ECIL-6
Antibacterial prophylaxis: critical appraisal of previous ECIL guidelines

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Quinolone prophylaxis for bacterial infections in afebrile high risk neutropenic patients ☆

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Table 3 – Recommendations for fluoroquinolone prophylaxis for prevention of bacterial infections in neutropenic patients with acute leukaemia or haematopoïetic stem cell transplant

Does fluoroquinolone prophylaxis prevent bacterial infections in patients with acute leukaemia?	Yes 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?	Start with chemotherapy and continue until resolution of neutropenia or initiation of empirical antibacterial therapy for febrile neutropenia (AII)

ECIL I; 2006

Published 2007

Background

- Prophylaxis with fluoroquinolones (FQ) widely recommended for high risk patients
- Its efficacy in the era of increasing resistance is unknown
- Potential impact on the selection of resistant strains should be carefully assessed

Leibovici et al. 2006:

- *The GIMEMA study was conducted in a population with* ***nearly 50% resistance to fluoroquinolones in all pathogens and 20% resistance in gram-negative isolates in the control group and in a country with a baseline resistance of approximately 20% in gram-negative isolates*** *from the community (Fadda et al. 2005) and medical departments (Luzzaro et al. 2002). Prophylaxis should be considered in locations that have similar or less resistance.*

Aims & methods

- Standardised systematic literature review of articles published since 2005 on antibiotic prophylaxis in neutropenic high risk haematological patients.
- Aim is producing a position paper, not a guideline
- Trying to answer the following questions:
  1. Is FQ prophylaxis still effective in reducing:
     a) mortality (overall or infection-related),
     b) bloodstream infections (BSI)
     c) febrile episodes
  2. Does discontinuation of FQ prophylaxis increase:
     a) mortality (overall or infection-related),
     b) bloodstream infections (BSI)
     c) febrile episodes
  3. Does FQ prophylaxis increase the rate of FQ resistance?
  4. Does FQ prophylaxis increase the rate of multidrug resistance (MDR)?
  5. What are other prophylactic regimens used, and what is their efficacy in reducing:
     a) mortality (overall or infection-related),
     b) bloodstream infections (BSI)
     c) febrile episodes

Literature review

- Period of publication: 2005 until now
- Search and selection performed independently by three subgroups of authors
- The following key words were used: prophylaxis, neutropenia, antibacterials/antibiotics, fluoroquinolones, haematology, febrile neutropenia.

Three steps

- Non-randomized prospective, observational and retrospective studies
- Prospective, randomized clinical trials
- Metaanalyses

Current guidelines were also examined

FQ prophylaxis
Guidelines and their application

- 7 guidelines published between 2007-2013
- Countries/groups:
  - Europe: ECIL, Germany (AGIHO, DGHO), UK (NICE)
  - Australia
  - USA: IDSA, ASCO, NCCN

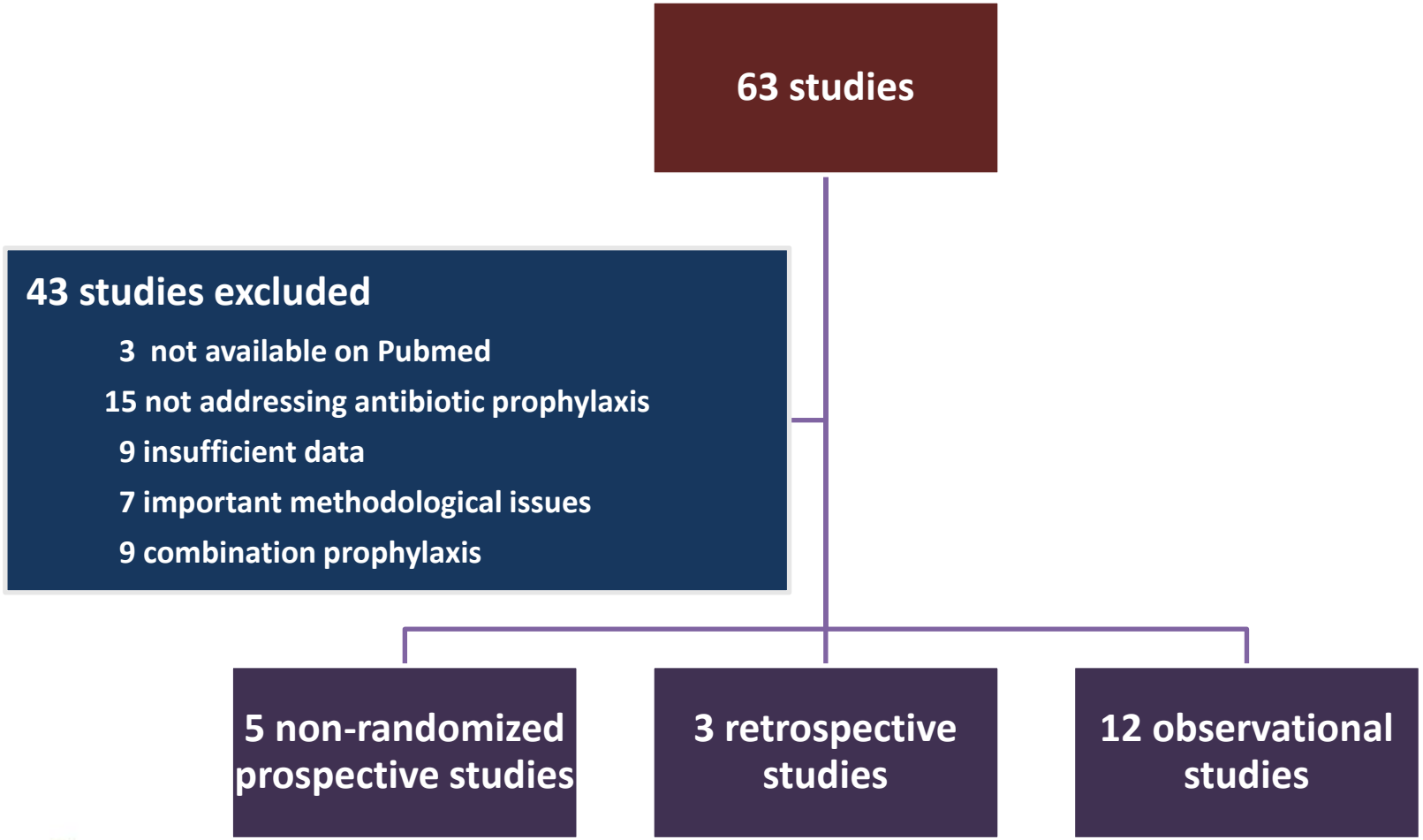
➢ **Recommended in high risk patients with neutropenia ≥ 7 days (ECIL, IDSA, NCCN, ASCO, Germany)**

- 7 surveys on management of infections, including FQ prophylxis, 5 in hematology patietns
- Use of FQ prophylaxis in hematology in **adult** patients
  - Chemotherapy (n=2) **42% and 58%**
  - HSCT (n=2) **76% and 85%**

Review of non-randomized prospective, observational and retrospective studies

F. Tissot, T. Calandra

Research results



Q1: efficacy of FQ prophylaxis
(n=7 studies)

- Studies: prospective (2), retrospective (5)
- Publication year: 2007-2014
- Median number of patients: 220 (range 45-1145)
- FQ prophylaxis: ciprofloxacin (5), levofloxacin (2)
- Historical controls: no prophylaxis (7)
- Baseline prevalence of Gram- FQ resistance:
  - 0.4-41%
  - > 20% in 1 study

Q1: Is FQ prophylaxis still effective in reducing mortality, BSI and febrile episodes?

(n=7 studies)

Outcome	Decrease	Increase	No difference	Answer
Overall or infection-related mortality (n=7)	0/7	0/7	7/7	**No**
BSI (n=7)	5/7	0/7	2/7	**Yes***
Febrile episodes (n=3)	2/3	0/3	1/3	**Inconclusive**

*also in 1 study with > 20% baseline FQ-resistance

BSI: bloodstream infection

Q2: discontinuation of FQ prophylaxis

Article	Prophylaxis discontinuation	Infection-related mortality	Bloodstream infections	Febrile neutropenia
Kern, EJCMID 2005 (Germany)	1996-1997: ofloxacin +/- po colistin 1998: discontinuation (6 mths) 1998-1999: levofloxacin	9% 14% 6%	28% 34% 19%	No data
Reuter, CID 2005 (Germany)	2002-2003: levofloxacin 2003: discontinuation (3 wks) 2003-2004: levofloxacin	1% 33% 1.4%	23.6% 55.6% 22.9%	66.5% 88.9% 67.1%
Saito, EJCMID 2008 (Japan)	2001-2003: levofloxacin (liberal = 56%) 2003-2005: levofloxacin (restricted to HSCT recipients = 28.8%)	3.8% 3.8%	10% 20.3% (p<0.01)	No data
Kanda, BMT 2010 (Japan)	2000-2004: levo, cipro, tosufloxacin 2004-2008: discontinuation	11% 10%	No data	No data
Chong, Int J Infect Dis 2011 (Japan)	2003-2005: levofloxacin 2006-2009: discontinuation	1.5% 1.3%	9% 17%	No data
Sohn, EJCMID 2012 (Korea)	2001-2005: ciprofloxacin 2004-2008: none (other HM protocol)	1 death 0	1.5x100 PD 1.7x100 PD	70.2% 94.1% (p<0.001)
Verlinden, Eur J Haematol 2014 Belgium	2009: ciprofloxacin 2009-2010: discontinuation (8 mths) 2010-2011: ciprofloxacin	3 deaths 0 death 0 death	33.3% 33.3% 32.8%	72.5% 80% 72.4%

Q2: Does discontinuation of FQ prophylaxis increase mortality, BSI and febrile episodes? (n=7 studies)

Outcome	Decrease	Increase	No difference	Answer
Overall and infection-related mortality (n=7)	0/7	2/7	5/7	**No**
BSI (n=6)	1/6	5/6	0/6	**Yes***
Febrile episodes (n=3)	0/3	3/3	0/3	**Yes****

*only 1 study with significant increase

**only 1 study with significant increase

BSI: bloodstream infection

Q3: Does FQ prophylaxis increase the rate of FQ resistance?

(n=10 studies)

- Studies: prospective (1), retrospective (9)
- Publication year: 2007-2015
- Median number of patients: 248 (range 45-543)
- FQ prophylaxis: ciprofloxacin (7), levofloxacin (3)
- Controls:
  - no prophylaxis cohort (8)
  - baseline rate in the same population (2)

Q3: Does FQ prophylaxis increase the rate of FQ resistance?
(n=10 studies)

- **FQ-resistant bacteria in surveillance swab (n=1):**
  - rectal swab before and after prophylaxis:
  decrease in Gram- colonization (36% vs. 10%) but no increase in FQ-resistance (16 vs. 19%)

- **Infections with FQ-resistant bacteria (n=9):**
  - increase 5/9 => higher proportion of FQ-resistant bacteria among MDI, only 2 studies with significant increased incidence of FQ-resistant MDI
  - no increase: 3/9
  - decrease: 1/9

Answer: inconclusive

Q4: Does FQ prophylaxis increase the rate of multidrug resistance (MDR)?
(n=5 studies)

- Studies: retrospective (4)
- Publication year: 2007-2014
- Median number of patients: 364 (range 113-543)
- FQ prophylaxis: ciprofloxacin (3), levofloxacin (1)
- Historical controls: no prophylaxis (4)

Q4: Does FQ prophylaxis increase the rate of multidrug resistance (MDR)? (n=5 studies)

- **ESBL bacteria in surveillance swab (n=1):**
  - rectal swab before and after prophylaxis:

no increase in ESBL (10% vs. 10%) among *E. coli*

- **Increase of infections with MDR bacteria (n=3)**
  - MRSA (n=1, NS)
  - VRE (n=2, $p<0.05$ and $p<0.01$)
  - ESBL (n=2, NS and $p=0.01$)
  - MDR Gram- in general (n=1, NS)

- **No increase of infections with MDR bacteria (n=1)**

Answer: inconclusive

Q5: What are other prophylactic regimens used, and what is their efficacy in reducing mortality (overall or infection-related), BSI and febrile episodes

(n=3 studies)

- Studies: retrospective (1), prospective (2)
- Publication year: 2010-2014
- Median number of patients: 171 (range 38-238)
- Prophylaxis regimens:
  - ceftriaxone or pip/tazo
  - TMP-SMX 20 mg/kg/qd
  - vancomycin + cefepime or pip/tazo
- Historical controls: no prophylaxis (3)

Q5: What are other prophylactic regimens used, and what is their efficacy in reducing mortality (overall or infection-related), BSI and febrile episodes

(n=3 studies)

Outcome	Decrease	Increase	No difference
Overall or infection-related mortality (n=3)	0/3	0/3	3/3
BSI (n=3)	2/3	0/3	1/3
Febrile episodes (n=3)	2/3	0/3	1/3

Answer: inconclusive

BSI: bloodstream infection

Review of prospective, randomized clinical trials

M. Mikulska, C. Viscoli

Results

11 RCT

8 Excluded

- 3 solid tumor
- 1 not enough data provided
- 2 non neutropenia (post-engraftment or MM)
- 1 Levo vs. cipro + phenethicillin
- 1 Cipro + vancomycin vs. placebo in ASCT

2 FQ vs. placebo

1 cefepime vs. none

Results 3- Randomised Trials

Study Country	Type and no. of pts	Years of study	Prophylaxis	Baseline FQ resistance in *E. coli* during study years
Vehreschild 2012 Germany	ASCT, n=66	2006-2008	Moxi 400 mg vs. placebo	29%-30%-23% per year (EARS)
Laoprasopwattana 2013 Thailand	Children ALL or lymphoma, n=95	2007-2010	Cipro 20 mg/kg/day vs. placebo	20 %
Slavin 2007 Australia	ASCT & allo HSCT, n=153	ND (26 months)	Cefepime 1g twice daily at the onset of neutropenia vs. at fever	unknown

Q1: Is FQ prophylaxis still effective in reducing mortality, BSI and febrile episodes?
(n=2 RCT)

Outcome	Decrease	Increase	No difference	Answer
Overall or infection-related mortality	0/2	0/2	2/2	Inconclusive
BSI	1/2*	0/2	1/2	Inconclusive
Febrile episodes	1/2**	0/2	1/2	Inconclusive

- ASCT 28% vs. 9% in a country with 20-30% FQ resistance in *E. coli* (EARS)

** 73% vs. 50% benefit only seen in ALL, not lymphoma, in a setting of 20% FQ resistance in *E. coli*

Question 2

Does discontinuation of FQ prophylaxis increase mortality, bloodstream infections and febrile episodes?

No data from RCT

Q3: Does FQ prophylaxis increase the rate of FQ resistance?

- **Increase in FQ-resistant bacteria in surveillance swab (1/1):**
  - At week 2 FQ-R from 23% to 97% for *E. coli* and
    from 29% to 86% for *K. pneumoniae*

- **No increase in infections with FQ-resistant bacteria (2/2)**

Answer: Yes colonisation, no infection

Q4: Does FQ prophylaxis increase the rate of multidrug resistance (MDR)?

- **No increase in ESBL+ bacteria in surveillance swabs (1/1):**
  - from 10% to 13% for ESBL+ *E. coli*
  - from 21% to 21% for *K. pneumoniae*

- **No increase in infections with MDR bacteria (2/2)**

Answer to Q4: No

Q5: What are other prophylactic regimens used, and what is their efficacy in reducing mortality (overall or infection-related), BSI and febrile episodes

Cefepime 1g x 2 at the onset of neutropenia vs. at fever in transplant patients

a) No effect on overall survival or infection-related mortality
b) Reduction in BSI (41% vs. 21%, $p<0.01$), with significantly fewer G- BSI (12 cases vs. 2 cases, $p<0.01$)
c) Reduction of FN (96% vs. 83%, $p=0.018$)

Answer to Q5: Yes inconclusive

Review of metaanalyses

D. Averbuch, M. Akova

Metaanalyses identified since 2005

- 8 metaanalyses published during 2005-2014
- Search for studies published: 1966 – 2012
- Number of studies included: 8 – 109
- Number of patients included: 1453 - 13579
- Underlying disease: HSCT, AL, ST (7); only HSCT (1)
- Intervention:
  - Any prophylaxis vs. placebo/no treatment/other prophylaxis (4)
  - Fluoroquinolones vs. placebo (3, one of them also vs. other antibiotics)
  - Oral systemic prophylaxis (FQ or co-trimoxazole (TMP-SMX) vs. no prophylaxis or vs. each other(1)
- Timing: both before and during neutropenia (7), only before neutropenia (1)

Metaanalyses identified since 2005: description

- Gafter-Gvili Cochrane 05:
  - 101 studies, 12599 patients;
  - Years of publication: 1973-2005;
- Van de Wetering 05
  - 22 studies, prophylaxis (FQ or TMP-SMZ) started before neutropenia (in some studies macrolide was added);
- Leibovici 06 – as GG 05, but FQ prophylaxis only
- Gafter-Gvili 07 focuses on colonization and MDI with FQ-resistant bacteria;
- **Gafter-Gvili Cochrane 12**
  - Update of the previous metaanalyses above;
  - Years of publication: 1973-2011;
  - 109 studies, 13579 patient;
  - 8 new studies since GG Cochrane 05, published 1989-2010 (5 on FQ prophylaxis vs. placebo/no treatment).

Metaanalyses identified since 2005: description (cont.)

- Imran 2008
- only double blind studies (only FQ monotherapy vs. placebo)
- 8 studies, 2721 patients
- Years 1987 – 2005

- Kimura 2014
- HSCT patients only, includes 2 studies in auto-HSCT not included in Gafter-Gvili Cochrane 12
- 17 studies, 1453 patients
- Years 1986 – 2012

Q1a: Is FQ prophylaxis still effective in reducing all-cause mortality

- Significant reduction (Gafter Gvili 2012):
  5.3% vs. 2.8%, p=0.00012

- No reduction (Imran 08):
  5.3% vs. 4%, p=0.13

- No reduction (Kimura 14):
  0% vs. 1.8%
  (3 studies, 243 patients, but *only 4 allogeneic HSCT* patients)

Q 1a: Is FQ prophylaxis still effective in reducing infection-related mortality

- Significant reduction (Gafter Gvili 2012):
  2.9% vs. 1.5%, p=0.002

- No mortality in FQ and in placebo/no prophylaxis arm (Kimura 14)
  (3 studies, 241 patients, only *4 allogeneic HSCT* patients)

Q 1c: Is FQ prophylaxis still effective in reducing the rate of bloodstream infections?

- Significant reduction (Gafter Gvili 2012):
  16.9% vs. 10.4%, p< 0.00001

- Significant reduction (Kimura 2014):
  OR 0.18 (CI 0.08;0.47)
  (4 studies, 288 patients, *3/240 allo HSCT* patients)

Q 1c: Is FQ prophylaxis still effective in reducing the rate of febrile episodes

- Significant reduction (Gafter Gvili 2012):
  53.8% vs. 41%, p<0.00001

- Significant reduction (Kimura 2014): OR 0.14 (CI 0.07;0.32)
  (4 studies, 267 patients, *only 4 allo HSCT* patients)

- No reduction (Imran 08):
  39.7% vs. 31%, p=0.08

Q 2: Does discontinuation of FQ prophylaxis increase mortality, bloodstream infections and febrile episodes?

Not addressed in metaanalyses

Q3: Does FQ prophylaxis increase the rate of FQ resistance?

- Patients on prophylaxis did not experience more infections caused by resistant strains
  (8 studies, 2712 patients, years of publication: 1987 – 2005)

	FQ prophylaxis	No prophylaxis	p
Overall study population	1358 patients	1354 patients	
Rate of FQ-R infections among study population	54 (4%)	51 (3.8%)	NS
Number of MDI	154	308	
Rate of FQ-R infections among MDI	54 (30%)	51 (16%)	<0.0001

- No increase in colonization by FQ-resistant bacteria:
  7.6% vs. 11%, p=0.24
  (3 studies, 161 patients, years of publication: 1987 – 1992)

Gafter Gvili 07

Q4: Does FQ prophylaxis increase the rate of multidrug resistance (MDR)?

Not addressed in metaanalyses

Q5: Which other prophylactic regimens have been studied in neutropenic patients and what is their efficacy

- Other prophylactic regimens included:
  - non-absorbable antibiotics
  - co-trimoxazole (TMP-SMX)
  - other systemic antibiotics

- Data on TMP-SMX and non-absorbable antibiotics did not change since 2005 (studies dated 1973-83 on non-absorbable; 78-93 on TMP-SMZ)

Q5a: what is the efficacy of the other prophylactic regimens in reducing all cause mortality?

Agent	Overall mortality
Non-absorbable AB	Yes (35.8% vs. 23.1%, p=0.02)
TMP-SMX	No (13.1% vs. 9.4%, p=0.06)
Other systemic antibiotic	No (7.8% vs. 10.8%, p=0.18)

Gafter Gvili 2012

Q5a: what is the efficacy of the other prophylactic regimens in reducing IRM?

Agent	IRM
Non-absorbable AB	Yes (33.7% vs. 20.7%, p=0.042)
TMP-SMX	Yes (11.9% vs. 7.1%, p=0.0077)
Other systemic antibiotic	No (2.5% vs. 2.2%, p=0.76)

Gafter Gvili 2012

Q5b: what is the efficacy of the other prophylactic regimens in reducing BSI?

Agent	MDI
Non-absorbable AB	Yea (34.6% vs. 21.6%, p=0.026)
TMP-SMX	Yes (26.7% vs. 11.2%, p<0.00001)
Other systemic antibiotic	Yes (26.9% vs. 13.7%, p=0.0019)

Gafter Gvili 2012

Q5c: what is the efficacy of the other prophylactic regimens in reducing febrile episodes?

Agent	Febrile episodes
Non-absorbable AB	No (56.7% vs. 54.3%, p=0.37)
TMP-SMX	Yes (66.5% vs. 51.5%, p=0.0024)
Other systemic antibiotic	No (85.5% vs. 77.2%, p=0.2)

Gafter Gvili 2012

Proposed conclusions: data from metaanalysis

1. Is FQ prophylaxis effective in reducing:
   a) Mortality (overall survival and infection related) **Possibly yes**
   b) Blood stream infections **Yes**
   c) Febrile episodes **Yes**
2. Does discontinuation of FQ prophylaxis result in an increase in febrile episodes and microbiologically documented infections? **Not addressed in metaanalyses**
3. Does FQ prophylaxis increase the rate of infections caused by FQ resistant bacteria? **No; but the proportion of FQ-resistant MDI among all MDI is significantly higher**
4. Does FQ prophylaxis increase the rate of infections due to MDR bacteria? Not addressed in metaanalyses
5. Which other prophylactic regimens have been studied in neutropenic patients and what is their efficacy in reducing:
   a) Mortality:
      overall **non-absorbable antibiotics only**
      infection related **non-absorbable antibiotics and TMP-SMX**
   b) Blood stream infections **non-absorbable, TMP-SMX and other systemic antibiotics**
   c) Febrile episodes **TMP-SMX only**

Conclusions

Questions	Observational	RCT	Meta analyses
1. Is FQ prophylaxis still effective in reducing …			
1a) overall or infection related mortality?	No	Inconclusive	Possible yes
1b) bloodstream infections?	Yes	Inconclusive	Yes
1c) febrile episodes?	Inconclusive	Inconclusive	Yes
2. **Does discontinuation of FQ prophylaxis increase …**			
2a) overall or infection related mortality?	No		
2b) bloodstream infections?	Yes		
2c) febrile episodes?	Yes		
3. Does FQ prophylaxis increase the rate of FQ resistance?	Inconclusive	Yes swabs No BSI	No
4. Does FQ prophylaxis increase the rate of MDR?	Inconclusive	No	
5. **What is the efficacy of other prophylactic regimens in reducing mortality, BSI and febrile episodes?**	Inconclusive	Inconclusive	See previous slide

Blank fields: not addressed by the studies

Proposed final considerations

- In terms of overall and infection-related mortality
  - The Cochrane metaanalyses suggest a large effect, but are mainly based on studies performed in the nineties
  - The study which included only double-blind placebo-controlled studies showed no significant advantage
  - No conclusion can be drawn from studies after 2005 (not enough data)
- In terms of reduction of BSI and fevers, almost all studies (especially the metaanalyses) show an advantage with FQ, but based on old studies.
- In terms of infection rate after discontinuation observational studies suggest an increase
- If FQ prophylaxis increase resistance in local settings remains controversial
- Data about prophylaxis with other drugs are inconsistent, because too old (TMP-SMZ and non-absorbable) or not powered enough
- New challenges are being posed by MDR colonizations

Additional data

Guidelines, surveys, KPC decolonisation