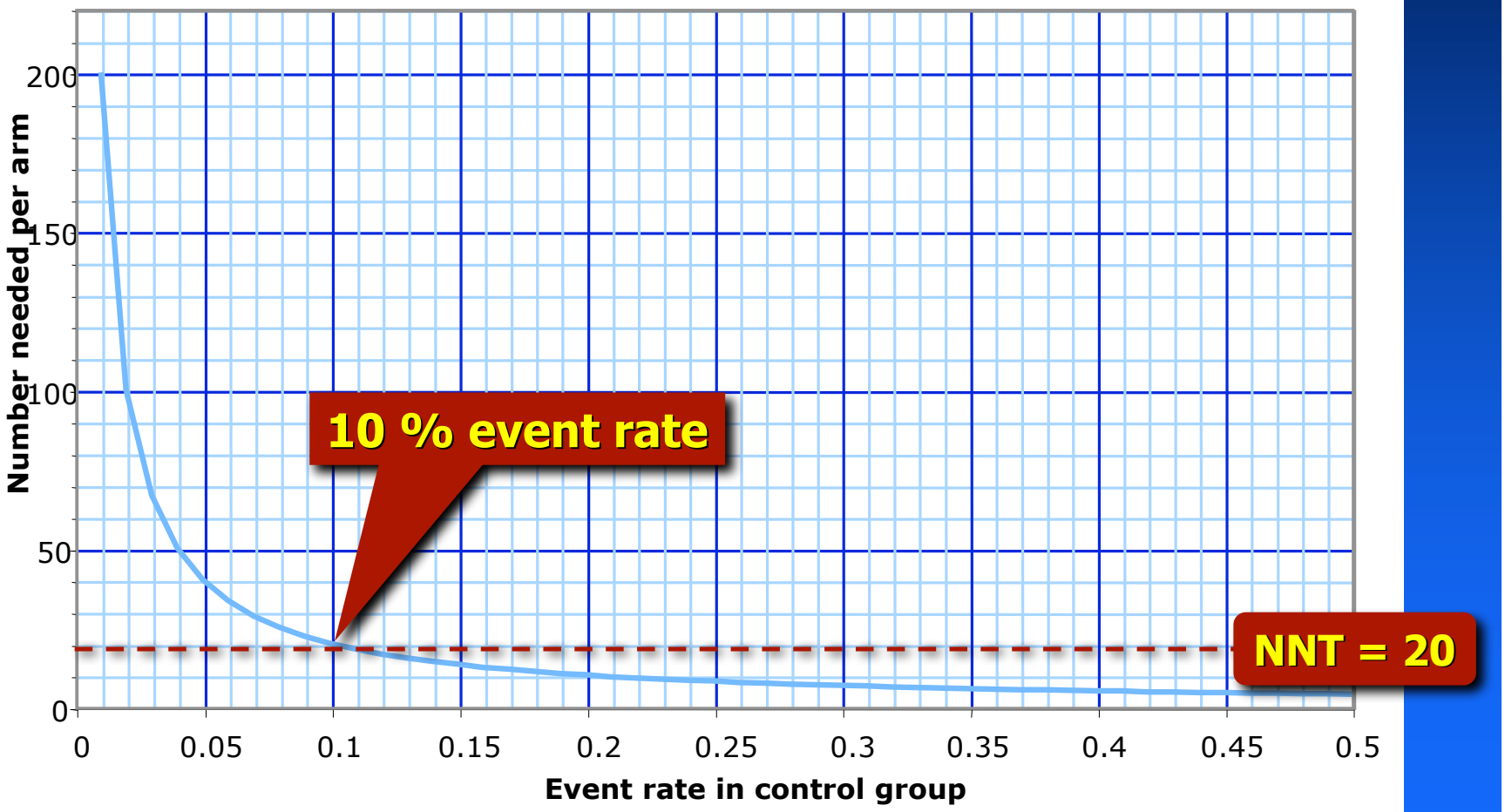
UMC St Radboud

Odds ratios for outcome of fluconazole prophylaxis in neutropenic patients in relation to incidence

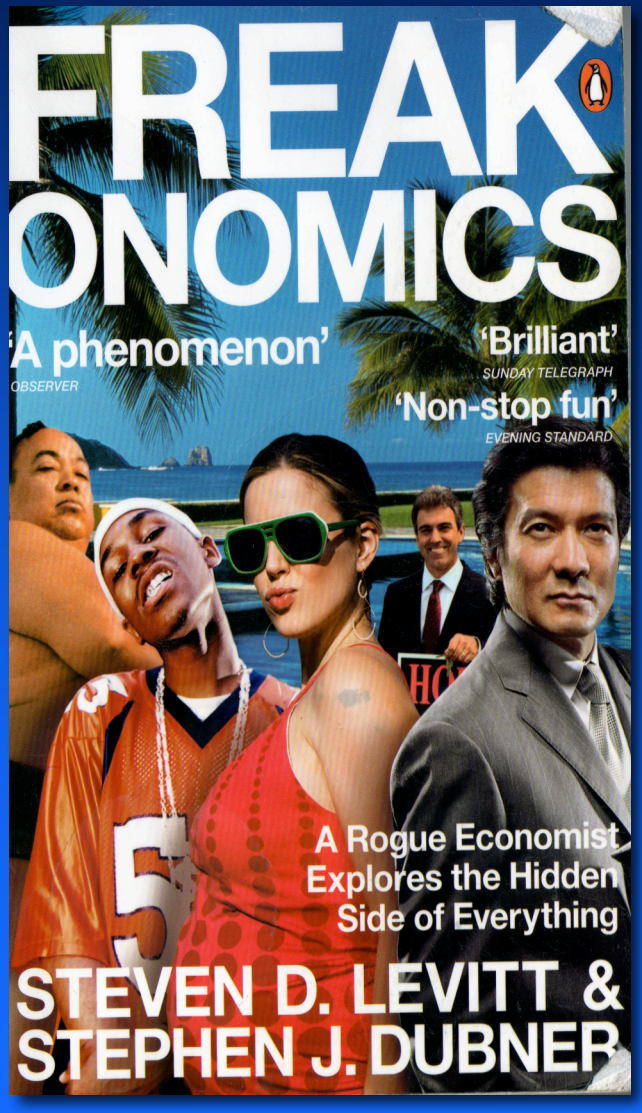


Kanda et al Cancer 2000 89;1611

Numbers needed to treat for a 50% reduction



Risk perception



Risk = hazard + outrage

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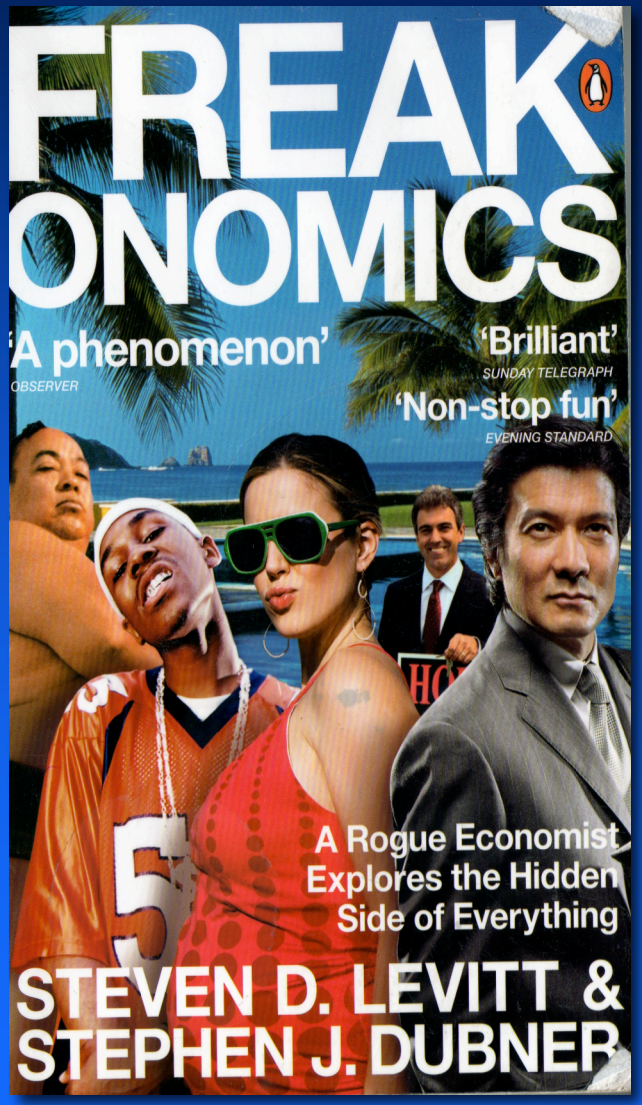
Childhood mortality

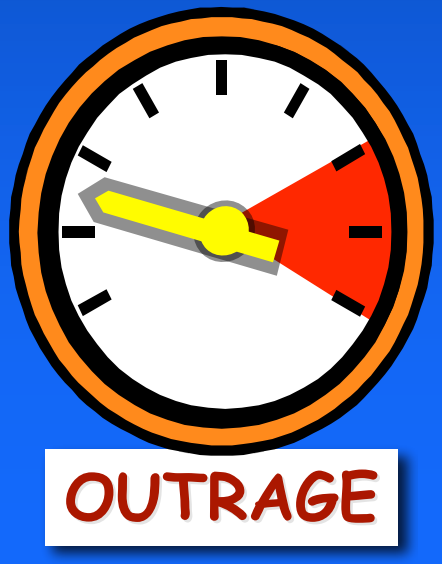


Drowning

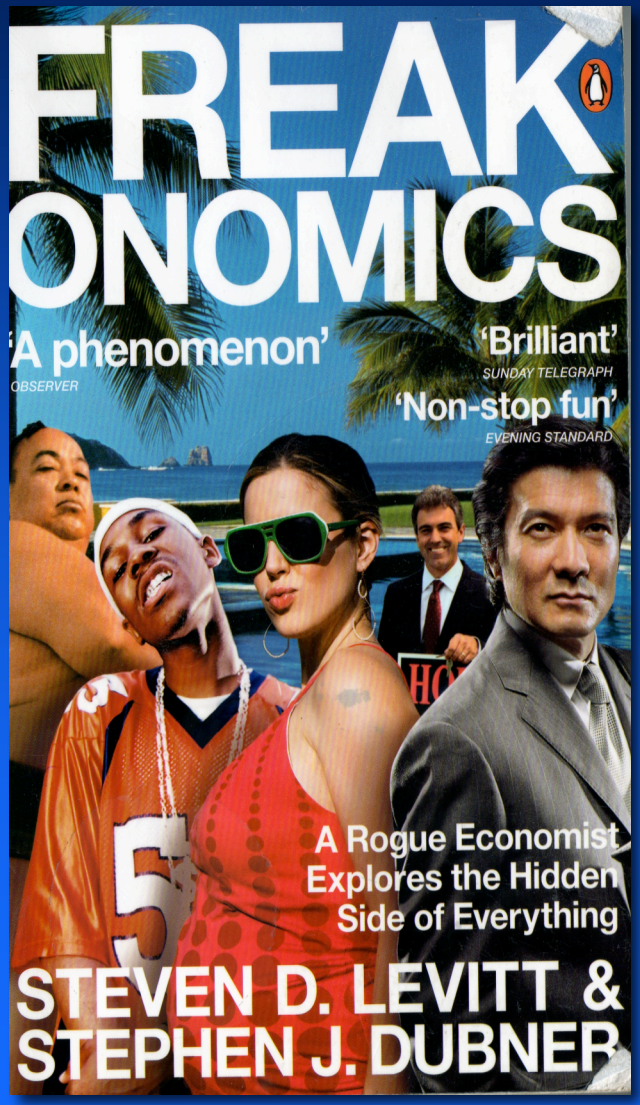
550 deaths/year

6,000,000 residential pools

1 death for every 11,000 residential pools



Childhood mortality



Drowning

550 deaths/year

6,000,000 residential pools

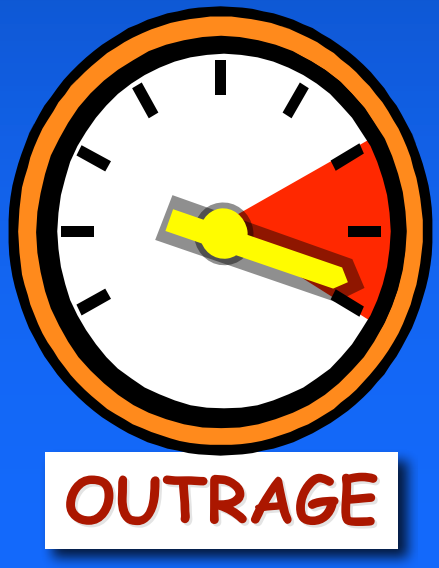
1 death for every 11,000 residential pools

Gunshots

175 deaths/year

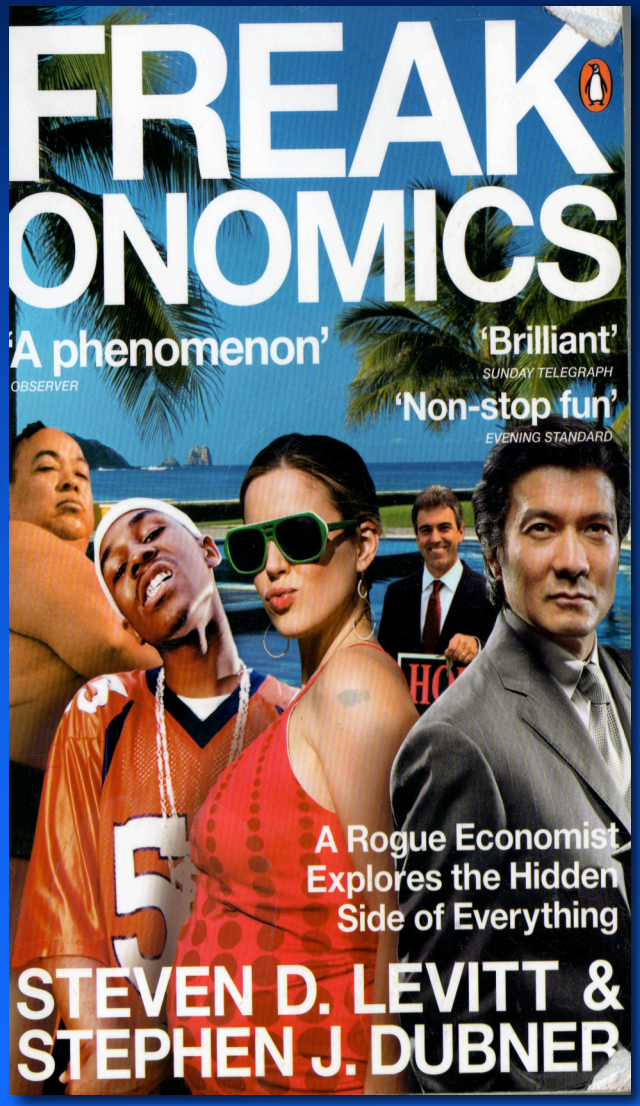
200,000,000 guns

1 death per 1,000,000 guns



UMC St Radboud

Childhood mortality



Drowning

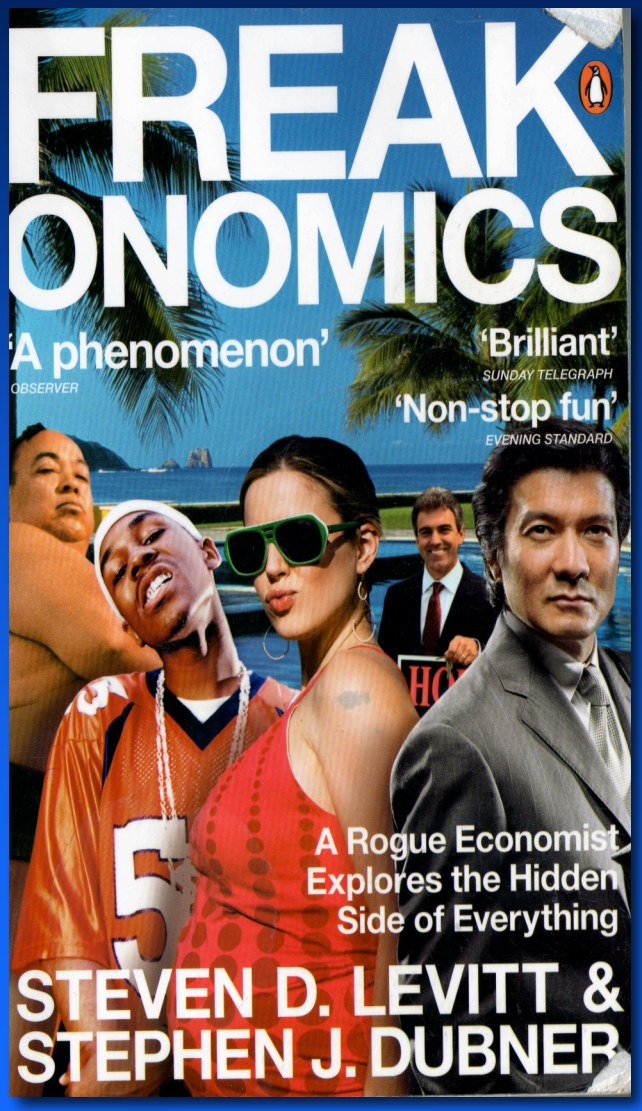
- 550 deaths/year
- 6,000,000 residential pools
- 1 death for every 11,000 residential pools

Gunshots

- 175 deaths/year
- 200,000,000 guns
- 1 death per 1,000,000 guns

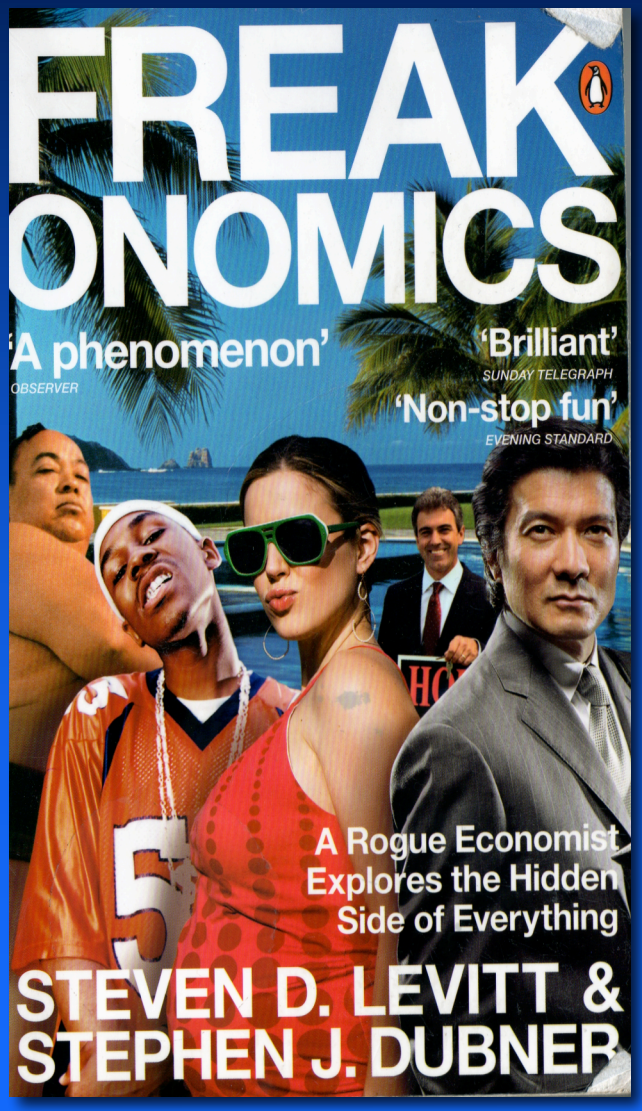
Odds 100 to 1 for drowning

Risk perception



Who is thought to be at high risk in your institute

Risk perception



Who is actually at high risk in your institute

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Do we use prophylaxis?

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Risk groups

HSCT allogeneic

AML/MDS

GVHD ≥ grade 2 **and** On haematology ward

Chronic GVHD

Steroid treatment

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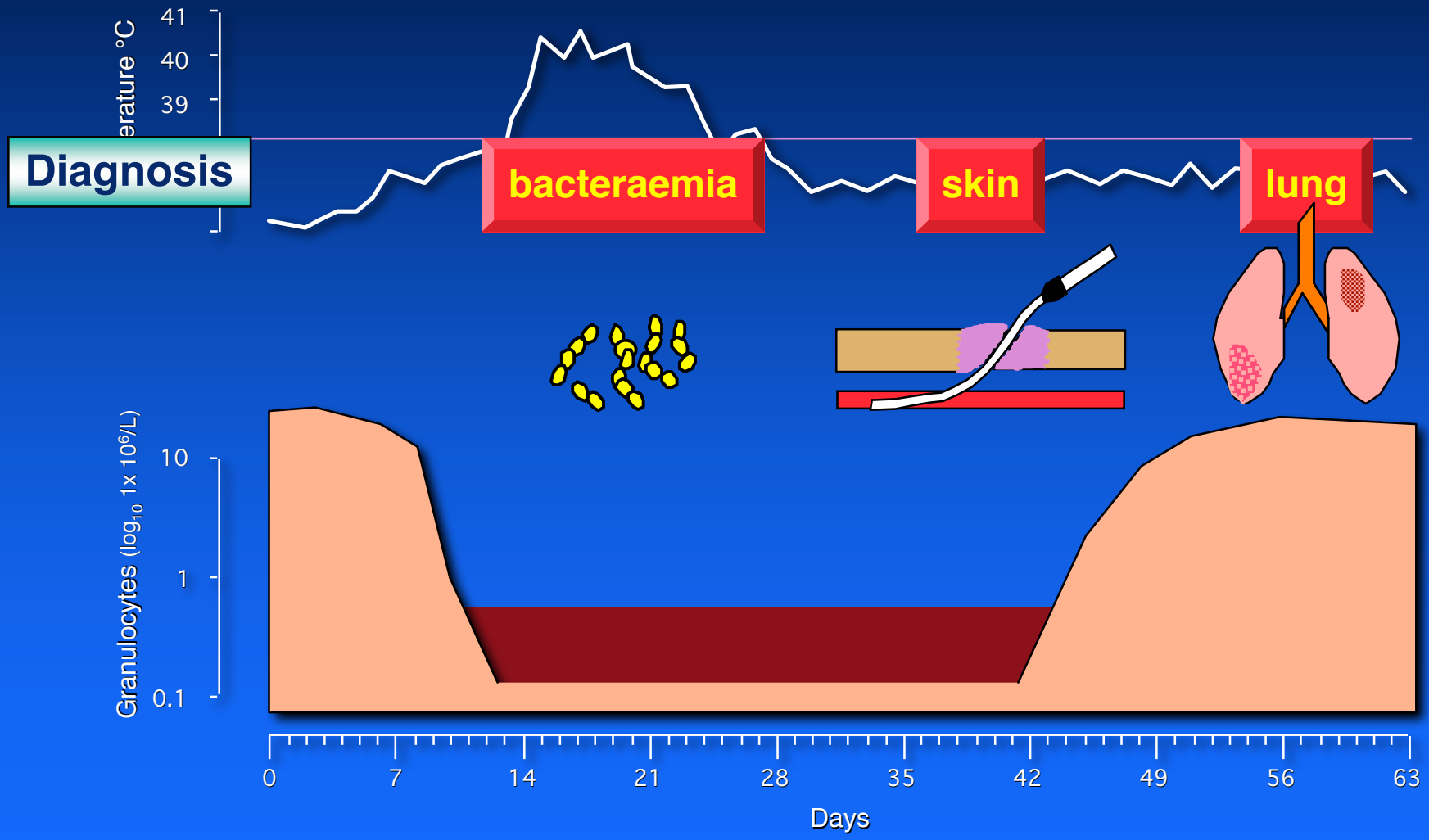
Infectious complications during neutropenia



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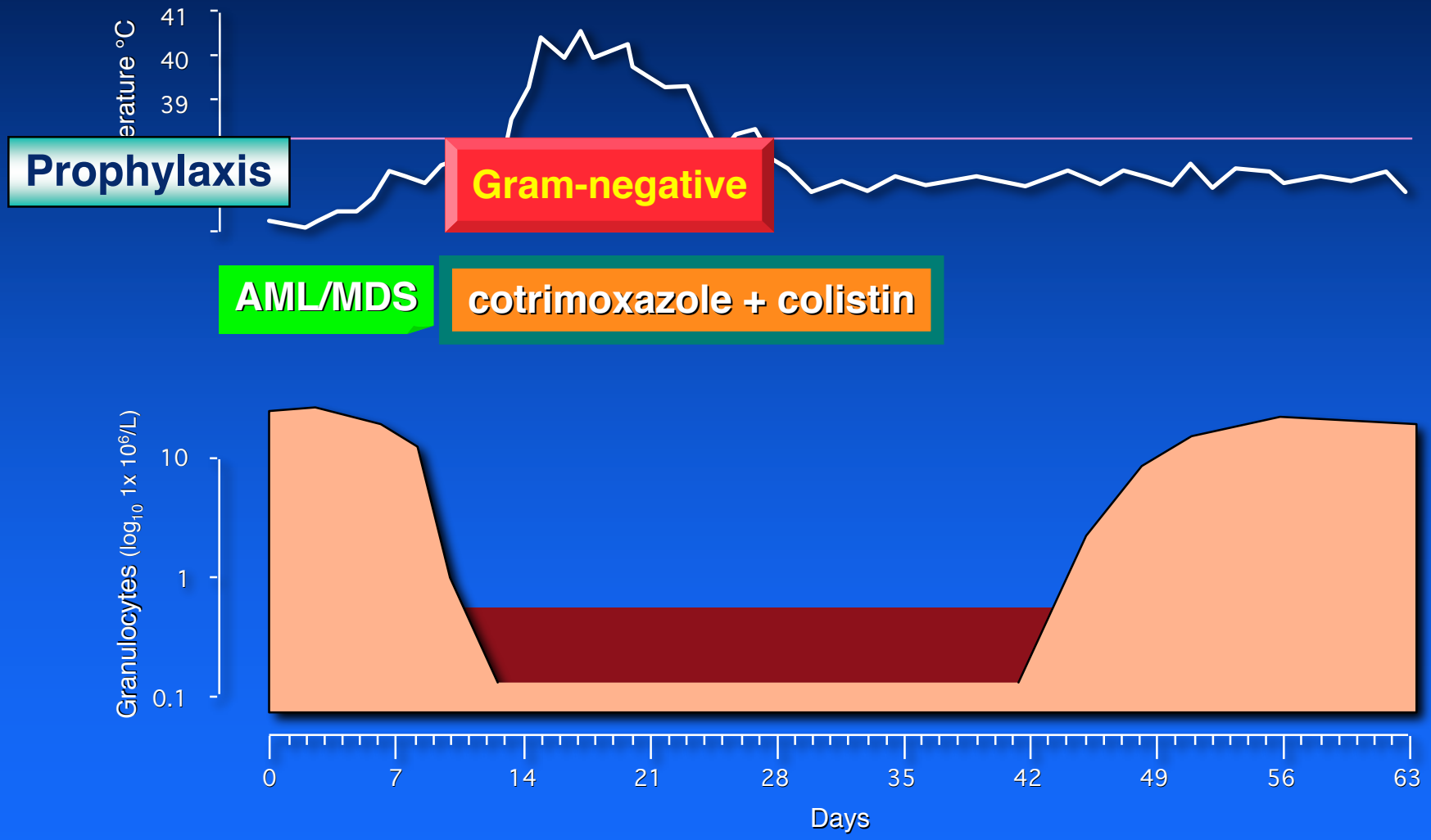
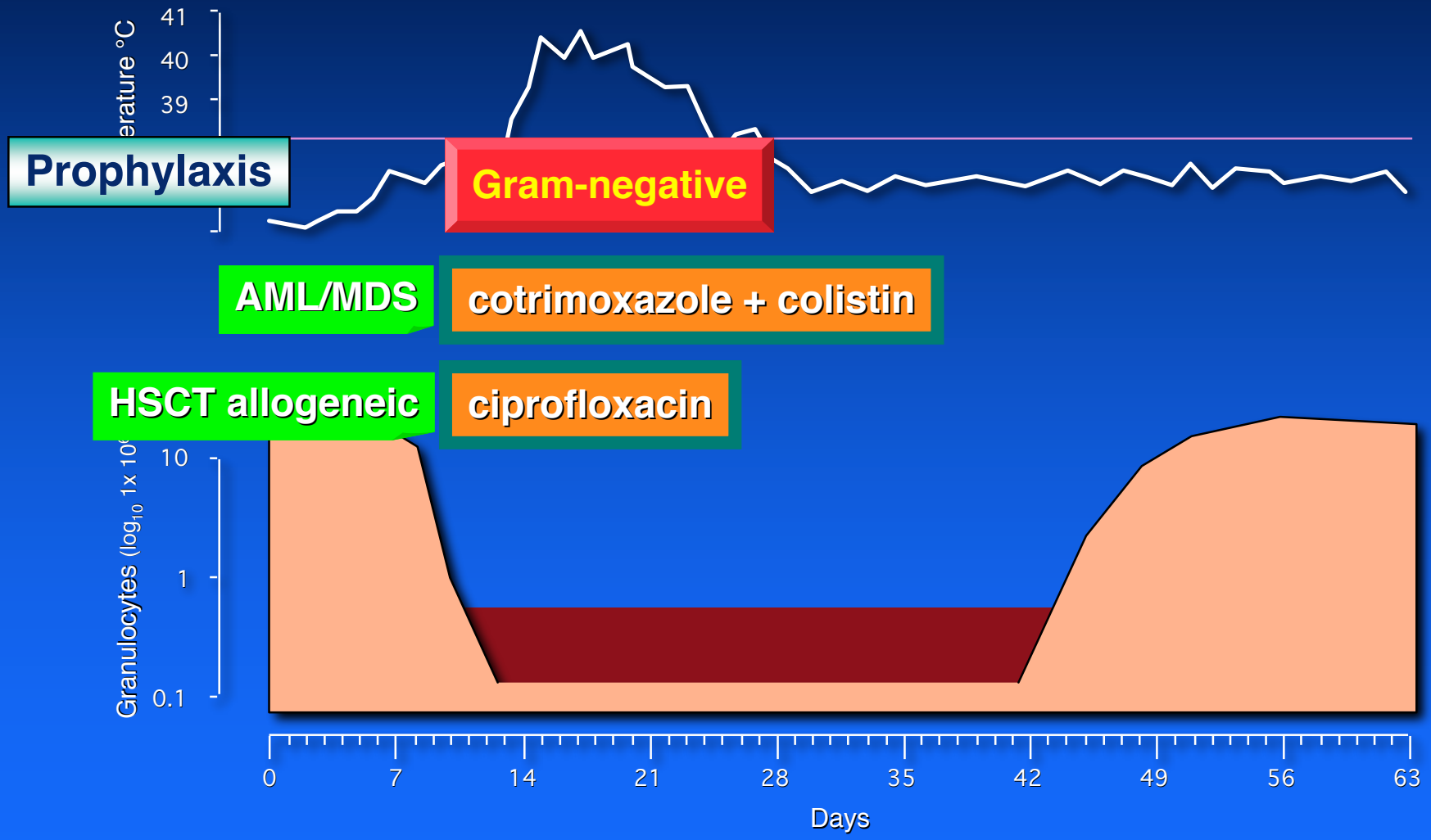
Antimicrobials for prophylaxis during neutropenia



UMC St Radboud

Antimicrobials for prophylaxis during neutropenia



UMC St Radboud

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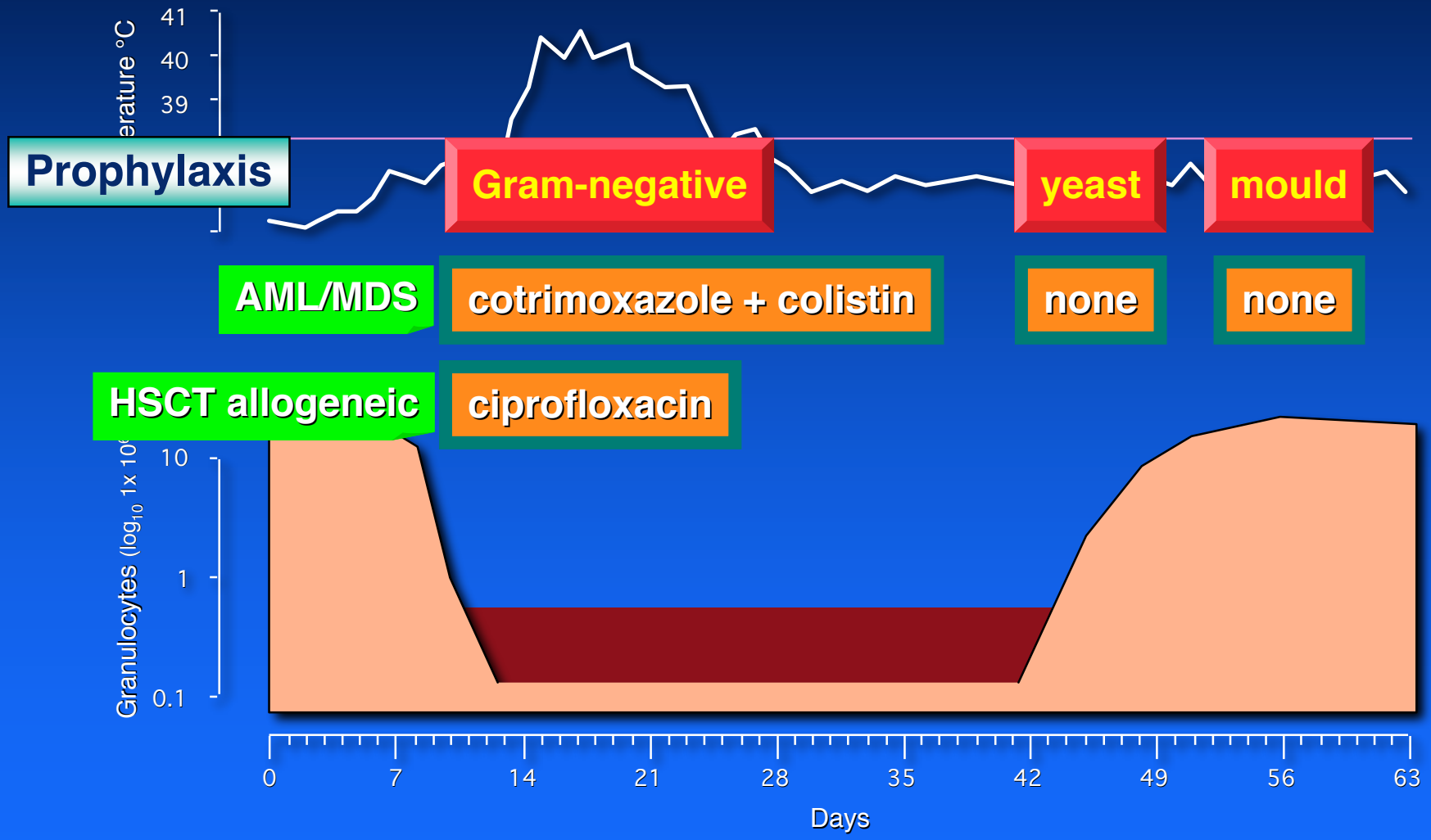

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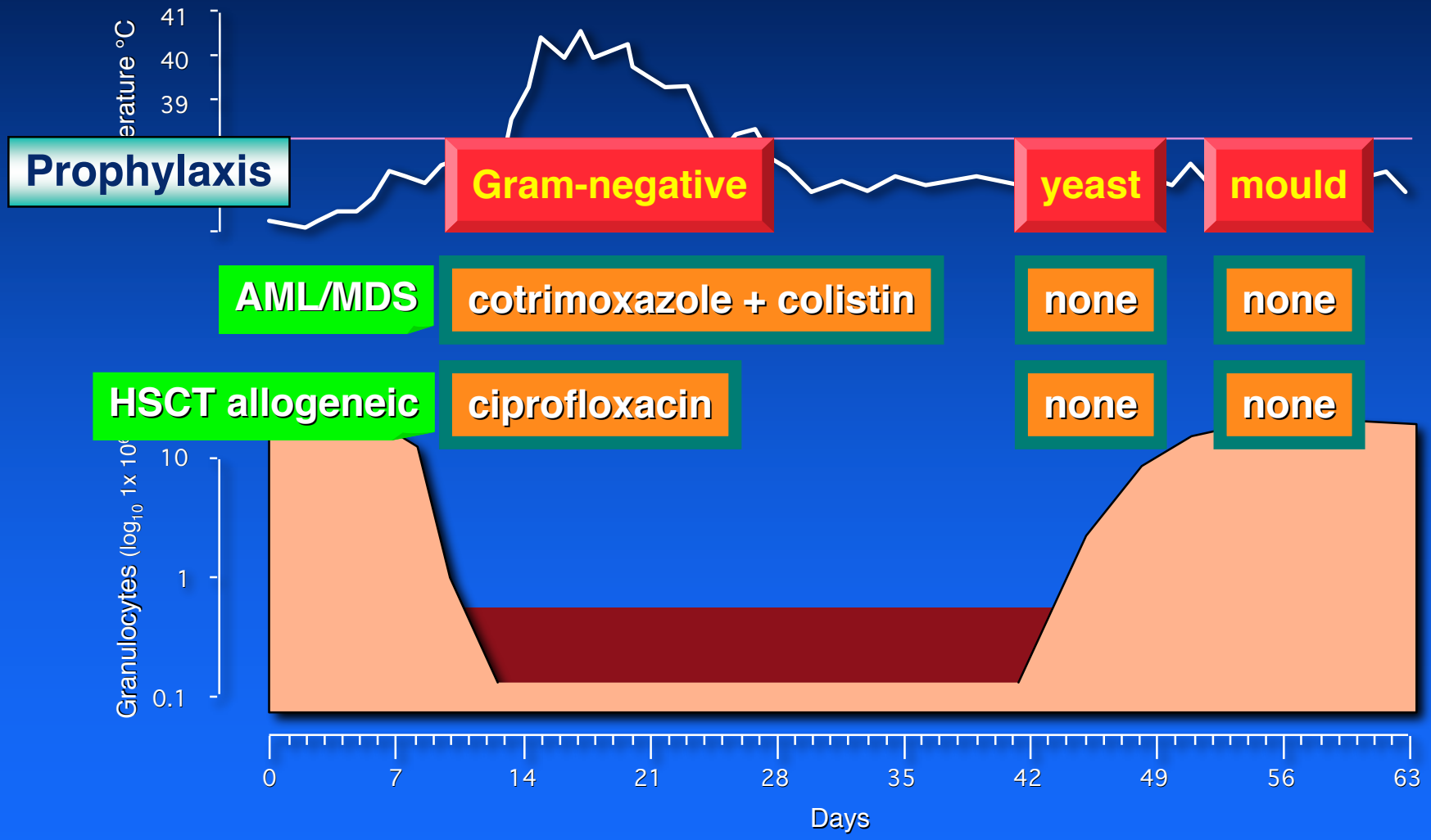
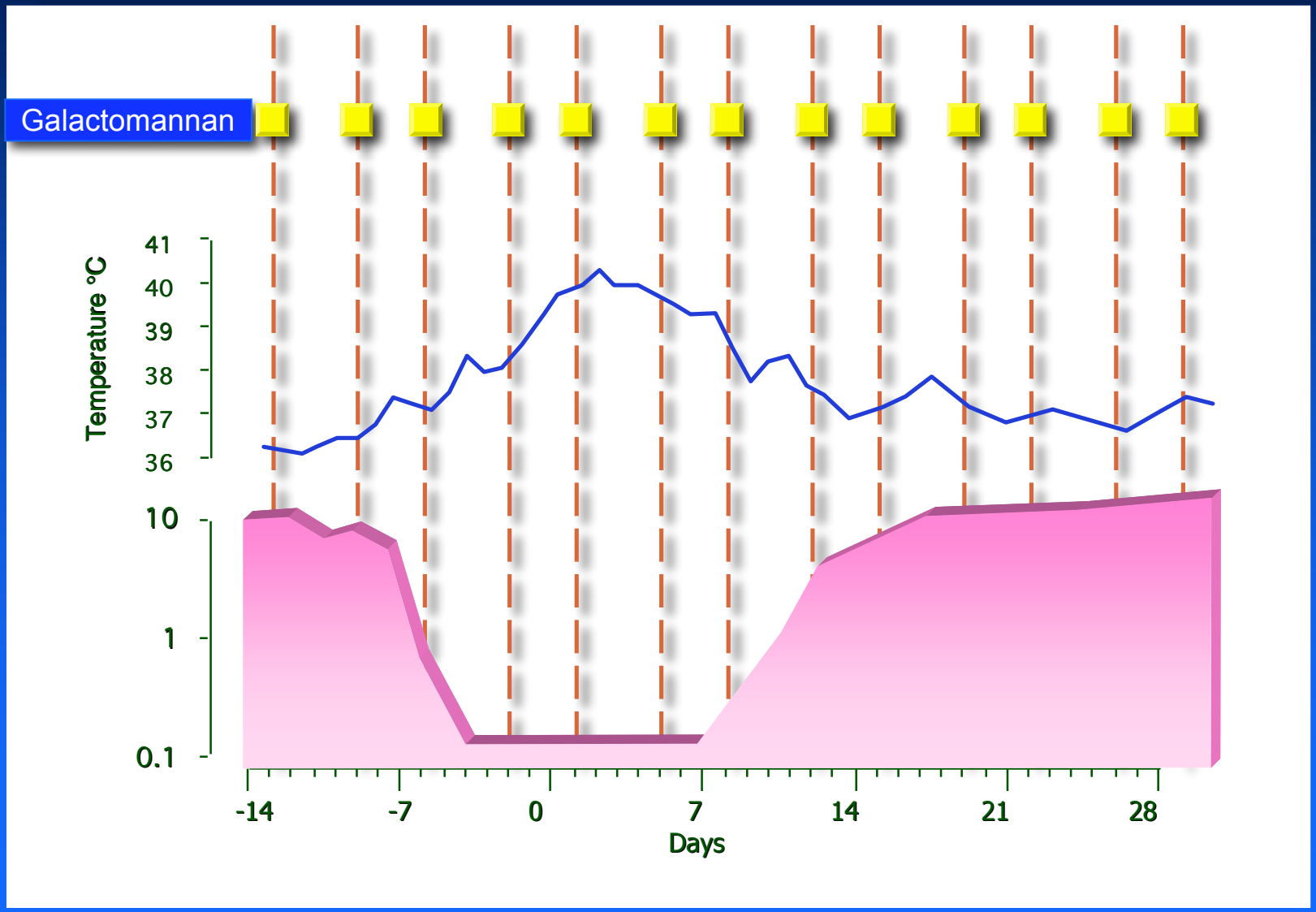


UMC St Radboud

Investigating invasive fungal disease



UMC St Radboud

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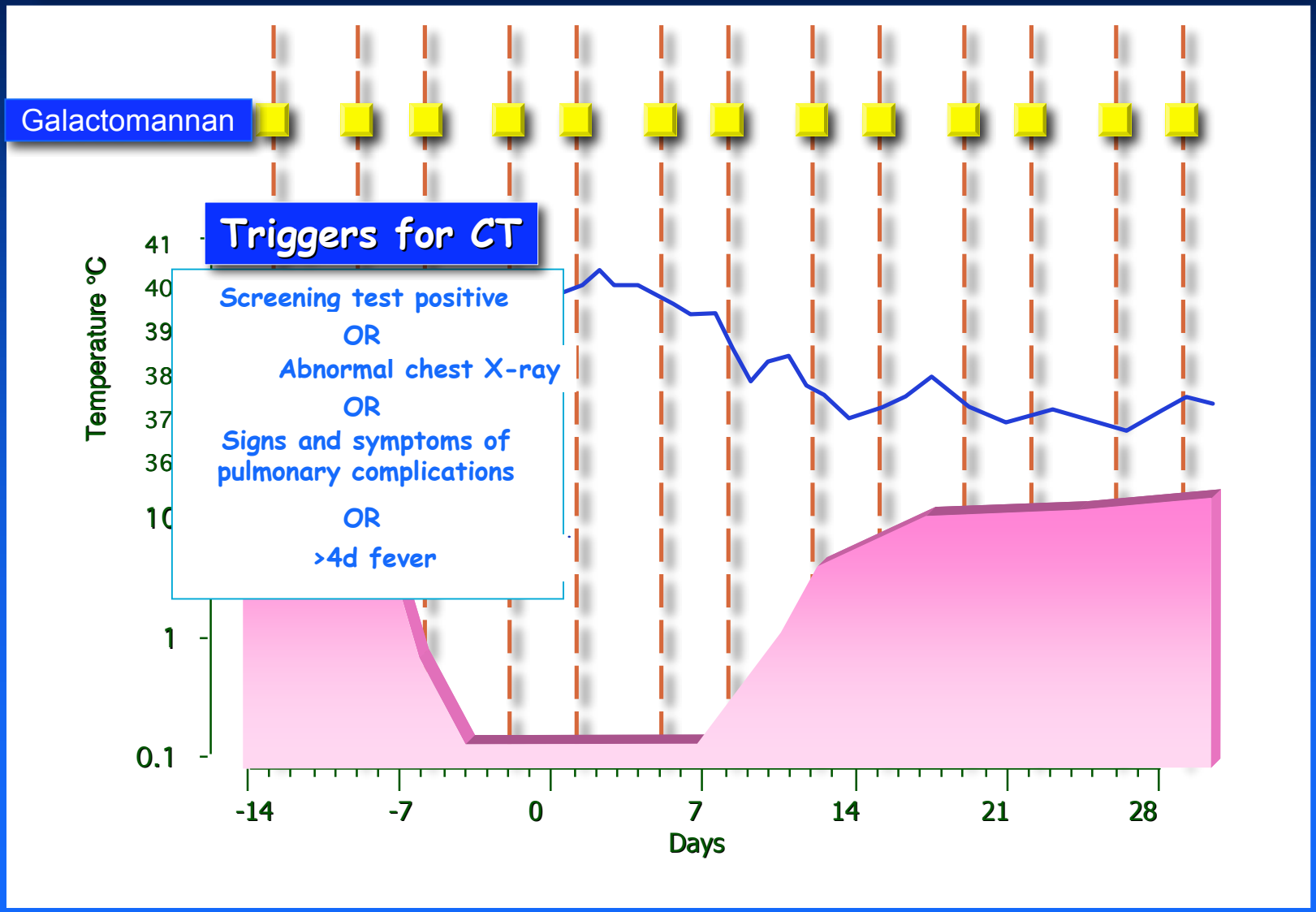
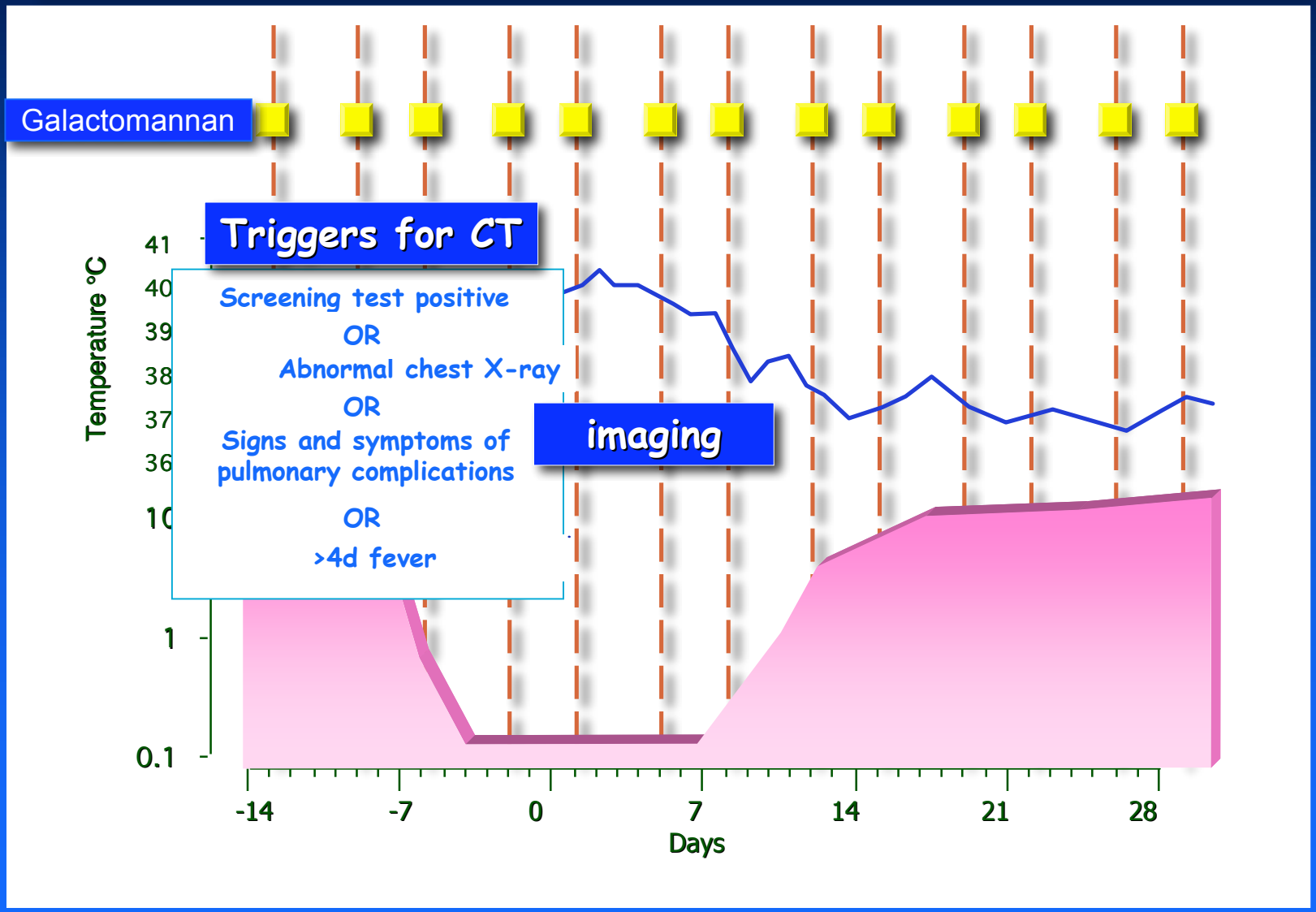


UMC St Radboud

Investigating invasive fungal disease



UMC St Radboud

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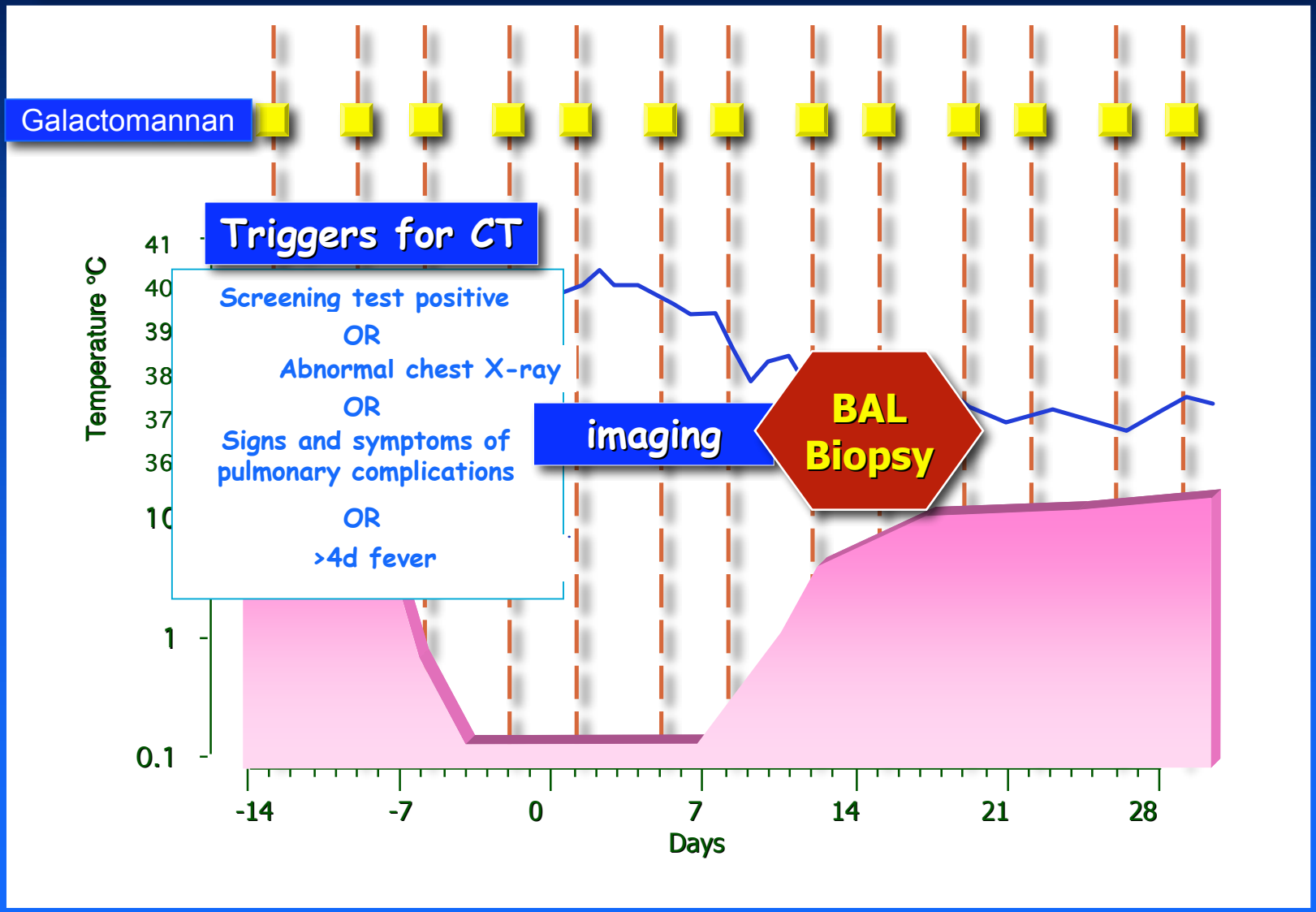
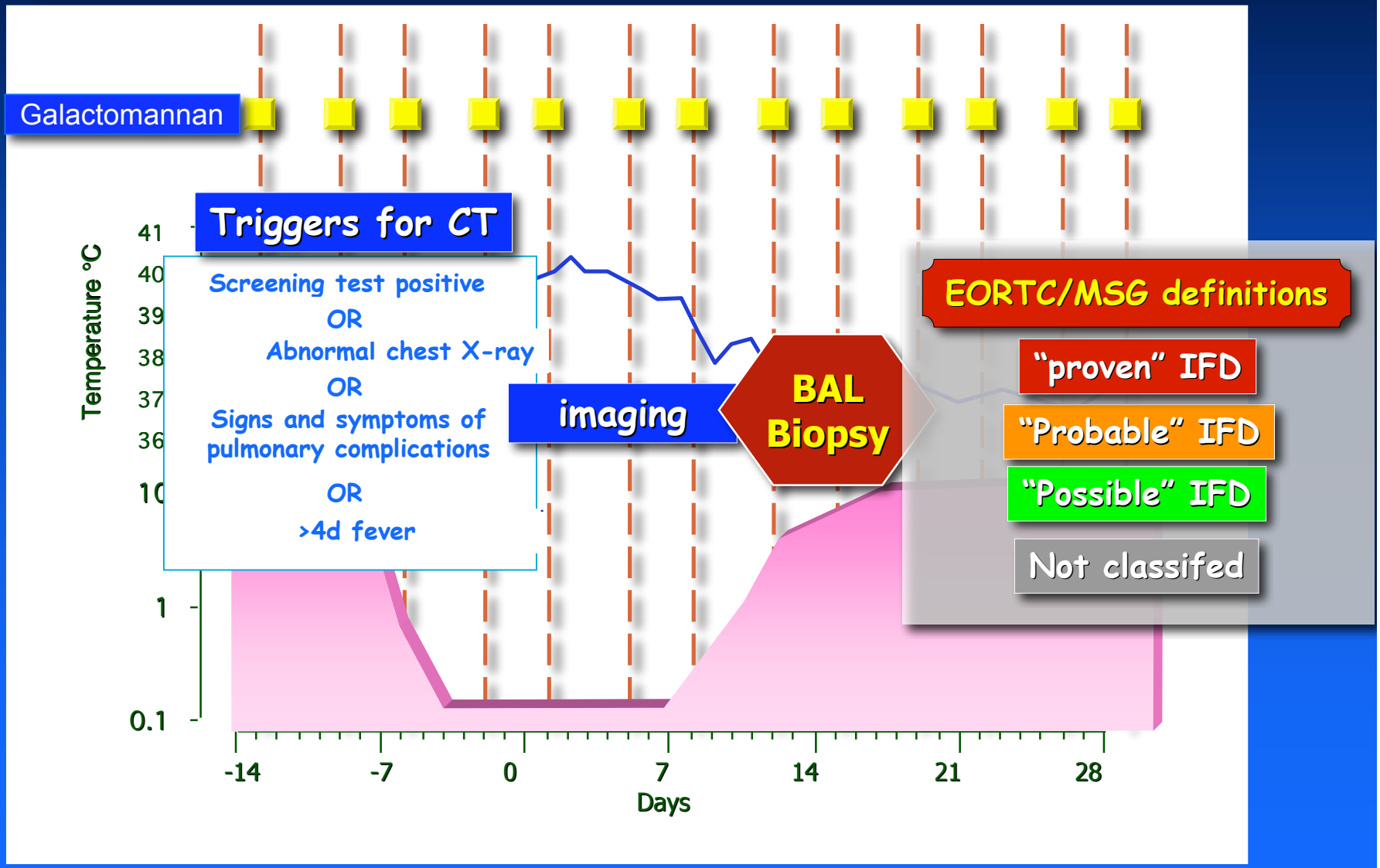


UMC St Radboud

Investigating invasive fungal disease



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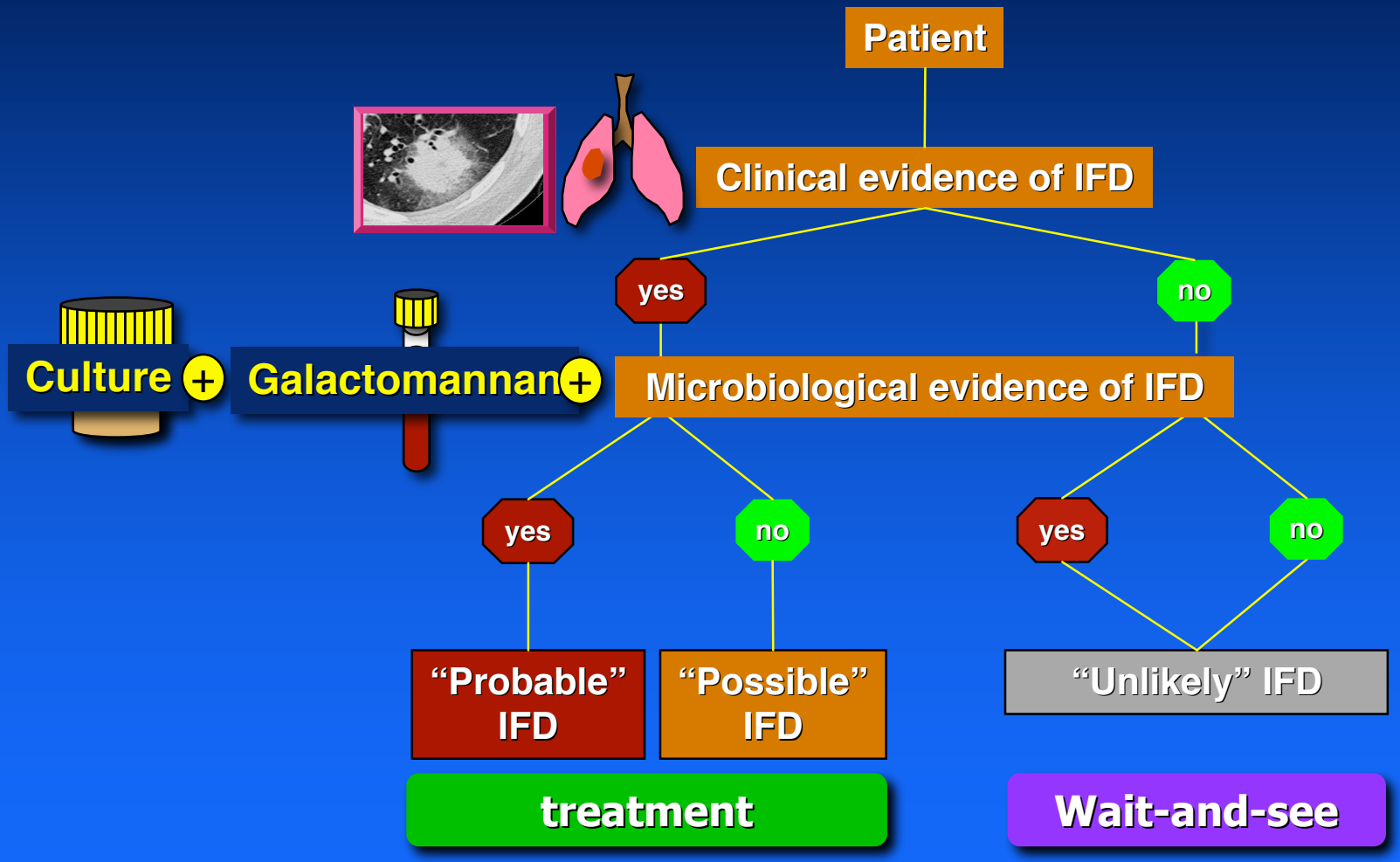
Scheme for managing high-risk patients



Conclusions

Antibacterial prophylaxis

- prevents infection in haematological patients
- reduces need for empirical therapy
- lowers mortality

But should be reviewed continuously

Conclusions

Antibacterial prophylaxis

- prevents infection in haematological patients
- reduces need for empirical therapy
- lowers mortality

But should be reviewed continuously

Antifungal prophylaxis

- prevents invasive fungal disease
- may lower mortality

But should only be used when the risk >10%