Quinolone –PROPHYLAXIS in neutropenic patients

The Cons..

Günter Weiss

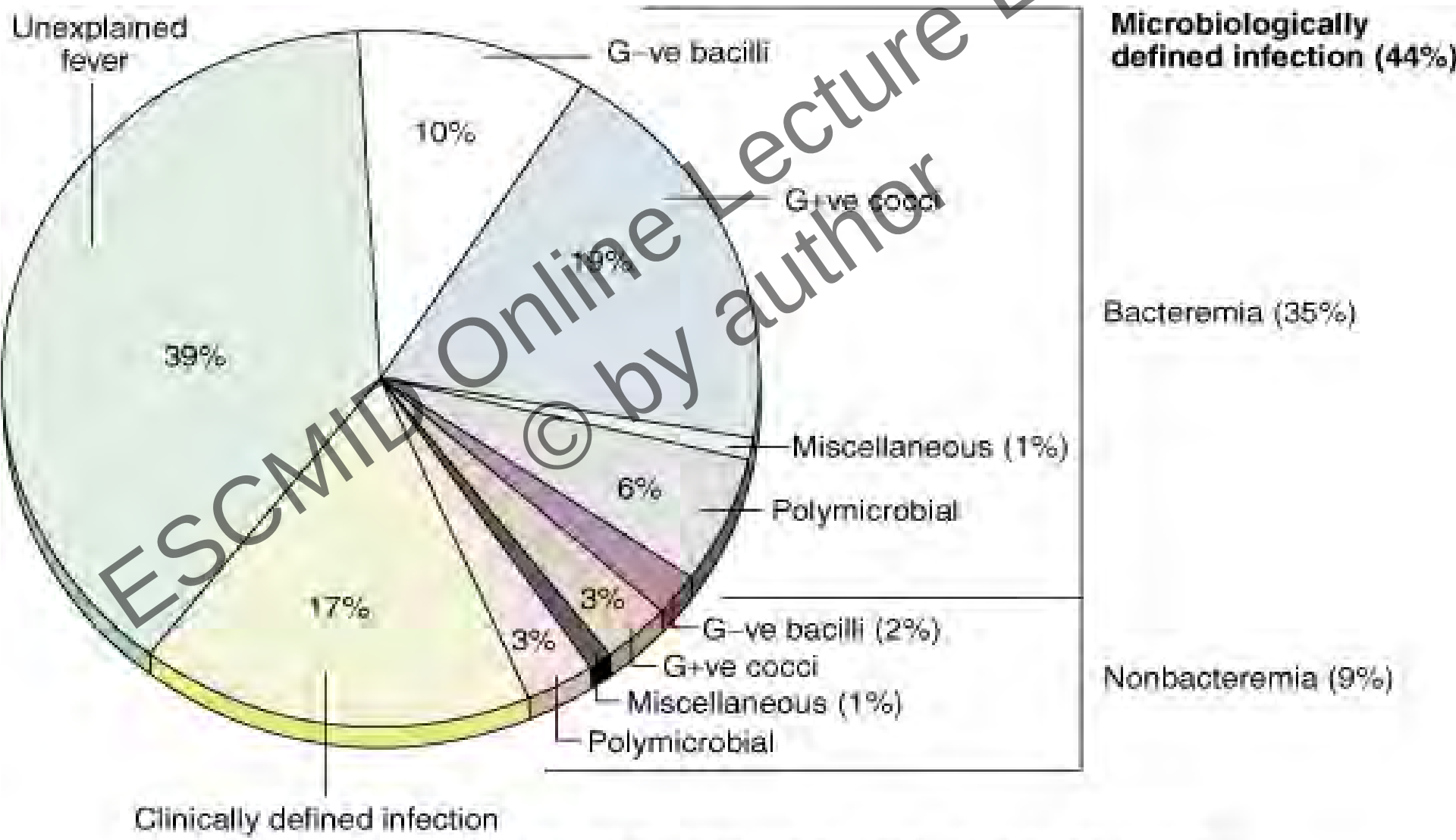
Department of Internal Medicine

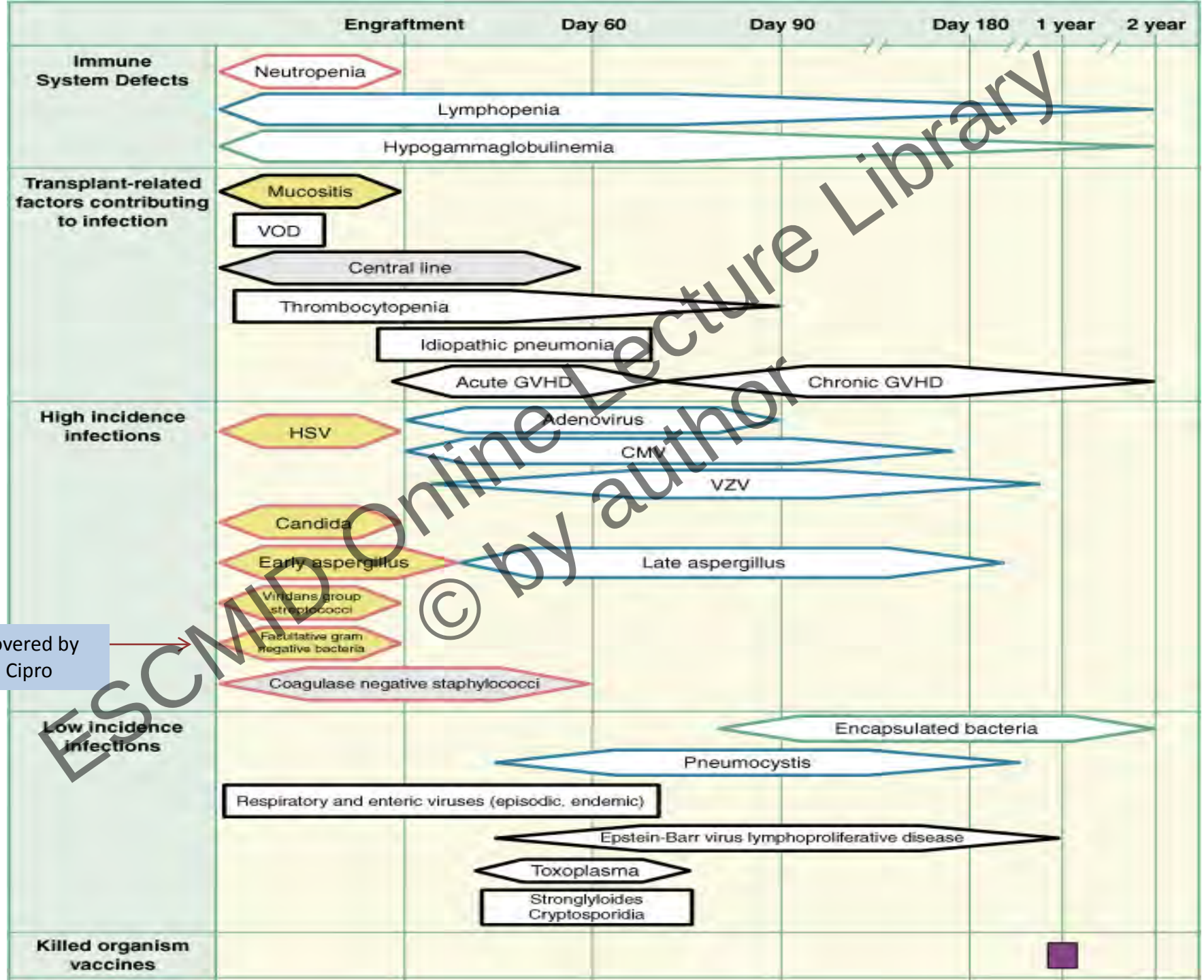
Clinical Immunology and Infectious Diseases

Medical University of Innsbruck, Austria

Infectious causes of neutropenic fever

Ann Intern Med. 1994;120:834-844.





Risk stratification

- Which patients may benefit?
- Local epidemiology
  - Most frequent pathogens in neutropenic patients
  - resistance pattern
  - Available diagnostic and therapeutic options

Metanalysis of 109 randomized controlled trials indidcated that in **high risk patients** (hematological malignancies, neutropenia> 7d)

Fluoroquinolone prophylaxis reduced all cause mortaltity (RR 0.54) as well as infected related mortality Gafter-Gvili et al Cochrane Databse 2012

NNT to prevent on febrile epidose

5 patients in leukemia

23 patients with solid tumors or lymphoma

Leibovici Cancer 2006

NNT to treat to prevent one death

43 for leukemia or HCT patients

132 for solid tumors and lymphoma

Tomblyn et al. Biol BMT 2009

.....BUT

….BUT

- …..most studies were conducted when chinolone resistance was not a serious problem—survival benefit in 2012?

Resistance in blood cultures

Gram-negative Bacteria (percentage of reistant pathogens in blood cultures-IBK 2007)

	Ciprofloxacin	Ceftazidim	Pip/Taz	Imipenem
E. coli	57% (34/64)	12% (11/94)	11% (10/94)	0% (0/64)
P. aeruginosa	30% (7/23)	28% (7/25)	12% (3/25)	26% (6/23)
Kleb. pneum.	5% (1/20)	5% (1/20)	25% (5/20)	0 % (0/20)
Enterobacter cl.	19% (3/16)	44% (7/16)	37% (6/16)	0 % (0/16)

Local epidemiology

….BUT

- …..most studies were conducted when chinolone resistance was not a serious problem—survival benefit in 2012?

- .. No benefit in low risk patients

- .. Borderline effects in intermediate risk patients (autologous HCT, neutropenia 7-10 days, CLL, MM,..) and no survival benefit (Eleutherakis- Papaiakovou et al. Am J Med 2010; Cullen et al. NEJM 2005)

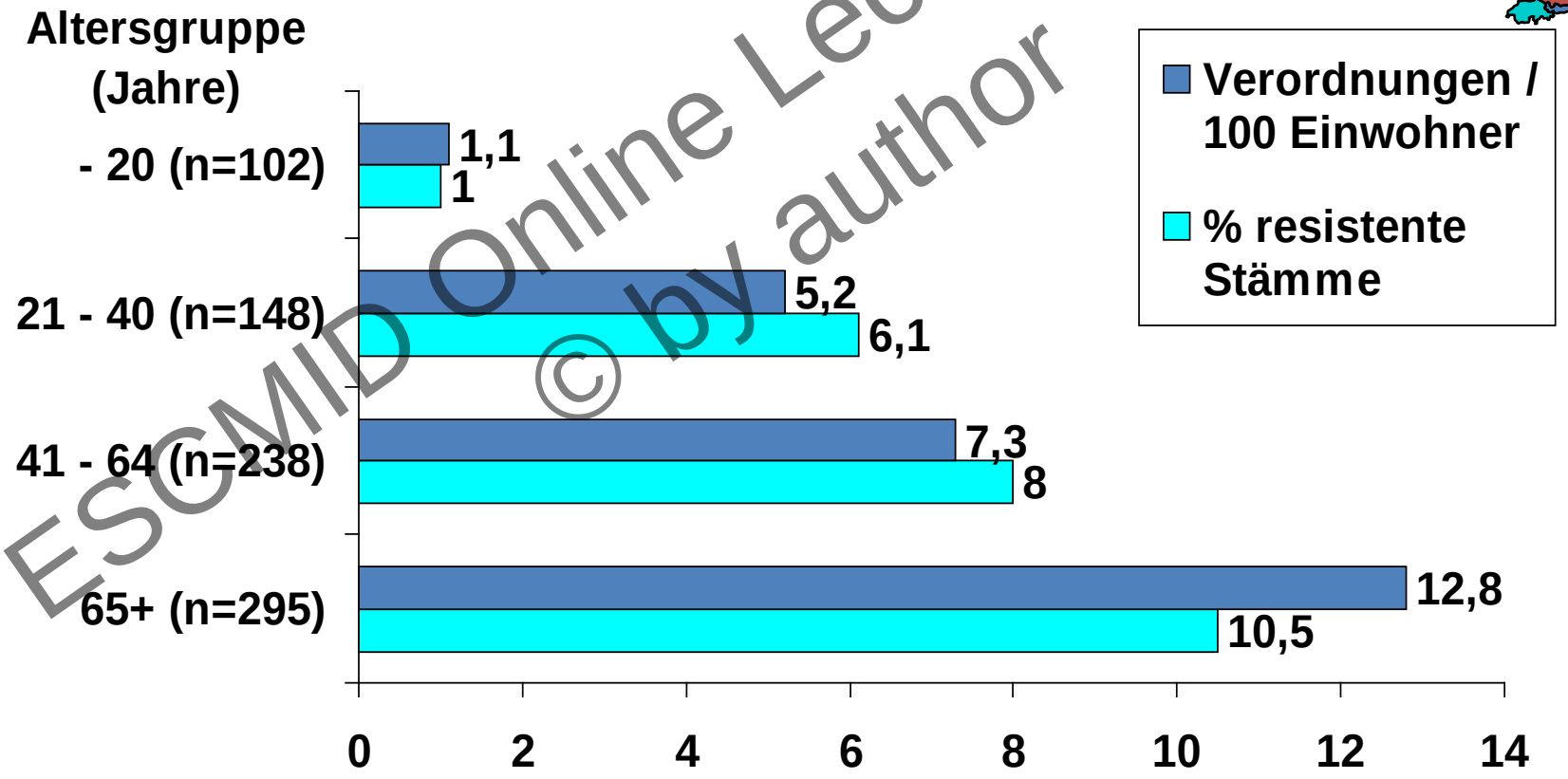
Dis-advantages of Ciprofloxacin Prophylaxis

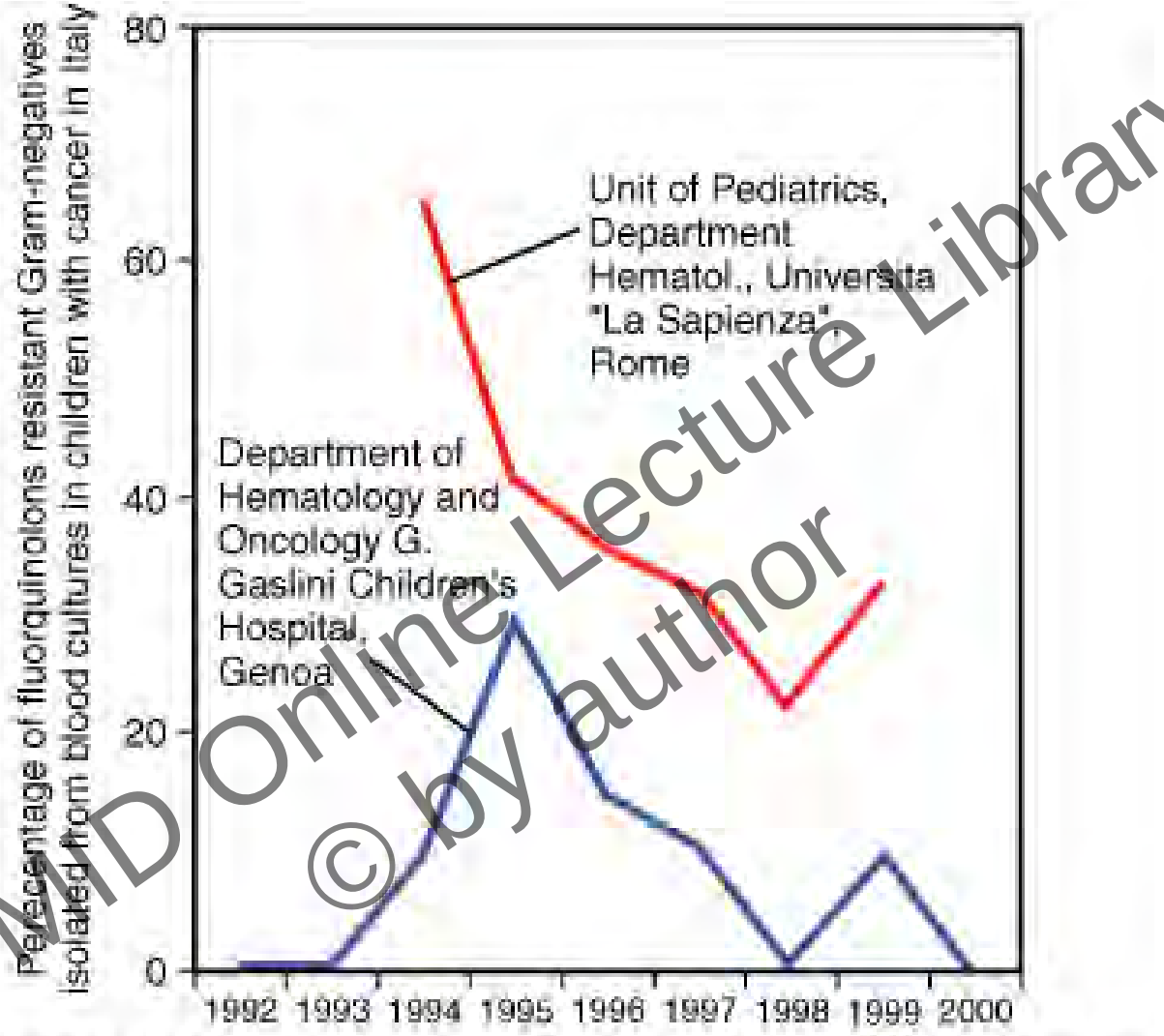
- EMERGE of RESISTANCE

Number and duration of antiboitic use is associated with emerge of resitance

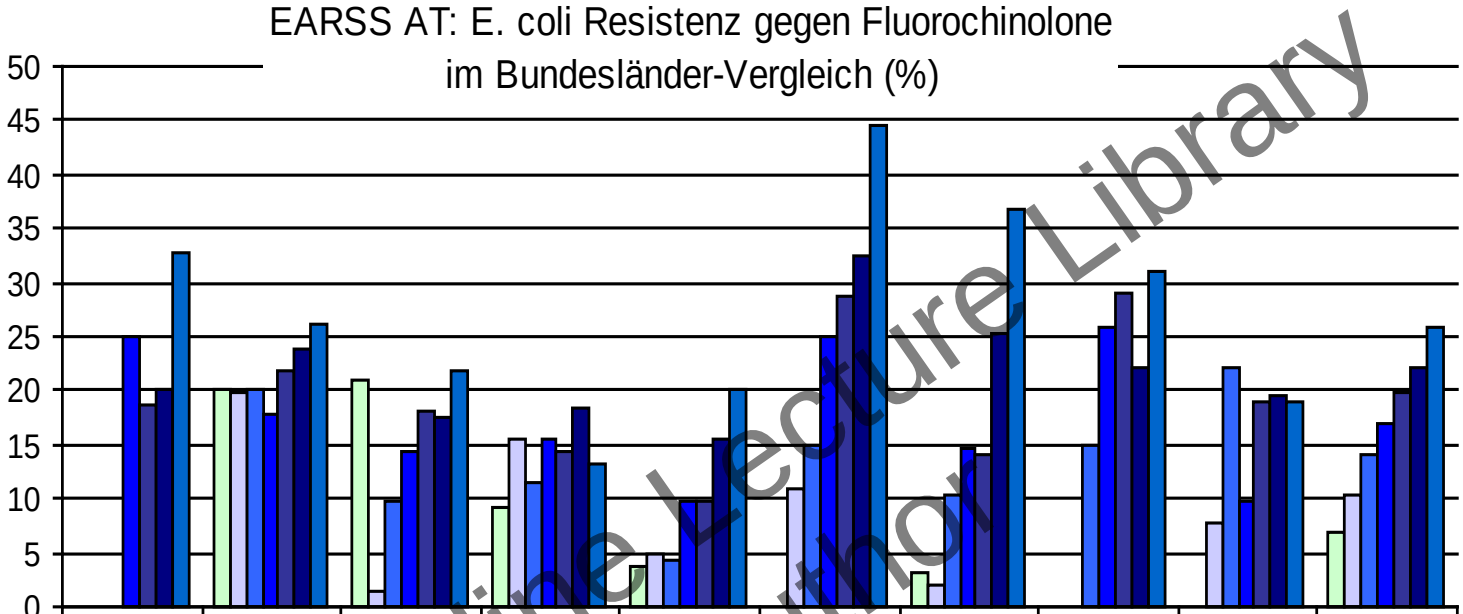
Ciprofloxacin-resistance in *E. coli* linked to Ciprofloxacin-use

PEG
AG Resistenz





Fluoroquinolone resistance is virtually absent among gram-negative isolates in Genoa, where no fluoroquinolone prophylaxis has ever been administered, but it is not negligible in Rome, where fluoroquinolone prophylaxis has been extensively used in adults.



	Bgld	Wien	Nö	Oö	Sbg	T	V	Stmk	K	Gesamt
2001		20	21,05	9,09	3,7		3,12	0	0	6,9
2002		19,74	1,49	15,52	4,88	10,84	2,04	0	7,69	10,27
2003		20	9,91	11,54	4,35	15,03	10,34	15	22	14,04
2004	25	17,75	14,42	15,54	9,78	25	14,52	25,93	9,78	17,02
2005	18,67	21,97	18,18	14,25	9,68	28,8	14,08	29,03	19,05	19,85
2006	20	23,95	17,65	18,49	15,5	32,34	25,33	22,22	19,48	22,25
2007	32,88	26,05	21,76	13,36	20,2	44,59	36,84	31,17	18,92	25,83

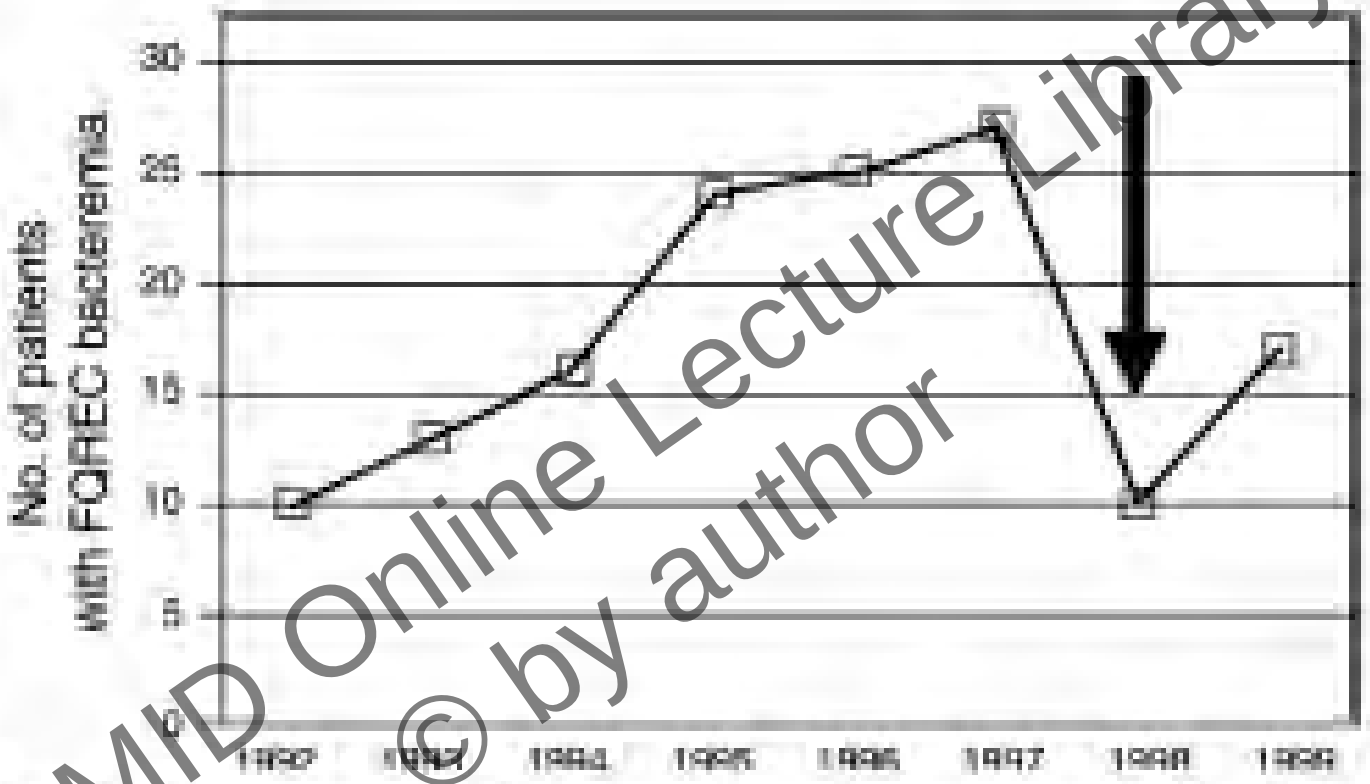


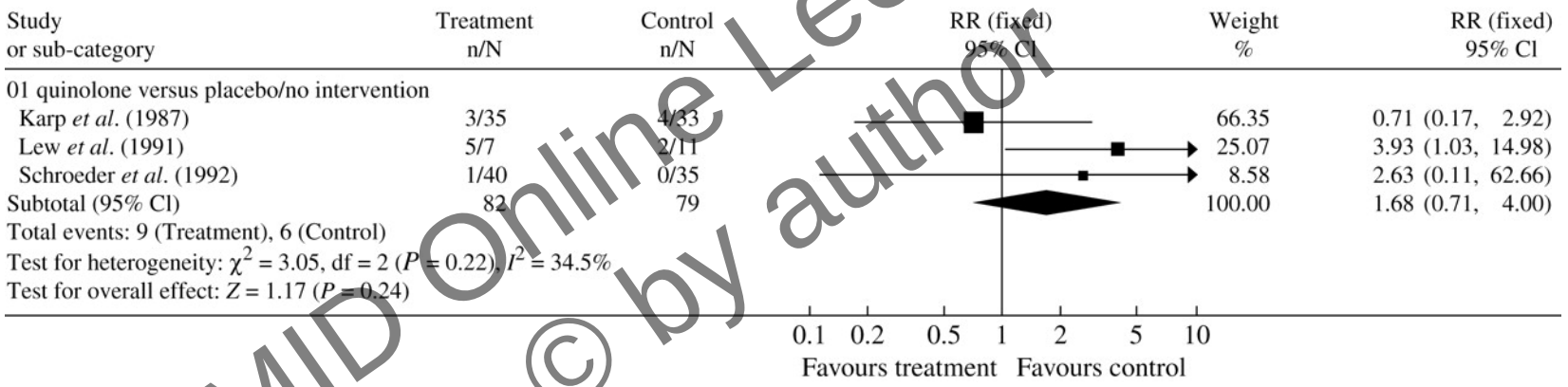
Fig. 1 Yearly number of hematology-oncology patients with one or more episodes of FQREC bacteremia. The arrow denotes the 6-month period of fluoroquinolone prophylaxis discontinuation

Kern WV et al. Eur J Clin Microbiol Infect Dis 2005

Dis-advantages of Ciprofloxacin Prophylaxis

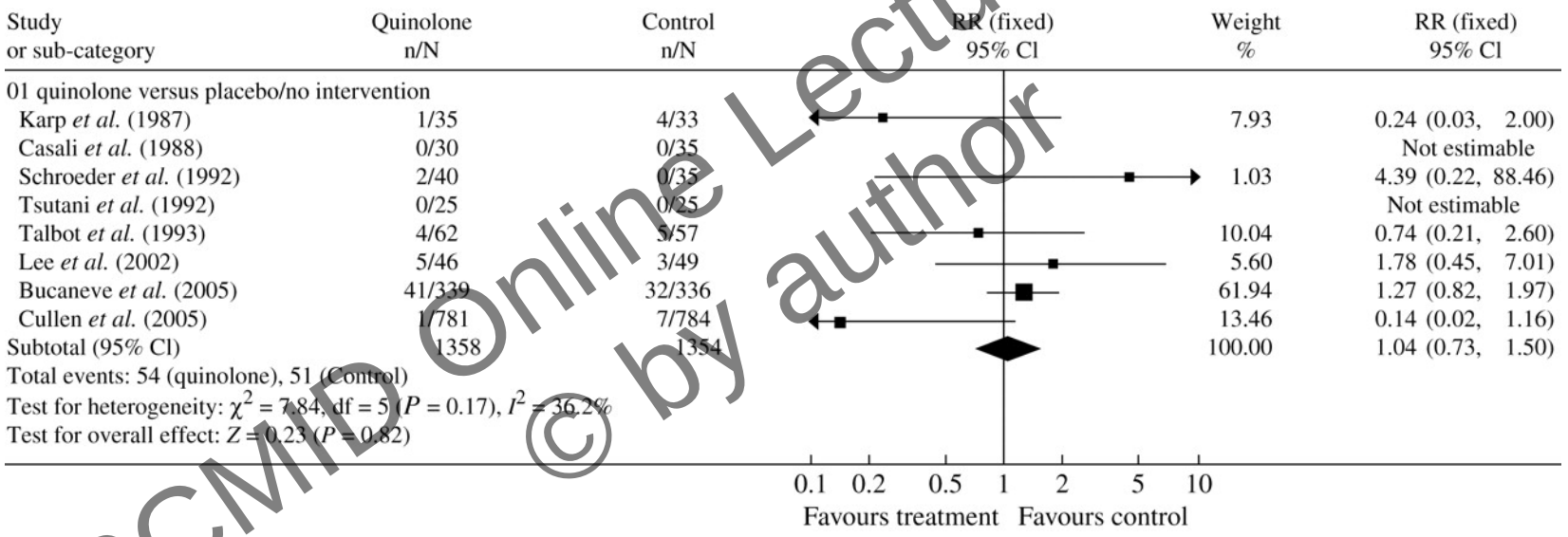
- SELECTION of bacteria (gram positive!)
  - Ciprofloxacin reduces infection with gram negativ pathogens but in increases the incidence of gram positive infection including MRSA *CID 1996; 23;795*
- C. difficile

Colonization with bacteria resistant to quinolones: quinolones versus placebo or no intervention.



Gafter-Gvili A et al. J. Antimicrob. Chemother. 2007;59:5-22

Infection with bacteria resistant to quinolones: quinolones versus placebo or no intervention.



Study or sub-category	Quinolone n/N	Control n/N	RR (fixed) 95% CI	Weight %	RR (fixed) 95% CI
01 quinolone versus placebo/no intervention					
Karp *et al.* (1987)	1/35	4/33		7.93	0.24 (0.03, 2.00)
Casali *et al.* (1988)	0/30	0/35			Not estimable
Schroeder *et al.* (1992)	2/40	0/35		1.03	4.39 (0.22, 88.46)
Tsutani *et al.* (1992)	0/25	0/25			Not estimable
Talbot *et al.* (1993)	4/62	5/57		10.04	0.74 (0.21, 2.60)
Lee *et al.* (2002)	5/46	3/49		5.60	1.78 (0.45, 7.01)
Bucaneve *et al.* (2005)	41/339	32/336		61.94	1.27 (0.82, 1.97)
Cullen *et al.* (2005)	1/781	7/784		13.46	0.14 (0.02, 1.16)
Subtotal (95% CI)	1358	1354		100.00	1.04 (0.73, 1.50)
Total events: 54 (quinolone), 51 (Control)					
Test for heterogeneity: $\chi^2 = 7.84$, df = 5 ($P = 0.17$), $I^2 = 36.2\%$					
Test for overall effect: $Z = 0.23$ ($P = 0.82$)					

Gafter-Gvili A et al. J. Antimicrob. Chemother. 2007;59:5-22

C. difficile-associated diarrhea (CDAD)

- Most frequent cause of nosocomial diarrhea
- Affects approx. 1% of all patients admited to hospitals (Buchner *Am J Gastro* 2001; Dallal *Annals Surgery* 2002)

accounts for approx 1% of in-hospital mortality

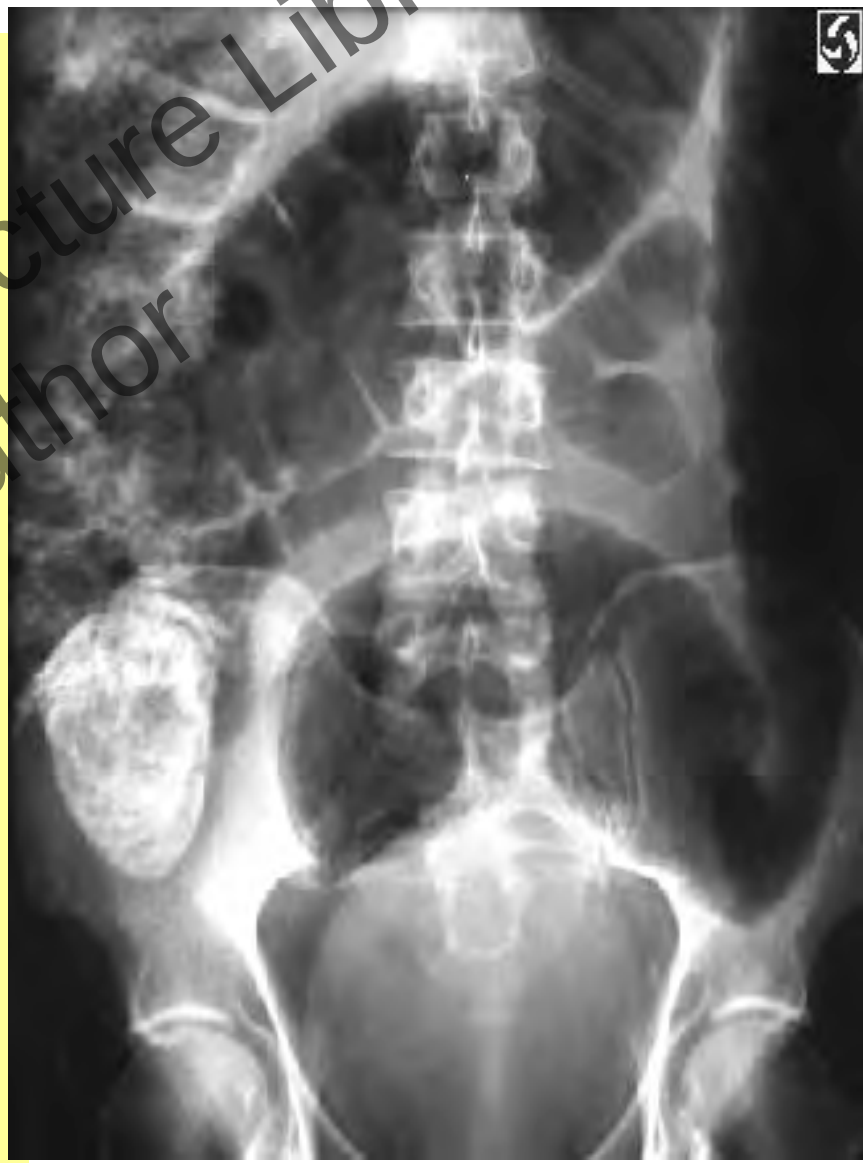


Table 4. Multivariate Model of the Risk of *Clostridium difficile*–Associated Diarrhea According to the Use of Antibiotics among Case Patients, as Compared with Matched Controls, January 11 through June 26, 2004.*

Antibiotic	Odds Ratio	95% Confidence Interval
Any cephalosporin	3.8	2.2–6.6
First-generation	2.4	1.2–4.6
Second-generation	6.0	2.1–17.5
Third-generation	3.0	1.4–6.8
Any fluoroquinolones	3.9	2.3–6.6
Ciprofloxacin	3.1	1.8–5.4
Gatifloxacin or moxifloxacin	3.4	1.5–7.7
Levofloxacin	0.6	0.2–1.9
Clindamycin	1.6	0.5–4.8
Aminoglycosides	0.7	0.3–1.9
Macrolides	1.3	0.6–2.9
Intravenous vancomycin	1.3	0.5–3.1
Penicillins combined with β-lactamase inhibitor	1.2	0.7–2.3
Penicillins	0.7	0.3–2.9
Carbapenems	1.4	0.3–6.3

* Values were adjusted for the use of all other antibiotics, age, sex, number of days at risk for *C. difficile*–associated diarrhea, the Charlson index, and the use feeding.

Loo V et al. N Engl J Med 2005;353:2442-2449

Baseline characteristics of participants in 7421 episodes of care of Clostridium difficile–associated diarrhea (CDAD).

Characteristic	Value
Sex	
Male	3451 (46.5)
Female	3970 (53.5)
Age, years	
18–64	2667 (35.9)
65–79	2457 (33.1)
⩾80	2297 (31.0)
Median years	72
Charlson comorbidity index	
0	1573 (21.2)
1–3	3426 (46.2)
4–6	1761 (23.7)
⩾7	661 (8.9)
Level of care	
Intensive care unit stay	1579 (21.3)
Surgery	1473 (19.8)
Oesophagogastroduodenoscopy	565 (7.7)
Colonoscopy prior to CDAD	474 (6.3)
Drugs received	
Any antibiotic	3432 (46.2)
Fluoroquinolones	1708 (23.0)
Second-generation cephalosporins	1001 (13.5)
First-generation cephalosporins	661 (8.9)
Narrow-spectrum penicillins	587 (7.9)
Third-generation cephalosporins	581 (7.8)
Metronidazole	535 (7.2)
Macrolides	376 (5.1)
Intravenous β-lactam/β-lactamase inhibitors	355 (4.8)
Aminoglycosides	278 (3.7)
Intravenous vancomycin	217 (2.9)
Trimethoprim-sulfamethoxazole	199 (2.7)
Amoxicillin–clavulanic acid	147 (2.0)
Clindamycin	147 (2.0)
Carbapenems	61 (0.8)
Nonsteroidal anti-inflammatory drugs	4088 (55.1)
Proton pump inhibitors	3134 (42.2)
Laxatives	3050 (41.1)
Corticosteroids	1389 (18.7)
H_2 blockers	1199 (16.2)
Antacids	756 (10.2)
Antimotility drugs	644 (8.7)
Immunosuppressive drugs	288 (3.9)
Enteral feeding	237 (3.2)

NOTE. Data are no. (%) of patients, unless otherwise indicated.

Pépin J et al. Clin Infect Dis. 2005;41:1254-1260

Adjusted hazard ratios of developing Clostridium difficile–associated diarrhea (CDAD), according to the duration of use of each class of antibiotics.

Antibiotic class	Adjusted hazards ratio (95% CI),[a] by duration of therapy		
	1–3 days	4–6 days	⩾7 days
Fluoroquinolones	2.42 (1.62–3.62)	2.99 (2.06–4.35)	4.33 (3.21–5.84)
First-generation cephalosporins	1.07 (0.66–1.75)	2.61 (1.28–5.31)	3.14 (1.98–4.98)
Cefuroxime and oral second-generation cephalosporins	1.20 (0.73–1.98)	1.80 (1.17–2.76)	1.80 (1.20–2.69)
Cefoxitin	3.41 (2.07–5.60)	2.58 (0.36–18.63)	2.14 (0.29–15.54)
Third-generation cephalosporins	1.41 (0.94–2.10)	1.53 (0.93–2.53)	1.75 (1.08–2.83)
Macrolides	1.38 (0.80–2.40)	1.62 (0.88–2.97)	2.09 (1.12–3.90)
Clindamycin	1.15 (0.47–2.83)	2.35 (0.86–6.43)	2.38 (1.15–4.93)
Intravenous β-lactam/β-lactamase inhibitors	1.75 (0.96–3.18)	1.98 (1.13–3.50)	1.82 (1.15–2.88)

[a] Adjusted for the independent correlates of CDAD shown in table 2.

Pépin J et al. Clin Infect Dis. 2005;41:1254-1260

Selection/persistance of gram positive bacteria by quinolone prophylaxis

Table 2 Species groups of viridans group streptococci isolated from patients before and after quinolone prophylaxis

Species group	No. (%) of patients with viridans group streptococci	
	Before prophylaxis: 74 isolates from 47 patients	After commencing prophylaxis: 27 isolates from 20 patients
S. mitis	32 (43)	14 (52)
S. sanguinis	31 (42)	8 (30)
S. salivarius	10 (14)	4 (15)
S. anginosus	1 (1)	1 (4)
S. mutans	0 (0)	0 (0)

Prabhu et al. EJCMID 2005

SELECTION of resistance in gram positive bacteria

Table 4 Susceptibility patterns of different species groups before and after quinolone prophylaxis

Species group	Levofloxacin[a]				Gatifloxacin[a,b]				Moxifloxacin[a,b]			
	No. (%) susceptible		No. (%) fully resistant[c]		No. (%) susceptible		No. (%) fully resistant[c]		No. (%) susceptible		No. (%) fully resistant[c]	
	Before	After	Before	After	Before	After	Before	After	Before	After	Before	After
S. mitis	29 (91)	5 (36)	3 (9)	9 (64)	29 (91)	5 (36)	3 (9)	9 (64)	29 (91)	5 (36)	3 (9)	9 (64)
S. sanguinis	26 (84)	0 (0)	5 (16)	7 (88)	26 (84)	0 (0)	4 (13)	6 (75)	27 (87)	1 (13)	2 (6)	6 (75)
S. salivarius	10 (100)	2 (50)	0 (0)	0 (0)	10 (100)	4 (100)	0 (0)	0 (0)	10 (100)	4 (100)	0 (0)	0 (0)
S. anginosus	1 (100)	1 (100)	0 (0)	0 (0)	1 (100)	1 (100)	0 (0)	0 (0)	1 (100)	1 (100)	0 (0)	0 (0)
S. mutans	–	–	–	–	–	–	–	–	–	–	–	–

S susceptible, *I* intermediate, *R* resistant, according to Clinical and Laboratory Standards Institute guidelines
[a]Breakpoints in µg/ml: gatifloxacin, moxifloxacin S≤1, R≥4; levofloxacin S≤2, I=4, R≥8
[b]No approved Clinical and Laboratory Standards Institute breakpoints
[c]Includes only R and not I isolates

Prabhu et al. EJCMID 2005

Dis-advantages of Ciprofloxacin Prophylaxis

- Toxicity and drug interactions

SIDE EFFECTS of QUINOLONES

Tendinopathia

QT- prolongation: multiple drug interactions; aggravated upon concomitant use of other QT prolonging agents/CytP 450 inhibitors such as voriconazole/posaconazole

Gastro-intestinal toxicity

SUMMARY
Chinolone prophylaxis

•Benefit shown in high risk groups!

• still relevant in 2012– new resistances?/ better treatments for bacteremia?!

• risk – benefit- ratio needs to be evaluated
  • Individually--- side effects, CDAD, selction of other bacteria..
  • institutionally– emerge of resistance, collateral damage in other patients

•Other options for infection control
  •Better diagnostic tests
  • hygiene measures
  • pro-biotics…