Revue de la littérature actualisée sur l'intérêt de la prophylaxie antibiotique par fluoroquinolones chez les patients leucémiques avec neutropénie.

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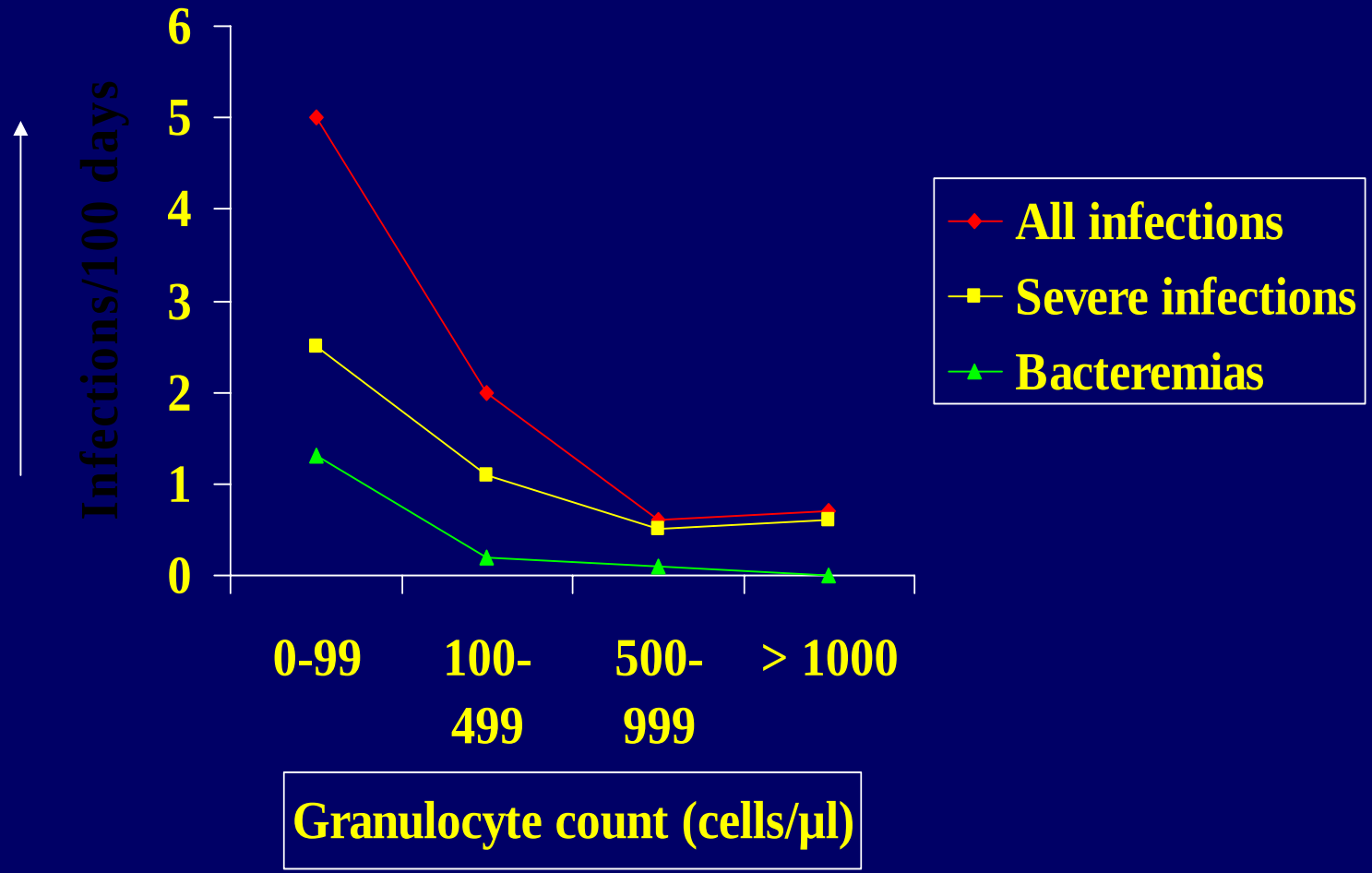
Séminaire de Pathologie Infectieuse UCL
24 novembre 2005
Mont-Godinne

Incidence of infections in acute non-lymphocytic leukemia during induction therapy



Clinical manifestation of pneumonia as influenced by the granulocyte count

	0-100/mm^3 (%)	101-1,000/mm^3 (%)	1,000/mm^3 (%)	
Cough	29/43 (67)	25/36 (69)	62/67 (93)	P=0.002
Sputum production	25/43 (58)	21/36 (58)	57/67 (85)	P=0.003
Rales	30/43 (70)	25/36 (69)	55/67 (82)	-
Consolidation	17/43 (40)	18/36 (50)	42/67 (63)	-
Purulent sputum (by Gram strain)	2/25 (8)	14/21 (67)	48/57 (84)	P<0.001
Bacteremia	23/42 (55)	7/34 (21)	10/58 (17)	P<0.001

Adapted from Sickes et al; Arch Intern Med 1975

Sites of involvement and microbial pathogens

Primary bacteremia

- Viridans streptococci
- Entérobacteriacae : E. coli, Klebsiella sp.
- Pseudomonas aeruginosa

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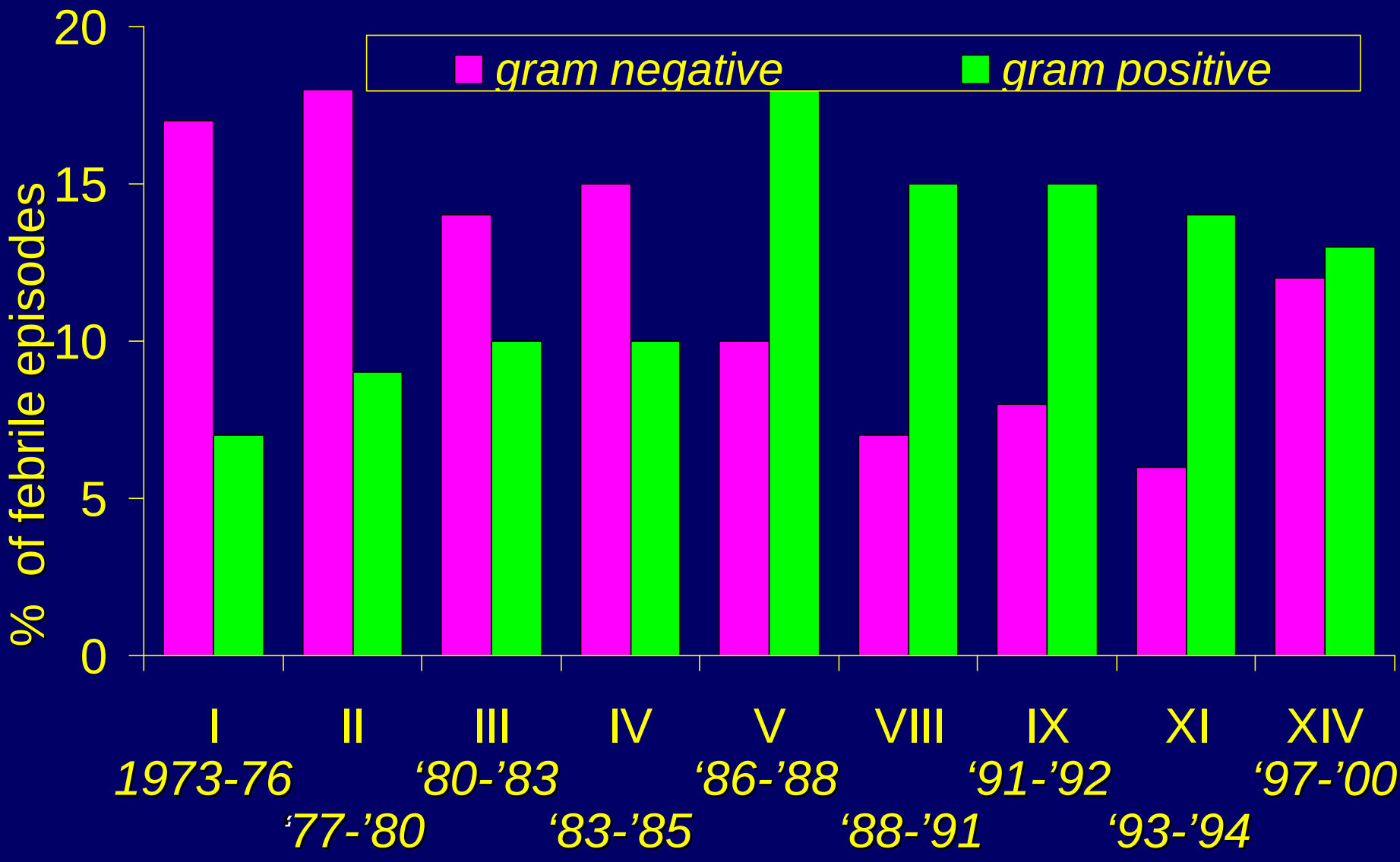
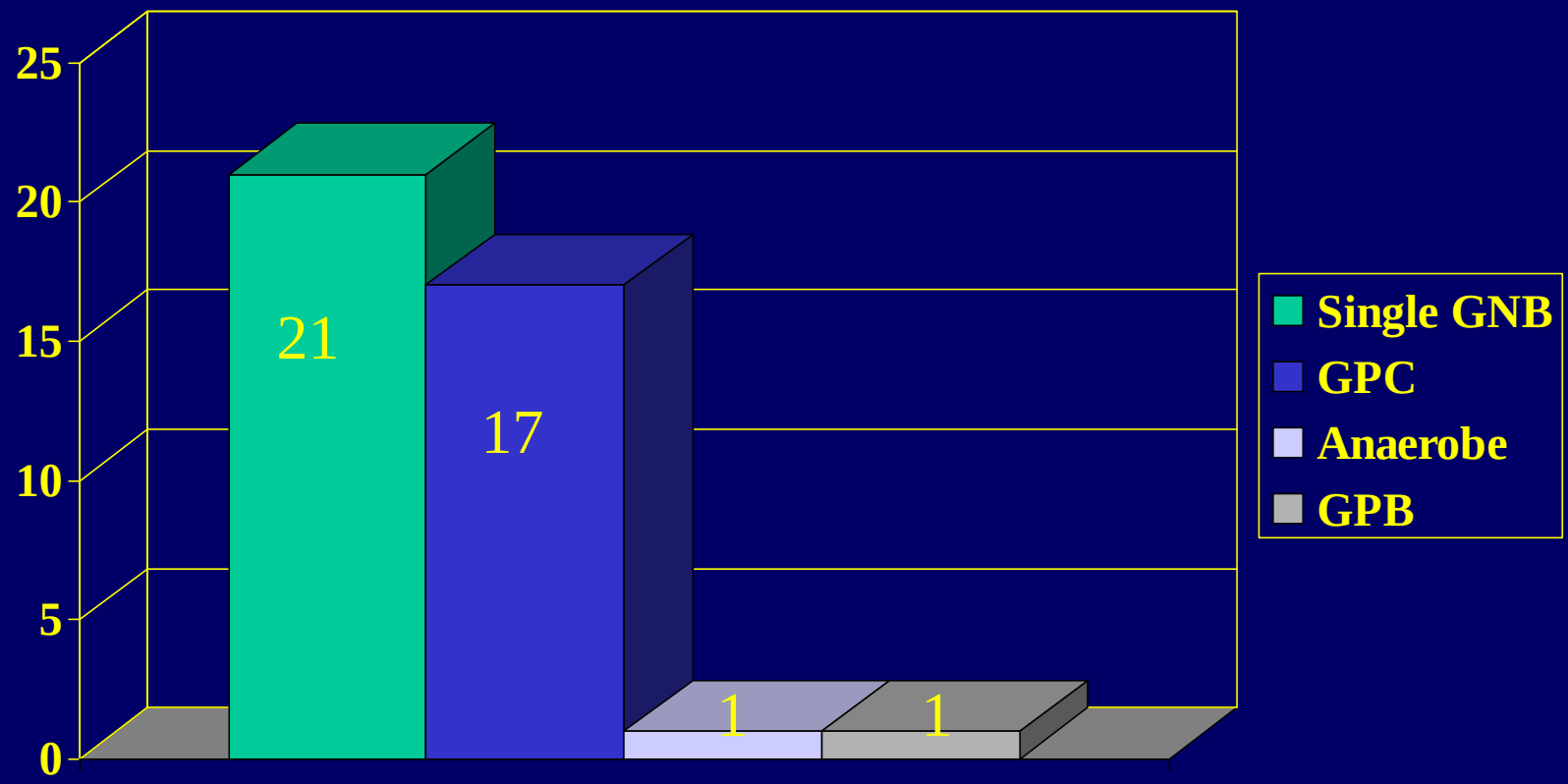
Single-Organisms Bacteremias in EORTC-IATG Trials of empirical therapy of febrile neutropenia



MASCC survey (1997-2003)

FN : 1026
Sepsis :102
Bacteremia : 40



Sites of involvement and microbial pathogens

Oral mucositis

- **Herpes simplex type 1**
- **Oral flora : v. Streptococci,**
  Fusobacterium,
  Stomatococcus,
  Rothia dentocariosa,
  Capnocytophaga,
  Eikenella corrodens
  Bacteroides oralis (necrotizing gingivitis)

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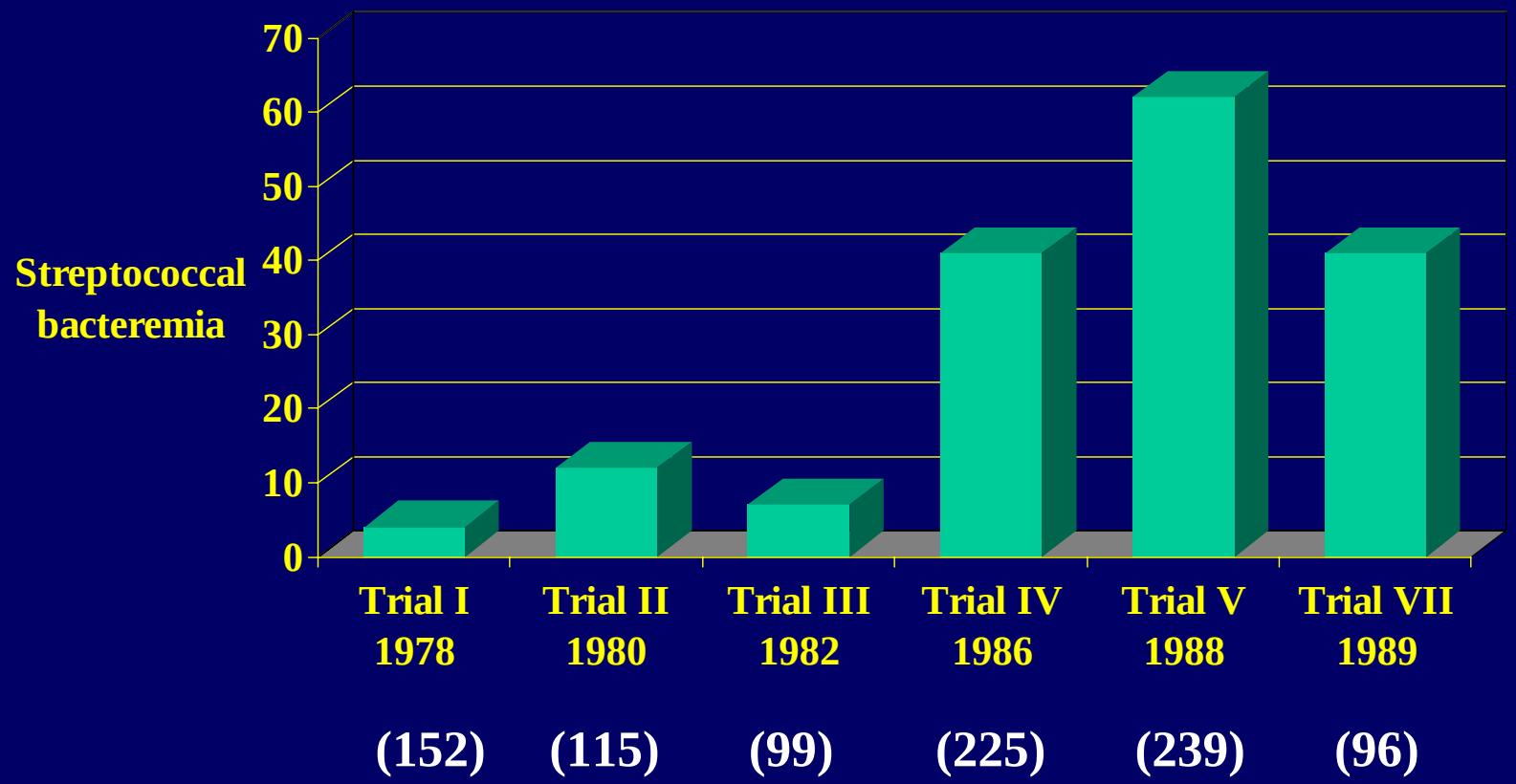
Streptococcal bacteremia in consecutive trials conducted by the E.O.R.T.C. Antimicrobial Therapy Project Group



Reasons of streptococcal increase

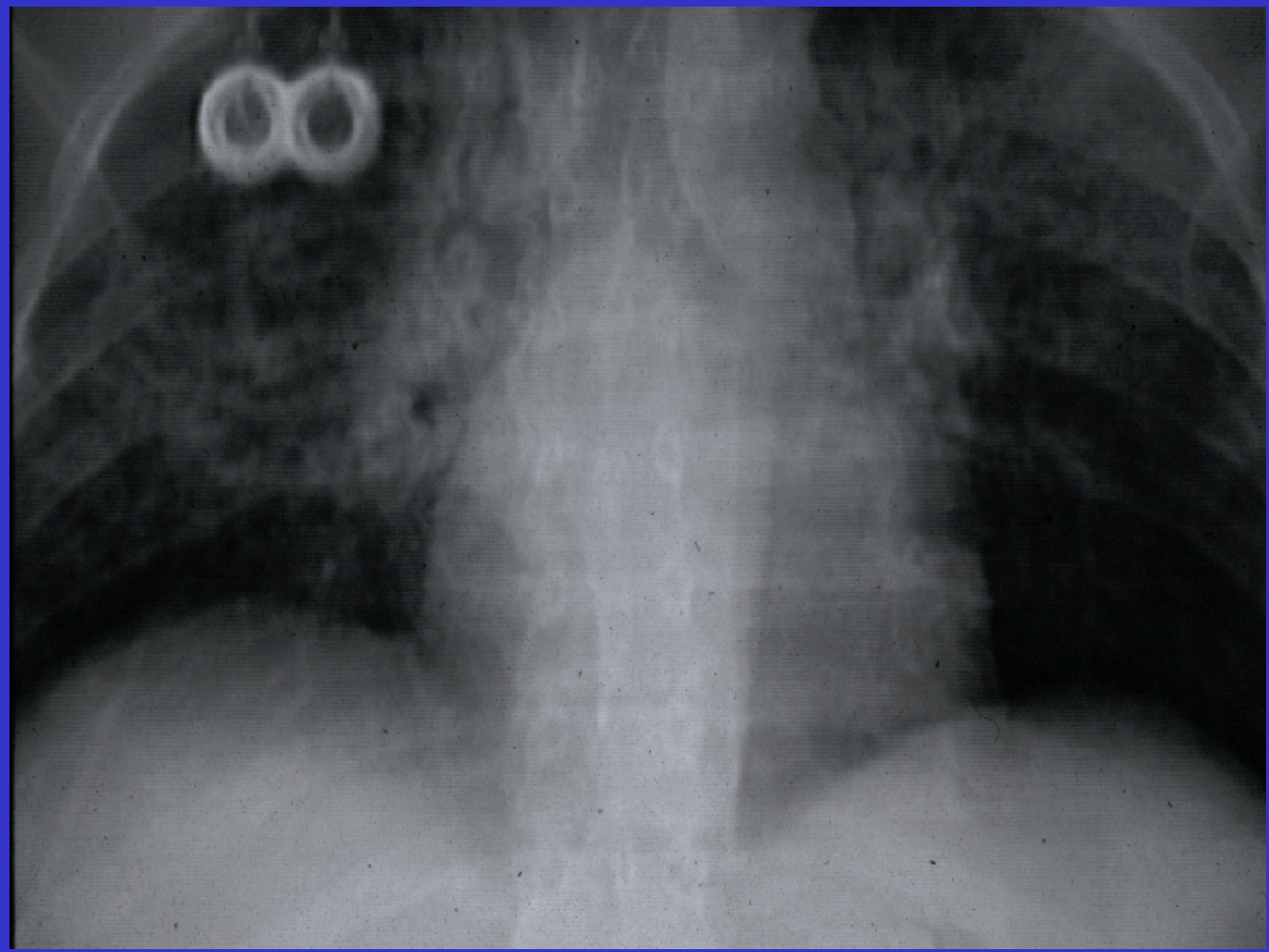
- Oral mucositis :
  - Chemotherapy
  - T.B.I.
  - HSV
- Antimicrobial prophylaxis and treatment
  - Directed against Gram-negative bacteria
  - Specific role of fluoroquinolones

Clinical features of 46 cases of viridans streptococcal septicemia and 92 control cases of septicemia involving other aerobic gram-positive bacteria

Feature	Percentage with feature		Odds ratio	95% Confidence limits	P*
	Controls	Cases			
Flushing	12	57	9.6	3.8, 24.9	<.0001
Chills	21	41	2.7	1.2, 6.3	.02
Hypotension	12	37	4.3	1.7, 11.3	.001
Rash	8	57	15.8	5.5, 47.0	.0001
Desquamation	1	13	13.7	1.5, 97.5	.009
Menstruation	2	20	10.9	2.1, 46.9	.001
ARDS	0	11	24.5	9.6, 62.7	.004
Endocarditis	1	7	6.3	0.6, 93.6	.20
Death	14	11	0.7	0.2, 2.5	.79

* values reflect univariate comparison of cases and controls

Elting LS et al, Clin Infect Dis 1992



α-Strep. Bacteremia and ARDS

- **ARDS may occur without shock**
- **Within 14 days after bacteremia**
- **No α-streptococci in the lungs**
- **Despite early and adequate therapy and negativation of blood cultures**
- **No toxin**
- **Coincidence with chemotherapy ?**
- **Mutual synergism between α-Strepto and Chemotherapy ?**

Sites of involvement and microbial pathogens

Typhlitis

- **Clostridium septicum**
- **Clostridium perfringens**
- **Other clostridia**

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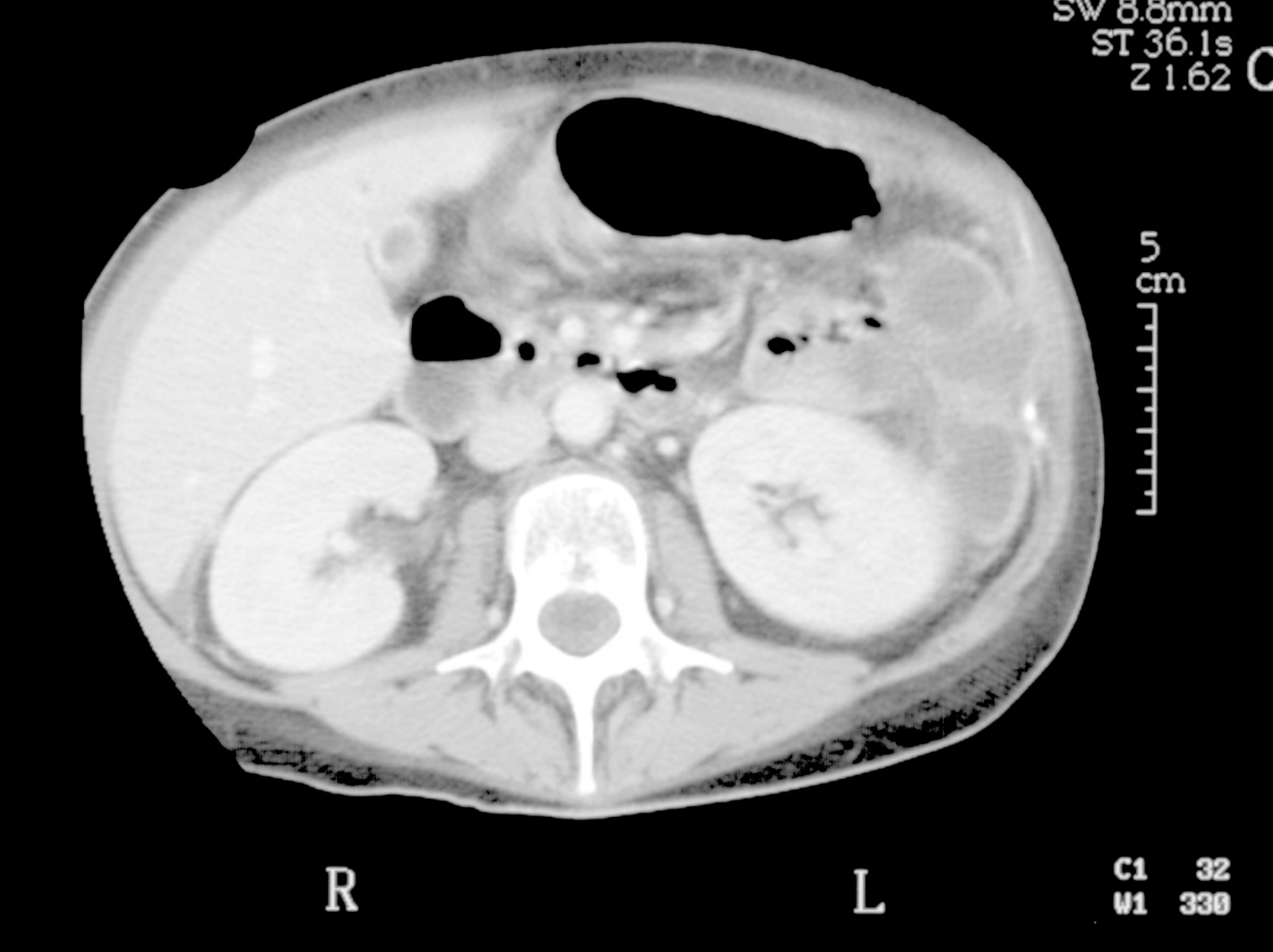
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cm
R
L
C1 32
W1 330


ST 36.1s
Z 1.62 C
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cm
R
L
C1 20
W1 273

Sites of involvement and microbial pathogens

Perianal abscess

Polymicrobial :

- GNB (E.coli),
- Anaerobes (B. fragilis)
- Enterococci

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Sites of involvement and microbial pathogens

Short duration of neutropenia (N<7 days)

Conventional bacteria (70 % associated bacteremia)

- S. pneumoniae
- H. influenzae
- Enterobacteriacae
- P. aeruginosa

Long duration of neutropenia (N>7 days)

Multiresistant organisms

- ESBL or AmpC GNB
- Multiresistant P. aeruginosa
- MRSA

Fungi

- Aspergillus, Mucor, Fusarium, …

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Sites of involvement and microbial pathogens

Skin and soft tissue

Catheter site

- CNS

- S. aureus

- Bacillus sp.

- Corynebacterium JK

Moisture-laden areas

- P. aeruginosa (ecthyma gangraenosum)

Secondary skin lesions

- Candida sp., Trichosporon sp., Fusarium, …

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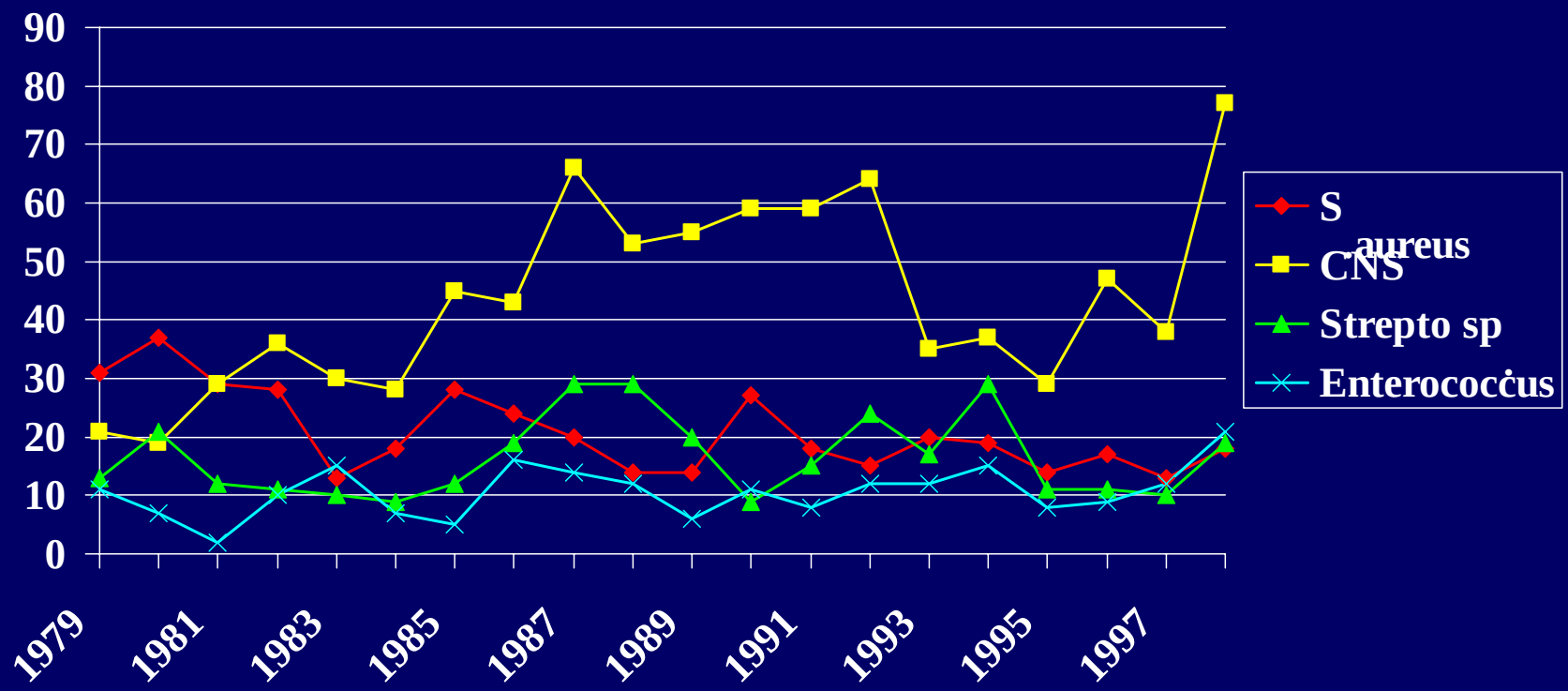
Institut Jules Bordet : bacteremic episodes

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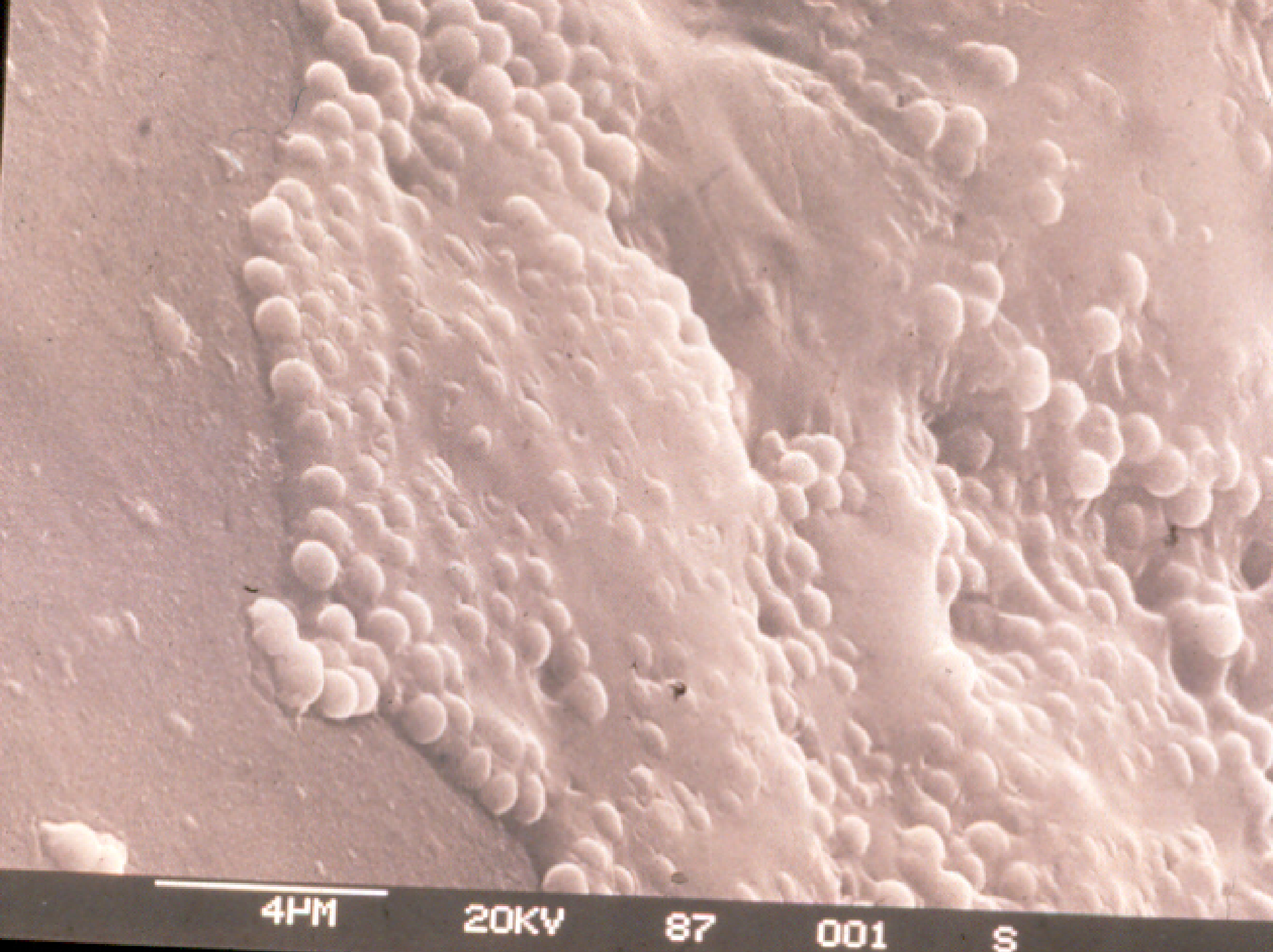
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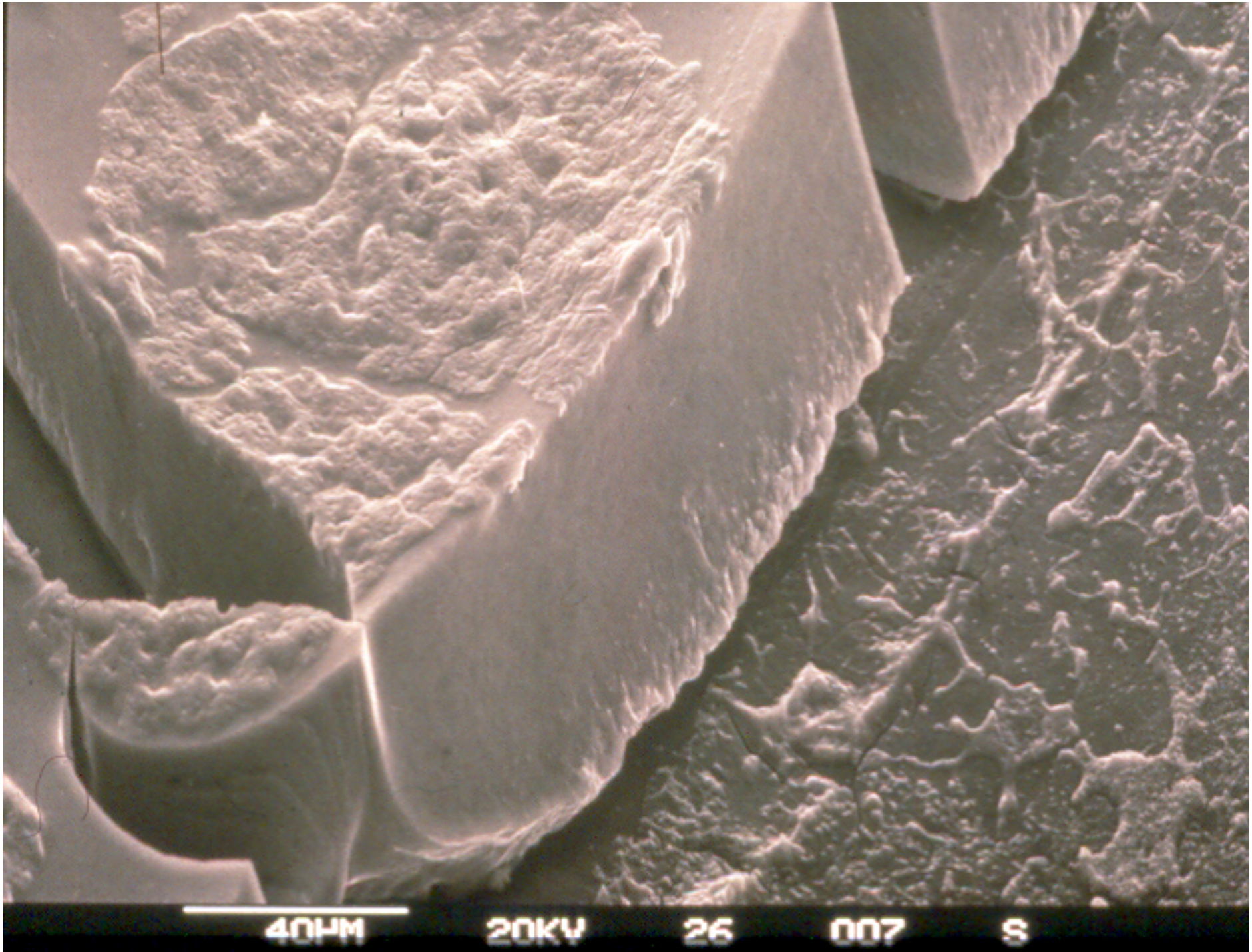
40UM
20KV
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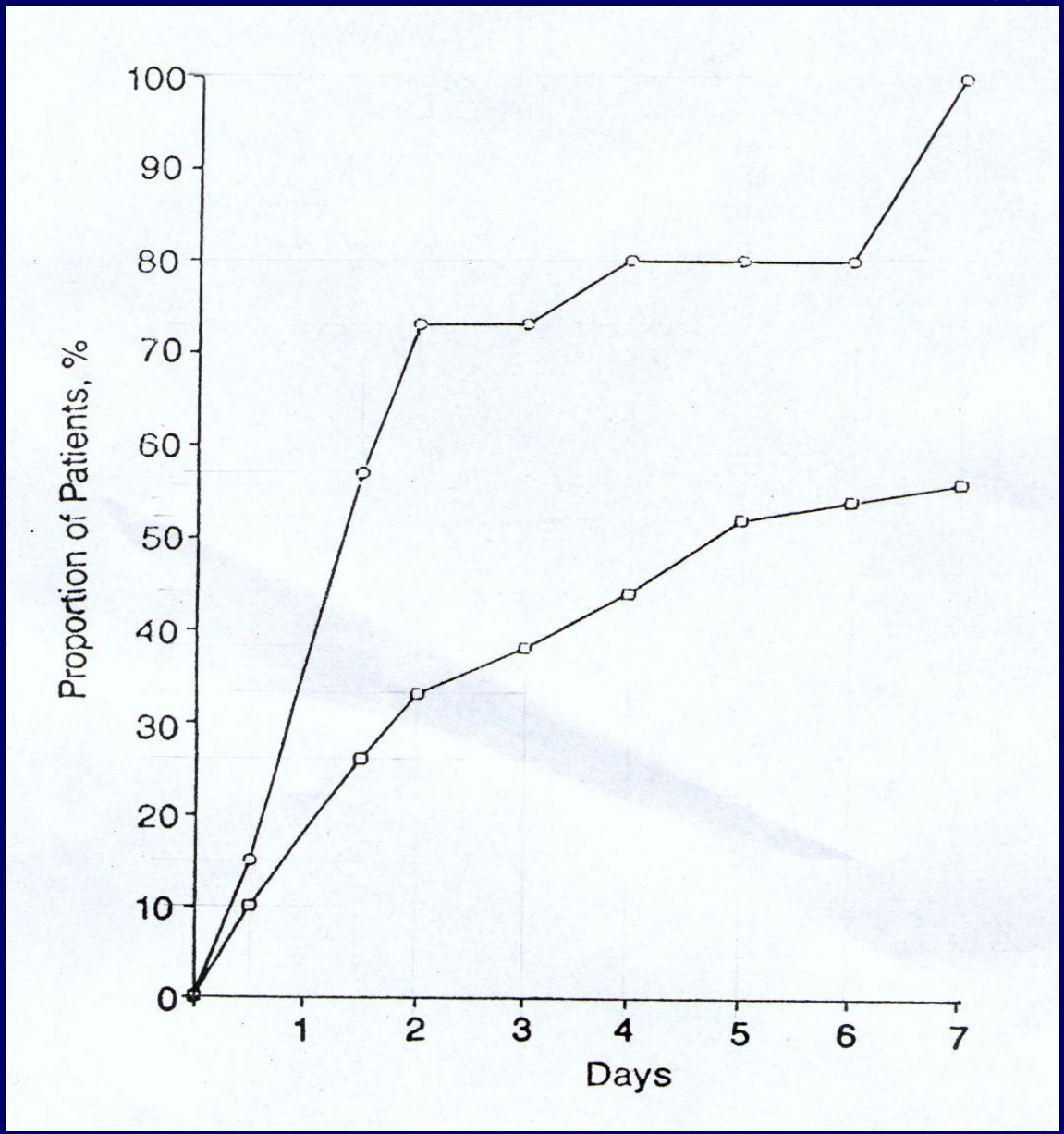
S

Risk of dying due to delay in administration of appropriate antibiotic therapy.



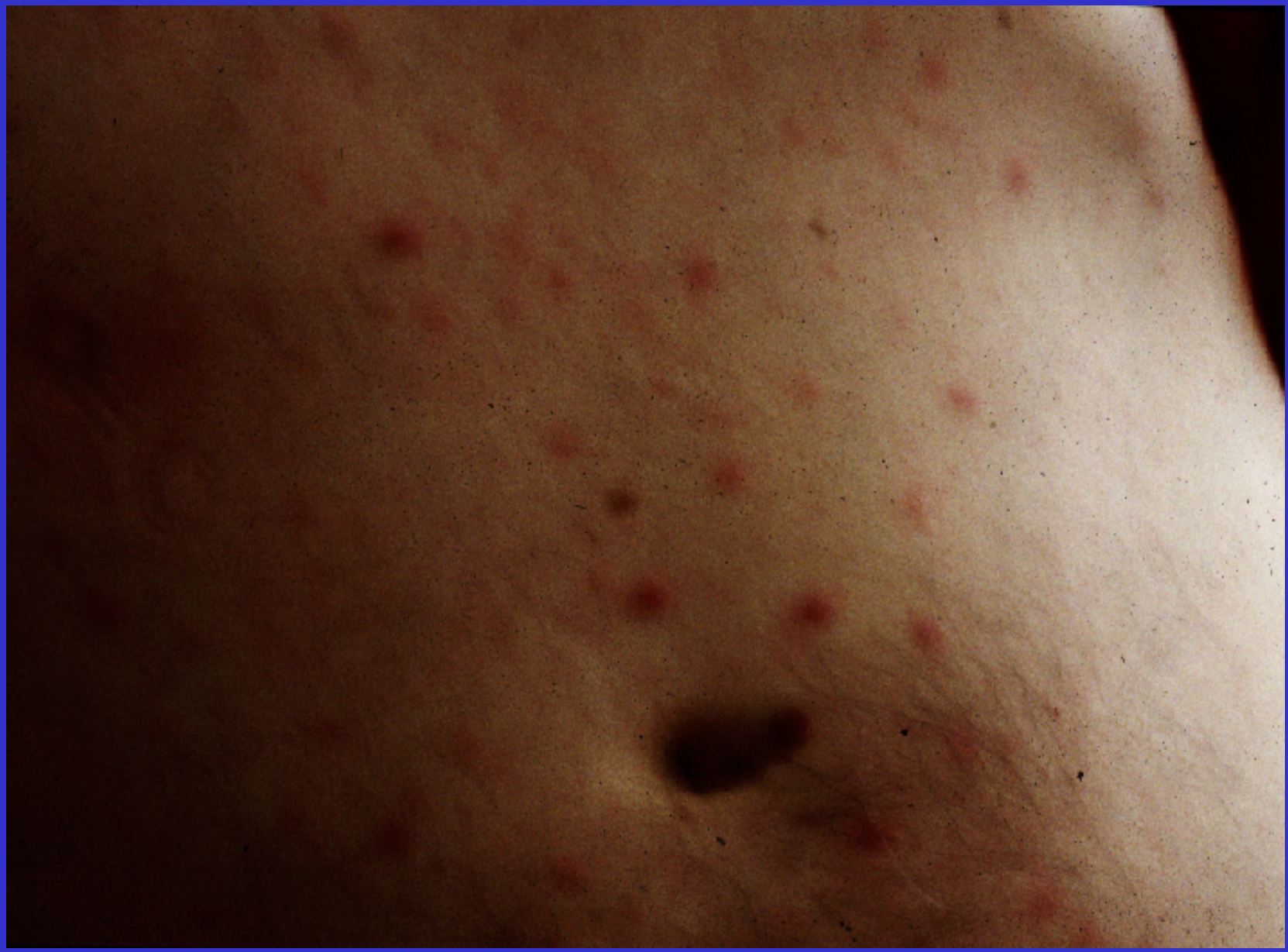
Circles : neutropenic patients

Squares : all patients

Bodey et al, Arch Intern Med 1985

Pseudomonas aeruginosa bacteremia EORTC Trials

	III (1981-1982)	IV (1983-1985)	Vb (1986-1987)	VI (1987)	VII (1989)	IX (1991-1992)	XI (1993-1994)	XII (1996-1997)	XIV (1998-2000)
Total n° of pts	742	1074	891	111	677	696	987	353	763
Pts with P. aeruginosa bacteremia	33	33	22	5	12	13	8	5	11
	(4,4%)	(3,1%)	(2,5%)	(4,5%)	(1,8%)	(1,9%)	(0,8%)	(1,4%)	(1,4%)



Autopsy series (Bodey 1992)

All fungal infections : 25 % in leukemia

25 % in BMT

- Candidiasis : 58 %
- Aspergillosis : 30 %
- Cryptococcosis : 2 %
- Not identified : 10 %

Another series :

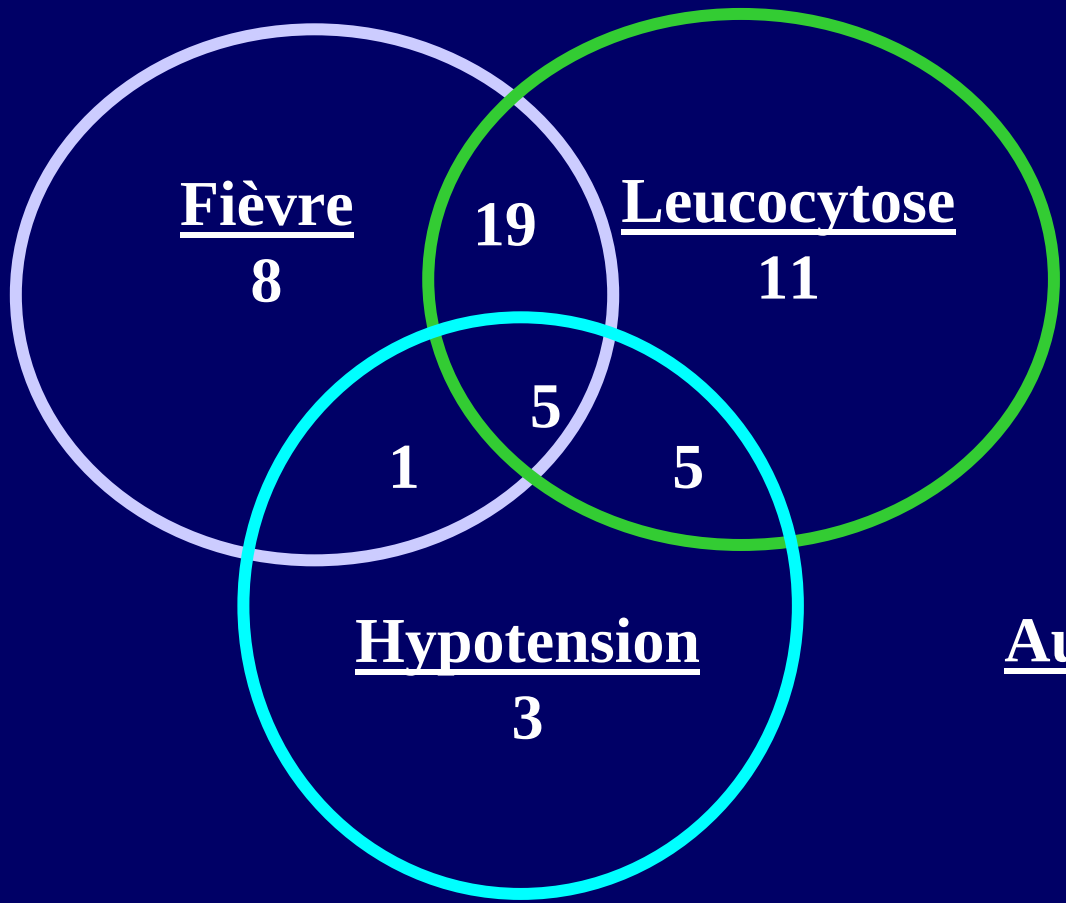
- Mucormycosis : 2 %

Les facteurs de risque de candidose d 'origine iatrogène

- **Le cathétérisme intraveineux**
- **Les antibiotiques à large spectre**
- **Traitement immunosuppresseur (corticoïdes, cyclosporine, azathioprine)**
- **L 'alimentation artificielle**
- **La durée du séjour à l 'hôpital**
- **Chimiothérapie aplasiante - mucosité**
  - neutropénie

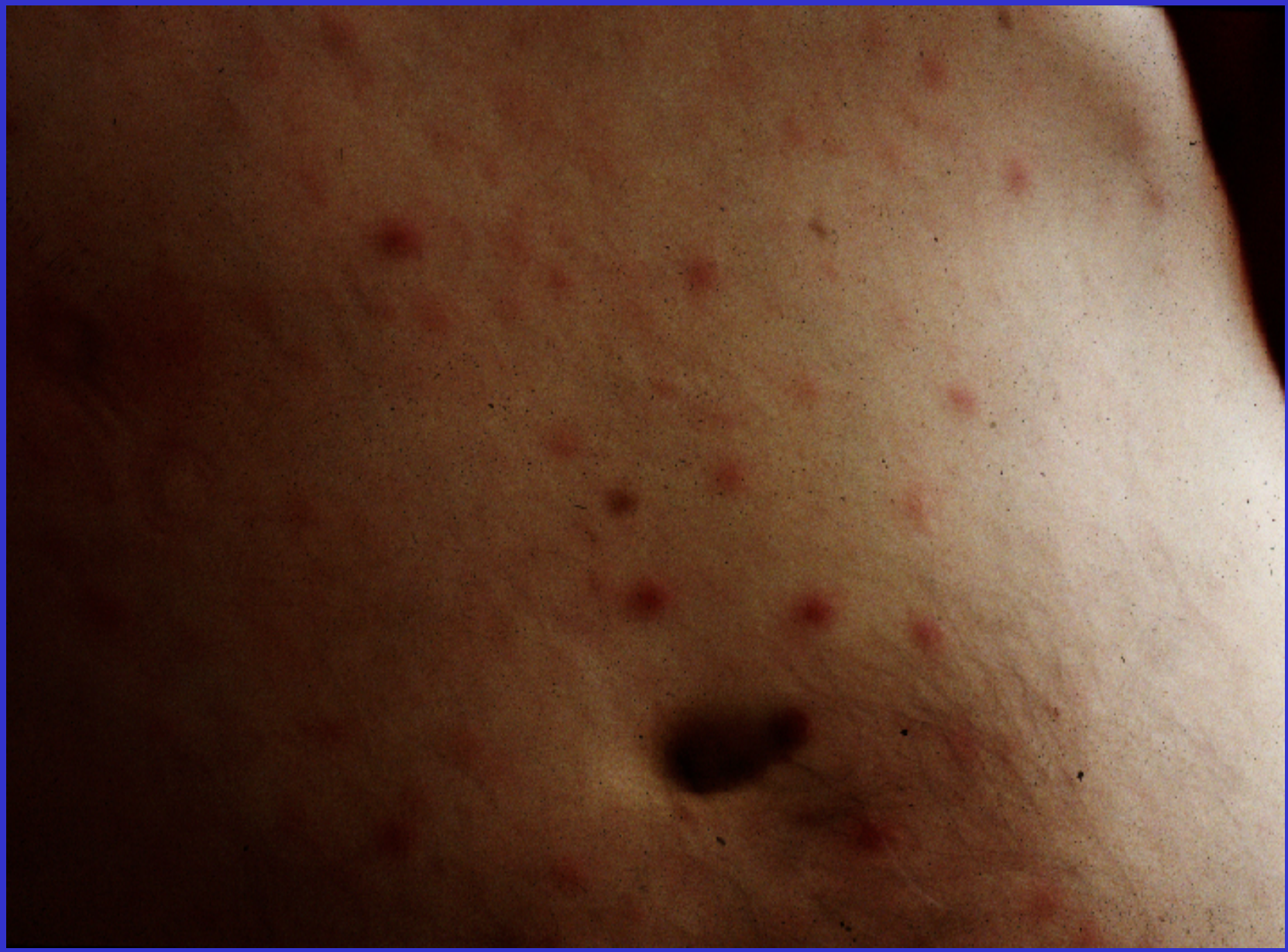
Fraser VJ e.a. Clin Infect Dis 1992
Sobel JD Crit Care Clin 1988
Edwards JE Jr N Engl J Med 1991
Komshian SV Rev Infect Dis 1989
Wey SB Arch Intern Med 1989

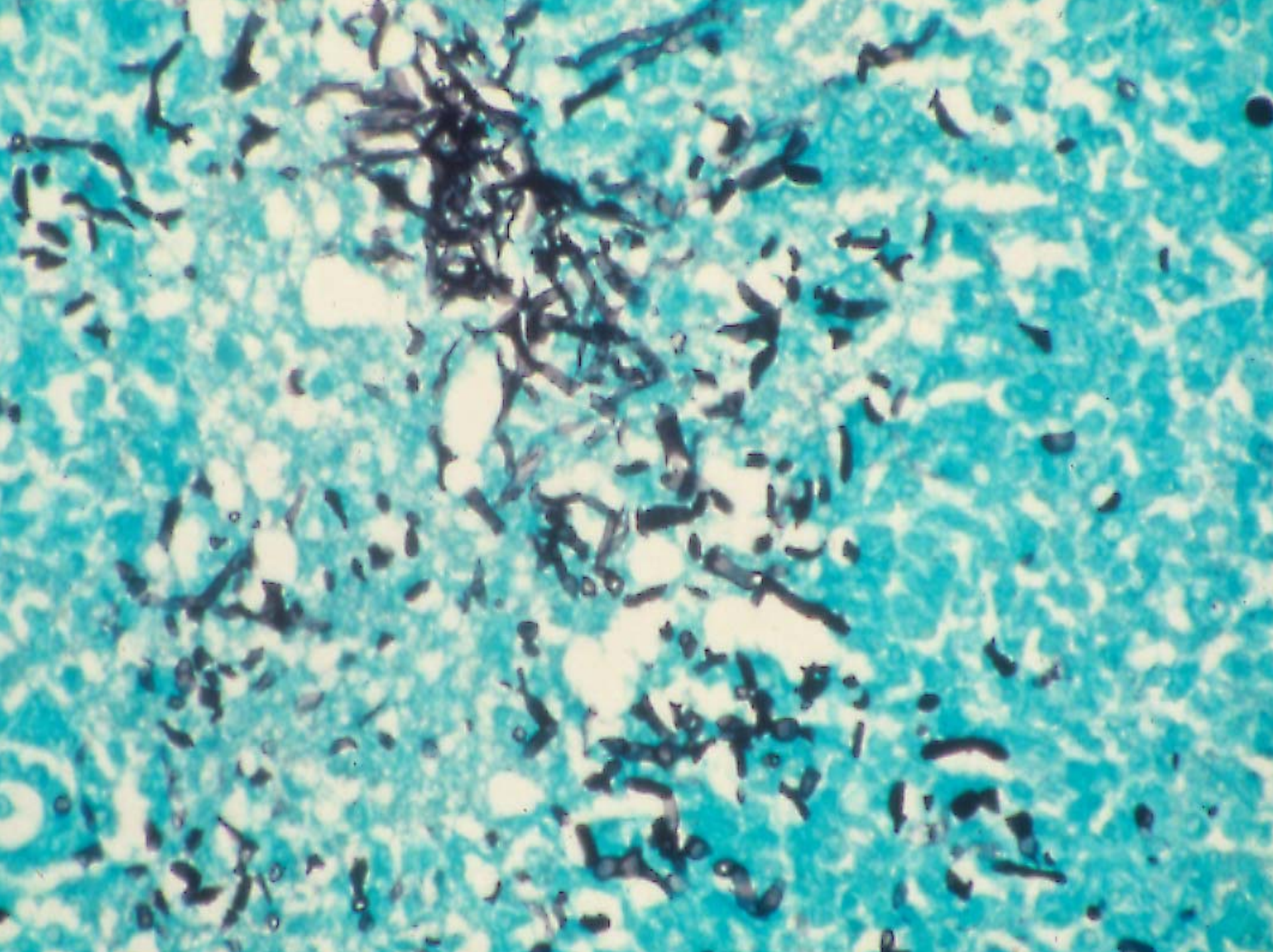
Les signes cliniques et biologiques de la candidose chez des patients opérés

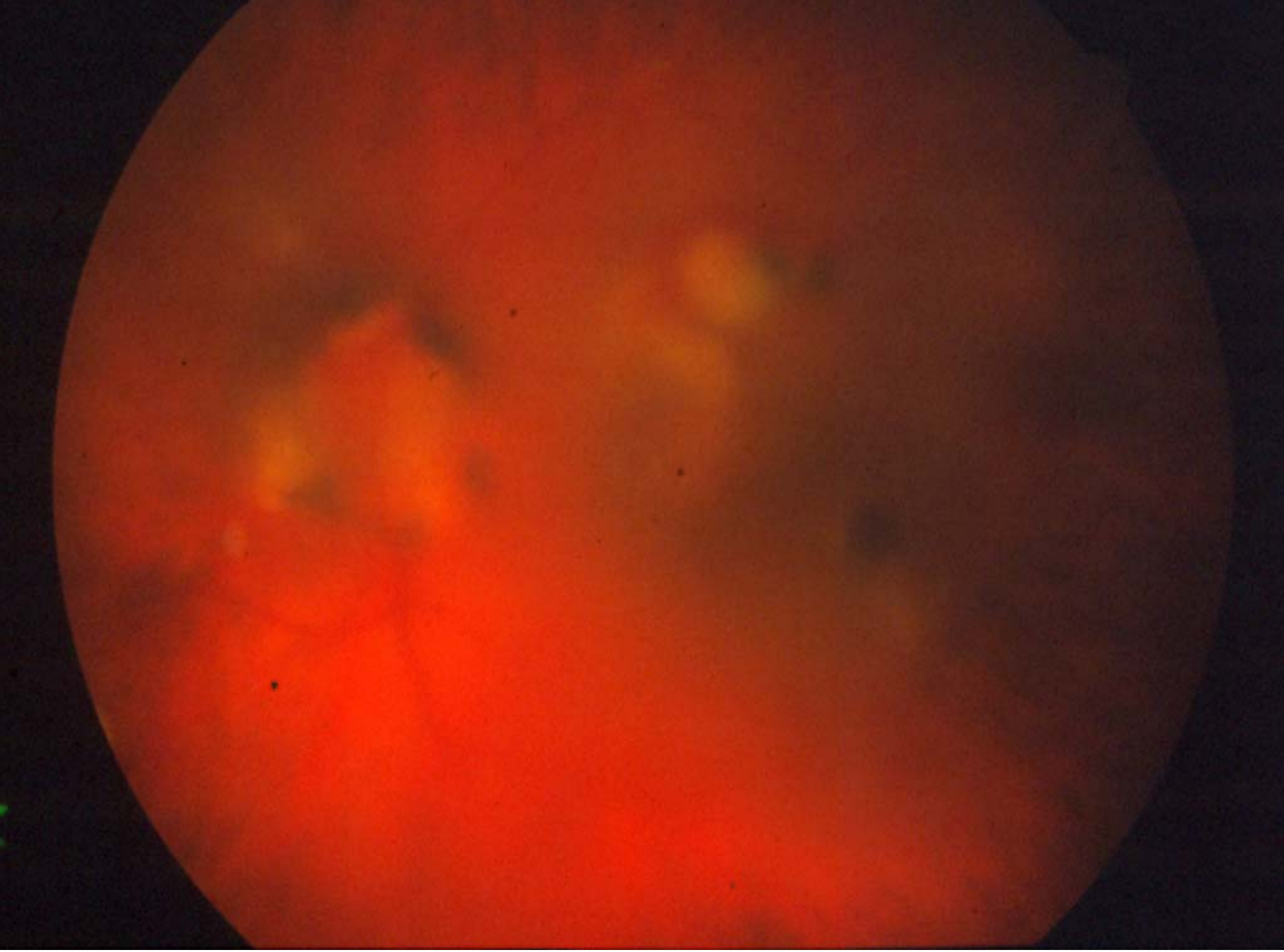


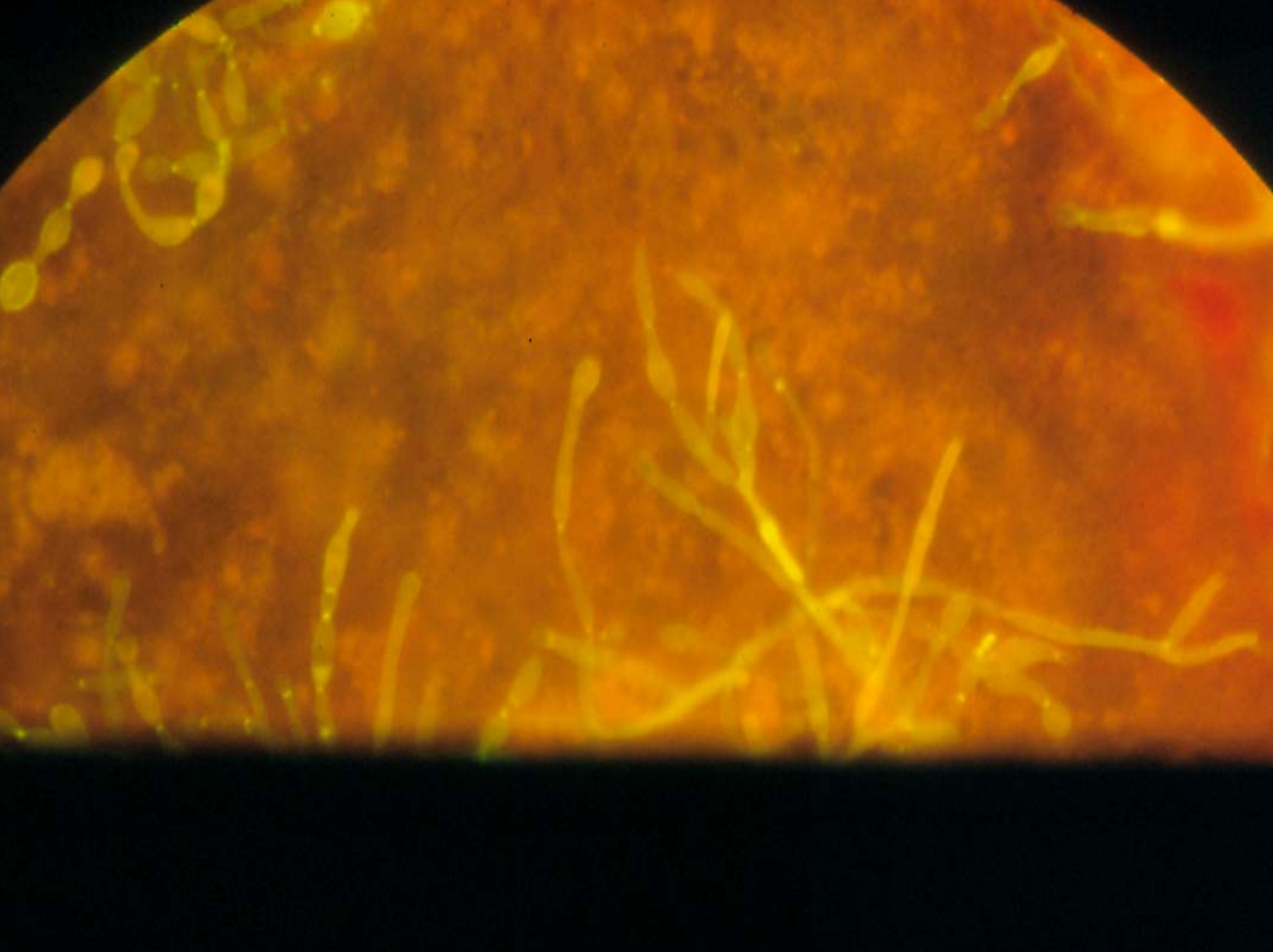
N= 55 patients soumis à une chirurgie

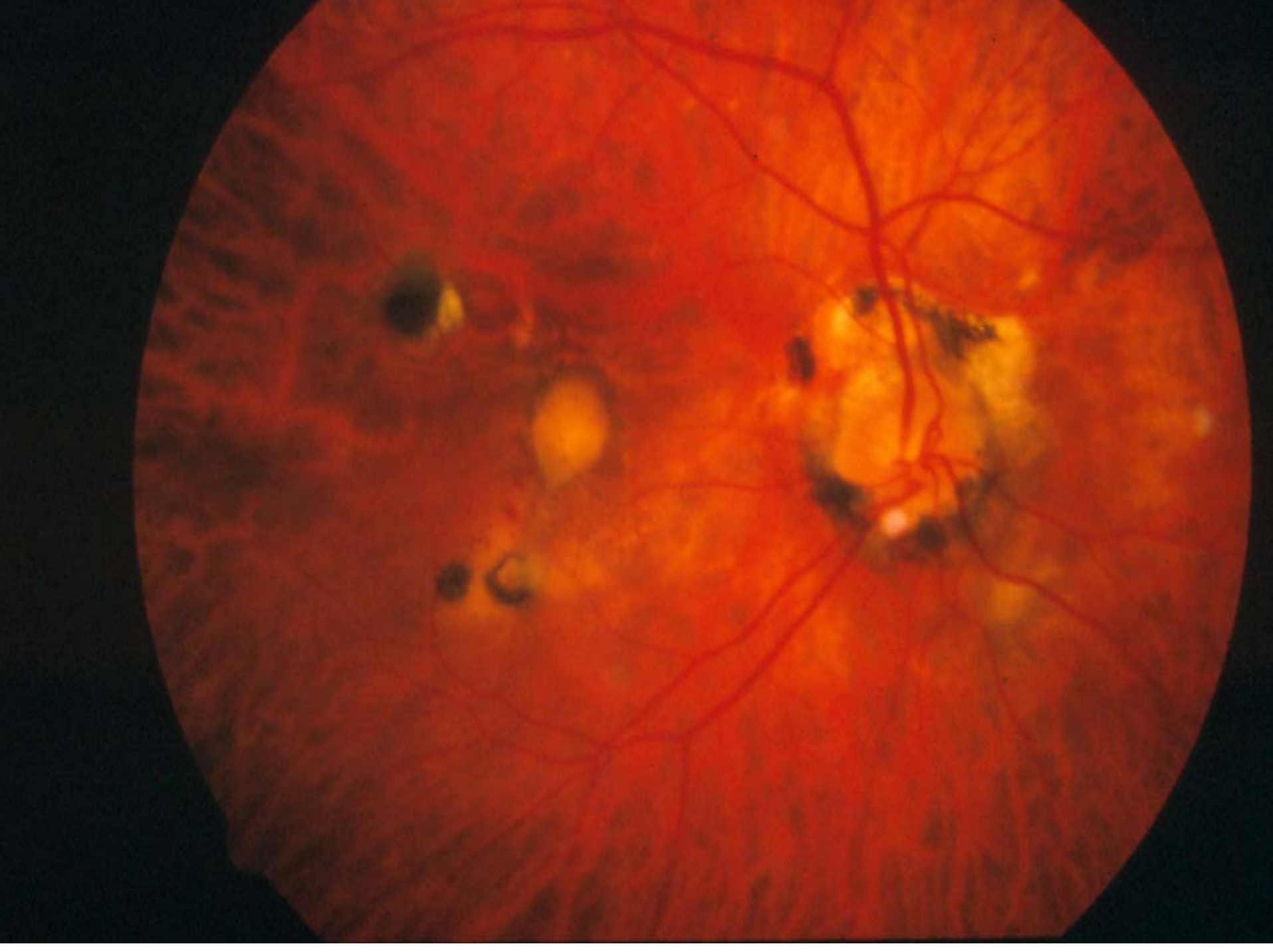
MARSH RB e.a. Ann. Surg 1983;198:42-47

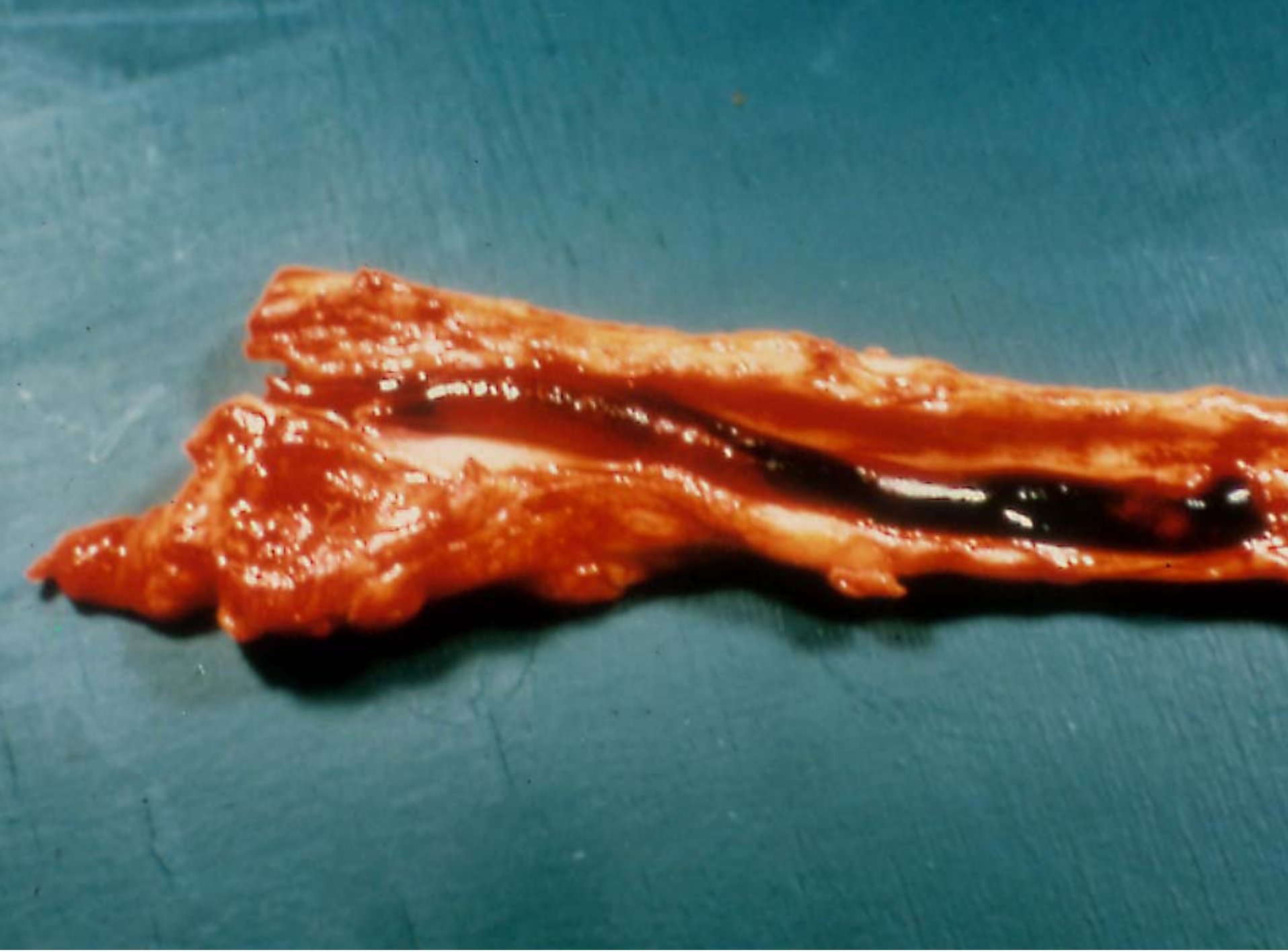








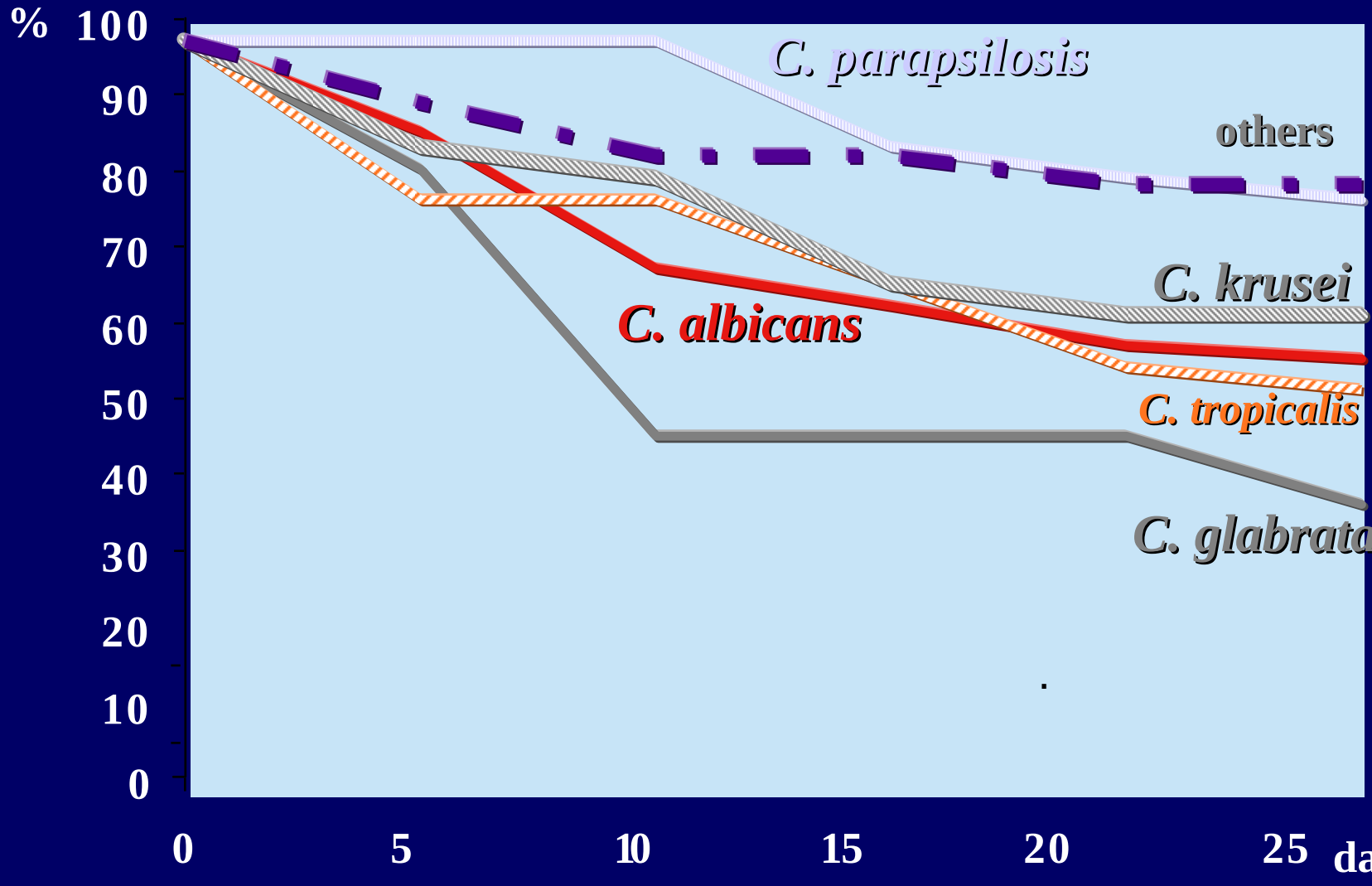




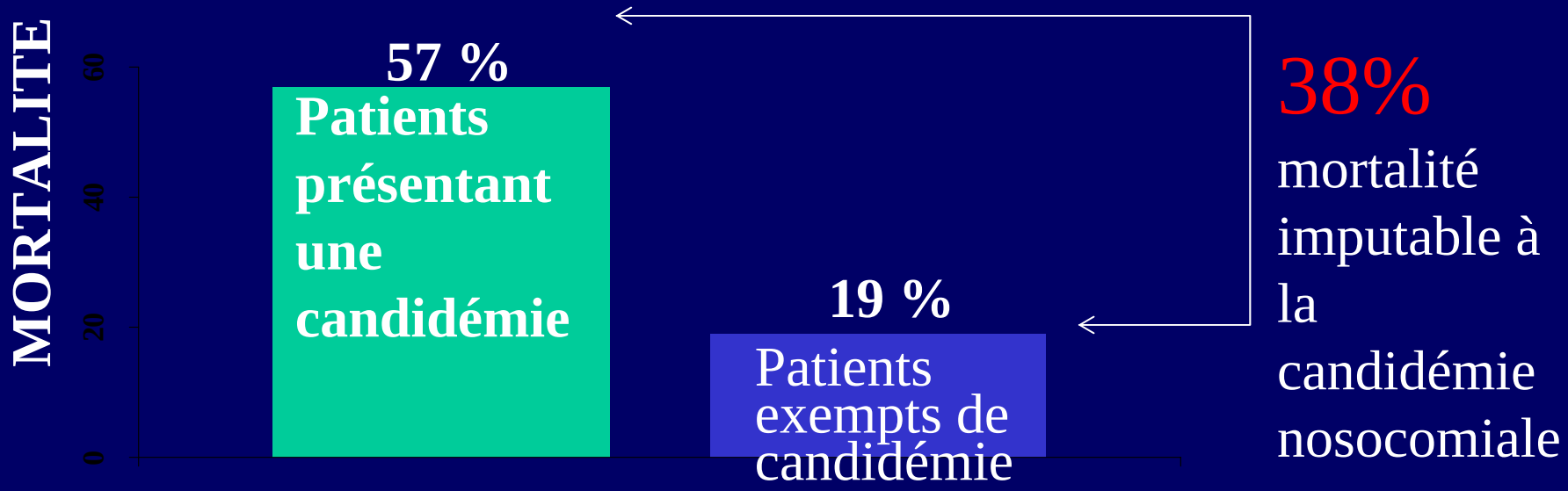
EORTC
IFICG

St Radboud

FUNGEMIA: SURVIVAL ACCORDING TO SPECIES
VISCOLI ET AL., Clin Infect Dis 1999

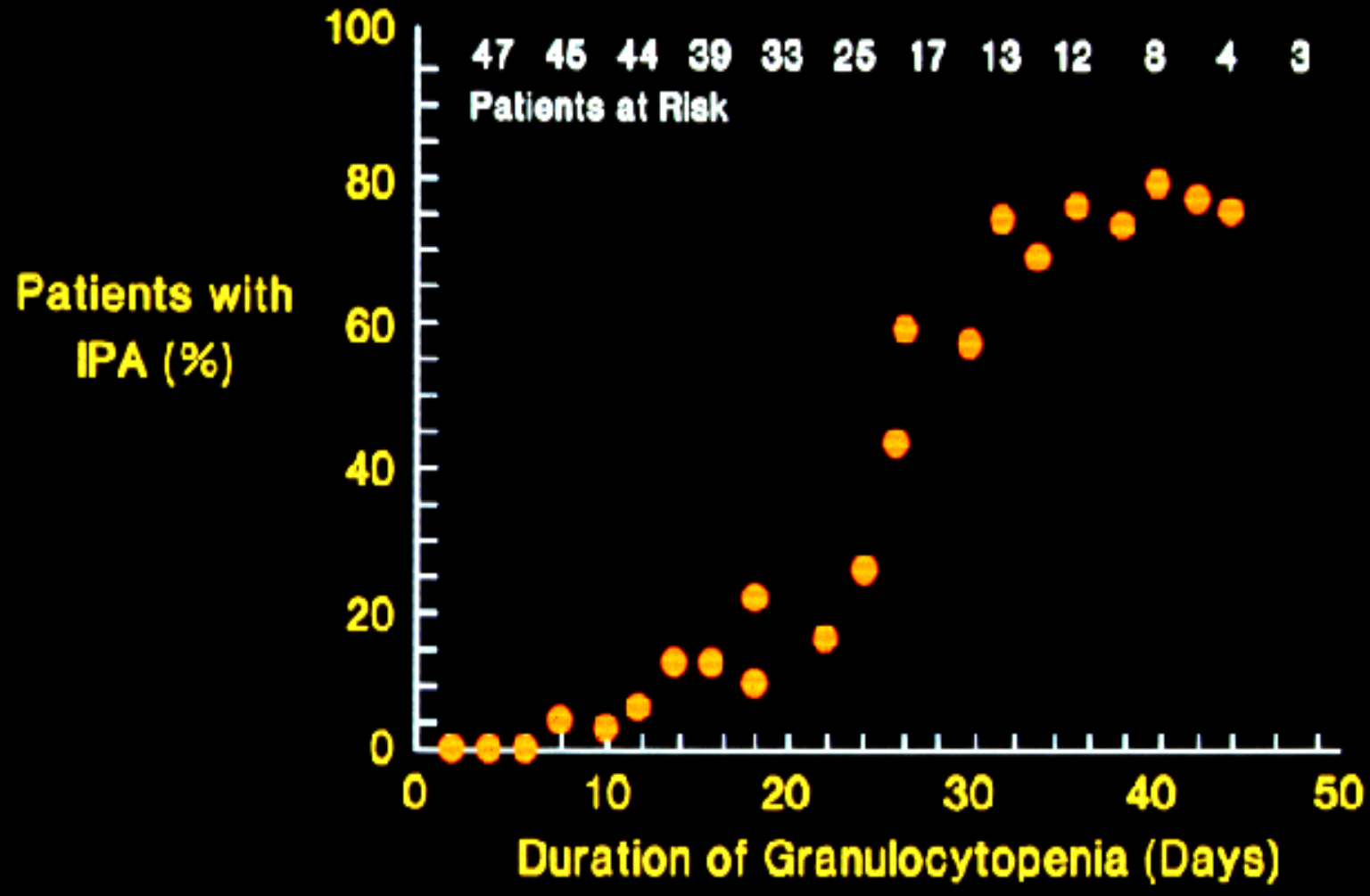


La mortalité due à la candidémie nosocomiale



Essai mené chez 176 patients appariés 2 par 2, chez lesquels la mortalité due à la candidémie à été étudiée

WEY SB e.a Arch Intern Med 1988; 148:2642-2645

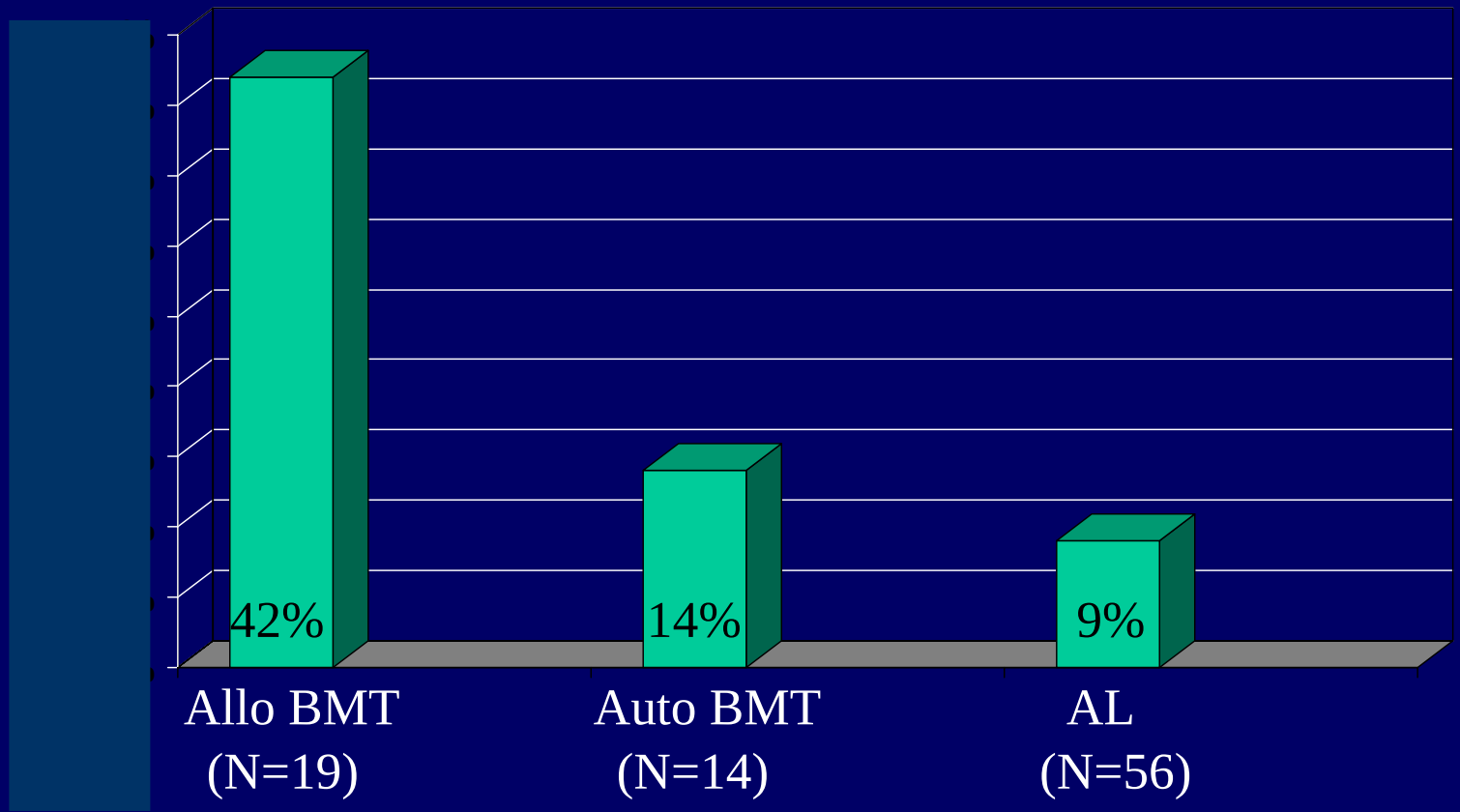


Percentage of all granulocytopenic patients who developed invasive pulmonary aspergillosis (IPA) as a function of duration of granulocytopenia. Two linear regression lines were calculated: one between the 1st and 22nd days, $y = 1.0X - 4.0$; the other between the 22nd and 36th days, $y = 4.3X \cdot 73$

Gerson et al., 1984

Institut Jules Bordet
Aspergillose invasive 2002-2003 (9 mois)

Incidence A.I.



Mortalité globale : 37 %

Directement liée à A.I. : 12.5 %

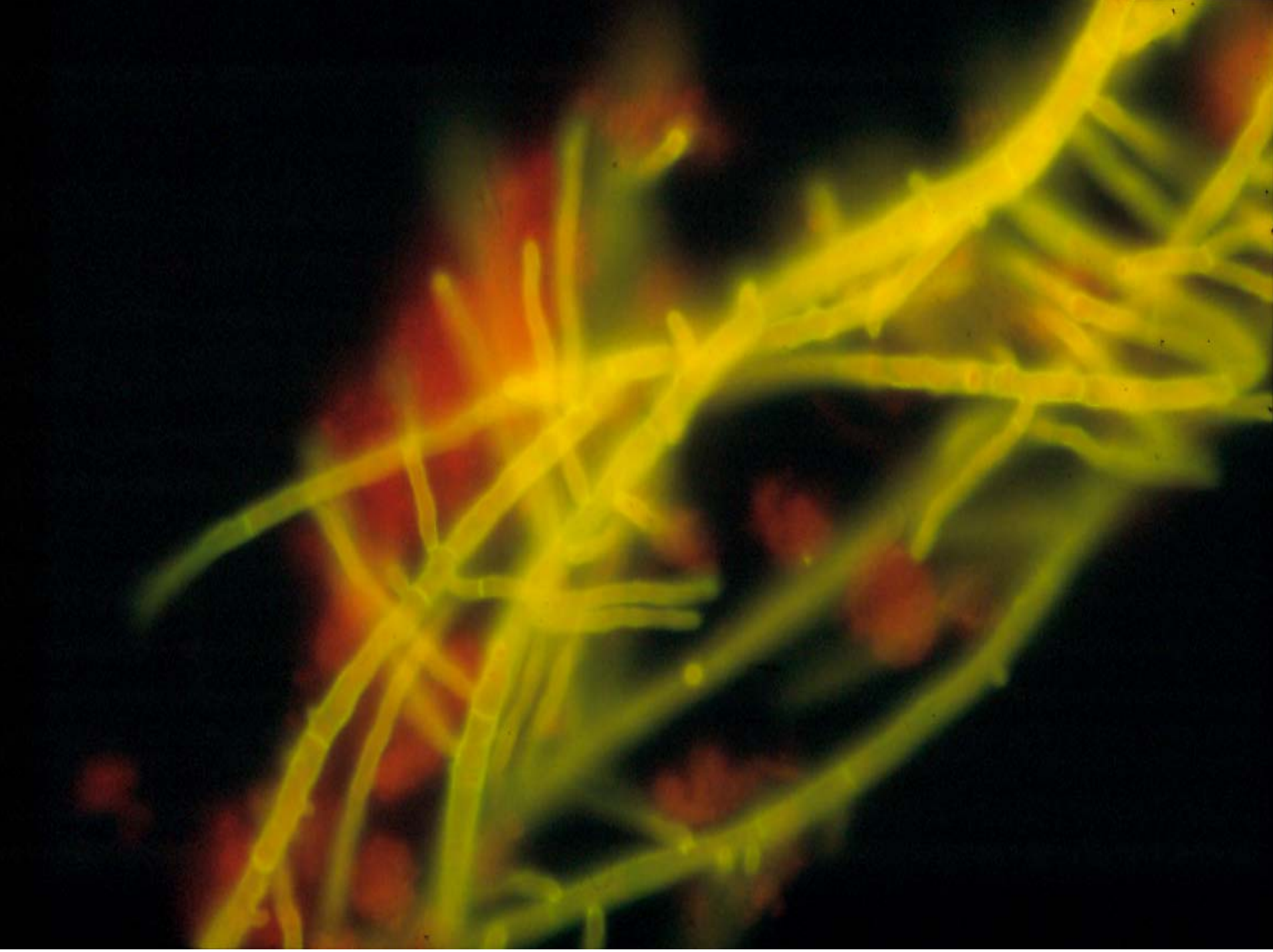
} allo BMT

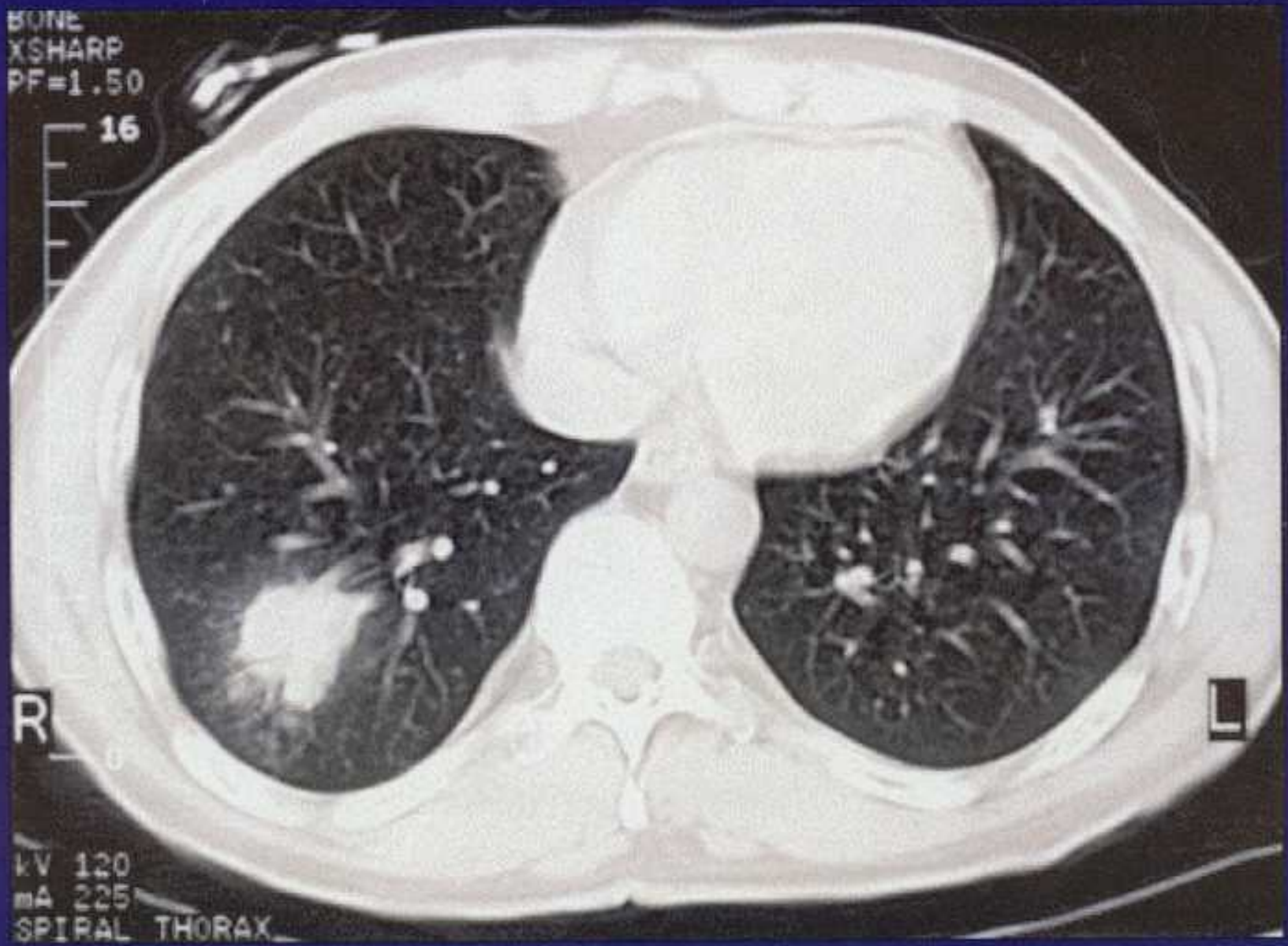
Invasive aspergillosis : clinical manifestations

Persistent fever

- Pneumonia : - Pleuritic chest pain
  - Cough
  - Dyspnea and hypoxia
- Sinusitis : - Nasal discharge
  - Epistaxis
  - Facial swelling and tenderness


09 / 01 / 02

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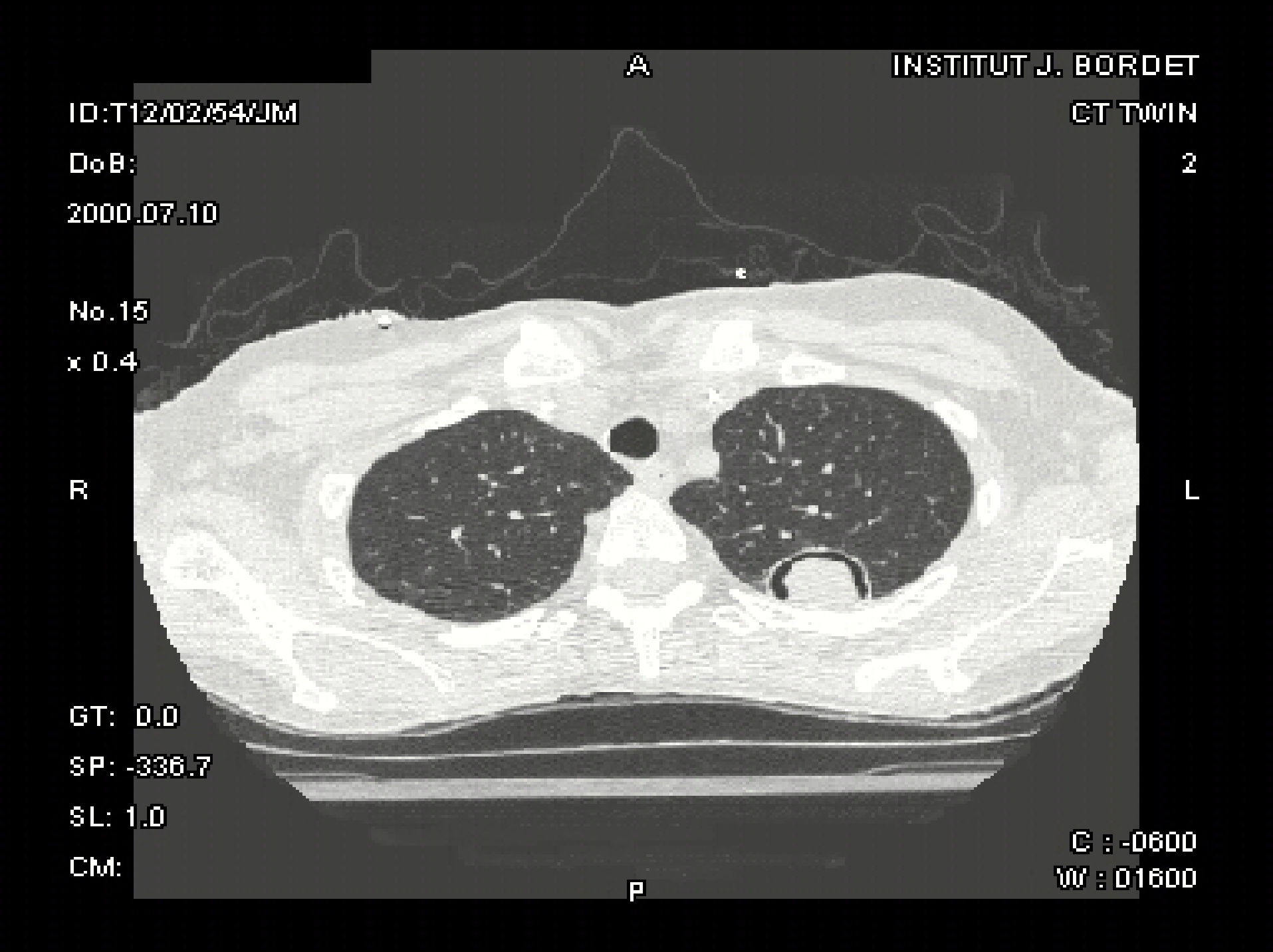
16
R
L
kV 120
mA 225
SPIRAL THORAX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INSTITUT J. BORDET
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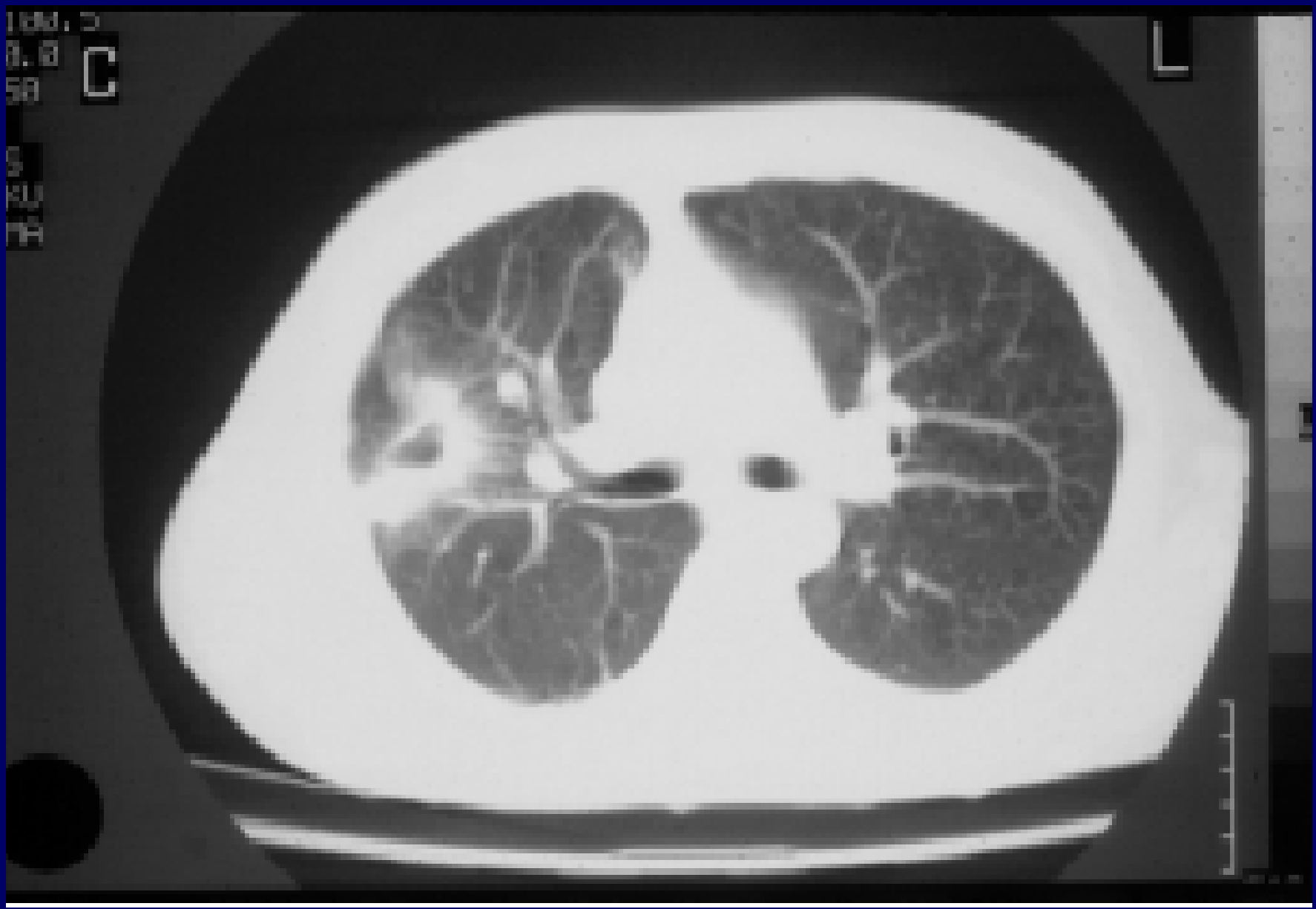

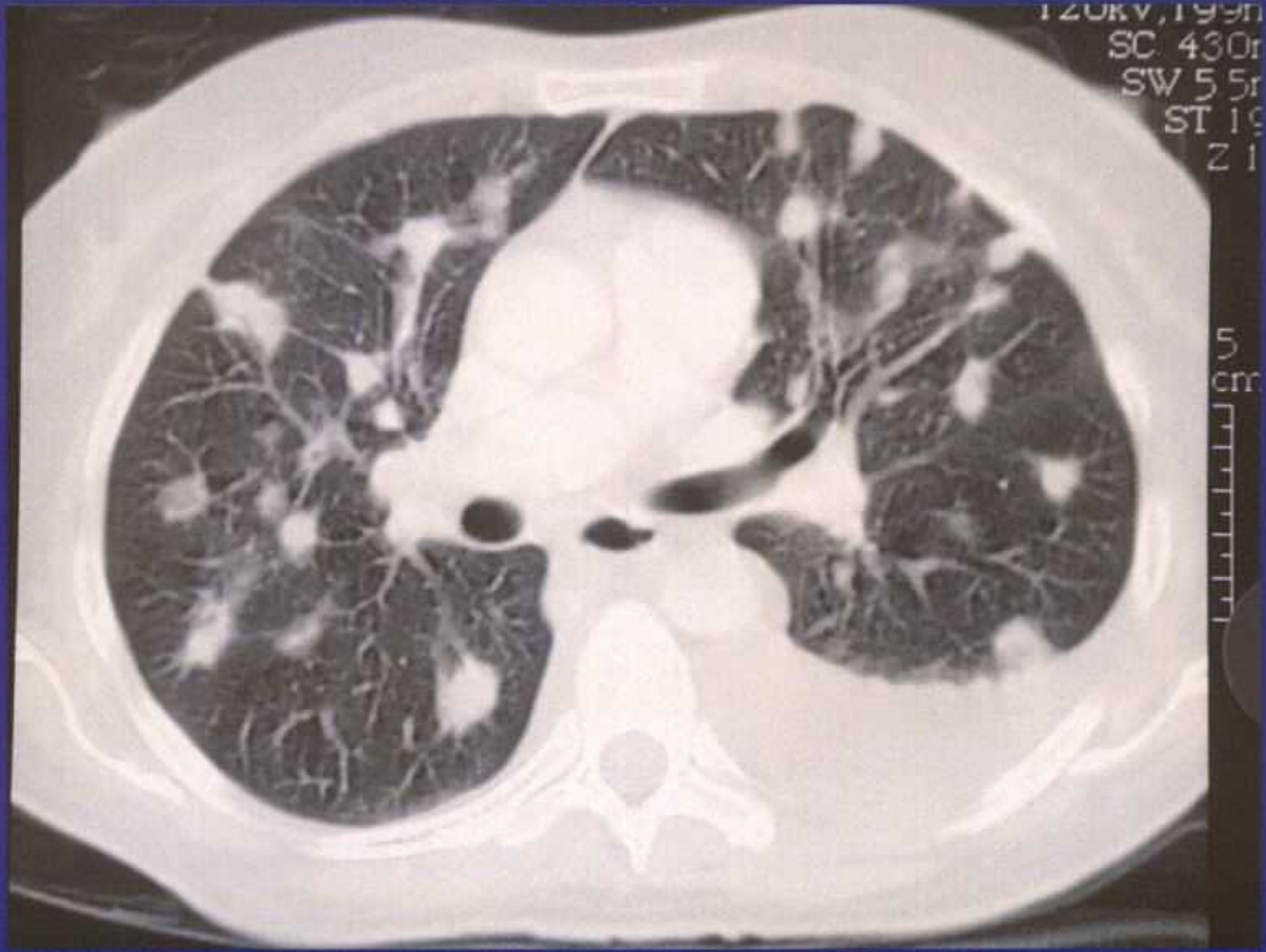
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CT TWIN
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No.21
x 0.7
R
L
GT: 0.0
SP: 113.1
SL: 1.1
CM:
C : 00150
W : 02500
P

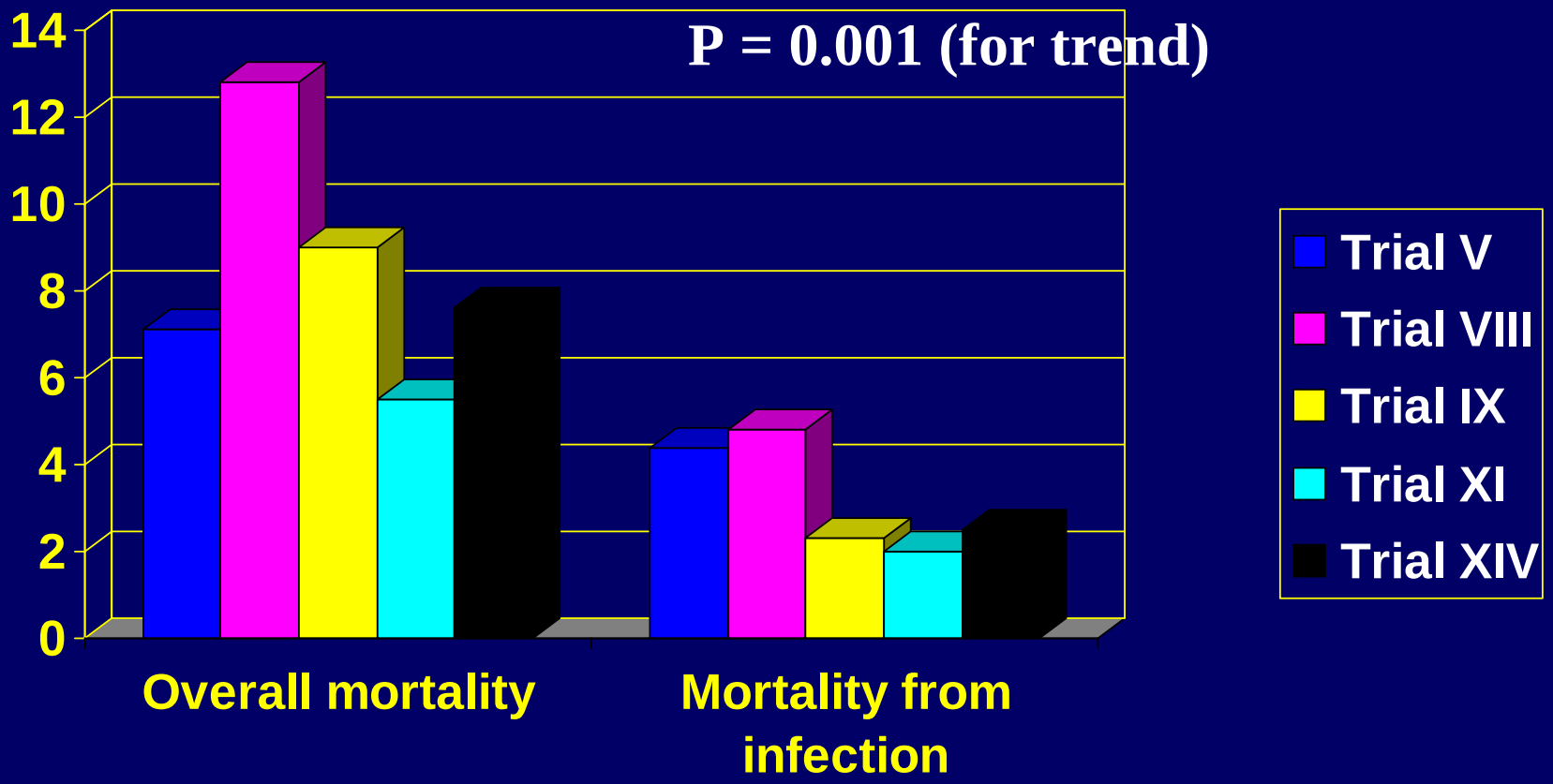
Patients avec greffe de moëlle

	Allogreffe	Autogreffe	Total
Aspergillose invasive	5	6	11
Succès	0	2	2
Echecs	5	4	9
Décès	5	5	10 (90.9 %)
N° d'autopsies/décès	0/5	5/5	5/10
Autopsies positives	-	4/5	4/5
Colonisation	1	1	2
Total	6	7	13

Mesures simples d 'hygiène

- Alimentation bien cuite
- Hygiène bucco-pharyngée stricte
- Hygiène corporelle soigneuse
- Eviter les lieux publics
- Eviter le jardinage
- Manipulation stérile du site d 'implantation du cathéter ainsi que la tubulure

Mortality rate in patients randomised in IATG trials (1985-2000)



MASCC survey (1997-2003) Mortality

	Sepsis on admission	Breakthrough sepsis	No sepsis
Nb of pts	27	75	919
Death	5 (18.5 %)	31 (41.3 %)	20 (2.2 %)

Major elements of standard care

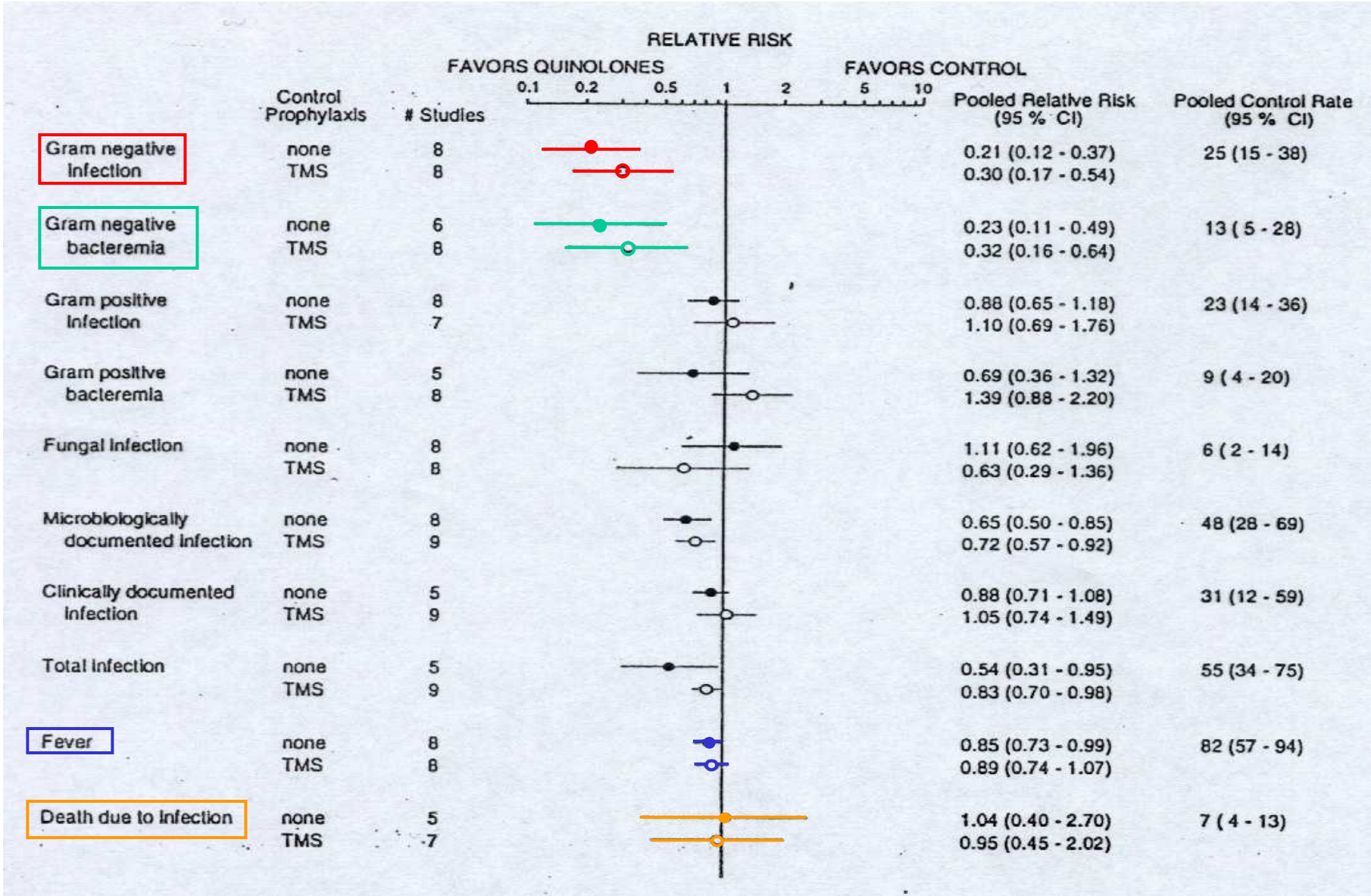
- Empiric therapy
- Double coverage with β-lactam and an aminoglycoside
- β-lactam monotherapy
- Risk-adapted therapy

Trial 1st investigator (Country, year)	Underlying condtions	Quinolon arm		Control arm		Definition Of neutropenia	Randomi-zation described	Blinded	Intent to Treat analysis
		Regimen	sub	Regimen	sub				
Hartlapp (Germany 1987) Karp (USA 1987)	Solid Some BMTs:: leuk	OFL 200mg bid NOR 400mg every 12h+P	84 35	No treatment Placeob+P	84 33	ND 100	No Yes	No Yes	No Yes
Casoli (Italy 1988) Law (USA 1991)	Solid leuk, lymph All BMT:solid, leuk	NOR 400mg every 8h CIP 750mg every 12h+ C,V	30 7	No treatment Placebo+C, V	35 11	1000 500	No Yes	No Yes	No No
Sampi (Japan, 1992) Bradley (Argentina, 1993)	Some BMTs: solid, leuk Leuk	NOR 200mg qid CIP 500mg bid or NOR 400mg bid+N	38 12	No treatment +N No treatment +N	35 13	100 500	Yes No	No No	No No
Maiche (Finland 1993)	Solid, lymph	CIP 750mg bid or OFL 200mg bid+G	44	No treatment +G	48	1000	No	No	No
Talbot (USA, 1993) Yamada (Japan 1993)	Leuk leuk	ENO 400mg every 12h NOR 200mg bid or qid+A	62 52	Placebo No treatment +A	57 57	500 1000	Yes No	Yes No	Yes No

Engels et al, J Clin Oncol 1998

Trial controlled With TMS prophylaxis	Underlying condtions	Quinolon arm		Control arm		Definition Of neutropenia	Randomi-zation described	Blinded	Intent to Treat analysis
		Regimen	sub	Regimen	sub				
Winston (USA 1987)	Leuk	NOR 400mg tid	26	TMS 160/ 800mg tid	28	100	No	No	No
Bow (Canada 1988)	Leuk	NOR 400mg every 12h	31	TMS 160/ 800mg every 12h	32	1000	Yes	No	No
Cruciani (Italy 1989)	Solid leuk, lymph	NOR 20mg/kg bid+A	21	TMS 15mg/ Kg bid+A	23	1000	Yes	No	No
Franci (Italy 1989)	Leuk	OFL 300mg every 12h	20	TMS 160/ 800mg every 12h	20	200	No	Yes	No
Liong (Hong-Kong 1990)	Leuk, lymph	OFL 300mg bid/N	50	TMS 160/ 800mg bid+N	52	500	No	No	No
Orlandi (Italy 1990)	Leuk	NOR 400mg every 12h+A	29	TMS 160/ 800mg every 12h+A	30	500	No	No	No
Kern Germany 1991)	Leuk	OFL 200mdg tid+A	70	TMS 160/ 800mg tid+A	58	1000	No	No	No
Macikova (Not stated 1992)	Leuk	OFL 400mg/d divided	22	TMS 2880mg D divided	20	500	No	No	No
Lew (USA 1995	All BMTs: solid, leuk,lymph	CIP 750mg every 12h+C	74	TMS 160/ 800mg every 12h+C	71	100	Yes	Yes	No

Engels et al, J Clin Oncol 1998



Pooled relative risk estimates and their 95 % Cls for each outcome, for trials controlled with no prophylaxis or TMS prophylaxis. Pooled control rate (%) is the proportion of subjects who received no prophylaxis who developed an outcome.

Engels EA et al, J Clin Oncol 1998

Year (ref)	Underlying condition	Regimen (dosage)		No. receiving fluoroquinolones /no. receiving control regimen	PMN count (mm3)	Duration (d) of neutropenia	
		Fluoroquinolones	Control			Recipients of fluoro.	Recipients of control regimens
1986	AL,CML, L	Norflox (400mg tid)	Vanco (500mg tid), polymyxin (100mg tid)	36/30	<1000 <500 <100	3.0 4.0 14.0	2.0 4.0 11.0
1987	AL	Cipro (500mg bid),	TMP-SMZ (960mg tid), colistin (200mg tid)	28/28	<500 <100	10.2 28.6	12.2 29
1987	AL,BMT	Norflox (400mg bid)	Placebo (bid)	35/33	<100	32	
1988	AL,CML, L	Norflox (400mg bid)	TMP-SMZ (960mg bid)	31/32	<1000 <500 <100	26.2 4.8 13.8	24.4 4.7 12.3
1990	AL	Oflox (200mg bid), or cipro (500mg bid)	TMP-SMZ (960mg bid), colistin (2 million U tid)	61/27	<500	13.0	20.0
1990	AL,L	Oflox (300mg bid),	TMP-SMZ (960mg bid)	50/52	<500	14.9	15.8

Cruciani et al, CID 1996

Year (ref)	Underlying condition	Regimen (dosage)		No. receiving fluoroquinolones /no. receiving control regimen	PMN count (mm3)	Duration (d) of neutropenia	
		Fluoroquinolones	Control			Recipients of fluoro.	Recipients of control regimens
1990	AL	Norflox (400mg tid)	TMP-SMZ (960mg tid)	29/30	<500	17.6	20.3
1990	AL,CML	Oflox (300mg bid),	Vanco (500mg tid), polymyxin (100mg tid)	30/32	<1000 <500 <100	2.0 5.0 10.0	2.0 4.0 12
1991	AL	Oflox (200mg tid)	TMP-SMZ (960mg bid)	70/58	<1000 <100	28.5 14.0	36.0 16.0
1991	AL,L,solid tumor, BMT	Cipro (750mg bid)	Placebo (bid)	7/11	<1000 <500 <100	22.4 18.9 9.7	23.5 20.4 11.8
1992	AL	Cipro (500mg bid)	TMP-SMZ (960mg bid), colistin (200mg q6h)	117/113	<1000 <500 <100	25.6 21.6 14.1	25.0 21.6 14.5
1993	AL	Enoxacin (400mg bid),	Placebo (bid)	62/57	<1000 <500 <100	9.0 13.0 3.0	8.0 8.0 5.0
1994	AL,CML, BMT	Cipro (500mg bid),	Neomycin (250mg q6h) polymyxin (100mg q6h) nalidixic acid (1g bid)	63/33	<500	20.6	21.2

Year (ref)	Underlying condition	Regimen (dosage)		No. receiving fluoroquinolones + gram-positive prophylaxis/no. receiving control regimen	PMN count	Duration (d) of neutropenia	
		Fluoroquinolones + gram-positive prophylaxis	Control			Recipients of fluoro. + gram-positive prophylaxis	Recipients of control regimens
1991	AL,CML,L, solid tumor, BMT	Peflox (800mg/d), vanco (800mg/d)	Genta (100mg/d), colistin (3 million U/d), vanco (800 mg/d)	76/74	<500 <100	22.0 15.0	21.0 15.0
1991	AL,aplastic anemia, BMT	Oflox (200mg bid), amoxy (1g bid)	Vanco (450mg/d), tobra (450mg/d), colistin (4.5million U/d)	22/22	<500	23.8	19.0
1993	AL,L,BMT	Cipro (500mg bid), amoxy (1g/d)	Cipro (500mg bid)	27/26	<1000	20.0	18.0
1994	AL,L,solid tumor,BMT	Norflox (400mg tid) + iv pen G (1million U tid) or iv vanco (750mg bid)	Norflox (400mg tid)	21/22	<500	NS	
1994	AL,CML,L, BMT	Oflox (200mg tid), roxithro (150mg bid)	Oflox (200mg tid)	67/64	<1000 <100	29.5 13.0	26.4 12.6
1994	AL,L,solid tumor,BMT	Peflox (400mg bid), pen V (500mg bid)	Peflox (400mg bid) placebo (bid)	268/268	NS	22.0	21.0

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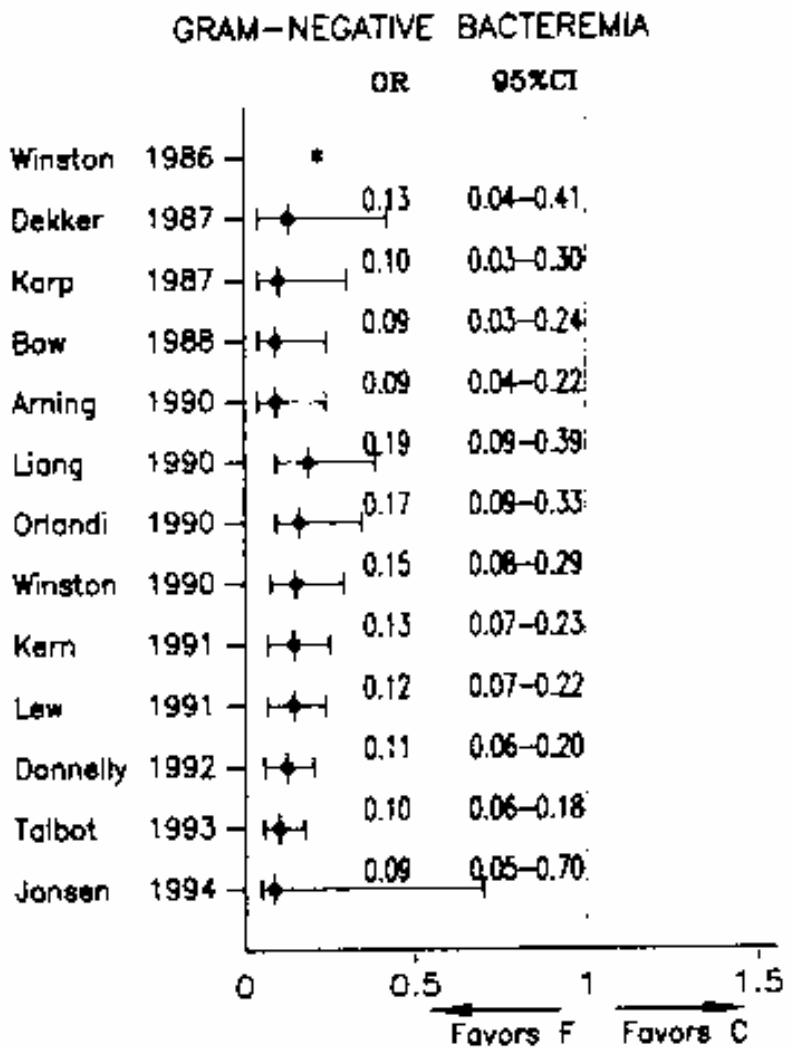

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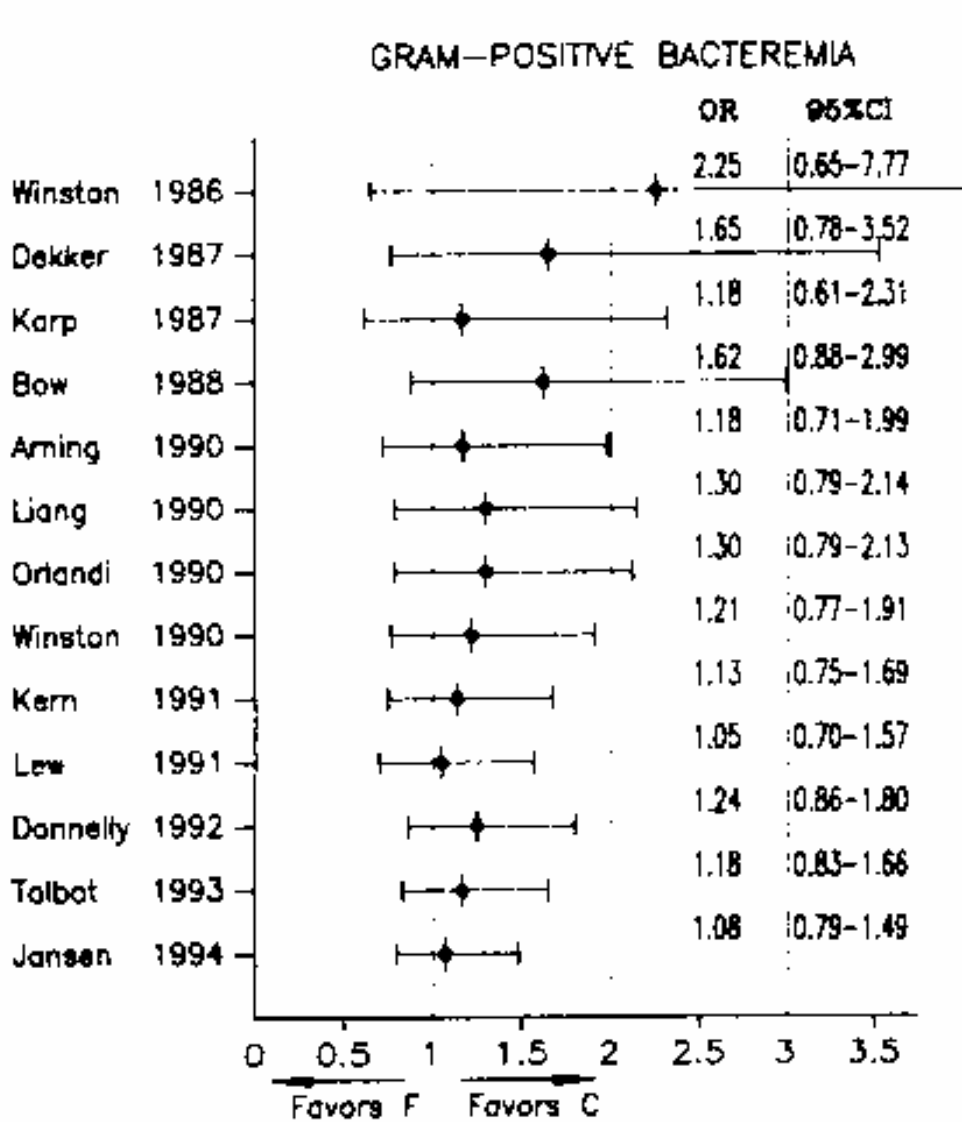

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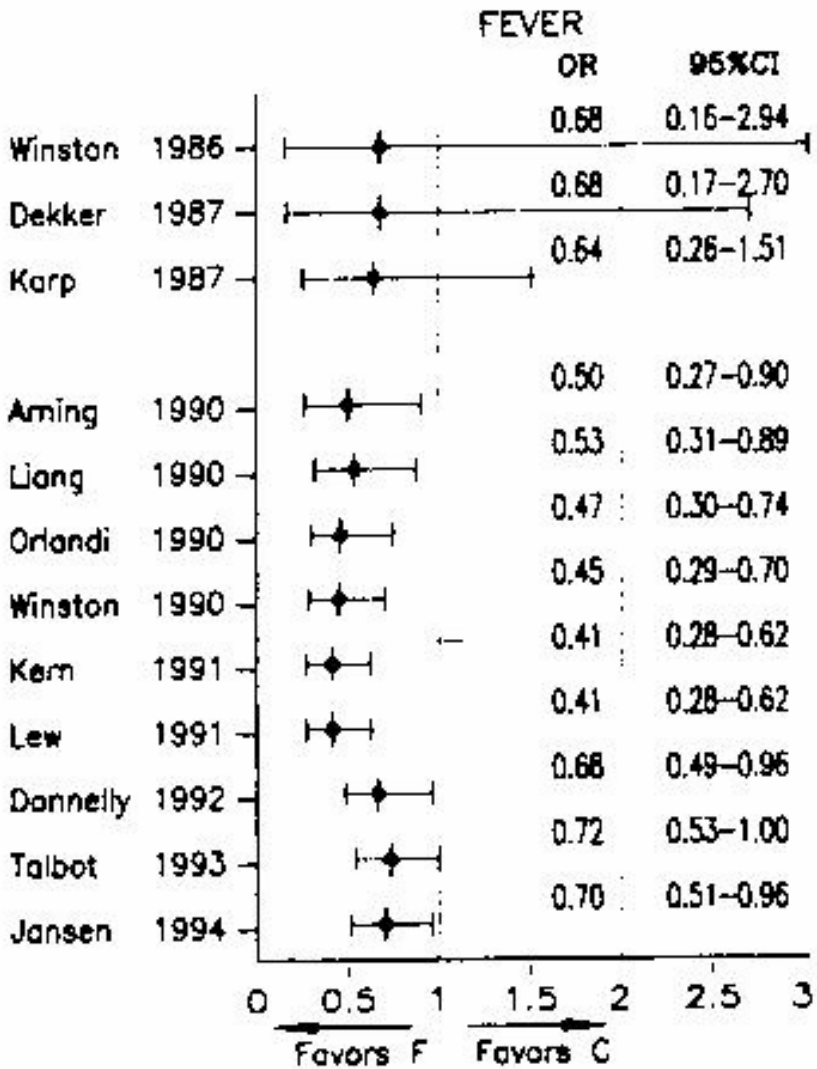

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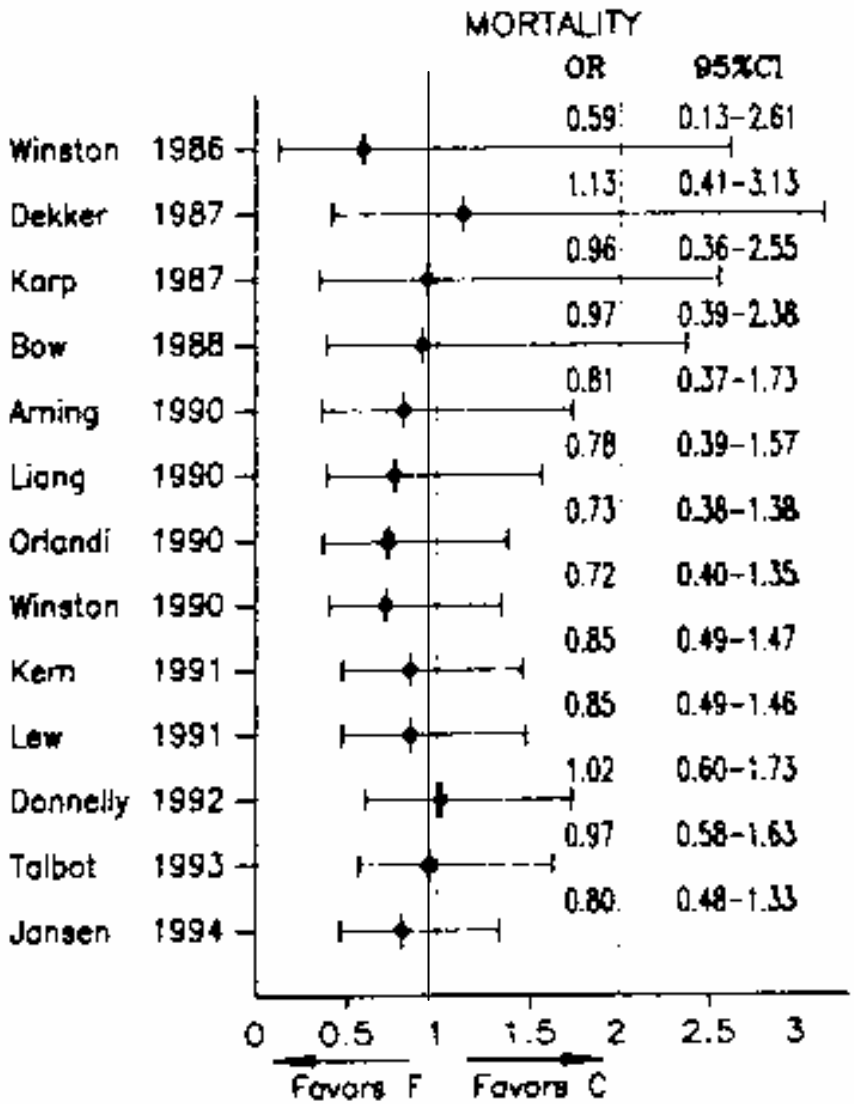

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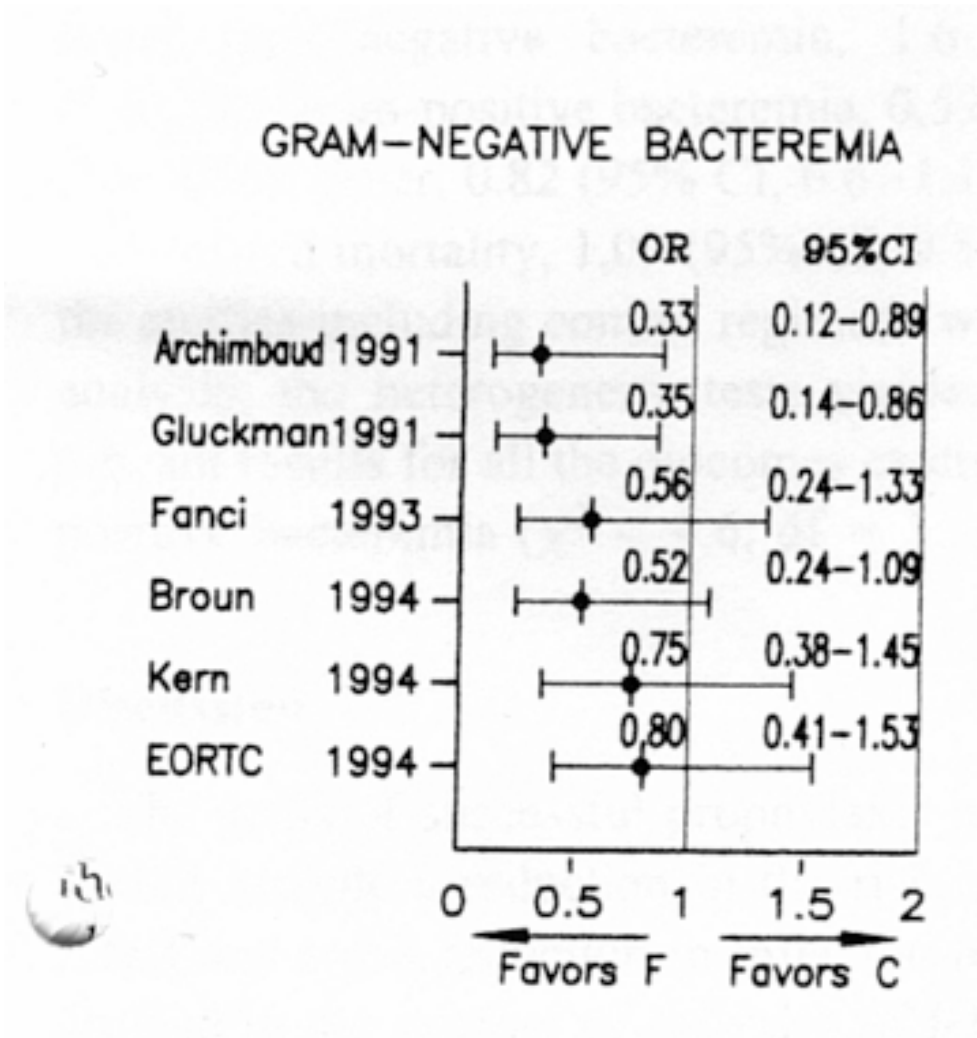

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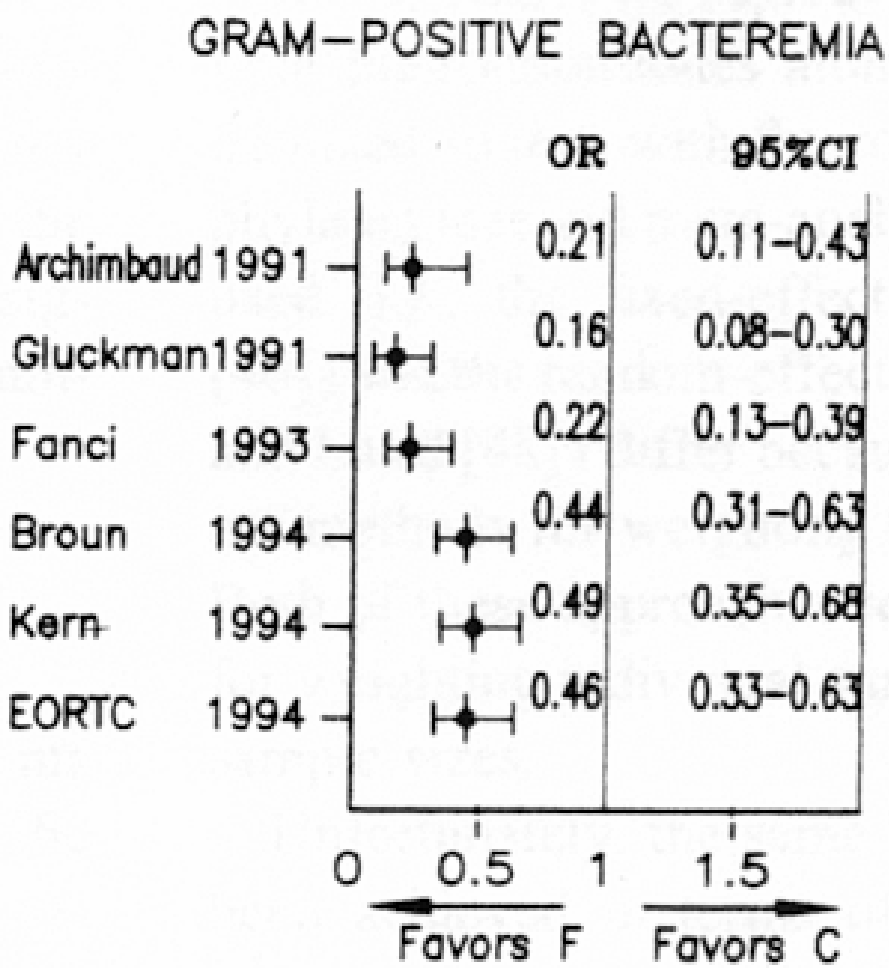

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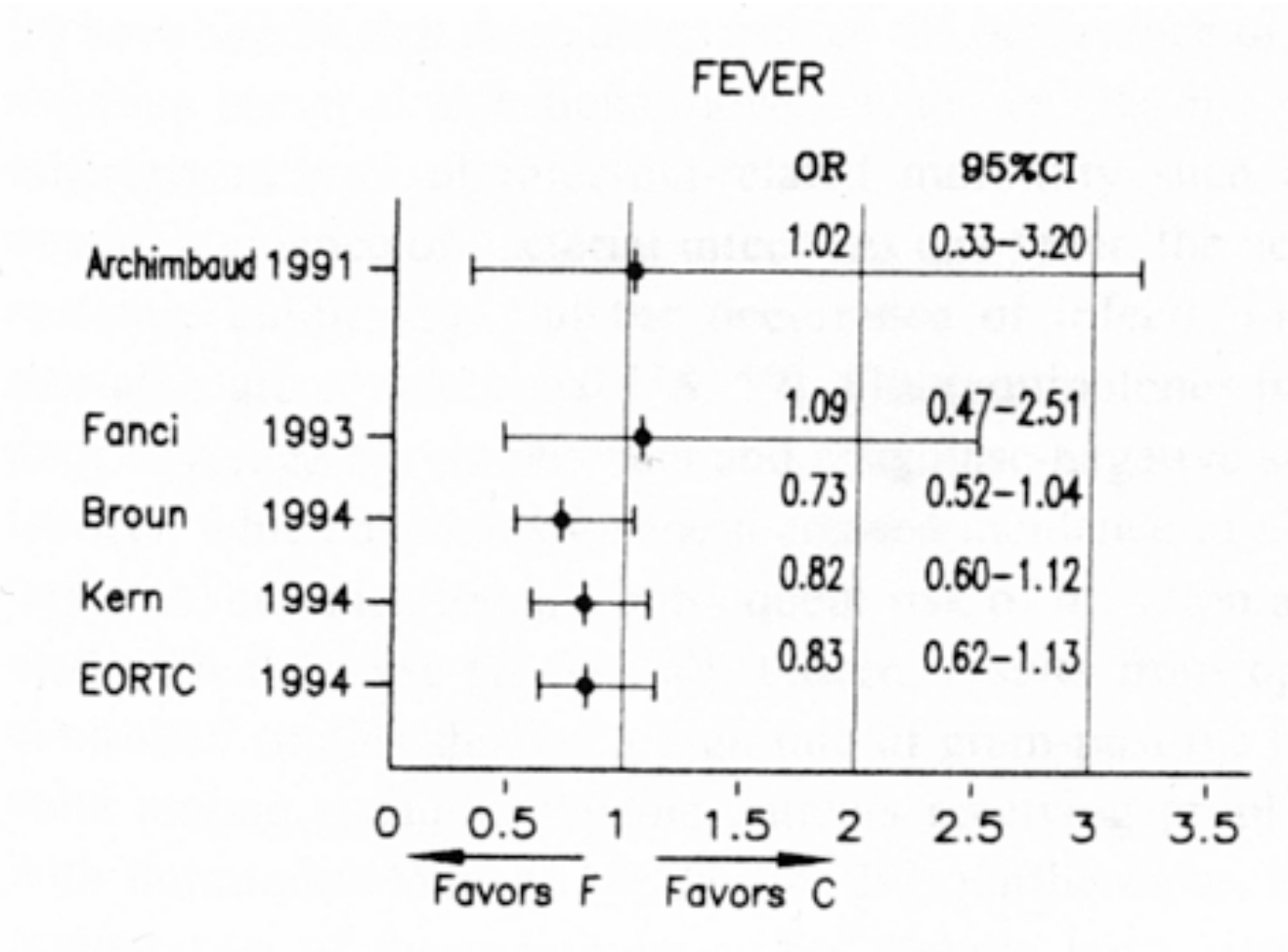

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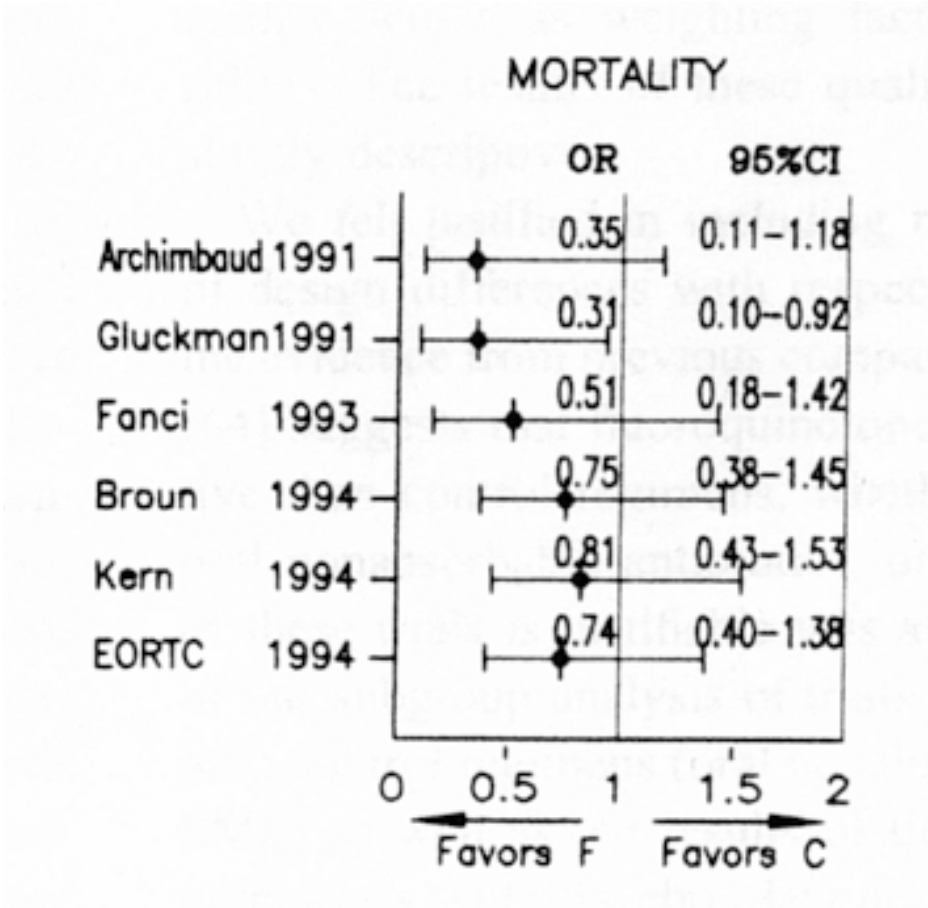

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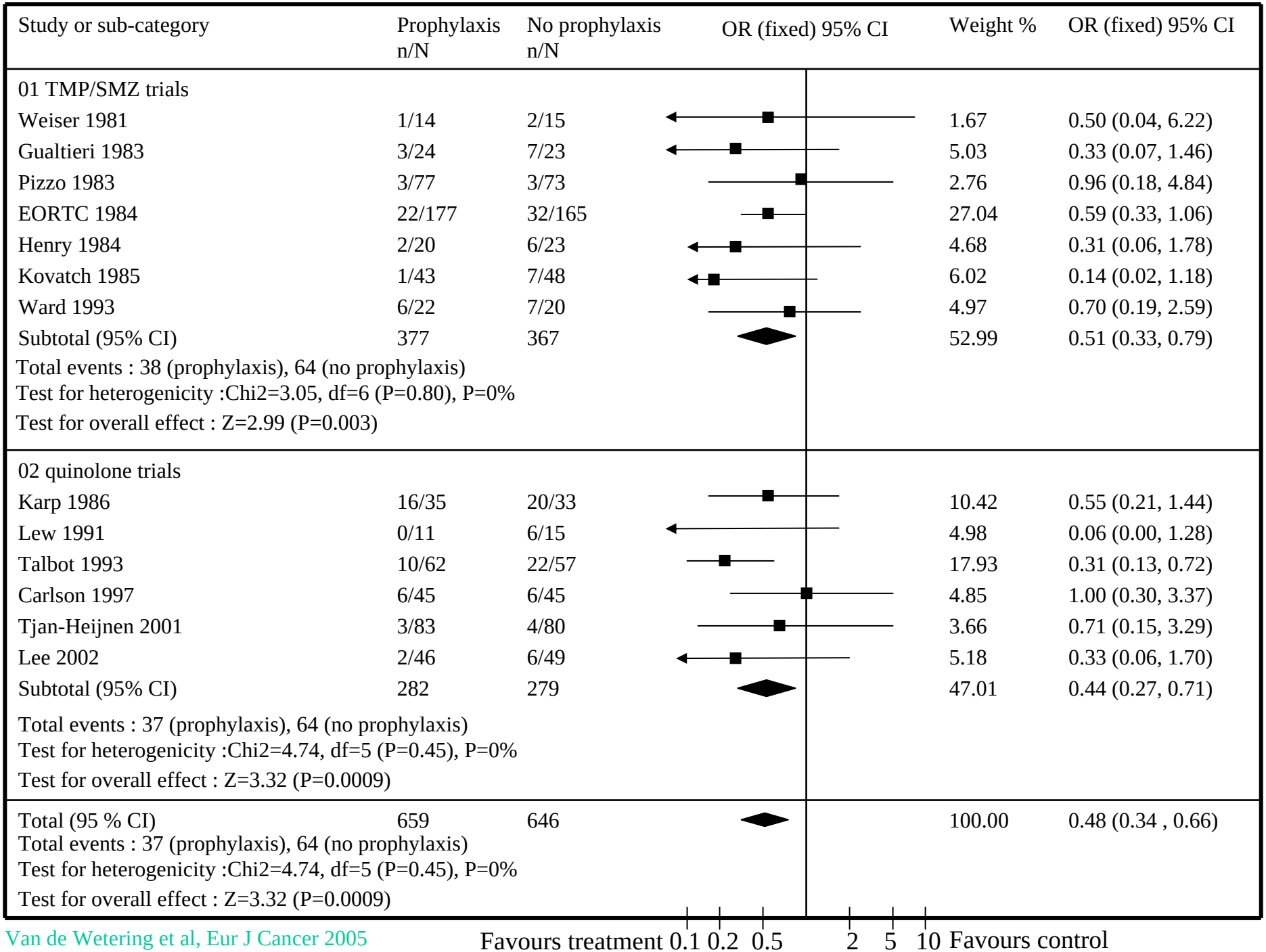

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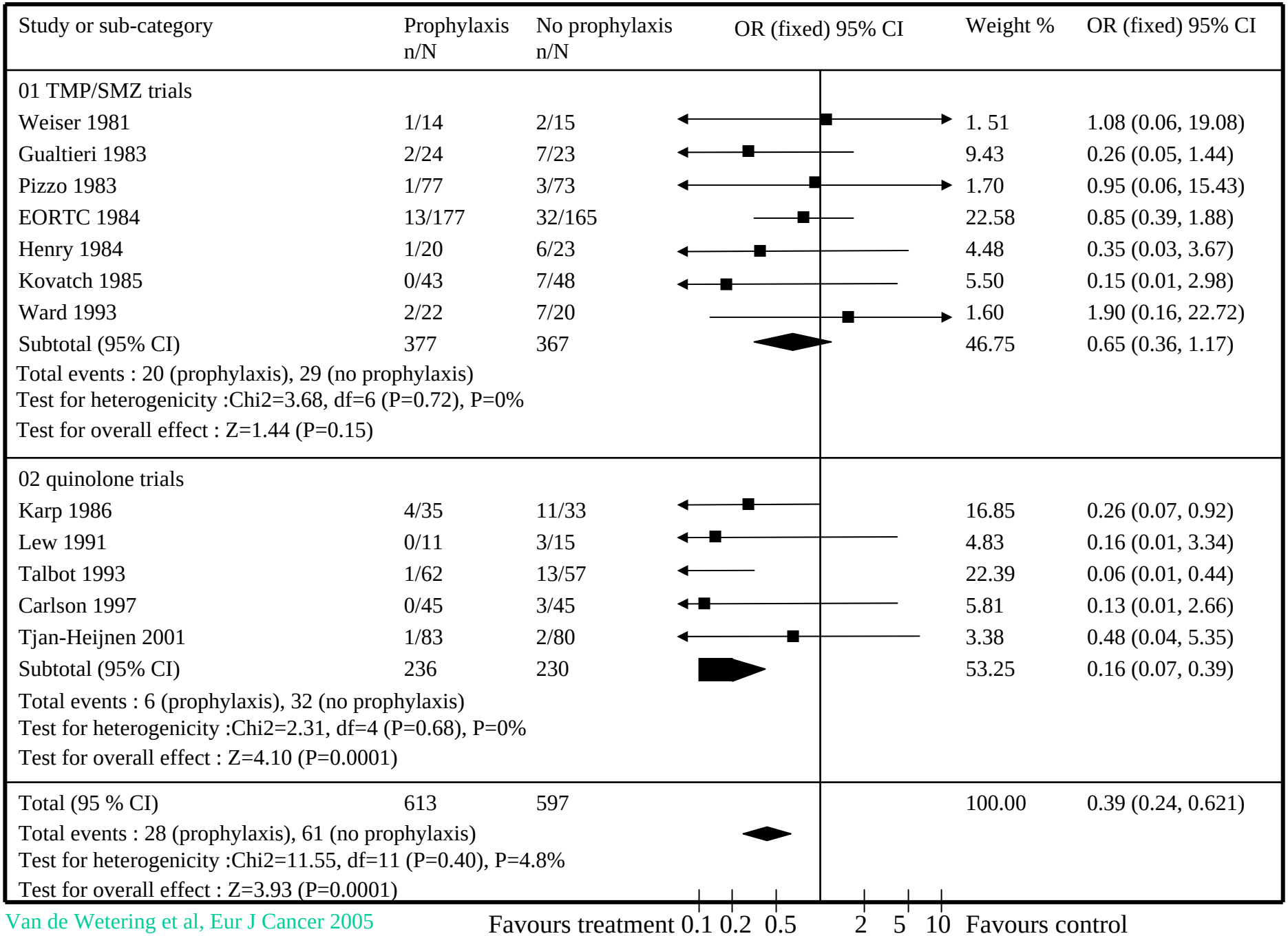

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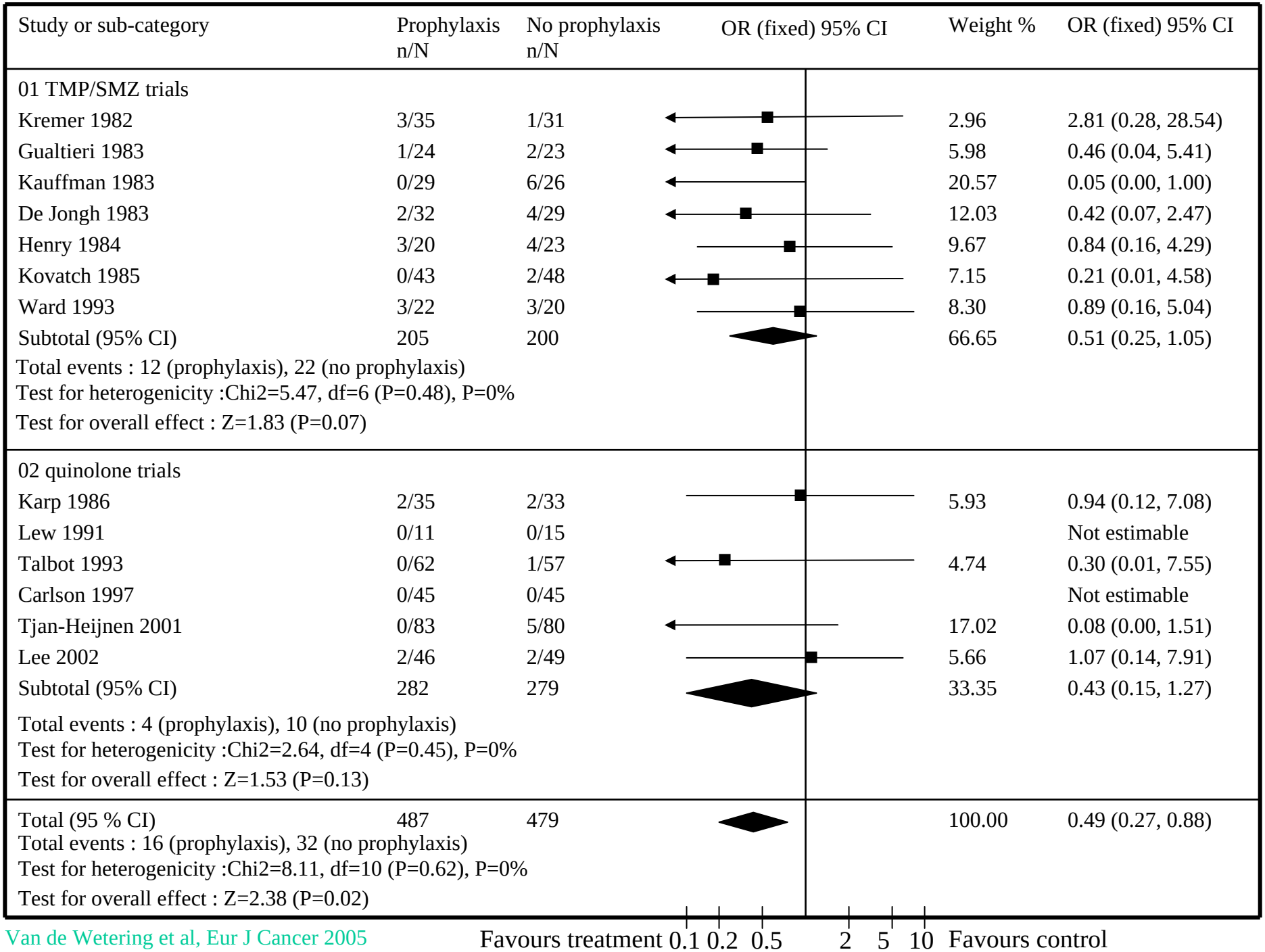

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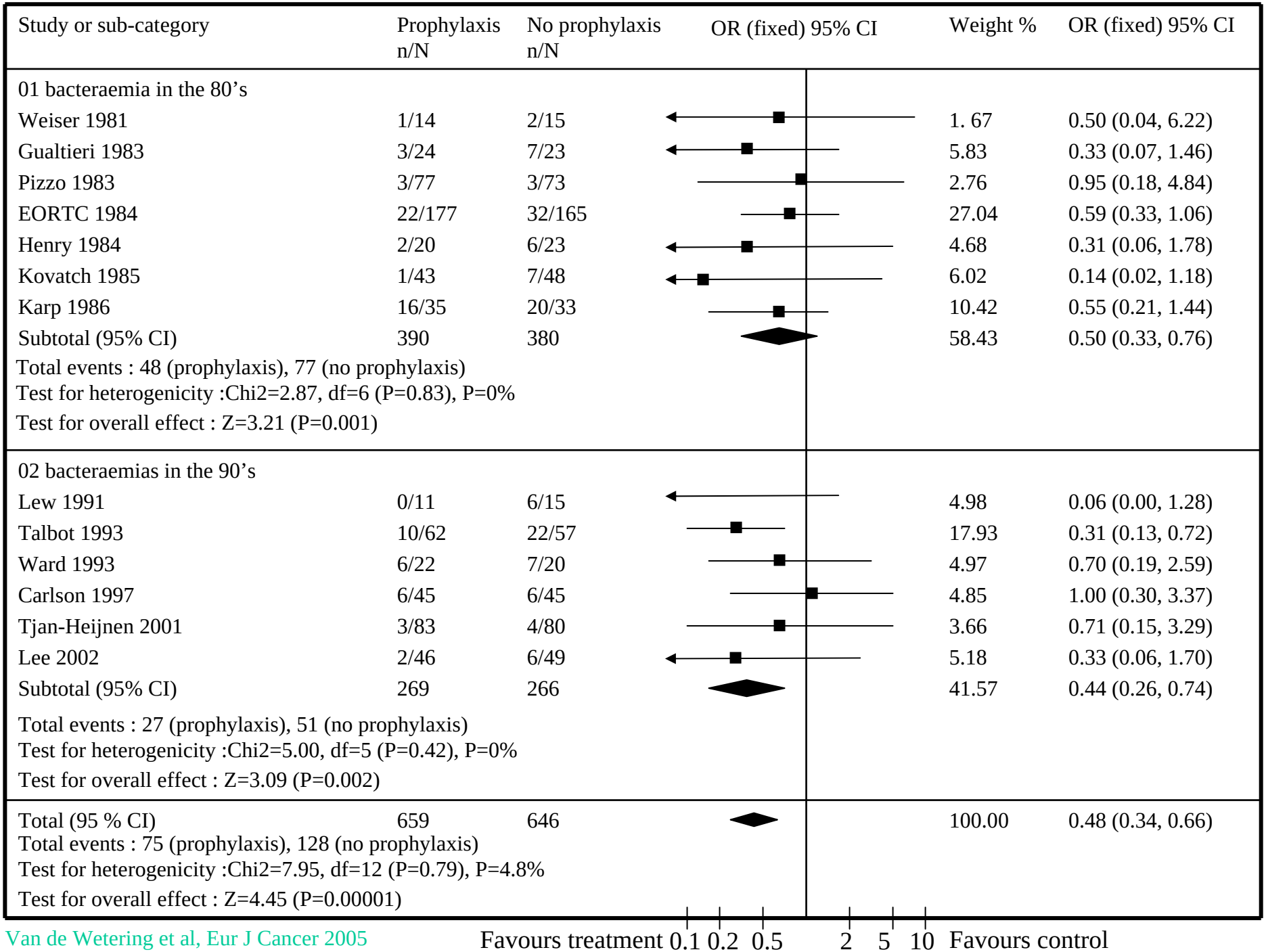

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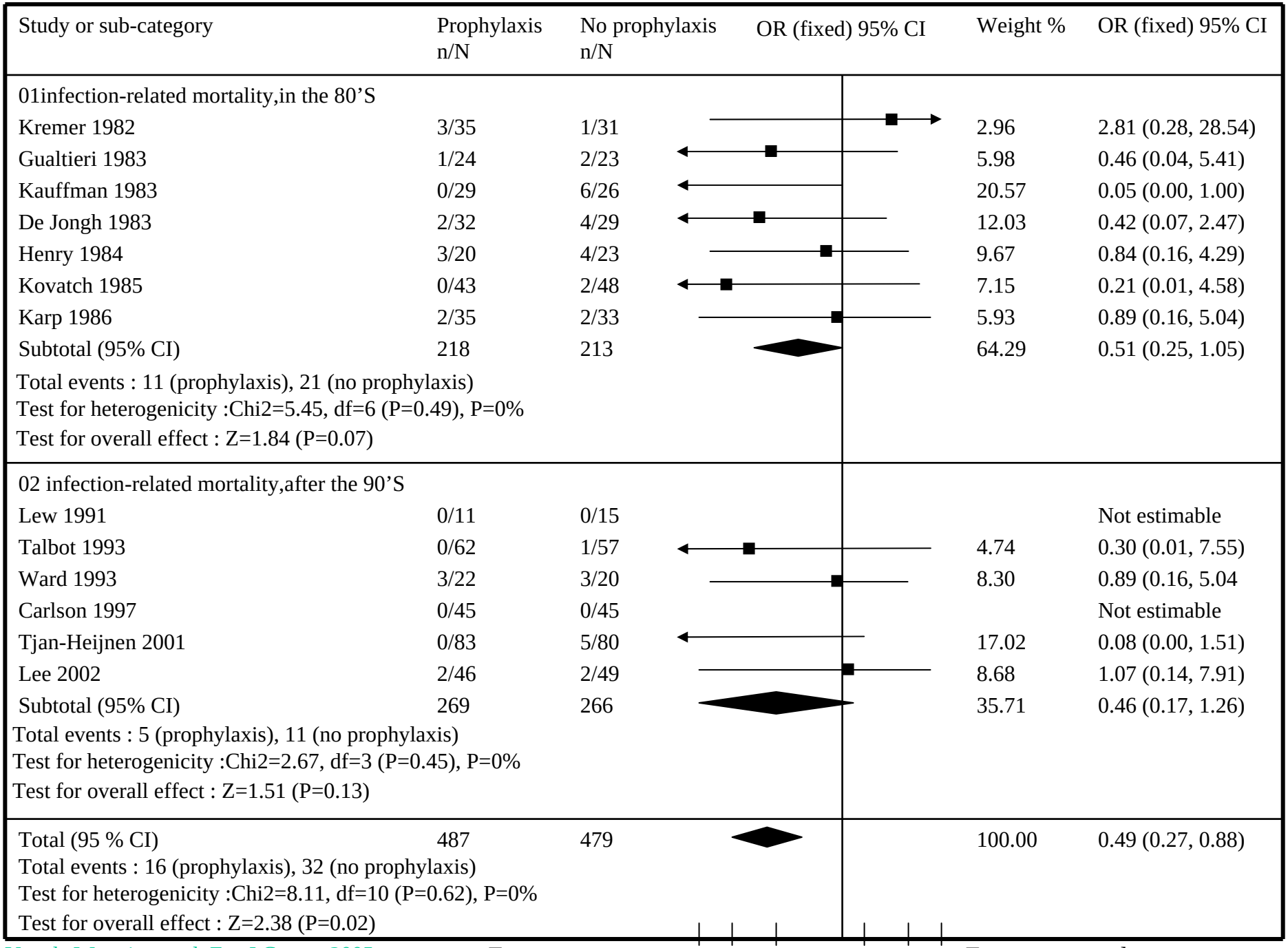

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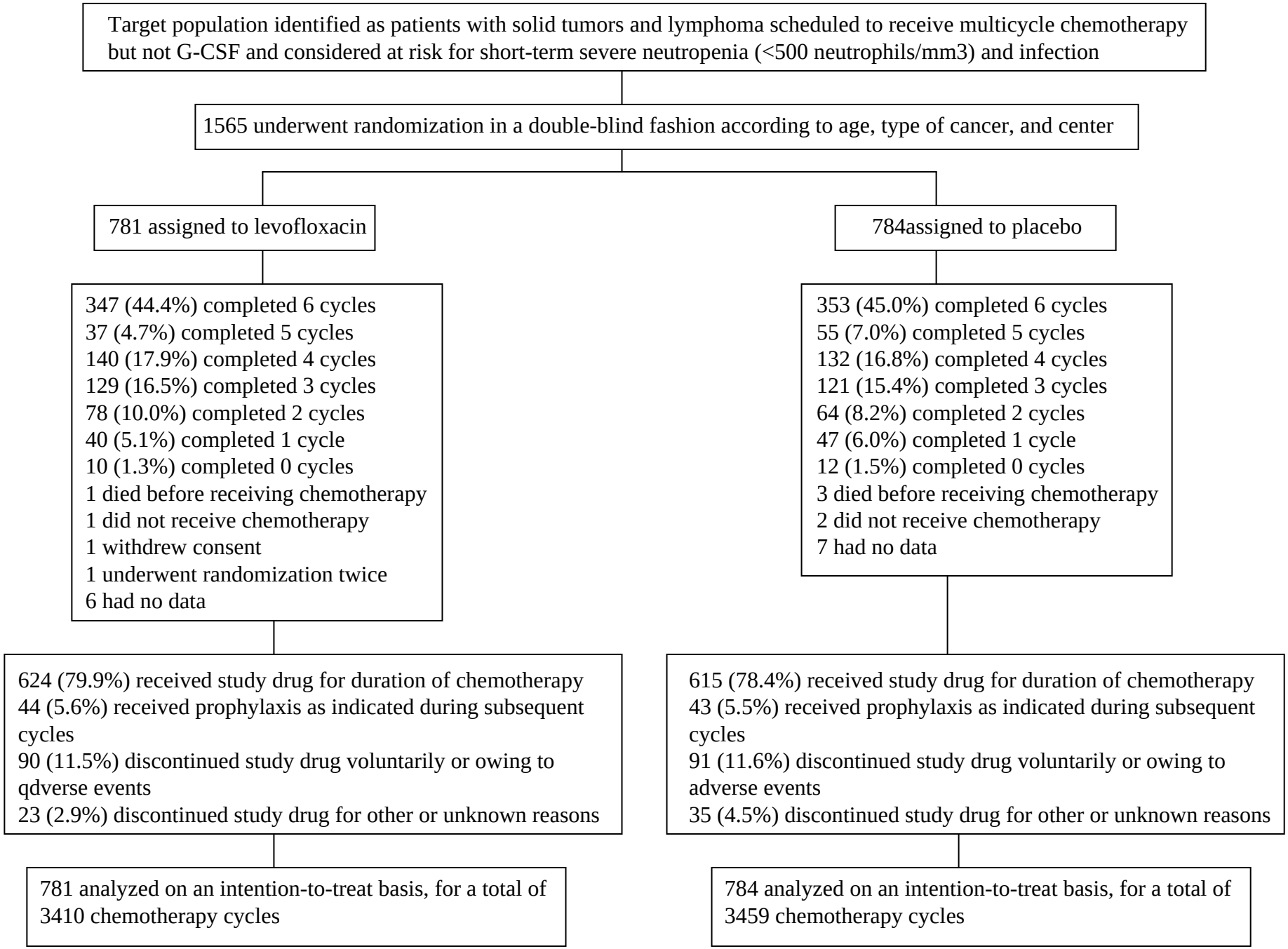

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Table 1. Baseline Characteristics of the Patients.*

Characteristic	Levofloxacin (N=781)	Placebo (N=784)
Sex — no. (%)		
Male	338 (43.3)	354 (45.2)
Female	443 (56.7)	430 (54.8)
Age		
16–39 yr — no. (%)	157 (20.1)	147 (18.7)
40–59 yr — no. (%)	336 (43.0)	337 (43.0)
≥60 yr — no. (%)	288 (36.9)	300 (38.3)
Median — yr	55	55
Interquartile range — yr	42–63	43–65
Range — yr	18–82	16–83
WHO performance status		
0	493 (63.1)	477 (60.8)
1	213 (27.3)	234 (29.8)
2	65 (8.3)	56 (7.1)
3 or 4	9 (1.2)	16 (2.0)
Unknown	1 (0.1)	1 (0.1)

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Table 1 (part 2)

Type of cancer and most commonly used chemotherapy regimens — no. (%)		
Breast cancer†	275 (35.2)	279 (35.6)
FEC	109	116
AC	64	51
Testicular cancer	114 (14.6)	111 (14.2)
BEP	96	93
EP	14	14
Small-cell lung cancer	110 (14.1)	110 (14.0)
PE	50	45
CAV	14	19
CAVE	14	18
Non-Hodgkin's lymphoma	79 (10.1)	72 (9.2)
CHOP	74	63
Hodgkin's disease	24 (3.1)	25 (3.2)
ABVD	20	15
Other‡	179 (22.9)	187 (23.8)
Chemotherapy being given in adjuvant setting — no. (%)§	354 (45.3)	335 (42.7)
Indwelling venous catheter present — no. (%)	59 (7.6)	70 (8.9)
Previous myelosuppressive chemotherapy given — no. (%)	73 (9.4)	88 (11.2)
Previous radiotherapy given — no. (%)	33 (4.2)	40 (5.1)¶

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Table 2. Characteristics of 817 Probable Infections among 6869 Cycles.

Variable	Focus of Infection	No Focus of Infection	No./Total No. (% of Cycles)
	no. of probable infections (% of total)		
Sign of probable infection			
Fever	144 (17.6)	104 (12.7)	248/6869 (3.6)
Other systemic signs	184 (22.5)	56 (6.9)	240/6869 (3.5)
No systemic signs	298 (36.5)	31 (3.8)*	329/6869 (4.8)
Focus of infection			
Upper respiratory tract	197 (24.1)	—	
Lower respiratory tract	105 (12.9)	—	
Gastrointestinal tract and anal abscesses	36 (4.4)	—	
Urinary tract	68 (8.3)	—	
Skin and soft tissue	86 (10.5)		
Venous catheter	39 (4.8)	—	
Oral mucosa and teeth	41 (5.0)	—	
Multiple sites	36 (4.4)	—	
Other sites	17 (2.1)		
Unspecified	1 (0.1)		
No focus of infection	—	191 (23.4)	

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Table 3. Incidence of Febrile Episodes, Probable Infections, and Hospitalization for Infection.*

Event	Levofloxacin (N=781)	Placebo (N=784)	Relative Risk (95% CI)	P Value†
	no. of patients (%)			
Events occurring in first cycle				
Febrile episode				
Yes	27 (3.5)	62 (7.9)	0.44 (0.28–0.68)	<0.001
No	736	699		
Unknown	18	23		
Probable infection				
Yes	109 (14.0)	152 (19.4)	0.72 (0.57–0.90)	0.005
No	658	614		
Unknown	14	18		
Hospitalization for infection				
Yes	52 (6.7)	81 (10.3)	0.64 (0.46–0.90)	0.01
No	712	681		
Unknown	17	22		

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Table 3 (part 2)

Events occurring at least once in any cycle				
Febrile episode				
Yes for ≥1 cycles	84 (10.8)	119 (15.2)	0.71 (0.55–0.92)	0.01
No for all cycles	661	623		
Unknown for ≥1 cycles	36	42		
Probable infection				
Yes for ≥1 cycles	267 (34.2)	325 (41.5)	0.82 (0.73–0.94)	0.004
No for all cycles	489	432		
Unknown for ≥1 cycles	25	27		
Hospitalization for infection				
Yes for ≥1 cycles	123 (15.7)	169 (21.6)	0.73 (0.59–0.90)	0.004
No for all cycles	623	575		
Unknown for ≥1 cycles	35	40		
Severe infection and/or death from infection	8 (1.0)	16 (2.0)	0.50 (0.22–1.17)	0.15

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Table 4. Treatment Compliance, Adverse Events, and Characteristics of Febrile Episodes and Probable Infections.

Variable	Levofloxacin	Placebo
All cycles — no. (%)	**3410**	**3459**
Compliance		
7 days of study drug	2470 (72.4)	2458 (71.1)
1–6 days of study drug	114 (3.3)	123 (3.6)
0 days of study drug	625 (18.3)	667 (19.3)
Unknown	201 (5.9)	211 (6.1)
Adverse event	78 (2.3)	40 (1.2)
Rash	22	13
Gastrointestinal effect	36	11
Central nervous system effect	6	6
Musculoskeletal effect	4	1
Multiple events, including those listed above	5	6
Other*	5	3
Unknown	31	27
Antifungal prophylaxis prescribed	271 (8.0)	266 (7.7)
Unknown	129	118
Incidence of mucosal candidiasis	159 (4.7)	176 (5.1)
Unknown	66	78

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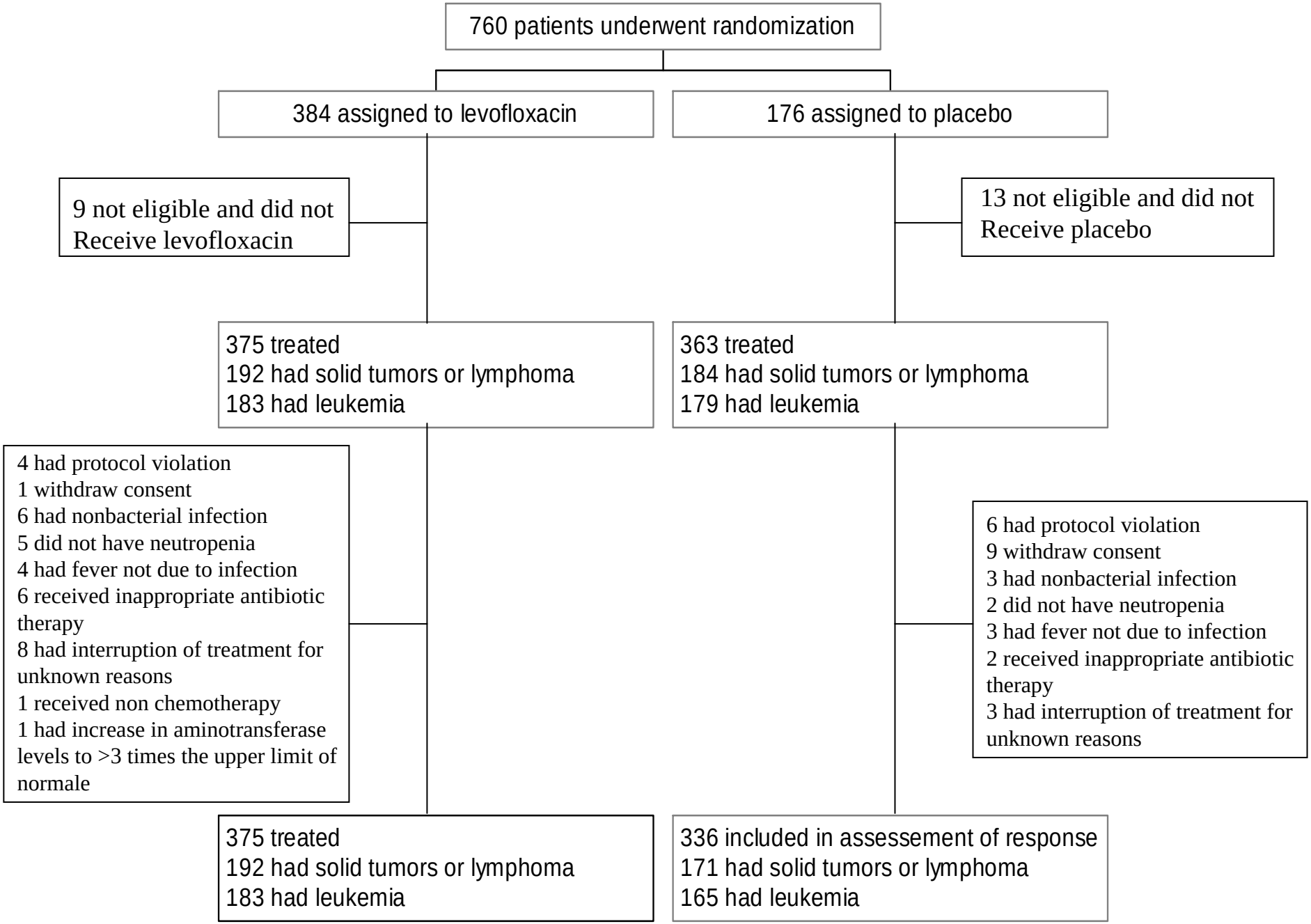

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Table 1. Characteristics of the 675 Patients Whose Response to Therapy Could Be Assessed.

Characteristic	Patients with Solid Tumors or Lymphoma		Patients with Leukemia	
	Levofloxacin (N=174)	Placebo (N=171)	Levofloxacin (N=165)	Placebo (N=165)
Age — yr				
Mean	47	49	48	49
Range	19–72	18–70	18–75	18–75
Sex — no. (%)				
Male	102 (59)	93 (54)	88 (53)	87 (53)
Female	72 (41)	78 (46)	77 (47)	78 (47)
Underlying cancer — no. (%)				
Acute leukemia	—	—	164 (99)	163 (99)
Lymphoma and Hodgkin's disease	112 (64)	100 (58)	—	—
Solid tumor	24 (14)	22 (13)	—	—
Other hematologic cancers	38 (22)	49 (29)	1 (1)	2 (1)
Chemotherapy — no. (%)				
First remission or induction	—	—	80 (48)	79 (48)
Reinduction	—	—	37 (22)	32 (19)
Augmentation	—	—	47 (28)	47 (28)
Stem-cell transplantation — no. (%)	158 (91)	149 (87)	12 (7)	9 (5)

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Table 1 (part 2)

Protective environment — no. (%)				
Single room	43 (25)	42 (25)	46 (28)	47 (28)
Reverse isolation	28 (16)	27 (16)	19 (12)	18 (11)
Laminar airflow room	25 (14)	26 (15)	11 (7)	13 (8)
Other	19 (11)	21 (12)	9 (5)	7 (4)
Intravenous catheter in situ — no. (%)	156 (90)	156 (91)	107 (65)	116 (70)
Antifungal prophylaxis — no. (%)	148 (85)	155 (91)	154 (93)	152 (92)
Antiviral prophylaxis — no. (%)	107 (61)	110 (64)	29 (18)	38 (23)
Duration of prophylaxis — days				
Mean	14	15	27	25
Range	4–36	5–61	9–65	6–70
Median	14	14	25	24
Duration of neutropenia (<1000 neutrophils/mm³) — days				
Mean	9	9	20	18
Range	4–28	2–51	3–54	3–67
Median	8	8	19	15
Duration of severe neutropenia (<100 neutrophils/mm³) — days				
Mean	6	6	11	10
Range	0–20	0–49	0–47	0–38
Median	6	5	10	8

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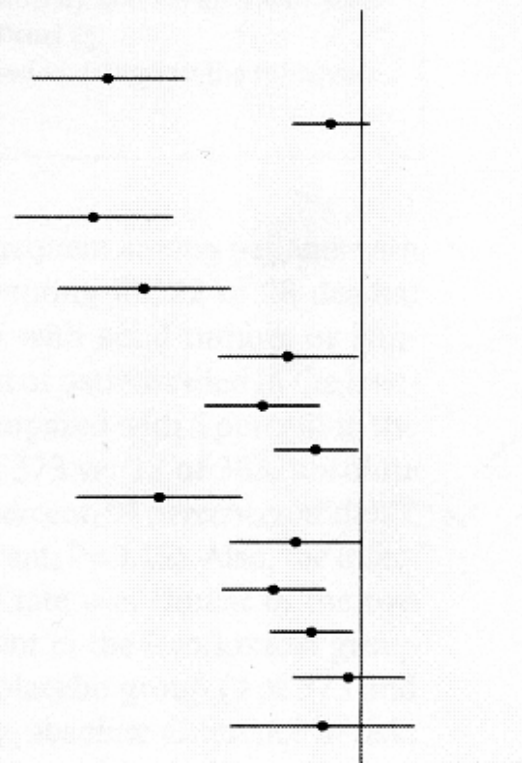
Group and Event	Levofloxacin	Placebo	Absolute Difference in Risk (95% CI)
	no./total no. (%)		
All treated patients			
Febrile episode	243/375 (65)	308/363 (85)	−0.20 (−0.26 to −0.14)
Death	10/373 (3)	18/363 (5)	−0.02 (−0.05 to 0.005)
All assessable patients			
Febrile episode	221/339 (65)	290/336 (86)	−0.21 (−0.27 to −0.14)
Microbiologically documented infection	74/339 (22)	131/336 (39)	−0.17 (−0.24 to −0.10)
Gram-positive	42/339 (12)	61/336 (18)	−0.06 (−0.11 to −0.003)
Gram-negative	21/339 (6)	47/336 (14)	−0.08 (−0.12 to −0.03)
Polymicrobial	11/339 (3)	23/336 (7)	−0.04 (−0.06 to −0.003)
Bacteremia	62/339 (18)	115/336 (34)	−0.16 (−0.22 to −0.09)
Gram-positive	37/339 (11)	54/336 (16)	−0.05 (−0.10 to 0.00)
Gram-negative	15/339 (4)	38/336 (11)	−0.07 (−0.10 to −0.02)
Polymicrobial	10/339 (3)	23/336 (7)	−0.04 (−0.07 to −0.01)
Clinically documented infection	30/339 (9)	33/336 (10)	−0.01 (−0.05 to 0.03)
Fever of unknown origin	117/339 (34)	126/336 (37)	−0.03 (−0.10 to 0.04)



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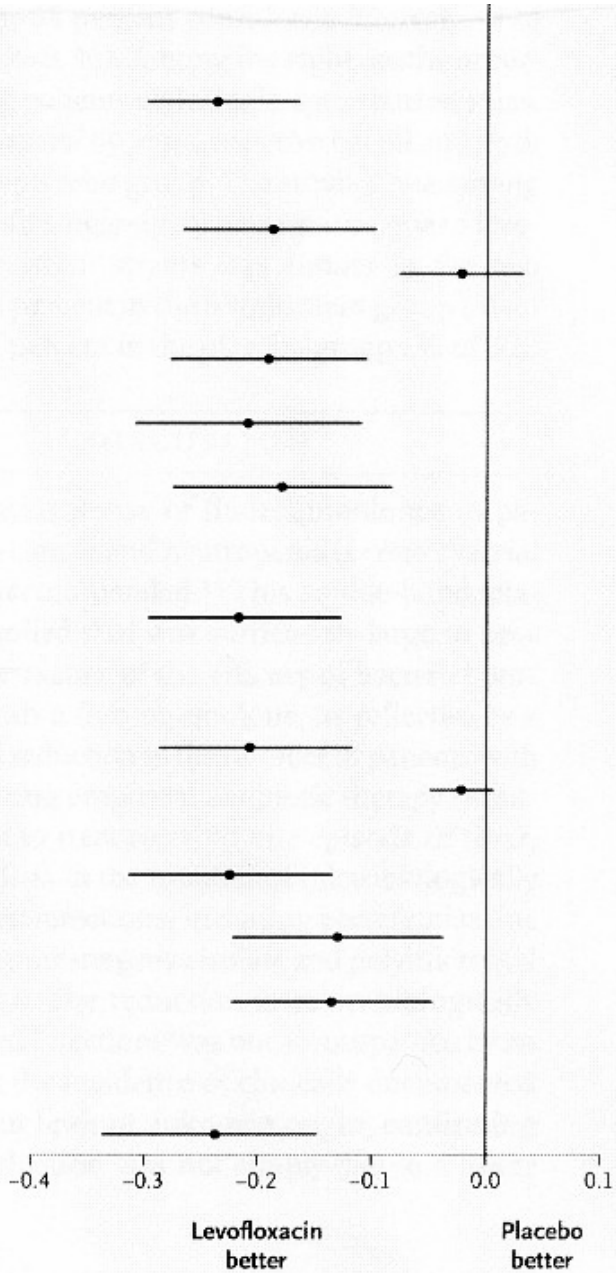
Assessable patients with neutropenia ≥7 days			
Febrile episode	200/300 (67)	252/280 (90)	−0.23 (−0.29 to −0.16)
Acute leukemia			
Treated patients			
Febrile episode	123/183 (67)	154/179 (86)	−0.19 (−0.27 to −0.10)
Death	9/182 (5)	13/179 (7)	−0.02 (−0.07 to 0.02)
Assessable patients			
Febrile episode	113/165 (68)	145/165 (88)	−0.20 (−0.28 to −0.10)
Microbiologically documented infection	39/165 (24)	74/165 (45)	−0.21 (−0.31 to −0.11)
Bacteremia	34/165 (21)	64/165 (39)	−0.18 (−0.27 to −0.08)
Assessable patients with neutropenia for ≥7 days			
Febrile episode	110/159 (69)	138/151 (91)	−0.22 (−0.30 to −0.13)
Solid tumors or lymphoma			
Treated patients			
Febrile episode	120/192 (62)	154/184 (84)	−0.22 (−0.29 to −0.12)
Death	1/191 (1)	5/184 (3)	−0.02 (−0.05 to 0.004)
Assessable patients			
Febrile episode	108/174 (62)	145/171 (85)	−0.23 (−0.31 to −0.13)
Microbiologically documented infection	35/174 (20)	57/171 (33)	−0.13 (−0.22 to −0.03)
Bacteremia	28/174 (16)	51/171 (30)	−0.14 (−0.22 to −0.04)
Assessable patients with neutropenia for ≥7 days			
Febrile episode	90/141 (64)	114/129 (88)	−0.24 (−0.34 to −0.15)



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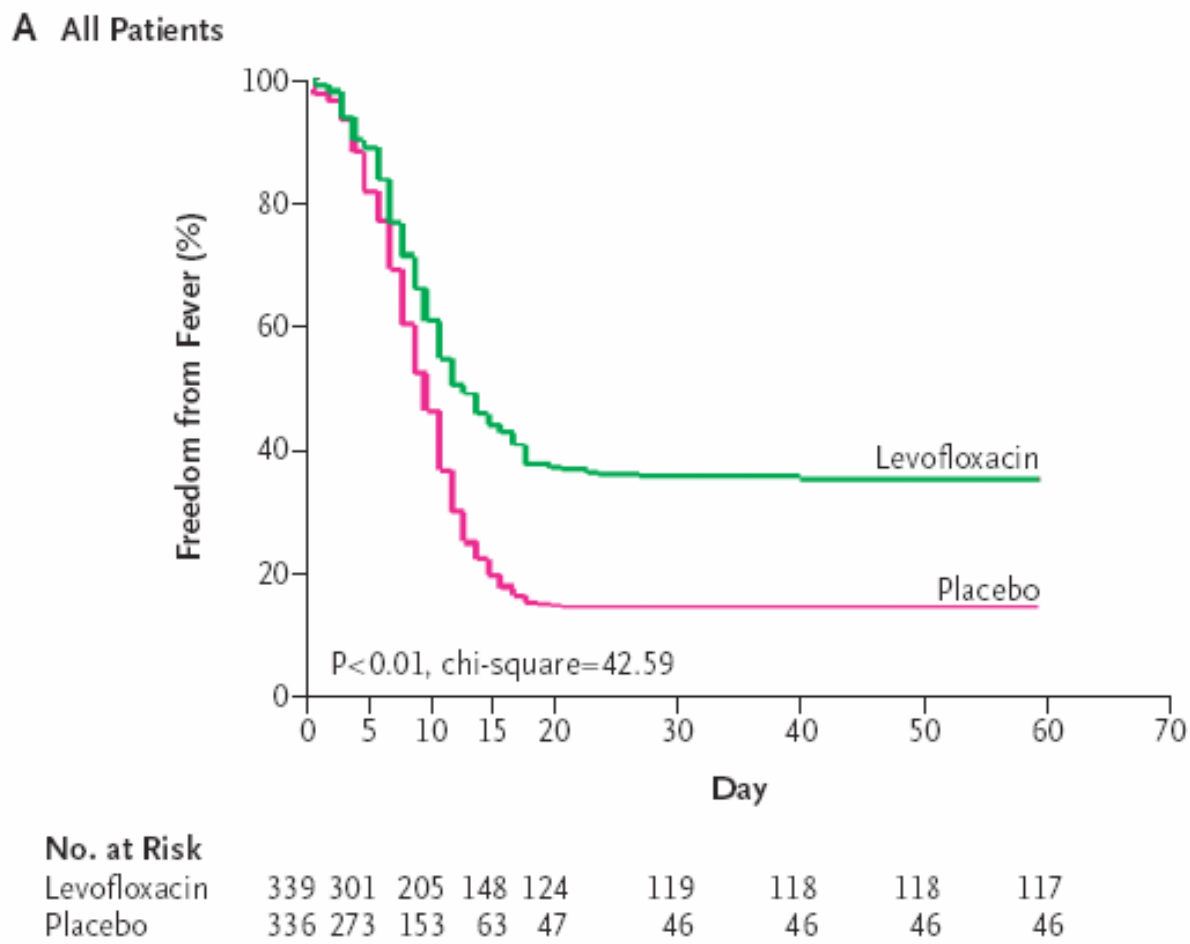

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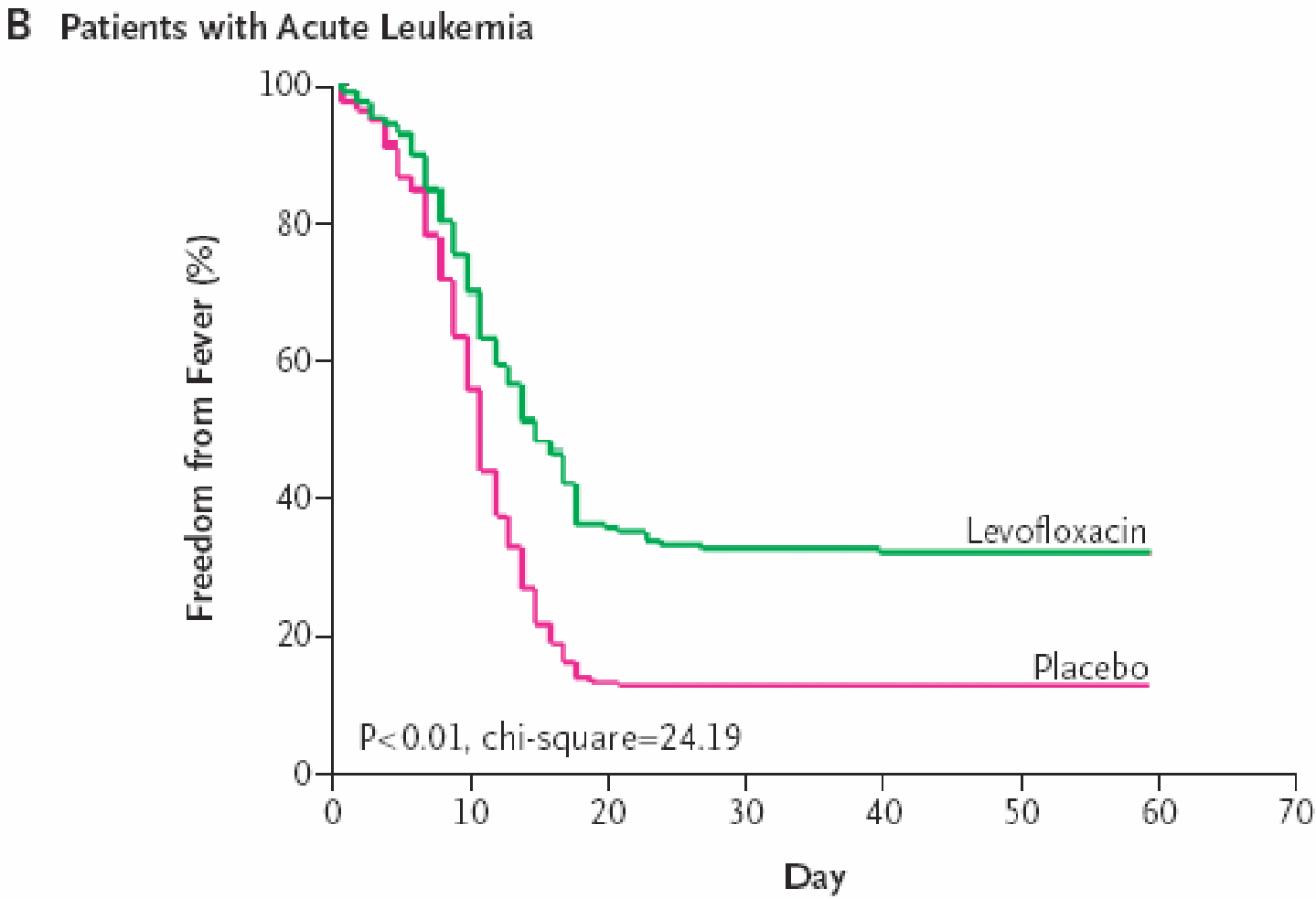

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C Patients with Solid Tumors or Lymphoma

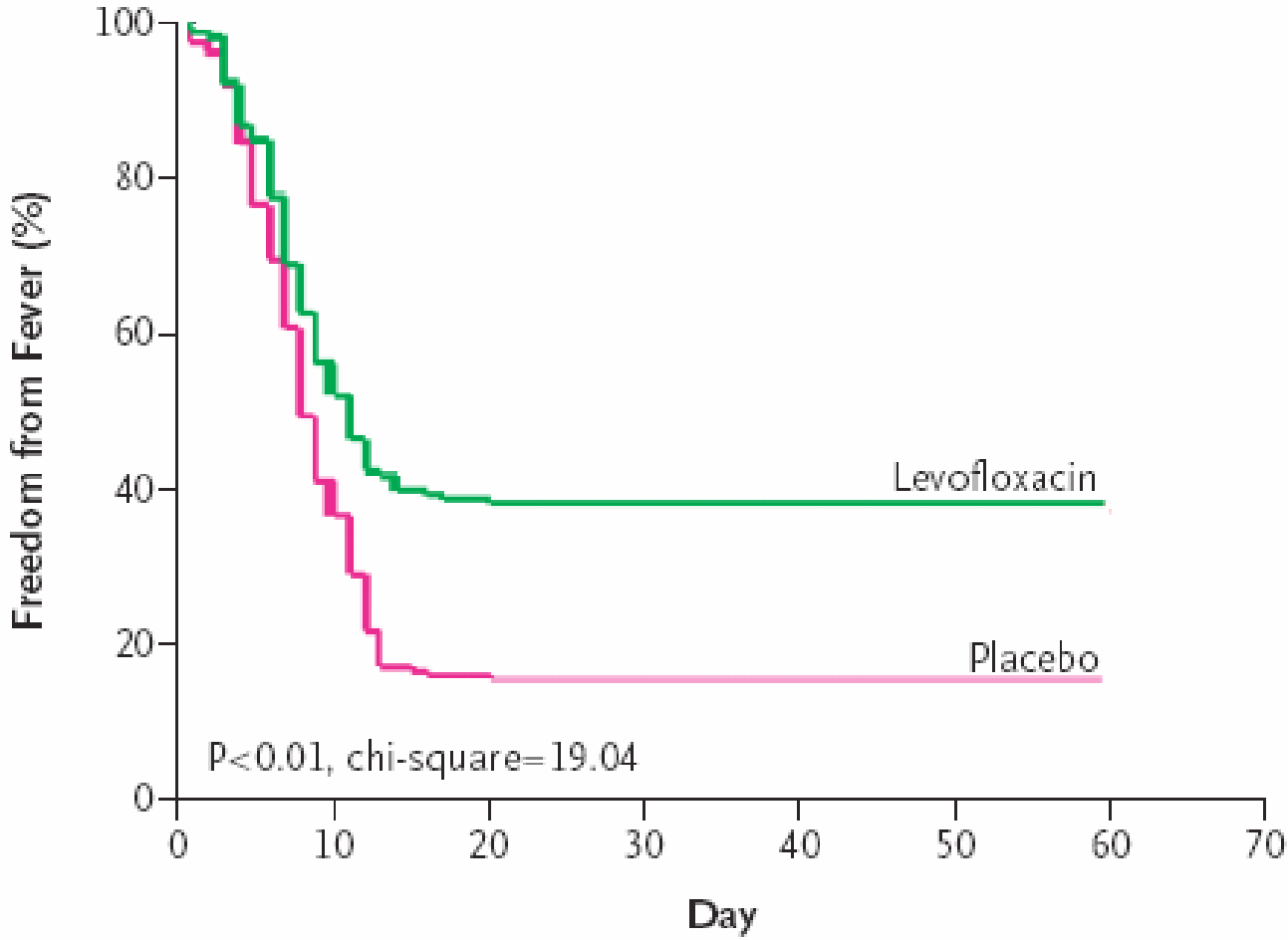

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Table 2. Characteristics of Bacterial Isolates and Number with Resistance to Levofloxacin.

Characteristic	Levofloxacin (N=339)	Placebo (N=336)
Microbiologically documented infection	74	131
No. with bacteremia	62	115
Single gram-positive isolate	37	54
S. aureus	0	10
Coagulase-negative staphylococcus	31	32
Streptococcus species	5	9
Other gram-positive organisms	1	3
Single gram-negative isolate	15	38
Pseudomonas species	6	8
E. coli	7	22
Other gram-negative organisms	2	8
Polymicrobial isolate	10	23
Gram-positive organisms only	5	5
Gram-positive and gram-negative organisms	5	18
No. without bacteremia	12	16
Single gram-positive isolate	5	7
Single gram-negative isolate	6	9
Polymicrobial isolate	1	0
Levofloxacin resistance in single-agent bacteremias — no. resistant/total no. available for analysis	41/47	32/68
Gram-positive isolate	31/34	28/44
S. aureus	0	1/7
Coagulase-negative staphylococcus	27/30	26/31
Streptococcus species	4/4	1/3
Other gram-positive organisms	0	0/3
Gram-negative isolate	10/13	4/24
Pseudomonas species	4/6	1/4
E. coli	5/5	2/16
Other gram-negative organisms	1/2	1/4

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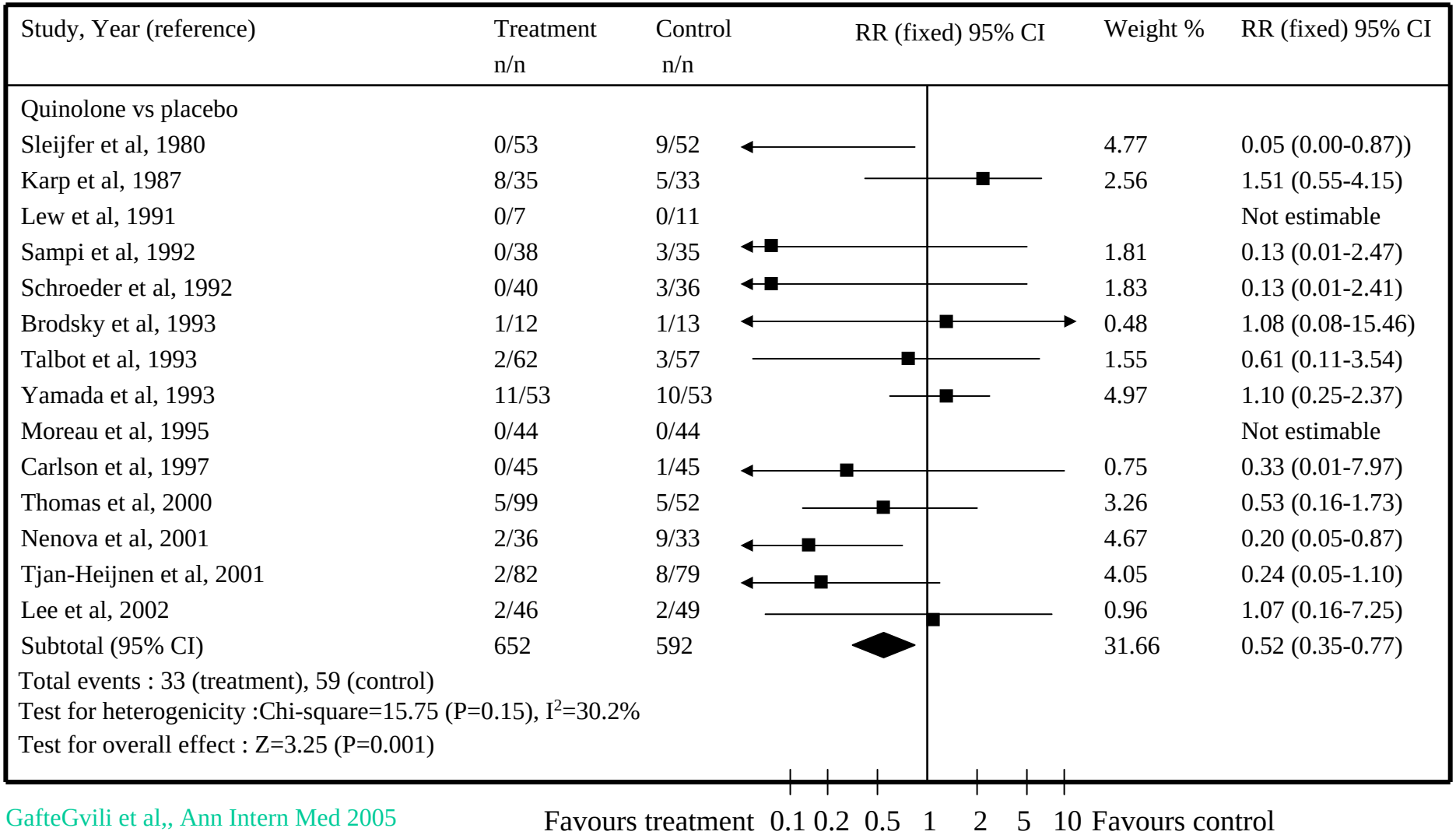
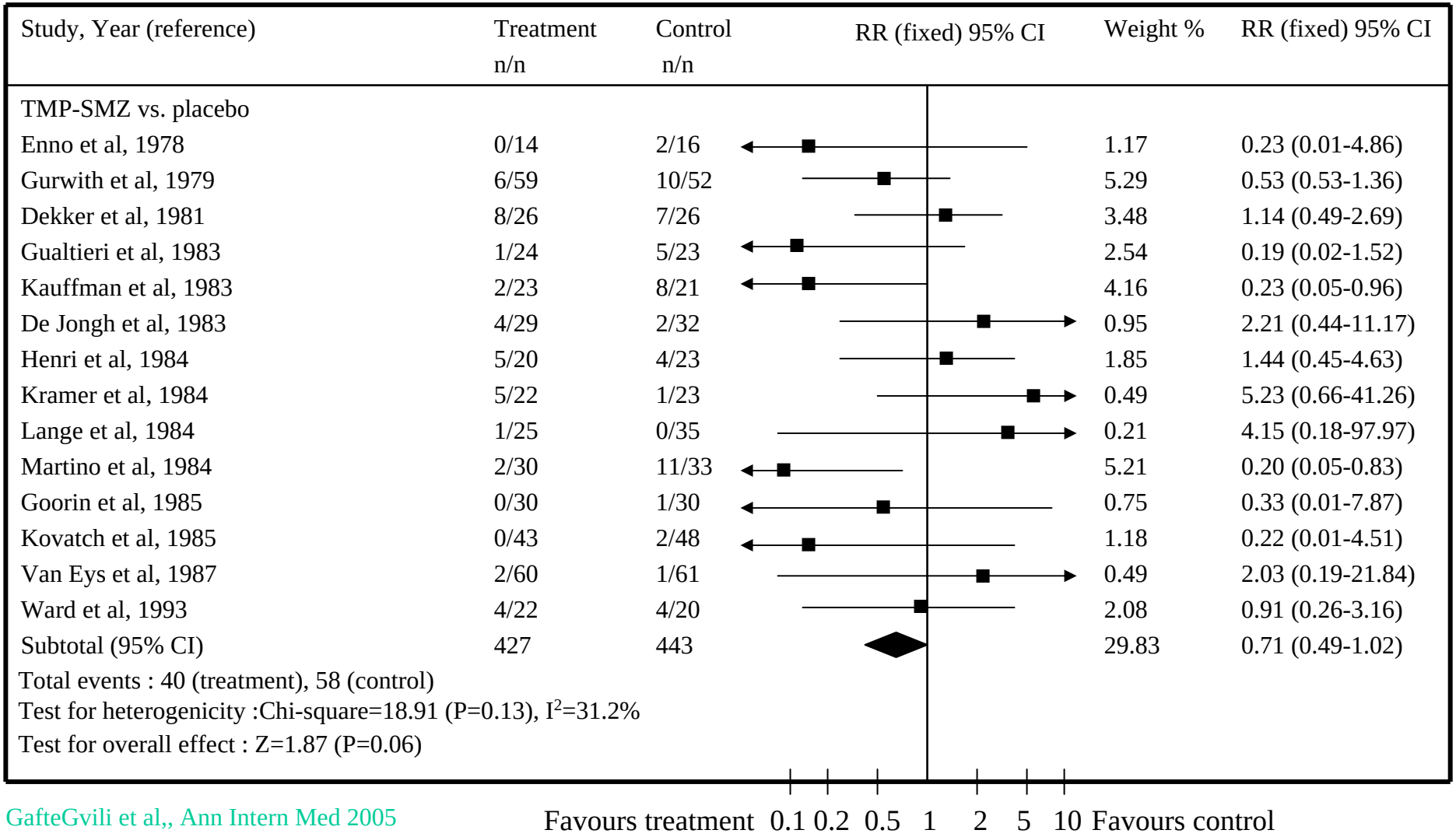
Table 3. Mortality Rates in the Treated Population.

Variable	Levofloxacin (N=373)*	Placebo (N=363)	P Value
	no. of patients		
Death	10	18	0.15
Death due to infection	9	14	0.36
Microbiologically documented infection	4	7	0.25
Microbiologically documented infection with bacteremia	3	5	0.34
Single gram-positive isolate	2	2	
Single gram-negative isolate	0	2	
Polymicrobial (gram-positive and gram-negative) isolate	1	1	
Microbiologically documented infection without bacteremia	1	2	0.48
Single gram-positive isolate	0	1	
Single gram-negative isolate	1	1	
Clinically documented infection	2	4	0.33
Lung	1	2	
Other site	1	2	
Fever of unexplained origin	3	3	0.64
Death from noninfectious causes	1	4	0.17

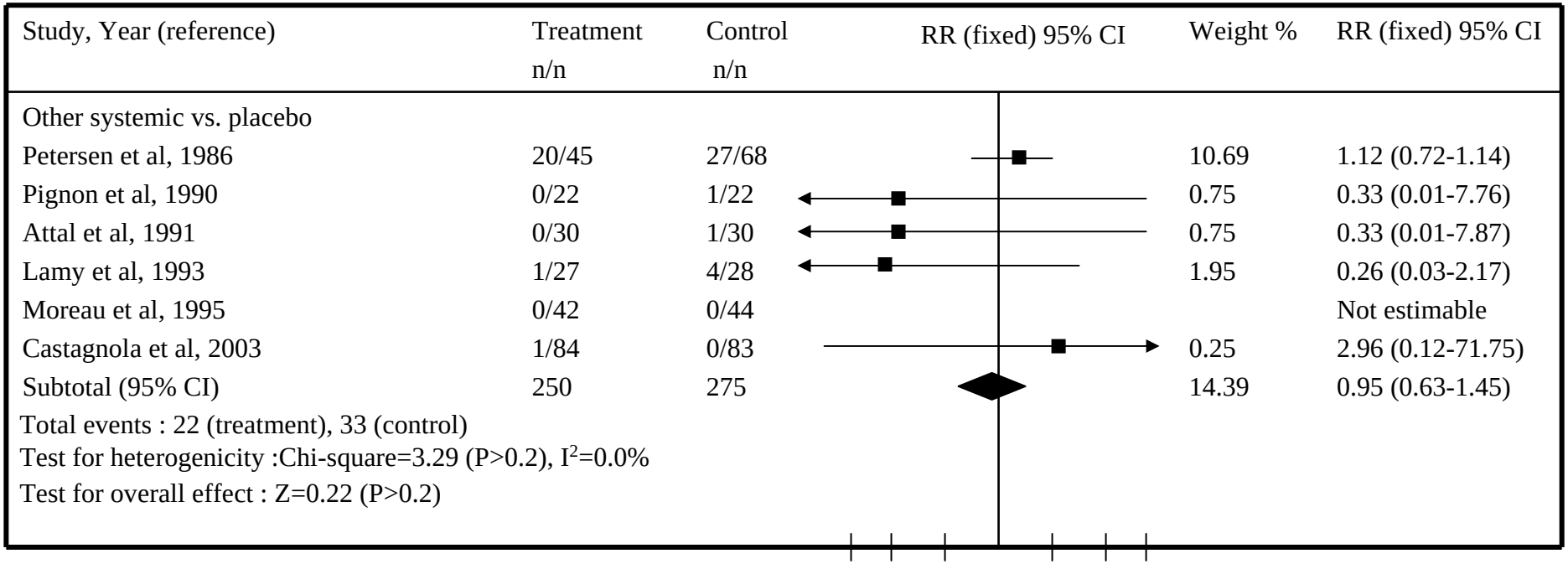
Bucaneve et al, N Engl J Med 2005



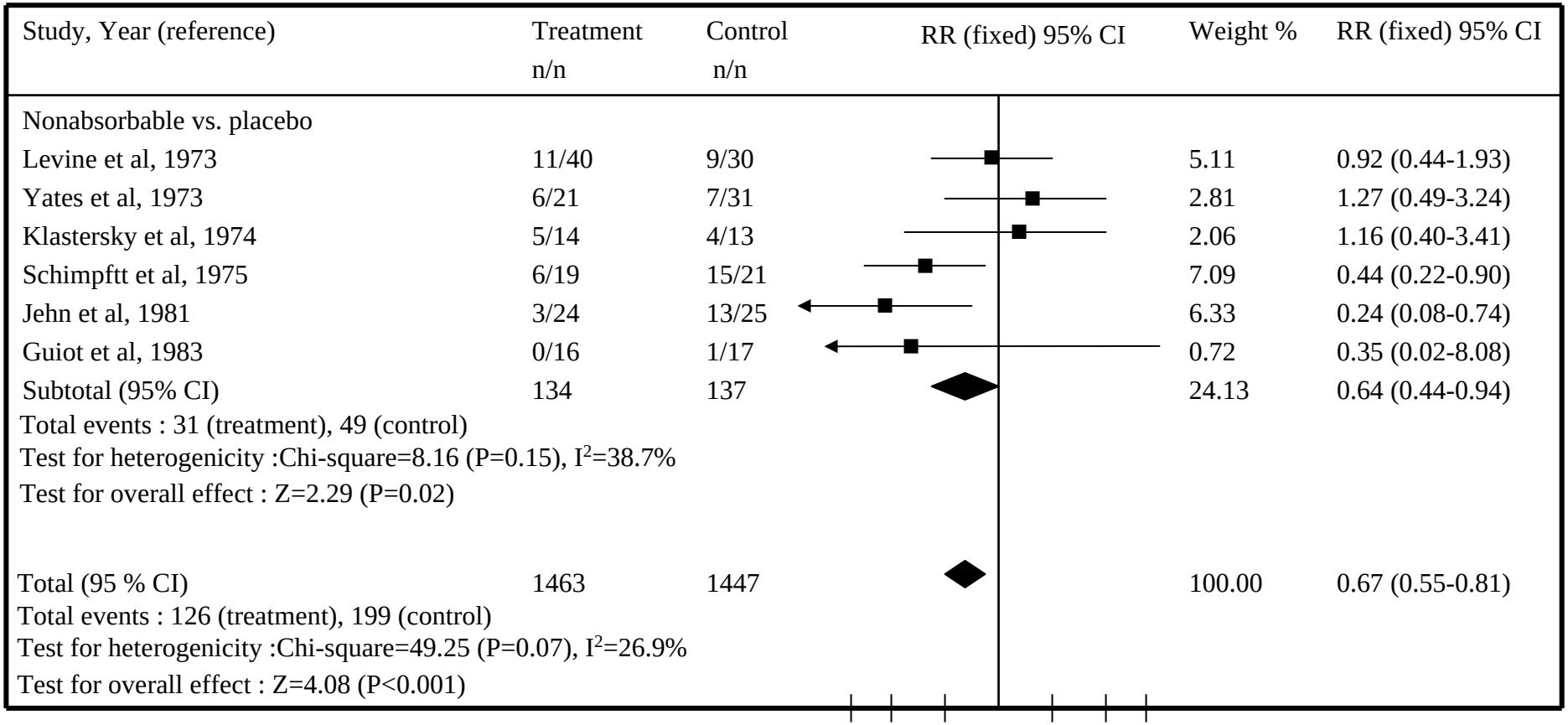
GafteGvili et al,, Ann Intern Med 2005



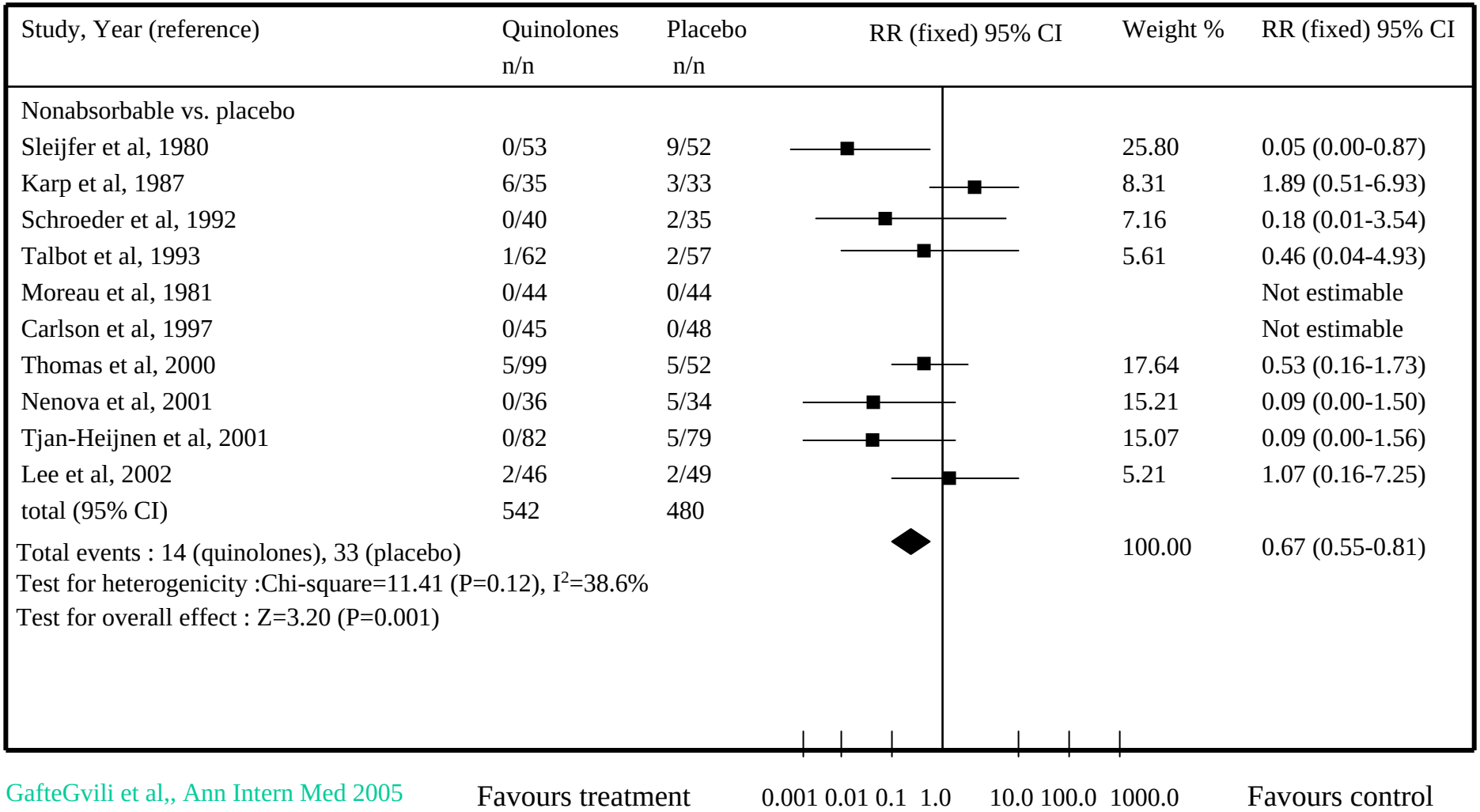
GafteGvili et al,, Ann Intern Med 2005



GafteGvili et al,, Ann Intern Med 2005



GafteGvili et al,, Ann Intern Med 2005



GafteGvili et al,, Ann Intern Med 2005

Variable	Period 1	Period 2	Period 3
Duration of period	12 months	3 weeks	3 months
Levofloxacin prophylaxis given	Yes	No	Yes
No.of patients	188	9	49
Patients age, median years	55	55	51
No.of neutropenic episodes	310	9	70
Duration of neutropenia in patient-days			
Total	3476	97	742
Per episode,			
mean (median)	11 (9)	11 (9)	11 (9)13 (11)
Per episode with fever,			
mean (median)	13 (11)	12 (10)	

Reuter et al, CID 2005

	Study period		
Complication, classification of isolate	Period 1 (n=310 neutropenic episodes)	Period 2 (n=9 neutropenic episodes)	Period 3 (n=70 neutropenic episodes)
Febrile neutropenia	206 (66.5)	8 (88.9)	47 (67.1)
Bacteremia			
Due to any bacteria	73 (23.6)	5 (55.6)	16 (22.9)
Due to gram negative bacteria			
No (%) of episodes	15 (4.8)	4 (44.4)	4 (5.7)
Fluoroquinolones resistance, no.of isolates			
Resistant	9	0	3
Intermediate	1	0	0
Susceptible	5	4	1
Due to Escherichia coli			
No (%) of episodes	9 (2.9)	3 (33.3)	2 (2.9)
Fluoroquinolones resistance, no.of isolates			
Resistant	9	0	2
Intermediate	0	0	0
Susceptible	0	3	0

Reuter S et al, CID 2005

	Study period		
Complication, classification of isolate	Period 1 (n=310 neutropenic episodes)	Period 2 (n=9 neutropenic episodes)	Period 3 (n=70 neutropenic episodes)
Due to gram-positive bacteria			
No (%) of episodes	58 (18.7)	3 (33.3)	12 (17.1)
Fluoroquinolones resistance, no.of isolates			
Resistant	48	1	11
Intermediate	4	0	1
Susceptible	6	2	0
Transfer to ICU because of infection	0 (0)	3 (33.3)	2 (2.9)
Death			
Due to any cause	9 (2.9)	3 (33.3)	1 (1.4)
Due to infection	3 (1)	3 (33.3)	1 (1.4)

Reuter S et al, CID 2005

Viridans streptococci resistance

To Levofloxacin

- Razonable CID 2002
  - breakthrough bacteremia 16 %
  - resistance to levofloxacin 17 %

Antimicrobial Prophylaxis

- IDSA 2002: …is not routine…
- Leibovici metaanalysis 2005:… reduces mortality…
- Bucaneve 2005: …prevents febrile episodes and other infection related outcomes…
- ECIL 1 meeting: ciprofloxacin and levofloxacin usefull restricted to high risk patients,+ monitoring.

Antimycotic Prophylaxis:

- Goodman, Slavin 1992,1995: set the trend of fluconazole prophylaxis in high risk pts
- CDC,ASBMT 2000: fluconazole should be administered
- IDSA 2002: fluconazole warranted in alloBMT.
- Ineffective for moulds, krusei and less effective for glabrata
- Glasmacher 2003: metaanalysis itraconazole: protects against IFI yeasts and Aspergillus when adequately dosed: oral solution, IV loading.