Fluoroquinolone prophylaxis: pro´s

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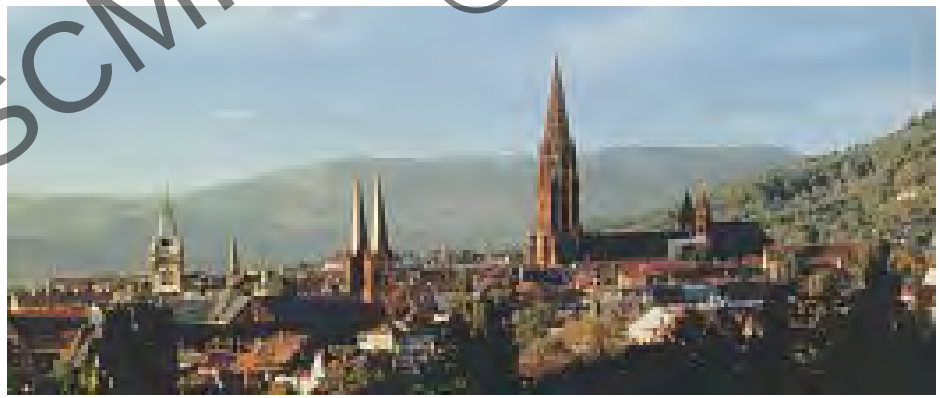


„in . ensch sieht ein –

und das ist wichtig –

und nichts ganz richtig“

Eugen Roth

„isn

completely right“

Eugen Roth

ORIGINAL ARTICLE ARCHIVE

A Comparison of Trimethoprim-Sulfamethoxazole plus Nystatin with Gentamicin plus Nystatin in the Prevention of Infections in Acute Leukemia

James C. Wade, M.D., Stephen C. Schimpff, M.D., Michael T. Hargadon, M.S., Clarence L. Fortner, M.S., Viola Mae Young, Ph.D., and Peter H. Wiernik, M.D.

N Engl J Med 1981; 304:1057-1062 | April 30, 1981

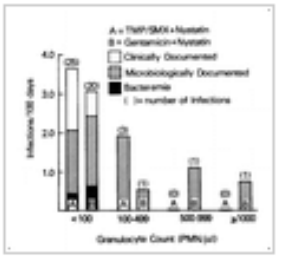
Abstract

Fifty-three profoundly granulocytopenic patients with relapsed acute leukemia who were undergoing reinduction chemotherapy were prospectively randomized to receive either trimethoprim–sulfamethoxazole plus nystatin or gentamicin plus nystatin for prevention of infections. The acquisition of new organisms per patient during the total study period was similar in both groups. Thirty-five symptomatic infections (five of which were bacteremias) occurred in patients receiving trimethoprim–sulfamethoxazole plus nystatin, whereas 31 infections (eight bacteremias) occurred in patients receiving gentamicin plus nystatin. Four deaths related to infection occurred in patients taking triethoprim–sulfamethoxazole, and eight occurred in patients taking gentamicin. We conclude that triethoprim–sulfamethoxazole plus nystatin was approximately as effective as gentamicin plus nystatin for prophylaxis against infection in relapsed acute leukemia. Furthermore, side effects were fewer and compliance was better with trimethoprim–sulfamethoxazole plus nystatin. (N Engl J Med. 1981; 304:1057–62.)

We are indebted to Paula Salvatore for her assistance in preparing the manuscript and to Dr. David Barry, of Burroughs–Wellcome,

MEDIA IN THIS ARTICLE

FIGURE 1



The Incidence of Infection for the Two Study Groups on Antibiotic Prophylaxis is Shown at Four Levels of Granulocyte Count.

TABLE 1

Patients' Characteristics.

Fluoroquinolones

- Norfloxacin was discovered in the late 70s
- It was licensed in Japan 1984, in USA 1986
- Other congeners followed soon (pefloxacin, ofloxacin, ciprofloxacin, enoxacin)

Fluoroquinolone (FQ) prophylaxis (Px) trials

- … in the mid-to-late 80s have shown better efficacy than cotrimoxazole and/or nonabsorbable antibiotics or no chemo-prophylaxis
- … considering the endpoint gram-negative bacteremia („sepsis“), being in 50% or more of the cases caused by *E.coli*

Large (>100 patients), evaluable, randomized, controlled trials (in the 80s) of FQ-Px for patients with neutropenia

Author/yr	Study drugs	N	Gram-negative bacteremia (%)
Liang 1990	Ofl *vs* TSX	102	2 *vs* 17
Cony-Mahoul 1990	Ofl *vs* TSX/C/V	122	3 *vs* 11
Kern 1991	Ofl *vs* TSX	128	1 *vs* 22
Donnelly 1992	Cip *vs* TSX/C	230	0 *vs* 4
Lew 1992	Cip *vs* TSX	145	0 *vs* 1
Talbot 1993	Enx *vs* Placebo	119	2 *vs* 25

… and the results of the first metaanalysis of FQ-Px trials

indicated that fluoroquinolones are effective in preventing:

- gram-negative bacteremia, OR 0.09 [0.05-0.16; P<.001]

but NOT:

- gram-positive bacteremia, OR 1.05 [0.76-1.45; P=0.7]
- fever, OR 0.76 [0.56-1.04; P=0.09]
- infection-related death, OR 0.79 [0.47-1.34; P=0.4]

Cruciani, Rampazzo, Malena, et al. *CID* 1996

Fluoroquinolone (FQ) prophylaxis (Px) trials

- … in the mid-to-late eighties (and earlier experience with cotrimoxazole) provided evidence that chemoprophylaxis is most effective and useful if the drugs used for it
  - have systemic activity
  - are and remain microbiologically most active against target microorganisms

Large (>100 patients) randomized, controlled trials (in the 80s) of FQ-Px for patients with neutropenia

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What about other and more recent randomized controlled trials ????

More recent large (>100) FQ-Px (vs placebo/no intervention) trials

- Thomas et al 2000
- Tjan-Heinen et al 2001
- Cullen et al 2005
- Bucaneve et al 2005

More recent large (>100) FQ-Px (vs placebo/no intervention) trials

- Thomas et al 2000
  - Pefloxacin+vancomycin (48 pts) vs pefloxacin alone (51 pts) vs placebo (52 pts)
  - Fewer gram-negative bacterial infection with pefloxacin
- Tjan-Heinen et al 2001
  - N=165 SCLC pts, cipro-roxi vs placebo
  - Few details regarding type of infection
- Cullen et al 2005
  - Largest placebo-controlled study to date (solid tumor [predominantly breast cancer]/lymphoma)
  - Difficult to interpret, some details regarding type of infection missing

More recent large (>100) FQ-Px (vs placebo/no intervention) trials

- Thomas et al 2000
- Tjan-Heinen et al 2001
- Cullen et al 2005
- Bucaneve et al 2005
  - Second largest placebo-controlled study

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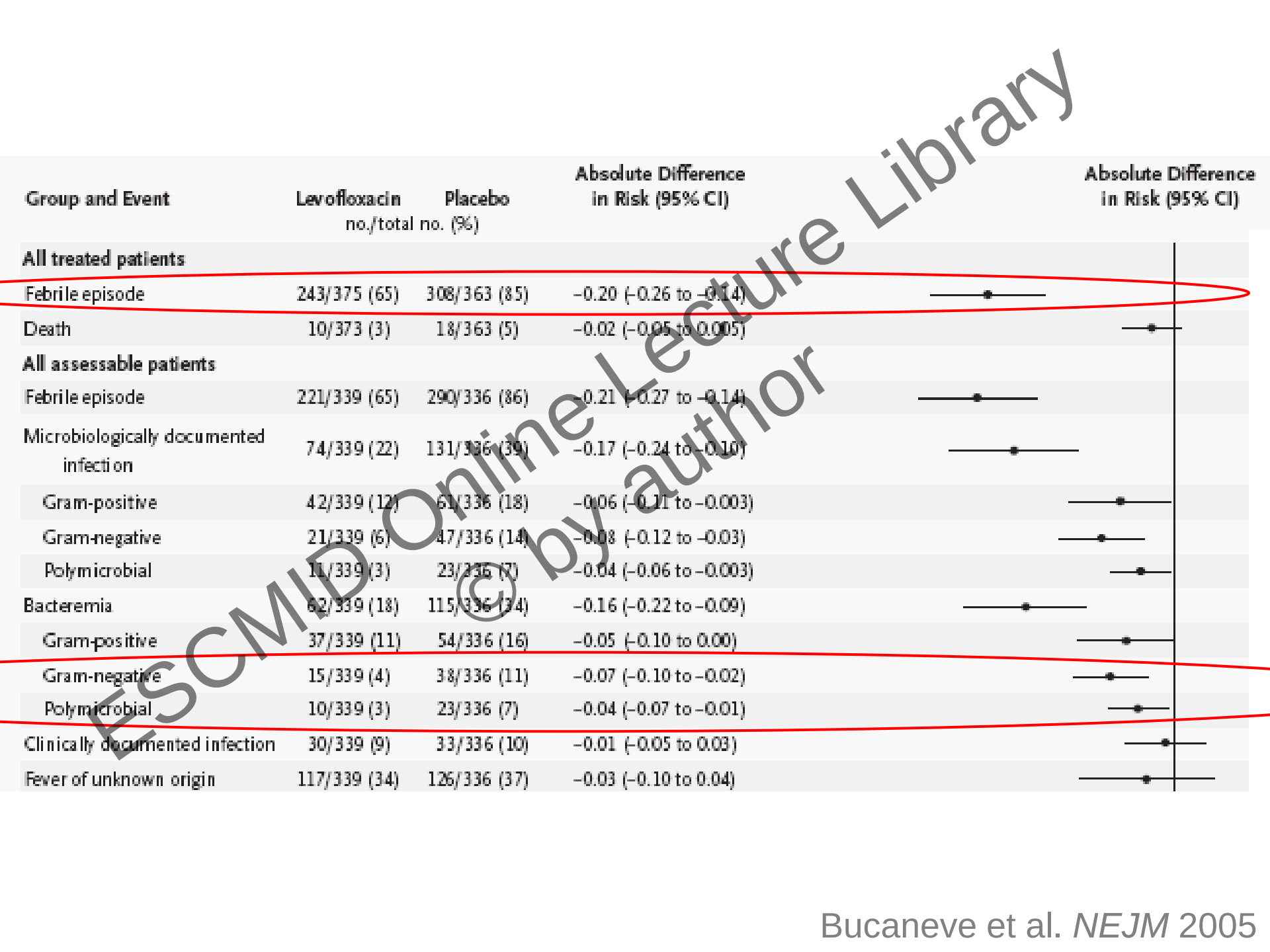
Levofloxacin to Prevent Bacterial Infection in Patients with Cancer and Neutropenia

Giampaolo Bucaneve, M.D., Alessandra Micozzi, M.D., Francesco Menichetti, M.D., Pietro Martino, M.D., M. Stella Dionisi, M.D., Giovanni Martinelli, M.D., Bernardino Allione, M.D., Domenico D'Antonio, M.D., Maurizio Buelli, M.D., A. Maria Nosari, M.D., Daniela Cilloni, M.D., Eliana Zuffa, M.D., Renato Cantaffa, M.D., Giorgina Specchia, M.D., Sergio Amadori, M.D., Francesco Fabbiano, M.D., Giorgio Lambertenghi Deliliers, M.D., Francesco Lauria, M.D., Robin Foà, M.D., and Albano Del Favero, M.D., for the Gruppo Italiano Malattie Ematologiche dell'Adulto (GIMEMA) Infection Program*

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)

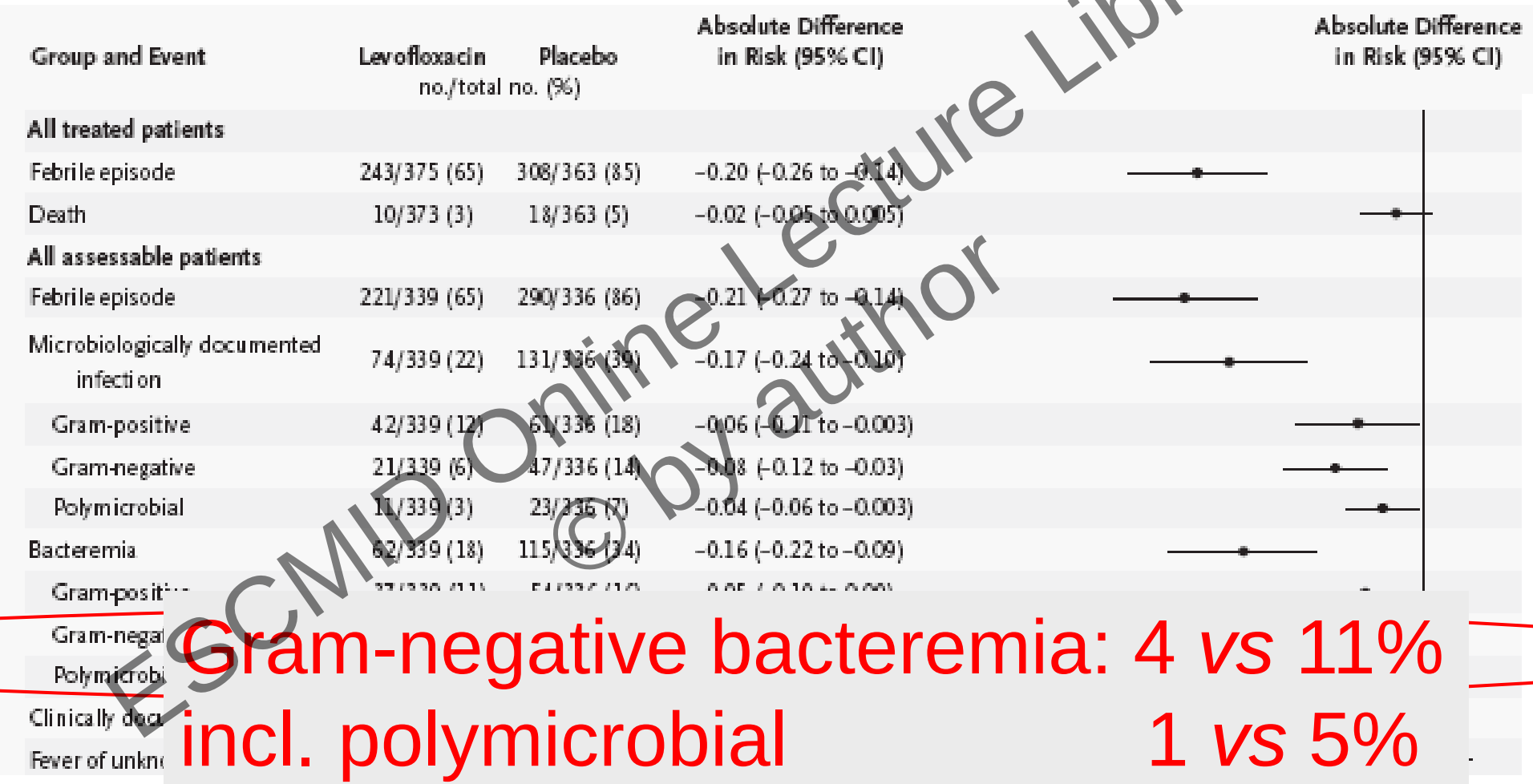


Bucaneve et al. *NEJM* 2005

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

Bucaneve et al. *NEJM* 2005



Gram-negative bacteremia: 4 *vs* 11%

incl. polymicrobial 1 *vs* 5%

Bucaneve et al. *NEJM* 2005

Antibiotic Prophylaxis in Neutropenic Patients

New Evidence, Practical Decisions

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Mical Paul, MD[1,2]
Michael Cullen, MD[3]
Giampaolo Bucaneve, MD[4]
Amat Gafter-Gvili, MD[1,2]
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Updated metaanalysis: FQ-Px impact on bacteremia

Gram-negative Bacteremia

META-ANALYSIS* 2949 patients	Fluoroquinolone	Placebo/No Treatment	RR (95%CI)	P
AL, BMT/SCT	38/598 (**6%**)	106/592 (**18%**)	**0.36** (0.25-0.50)	**<0.001**
Solid Tumors	2/842 (**0.2%**)	8/840 (**0.9%**)	**0.32** (0.09-1.18)	**0.11**

Gram-positive Bacteremia

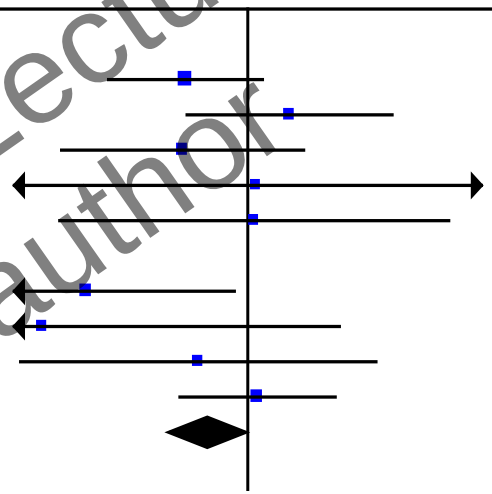
META-ANALYSIS* 2949 patients	Fluoroquinolone	Placebo/No Treatment	RR (95%CI)	P
AL, BMT/HSCT	108/605 (**18%**)	133/603 (**22%**)	**0.81** (0.65-1.01)	**0.07**
Solid Tumors	4/842 (**0.5%**)	12/840 (**1.4%**)	**0.35** (0.12-1.04)	**0.07**

Leibovici et al. *Cancer* 2006

Updated metaanalysis: FQ-Px impact on overall survival

(AL, BMT/SCT)

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	10/373	18/363		21.16	0.54 [0.25, 1.16]
Karp 1987	8/35	5/33		5.97	1.51 [0.55, 4.15]
Thomas 2000	5/99	5/52		7.60	0.53 [0.16, 1.73]
Brodsky 1993	1/12	1/13		1.11	1.08 [0.08, 15.46]
Lee 2002	2/46	2/49		2.25	1.07 [0.16, 7.25]
Moreau 1995	0/44	0/44			Not estimable
Nenova 2001	2/36	9/33		10.89	0.20 [0.05, 0.87]
Sampi 1992	0/38	3/35		4.22	0.13 [0.01, 2.47]
Talbot 1993	2/62	3/57		3.63	0.61 [0.11, 3.54]
Yamada 1993	11/53	10/53		11.60	1.10 [0.51, 2.37]
Subtotal (95% CI)	798	732		68.43	0.67 [0.46, 0.98]
Total events: 41 (Treatment), 56 (Control)					



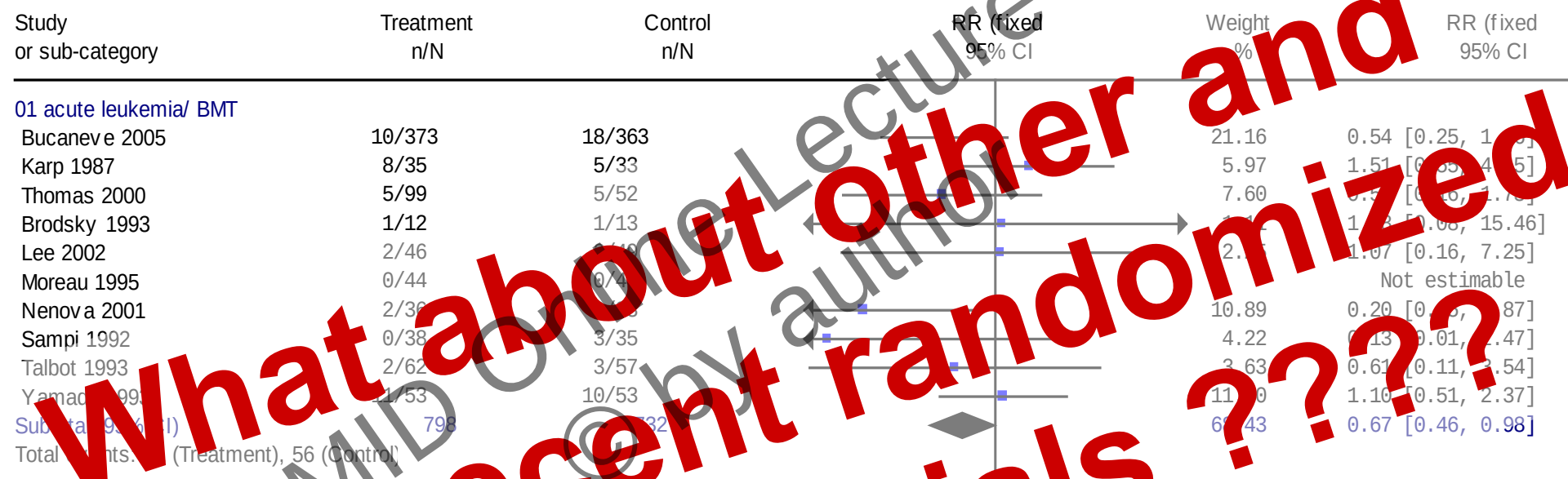
RR = 0.67 (95% CI 0.46-0.98)

NNT = 55

Leibovici et al. *Cancer* 2006

Updated metaanalysis: FQ-Px impact on overall survival

(AL, BMT/SCT)



RR = 0.67 (95% CI 0.46-0.98)

NNT = 55

What about other and more recent randomized controlled trials ????

Leibovici et al. *Cancer* 2006

Antibiotic prophylaxis for bacterial infections in afebrile neutropenic patients following chemotherapy (Review)

Gafter-Gvili A, Fraser A, Paul M, Vidal L, Lawrie TA, van de Wetering MD, Kremer LCM, Leibovici L

THE COCHRANE COLLABORATION®

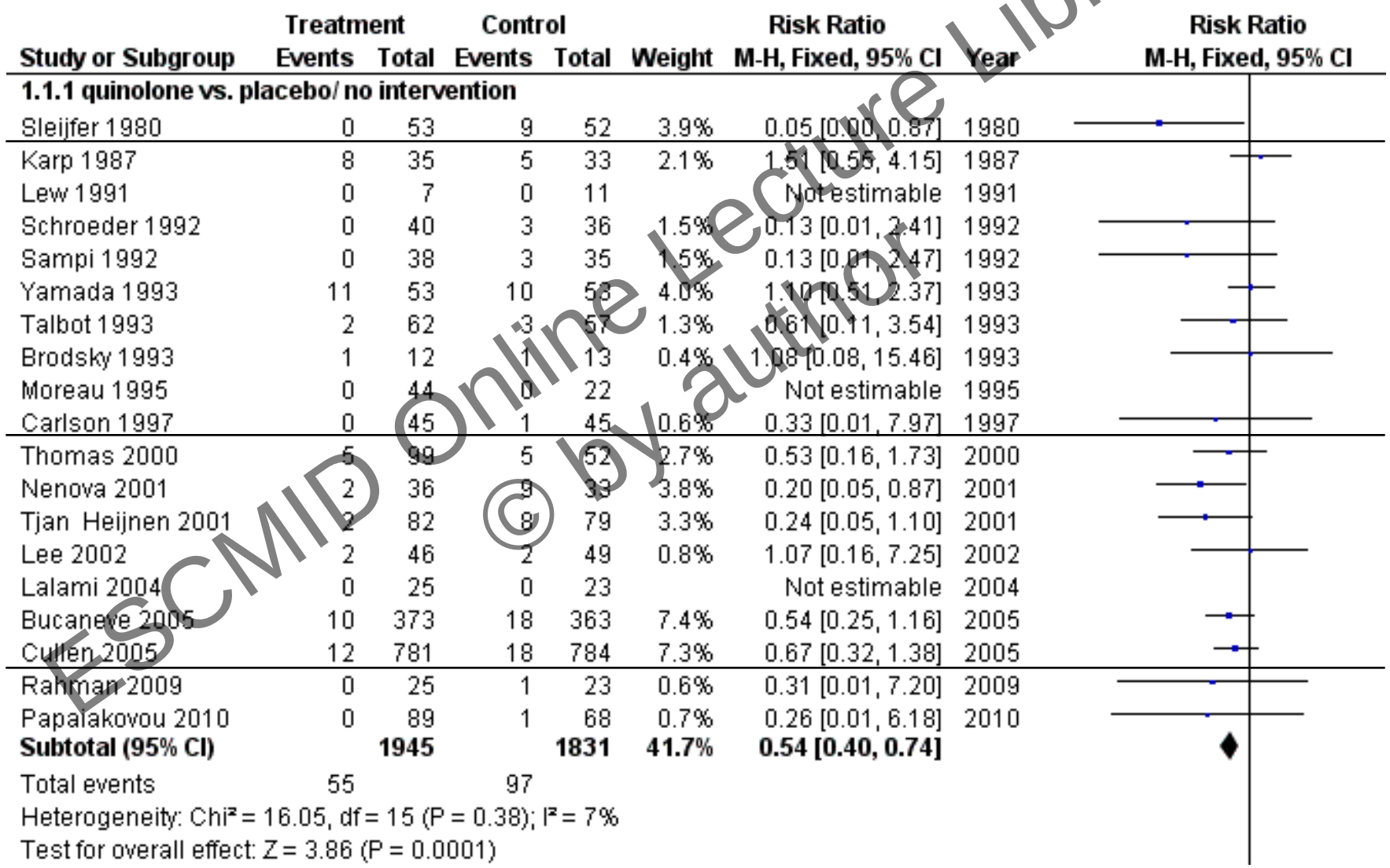
Study or Subgroup	Treatment Events	Treatment Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
3.1.1 quinolone vs. placebo/ no intervention							
Sleijfer 1980	10	53	24	52	1.0%	0.41 [0.22, 0.77]	1980
Hartlapp 1987	3	21	16	21	0.4%	0.19 [0.06, 0.55]	1987
Karp 1987	35	35	33	33	2.8%	1.00 [0.95, 1.06]	1987
Casali 1988	6	30	24	35	0.8%	0.29 [0.14, 0.62]	1988
Rafecas 1989	13	17	15	18	1.9%	0.92 [0.66, 1.28]	1989
Lew 1991	7	7	11	11	2.3%	1.00 [0.81, 1.24]	1991
Sampi 1992	20	38	29	35	1.9%	0.64 [0.45, 0.89]	1992
Tsutani 1992	8	25	20	25	1.1%	0.40 [0.22, 0.73]	1992
Schroeder 1992	2	40	11	35	0.3%	0.16 [0.04, 0.67]	1992
Talbot 1993	48	62	46	57	2.5%	0.96 [0.80, 1.15]	1993
Maiche 1993	6	29	15	30	0.7%	0.41 [0.19, 0.92]	1993
Yamada 1993	38	52	44	51	2.4%	0.85 [0.69, 1.03]	1993
Brodsky 1993	11	12	13	13	2.3%	0.92 [0.74, 1.14]	1993
Moreau 1995	36	44	22	22	2.6%	0.83 [0.71, 0.97]	1995
Carlson 1997	12	45	15	45	1.0%	0.80 [0.42, 1.51]	1997
Thomas 2000	93	99	51	52	2.8%	0.96 [0.90, 1.02]	2000
Ruiz 2001	21	26	23	25	2.4%	0.91 [0.74, 1.12]	2001
Tjan Heijnen 2001	39	82	49	79	2.1%	0.77 [0.58, 1.02]	2001
Nenova 2001	3	36	16	34	0.4%	0.18 [0.06, 0.55]	2001
Lee 2002	38	46	44	49	2.5%	0.92 [0.78, 1.08]	2002
Lalami 2004	1	25	0	23	0.1%	2.77 [0.12, 64.76]	2004
Bucaneve 2005	221	339	290	336	2.7%	0.76 [0.69, 0.83]	2005
Cullen 2005	109	781	152	784	2.3%	0.72 [0.57, 0.90]	2005
Rahman 2009	17	25	18	23	1.8%	0.87 [0.62, 1.23]	2009
Dickgreber 2009	36	99	59	93	2.0%	0.57 [0.42, 0.78]	2009
Papaiakovou 2010	50	89	62	68	2.4%	0.62 [0.51, 0.75]	2010

Gafter-Gvili et al *Cochrane Database of Systematic Reviews* 2012

Most recent FQ-Px (vs placebo/no intervention) trials

- Rahman et al 2009
  - N=80 pts with AL (Bangladesh single-center)
  - Placebo-controlled, many excluded (only 48 evaluable)
- Dickgreber et al 2009 (now fully published: Schuette et al 2011)
  - N=187 NSCLC pts (German multicenter)
  - Placebo-controlled, fewer grade 3/4/5 infections (10 *vs* 28%)
- Eleutherakis-Papaiakovu et al 2010
  - N=157 pts with auto-SCT (Athens single-center, 1997-2008)
  - Cipro+vanco vs no intervention
  - No (!?) gram-negative bacteremia with cipro+vanco

Updated metaanalysis: FQ-Px impact on overall survival



Study or Subgroup	Treatment Events	Treatment Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI	Year
1.1.1 quinolone vs. placebo/ no intervention							
Sleijfer 1980	0	53	9	52	3.9%	0.05 [0.00, 0.87]	1980
Karp 1987	8	35	5	33	2.1%	1.51 [0.55, 4.15]	1987
Lew 1991	0	7	0	11		Not estimable	1991
Schroeder 1992	0	40	3	36	1.5%	0.13 [0.01, 2.41]	1992
Sampi 1992	0	38	3	35	1.5%	0.13 [0.01, 2.47]	1992
Yamada 1993	11	53	10	53	4.0%	1.10 [0.51, 2.37]	1993
Talbot 1993	2	62	3	57	1.3%	0.61 [0.11, 3.54]	1993
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Carlson 1997	0	45	1	45	0.6%	0.33 [0.01, 7.97]	1997
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Rahman 2009	0	25	1	23	0.6%	0.31 [0.01, 7.20]	2009
Papalakovou 2010	0	89	1	68	0.7%	0.26 [0.01, 6.18]	2010
Subtotal (95% CI)		**1945**		**1831**	**41.7%**	**0.54 [0.40, 0.74]**	
Total events	55		97				

Heterogeneity: $Chi^2 = 16.05$, $df = 15$ ($P = 0.38$); $I^2 = 7\%$

Test for overall effect: $Z = 3.86$ ($P = 0.0001$)

Gafter-Gvili et al *Cochrane Database of Systematic Reviews* 2012

Summary/Conclusions

- The efficacy of FQPx in cancer pts with neutropenia (as indicated by GNB) has been demonstrated – with impact on morbidity and utilization of therapeutic antibiotics
- … still - if they work – they could even provide a survival benefit with an acceptable number needed to treat in high-risk patients

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PRO

PRO

Summary/Conclusions

- The efficacy of FQPx in cancer pts with neutropenia (as indicated by GNB) has been demonstrated – with impact on morbidity and utilization of therapeutic antibiotics
- … still - if they work – they could even provide a survival benefit with an acceptable number needed to treat in high-risk patients
- The efficacy appears to diminish … as FQR rates in *E. coli* increase → local/regional epidemiology important