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Fluoroquinolone prophylaxis in haematological cancer patients with neutropenia: ECIL critical appraisal of previous guidelines

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Summary *Objectives:* Fluoroquinolone (FQ) prophylaxis was recommended in 2005 by European Conference on Infections in Leukemia (ECIL) for patients with prolonged neutropenia. In consideration of a worldwide increase in antibiotic resistance, the issue of FQ prophylaxis during neutropenia was re-evaluated.
Methods: Literature review of randomised controlled trials (RCT) and observational studies published in years 2006–2014 was performed. Their results were analysed in meta-analysis. Meta-regression model was applied to evaluate whether the rates of FQ resistance in community and hospital settings influenced the efficacy of FQ prophylaxis. The impact of FQ prophylaxis on colonisation and infection with resistant bacteria was reviewed.
Results: Two RCTs and 12 observational studies were identified. FQ prophylaxis did not have effect on mortality (pooled OR 1.01, 95%CI 0.73–1.41), but was associated with lower rate of bloodstream infections (BSI) (pooled OR 0.57, 95%CI 0.43–0.74) and episodes of fever during neutropenia (pooled OR 0.32, 95%CI 0.20–0.50). No effect of the background rate of FQ resistance on the efficacy of FQ prophylaxis was observed. In few studies, FQ prophylaxis resulted in an increased colonisation or infection with FQ- or multi-drug resistant strains.
Conclusions: The possible benefits of FQ prophylaxis on BSI rate, but not on overall mortality, should be weighed against its impact in terms of toxicity and changes in local ecology in single centres.

Introduction

In 2007, antibacterial prophylaxis with fluoroquinolones (FQs) was recommended by the European Conference on Infections in Leukemia (ECIL) group for high-risk neutropenic patients with an expected length of neutropenia longer than 7 days.[1] It was discussed in the first ECIL meeting in September 2005 while the full paper was published in 2007.[1] These recommendations were based primarily on the results of two randomised studies[2,3] and a meta-analysis,[4] while the results of an updated meta-analysis published in 2006[5] were also considered in the final ECIL publication. However, already in those years, the concerns were raised on the possibility that the extensive use of FQs might lead to an increased resistance, either to FQs only or to FQs and other drugs, and that an increasing antimicrobial resistance in the community might have a negative impact on the efficacy of prophylaxis in haematology.[6,7] In fact, an association between the use of FQs and the emergence of extended spectrum beta-lactamase (ESBL) producing Enterobacteriaceae had been reported.[8–11]

Already in 2006, Leibovici and colleagues stated that since the largest and the most recent study by Bucaneve and colleagues published in 2005 had shown the efficacy of FQs prophylaxis in a population with a 20% resistance rate to FQs in Gram-negatives, the FQ prophylaxis should be considered in locations with similar or lower resistance rates.[2,3,5,12–14]

Currently, in the era of increasing antibiotic resistance among Gram-negative bacteria worldwide, there are even more concerns about the efficacy of FQ prophylaxis and the negative impact of a widespread use of FQ on resistance rates. Thus, the ECIL group decided to re-evaluate this topic after ten years to examine whether the ECIL 1 recommendations were still valid. With this aim, recent available data were reviewed and the efficacy of FQ prophylaxis in neutropenic haematological cancer patients in reducing mortality and infections and its impact on antibacterial resistance were re-assessed.

Methods

Data collection

A systematic literature review of articles on FQ prophylaxis in neutropenic patients with haematological malignancies or following HSCT was performed. Literature search for studies published between 2006 and 2014 (including e-publications available ahead of print) was carried out using PubMed database and the article selection was performed independently by three authors (MM, DA, FT). The following key words were used: prophylaxis, neutropenia/neutropenic, antibacterial/antibiotics, fluoroquinolones, haematology, febrile neutropenia. References of all included trials and reviews were examined for additional data. The retrieved studies were divided into randomised controlled trials (RCT) and observational studies (both prospective and retrospective). For observational studies, publications were excluded if: (i) antibiotic prophylaxis was not specifically addressed; (ii) research question was impossible to assess due to insufficient data or methodological limitations (such as, indication for antibiotic prophylaxis not mentioned) and (iii) a non-FQ antibiotic was used either as the only agent for prophylaxis or in combination with an FQ. Particular attention was paid to the impact of antibiotic prophylaxis on the local ecology of bacterial strains and to possible increase in infections caused by resistant bacteria. Additionally, published meta-analyses and guidelines on antibiotic prophylaxis during neutropenia were also reviewed. The preliminary results of this review were presented and discussed during the ECIL 6 meeting held in September 2015.

First objective: assessment of the efficacy of FQ prophylaxis

Two aspects of FQ prophylaxis were considered, i.e. its direct efficacy in reducing infection-related outcomes (see below) and if there was evidence of a decreased efficacy related to increased FQ resistance.

Efficacy of FQ prophylaxis in studies published after 2005

The following endpoints were selected as parameters for the efficacy of FQ prophylaxis: a) overall mortality; b) rate of bloodstream infections (BSI); and c) rate of episodes of fever during neutropenia (FN). The identified studies were reviewed to determine whether FQ prophylaxis was effective in reducing the aforementioned endpoints. The results were presented in tables and the effect of FQ prophylaxis was also assessed in a meta-analysis.

Meta-analysis was performed by means of the random effects model following the method of DerSimonian and Laird.[15] The Higgins' I^2 index was computed to assess the percentage of total cross-study variation due to heterogeneity rather than chance.[16] A forest plot was generated to display results. As effect size of each study, the Odds Ratio (OR) between treated individuals and controls was computed for every of the three aforementioned endpoints.

Sensitivity analysis was carried out by iteratively recalculating the pooled-OR estimate after exclusion of each study at a time. This analysis inspected whether the pooled estimate was strongly dependent on one of the studies collected. Evaluation of the publication bias was done by using the funnel plot. The increased chance of a smaller study being published if it shows a stronger effect (small-study effect) was assessed by means of the Peters test.[17]

Impact of the background FQ resistance on the efficacy of FQ prophylaxis

In order to evaluate if the efficacy of FQ prophylaxis was significantly influenced by the rate of background FQ resistance, a meta-regression model was chosen.[18] Meta-regression is a tool used in meta-analysis which uses regression-based techniques to examine the impact of trial level moderator variables (in our case the background level of FQ resistance) on the study effect size. To stabilise the within-study variances, the analysis was performed transforming the OR in its natural logarithm (ln (OR)). Each ln (OR) was weighed by the inverse of its within-study variance. The coefficient (β) estimated by the meta-regression model represents the change in the ln (OR) of the efficacy endpoint associated with a 1% increase in the prevalence of background resistance. In figures, the coefficient β was converted into the percentage change (PC) via the formula $PC = [e^{\beta} - 1] \times 100$. PC has the most immediate meaning of percent change in the Odds Ratio by 1% change in the FQ rate. Percent change > 0 indicates a reduction in the efficacy of FQ prophylaxis.

For the purpose of the meta-regression, two types of studies were included: 1) RCTs which compared FQ vs. placebo or vs. no treatment, both those published before and after 2005, and 2) observational studies published between 2006 and 2014, since by including recent experiences, higher rate of background FQ resistance could be expected. The RCT published before 2005 were identified from previously published meta-analyses and reviewed by one of the authors (MM). Data on blinding, placebo and number of patients lost to follow up or excluded were noted for validity assessment (performance and attrition bias). In case of RCT comparing FQs and antifungals vs. placebo, BSI was the only endpoint analysed.

To establish if the FQ resistance in the community or in the hospital setting influenced the efficacy of FQ prophylaxis during neutropenia, two separate meta-regressions were performed, considering the trial level moderator variables as prevalence of FQ resistance in community and the hospital setting.

For each study, data on background prevalence of FQ resistance in the main Gram-negatives were obtained. They were either provided by the original publications (for example, resistance to FQ in surveillance swabs before administering FQ prophylaxis) or obtained from independent sources, consistently with previous studies.[5,13] Background resistance rates to FQ were retrieved from different published sources, according to the following criteria: 1) data for *E. coli* or, if not available, for all Enterobacteriaceae; 2) data for the same FQ; 3) data for the same study observation period; 4) data from the community and from hospital setting. The meta-regressions were performed separately for RCT and for observational studies.

Second objective: impact of FQ prophylaxis on antibiotic resistance

In order to fully evaluate the benefits and risks of FQ prophylaxis, its potential impact on the selection of resistant strains and on inducing resistance was assessed. A systematic review of data from the identified studies was performed with the aim of describing the rate of colonisation or BSI due to FQ resistant and multidrug resistant bacteria in the groups with and without FQ prophylaxis. In order to report absolute and not relative changes in antibiotic resistance, the denominator for the rate of colonisation and infection due to resistant bacteria was the number of patients included in the study and not the number of pathogens isolated in surveillance swabs or blood cultures. Additionally, data from the meta-analysis focusing exclusively on FQ resistance were reported.[19]

Results

Identified studies

After an initial literature research, 68 original studies were selected and reviewed based on the title and/or abstract as potentially appropriate for the purposes of this study. Among these, 11 were RCTs and 57 were observational. Observational studies included two types of studies on the efficacy (those with classical design comparing the results of FQ prophylaxis to data from historical cohort and those with discontinuation design comparing the data from the cohort, where FQ prophylaxis was discontinued to those from previous period when FQ prophylaxis was in place) and studies reporting data only on resistance. The description of the selection process of RCTs and observational studies is reported in Figure S1 in supplementary material.

Five meta-analyses were published between 2006 and 2014 (Table S1 in supplementary material).[5,20–23] Among them, one focused only on colonisation and infections with FQ-resistant bacteria,[23] while the remaining 4 focused on the efficacy of prophylaxis. Two of them were performed by the same group of investigators,[5,20] thus only the more recent one, which included all the studies from the older one, was considered.[20]

Finally, 8 guidelines on FQ prophylaxis in neutropenic patients were identified and are reported in Table S2.[1,24–30]

First objective: assessment of the efficacy of FQ prophylaxis

Efficacy of FQ prophylaxis in studies published after 2005

In Table 1, 14 studies (2 RCTs, 12 observational) reporting data on the efficacy of FQ prophylaxis on the rates of mortality, BSI, and episodes of fever during neutropenia are described.

Among two RCTs, the one performed in adults undergoing autologous HSCT reported a benefit of FQ prophylaxis on the BSI rate,[31] and the one in children with acute lymphoblastic leukaemia or lymphoma reported the benefit on the rate of episodes of fever during neutropenia.[34]

A total of 7 classical observational studies (2 prospective and 5 retrospective) on FQ prophylaxis (ciprofloxacin in 5 and levofloxacin in 2) were published between 2007 and 2014, including one study being an update of a previous one. They included a median of 220 patients per study (range: 45–1145) and used historical cohorts of patients not receiving antibiotic prophylaxis as the comparator group.[35,38,39,42,43,46,47] None of these studies reported any benefit of FQ prophylaxis on the overall mortality. Amongst them, four reported a reduction in the rate of any BSI and one reported a reduction in the rate of Gram-negative BSI. The impact of FQ prophylaxis on the occurrence of febrile episodes during neutropenia was analysed in only 2 studies, one reporting no effect and the other reporting a significant reduction.[39,43] In addition, 5 centres reported their experience upon discontinuation of FQ prophylaxis in comparison to historical cohorts of patients receiving FQ prophylaxis.[48,51,52,54,57] Two studies reported an increase in BSI rate,[48,52] and one in episodes of fever during neutropenia.[54]

Considering together these RCT and observational studies, our meta-analysis showed no benefit of FQ prophylaxis on the overall mortality (pooled OR 1.01, 95%CI 0.73–1.41), a significant reduction of the rate of BSI (pooled OR 0.57, 95%CI 0.43–0.74) and of episodes of fever during neutropenia (pooled OR 0.32, 95%CI 0.20–0.50) (Figs. 1, 2, 3). The number needed to treat (NNT) to prevent one episode of BSI was 15.

Among three previous meta-analyses published after 2005,[20–22] only one reported a benefit on the overall mortality, with a reduction from 5.3% to 2.8% ($p < 0.001$).[20] Of note, when limiting the analysis to patients with acute leukaemia or allogeneic HSCT, the overall mortality was reduced from 7.8% to 4.2% ($p = 0.0024$).[20] Two meta-analyses reported the benefit on the rate of BSI and episodes of fever during neutropenia.[20,22] The third one, which included only RCTs, found no benefit on the overall mortality and only a trend toward a lower risk of episodes of fever, but did not analyse the impact on BSI rate.[21] The results of previous meta-analyses are reported in Table 2.

Sensitivity analysis revealed that in RCTs by removing the Karp 1987 or Yamada 1993 study, the overall mortality was significantly reduced in patients undergoing prophylaxis (OR 0.58, 95%CI 0.35–0.96 and OR 0.58, 95%CI 0.34–0.98 respectively). No other relevant findings were shown by sensitivity analysis. Furthermore, in all investigated endpoints, the funnel

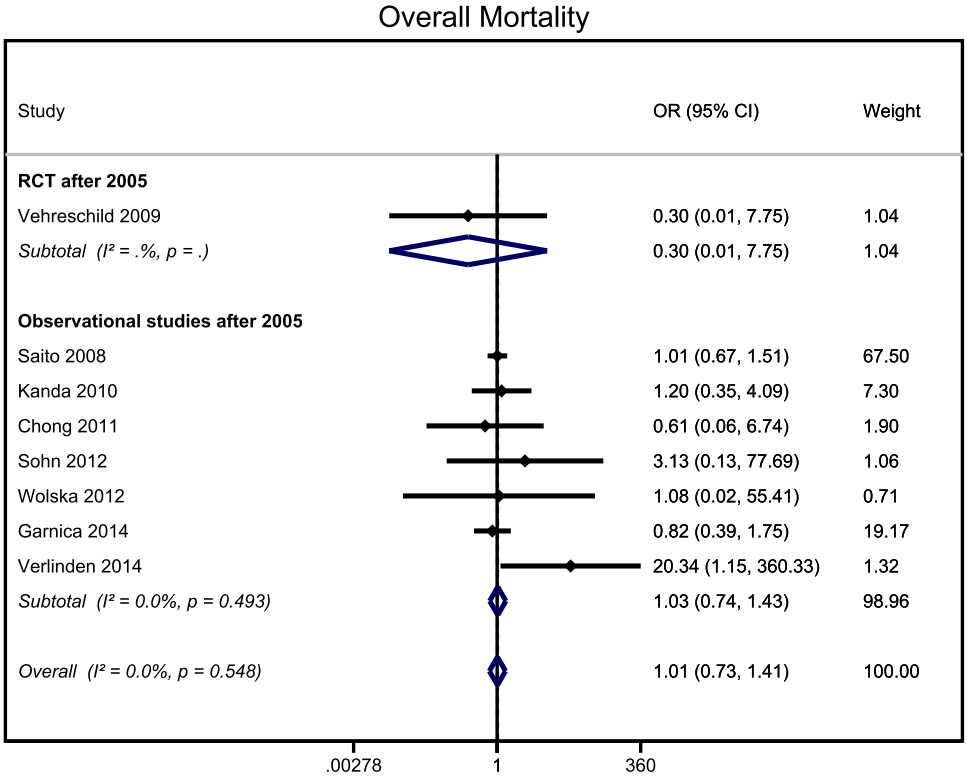

Figure 1 The impact of the prophylaxis with FQ on the rate of overall mortality in studies published after 2005. RCT, randomised controlled trials.

Table 1 Studies on the efficacy of FQ prophylaxis in neutropenic haematological patients published between 2006 and 2014

Study, country	Study type	Type of patients	Number of patients (episodes of neutropenia)	Years of observation and type of prophylaxis	Background resistance in community and hospital setting	Reported outcome		
						Overall mortality	BSI	Episodes of fever during neutropenia
Vehreschild 2012, Germany[31]	Randomised controlled, double blind, placebo controlled, no lost to follow-up patients	Auto-HSCT	66	2006–2008 randomised moxifloxacin 400 mg/day vs. placebo	4%[32] and 27%[33]	0% (0/34) vs. 3% (1/32), NS	**9% (3/34) vs. 28% (9/32), p = 0.042**	65% (18/34) vs. 75% (23/32), NS
Laoprasopwattana 2013, Thailand[34]	Randomised controlled, double blind, placebo controlled, no lost to follow-up patients	ALL or lymphoma children	95 randomised but only 71 neutropenic and included	2008–2009 randomised ciprofloxacin 20 mg/kg/day oral (max 750 mg bid) vs. placebo	20% of *E. coli*	ND	6% (2/34) vs. 3% (1/37), NS	**50% (17/34) vs. 73% (27/37), p = 0.046 (benefit only in ALL)**
Halim 2007, Canada[35]	Retrospective observational	AML outpatients vs. inpatients	294 (634)	1998–2001: none (inpatients) 2001–2004: ciprofloxacin (outpatients)	14% of *E. coli* UTI[36] and 14%[37]	ND[a]	**22% (92/426) 13% (21/157), p < 0.05**	ND
Craig 2007, USA[38]	Retrospective within prospective trial on empirical therapy	HM	543	1999–2002: none 2002–2004: levofloxacin (+ 8 month cycling of antibiotics for empirical therapy)	0.1 FQ-resistant Enterobacteriaceae x 1000 PD	17% (37/217) 22% (72/326), NS	**Gram- BSI 4.7 vs. 1.8 per 1000 PD, p < 0.05** Gram+ BSI 4.9 vs. 4.4 per 1000 PD, NS	ND
Wolska 2012, Poland[39]	Retrospective observational	Auto- HSCT	104	2005–2007: none 2007–2008: ciprofloxacin	8%[40] and 17%[33,41]	0% (0/54) 0% (0/50), NS	22% (12/54) 10% (5/50), NS	85% (46/54) 70% (35/50), NS
Cumpston 2013, USA (continuation of Craig 2007)[42]	Retrospective within prospective trial on empirical therapy	HM	1145	1999: none 2002–2004: levofloxacin (+ 8 month cycling) 2005–2009: levofloxacin (+ 3 month cycling)	0.1 FQ-resistant Enterobacteriaceae x 1000 PD	17 x 100 PD 20 x 100 PD 19 x 100 PD, NS	**5.3 for 1000 PD 2.1 for 1000 PD 3.3 for 1000 PD (p < 0.0001)**	ND
Garnica 2014, Brasil[43]	Retrospective observational, from a prospectively collected database	HM	220 (329)	2005: none 2005–2009: ciprofloxacin	3% (Gram+ and Gram-), 0.38% Enterobacteriaceae per 1000 PD; 11%[44] and 27%[45]	11% (12/110) 9% (20/219), NS	**33% (36/110) 22% (49/219), p = 0.04**	**93% (102/110) 73% (159/219), p < 0.01**
Yeh 2014, Taiwan[46]	Retrospective observational	AML and ALL children	113 (600)	2005–2009: none 2010–2012: ciprofloxacin 300 mg/m2 bid	17–41% among different Gram- species, 20% in 30.764 *E.coli* strains from the same institution	ND[b]	**13% (44/340) 4% (10/260), p < 0.01**	ND[2]

(*continued*)

Table 1 (*continued*)

Study, country	Study type	Type of patients	Number of patients (episodes of neutropenia)	Years of observation and type of prophylaxis	Background resistance in community and hospital setting	Reported outcome		
						Overall mortality	BSI	Episodes of fever during neutropenia
Felsenstein 2015, USA[47]	Retrospective observational	AML children	45 (153)	2008–2010: none 2010–2012: ciprofloxacin	ND	ND	32 % (28/89) 33% (21/64), NS	ND
Saito 2008, Japan[48]	Observational with discontinuation design	HM	807	2001–2003: levofloxacin (liberal = 56% of patients) 2003–2005: levofloxacin (restricted to HSCT recipients = 28.8% of patients)	8% in 2002[49] and 12%[50]	4% (61/442) 4% (50/365), NS	**10% (42/442)** **20% (69/365), p < 0.01**	ND
Kanda 2010, Japan[51]	Observational with discontinuation design	HSCT	128	2000–2004: levofloxacin or ciprofloxacin or tosufloxacin 2004–2008: discontinuation (none)	9%[49] and 12%[50]	11% (10/87) 10% (4/41), NS	7% (6/87) 15% (6/41), NS[c]	ND
Chong 2011, Japan[52]	Observational with discontinuation design	Allo-HSCT	1981	2003–2005: levofloxacin 2006–2009: discontinuation	10%[53] and 12%[50]	1.5% (1/762) 1.3% (2/931), NS	**9% (67/762)** **17% (156/931), p < 0.001**	ND
Sohn 2012, Korea[54]	Observational with discontinuation design	Auto-HSCT	277	2001–2005: ciprofloxacin 2004–2008: none (other HM protocol)	13% or 15%[55] and 28%[56]	1% (1/114) 0% (0/118), NS	12% (14/114) 14% (16/118), 1.5x100 PD 1.7x100 PD, NS	**70% (80/114)** **94% (111/118), p < 0.01**
Verlinden 2014, Belgium[57]	Observational with discontinuation design	HM	112 (154)	2009: ciprofloxacin 2009–2010: discontinuation (8 months) 2010–2011: ciprofloxacin	4%[58] and 20%[59]	18% (9/51) 0% (0/45) 3% (2/58), NS	33% (17/51) 33% (15/45) 33% (19/58), NS	73% (37/51) 80% (36/45) 72% (42/58), NS

ALL: acute lymphoblastic leukaemia; allo-HSCT: allogeneic HSCT; AML: acute myelogenous leukaemia; Auto-HSCT: autologous stem cell transplant; BSI: bloodstream infection; HM: haematological malignancy; HSCT: haematopoietic stem cell transplant; ND: no data; NS: not significant statistically; PD: patients-days.

[a] The overall survival outcome was not analysed since patients in the prophylaxis group needed to be clinically stable to be followed as outpatients, therefore introducing the bias of better clinical conditions.

[b] The overall survival and episodes of fever during neutropenia outcomes were not analysed since patients in the ciprofloxacin arm also received voriconazole prophylaxis, thus only the impact on infection-related mortality caused by bacterial infections was assessed.

[c] Including one case of microbiologically-documented pneumonia.

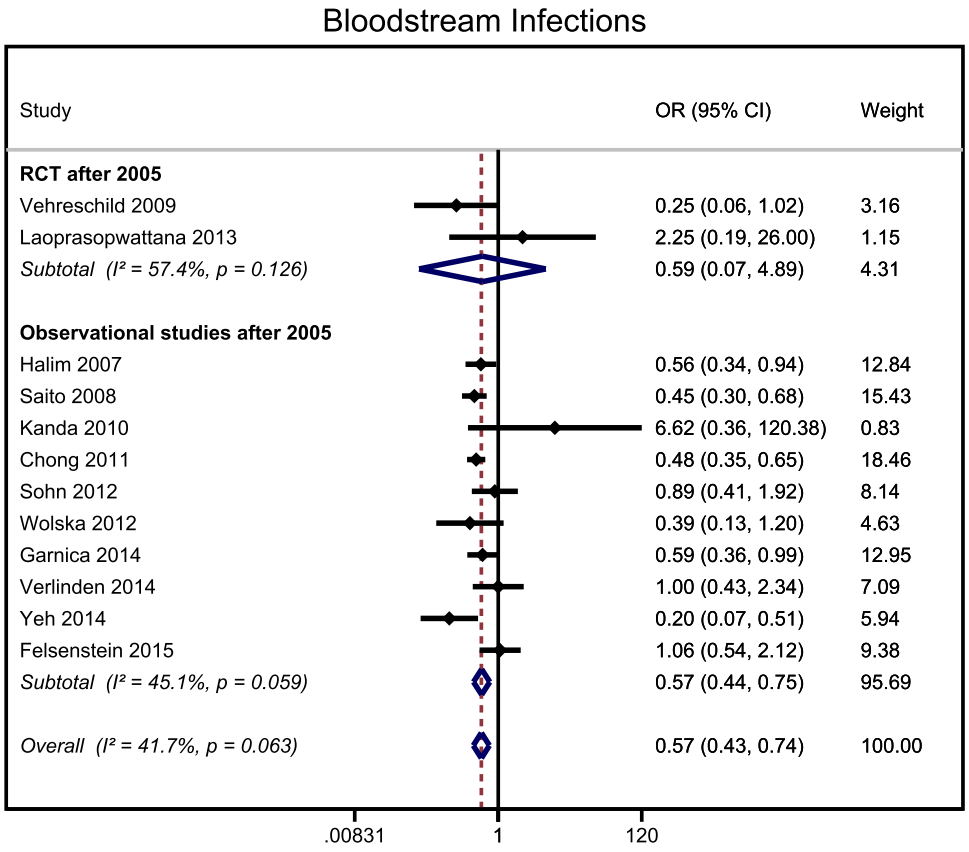

Figure 2 The impact of the prophylaxis with FQ on the rate of bloodstream infections. RCT, randomised controlled trials.

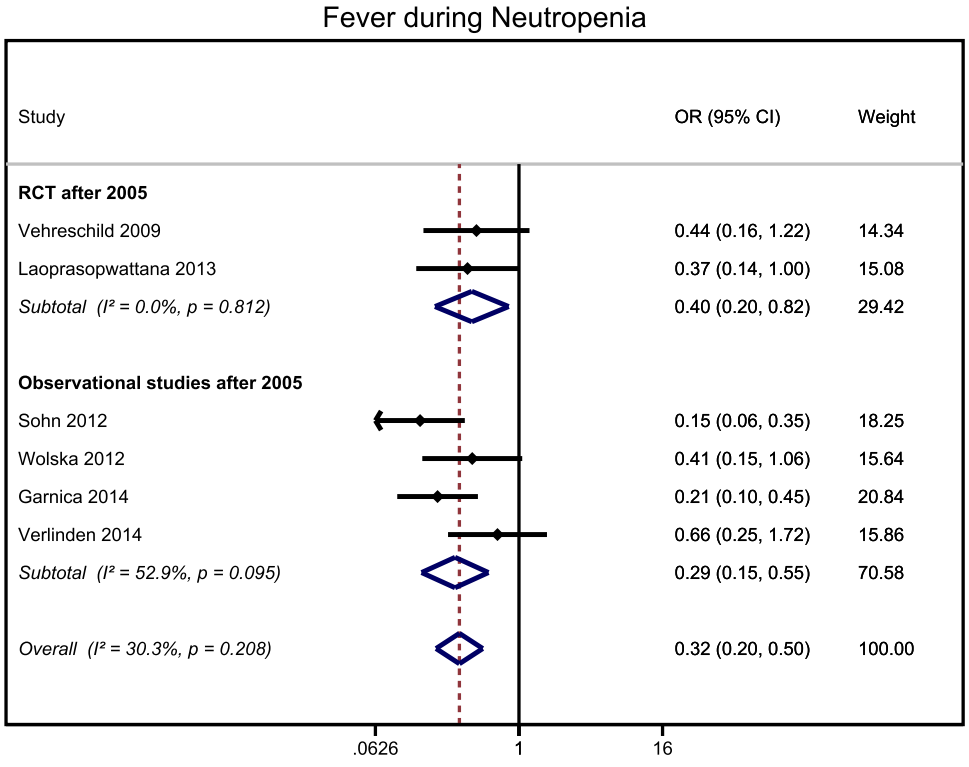

Figure 3 The impact of the prophylaxis with FQ on the rate of episodes of fever during neutropenia. RCT, randomised controlled trials.

Table 2 The efficacy of FQ prophylaxis on the overall mortality, rate of BSI and episodes of fever during neutropenia in the main meta-analyses published between 2006 and 2014.

Author, year of publication	Type of studies and patients included	Number of patients, number of studies	Reported outcome, FQ prophylaxis vs. placebo		
			Overall mortality	Bloodstream infections	Episodes of fever during neutropenia
Imran 2008[21]	RCT FQ vs. placebo, double blind only	2721 patients, 8 studies	4% vs. 5.3%, p = 0.13	ND	31% vs. 39.7%, p = 0.08
Gafter-Gvili 2012[20]	RCT FQ vs. placebo	3776 patients, 19 studies	2.8% vs. 5.3%, p = 0.00012	10.4% vs. 16.9%, p < 0.00001	41% vs. 53.8%, RR 0.74, p < 0.00001
Kimura 2014[22]	RCT FQ vs. placebo, HSCT recipients	243 patients, but only 4 allo-HSCT recipients, 3 studies	0% vs. 1.8%, NS	6.9% vs. 31.5% (OR 0.18, 95%CI 0.08–0.47)	66.2% vs. 93.7% (OR 0.14, 95%CI 0.07–0.32)

Allo-HSCT: allogeneic haematopoietic stem cell transplant; 95%CI: confidence interval of 95%; FQ: fluoroquinolones; NS: not significant; OR: odds ratio; RR: risk ratio.

Table 3 Randomised controlled trials included in the meta-regression analyses.

First author, year of publication and country	Placebo	Blinding	Number of patients lost to follow-up or excluded	Type of patients	Number of patients (on prophylaxis, without prophylaxis)	Years of observation	Prophylactic drug	Background rate of FQ resistance (reference) in community and hospital setting
Karp 1987, US, Baltimore[60]	Yes	Yes	14	AML, ALL, Auto-HSCT	68 (35, 42)	1984–1985	Norfloxacin	1%[61,62] and 1%[63,64]
Lew 1991, US, Boston[65]	Yes	Yes	8 in 26	HSCT	18 (7, 11)	Before 1991	Ciprofloxacin	1%[61,62] and 1%[64,66]
Tsutani 1992, Japan[67]	No	No	ND	HM	22, 50 episodes (25, 25)	1989–1990	Ofloxacin	2%[50] and 2%[68]
Brodsky 1993, Argentina[69]	No	No	ND	AL outpatients	14, 25 episodes (12, 13)	Before 1993	Ciprofloxacin or ofloxacin	2%[70] and 6%[70]
Talbot 1993, US multicentre[71]	Yes	Yes	0	AML	119 (62, 57)	Before 1993	Enoxacin	1%[61,62] and 1%[64,66]
Yamada 1993, Japan[73]	No	No	5	AL	103 (52, 51)	1988–1991	Norfloxacin	2%[50] and 2%[68]
Thomas 2000, France, Lyon[74]	Yes	Yes	9	mainly AL (MM)	103 (51, 52)	1996–1998	Pefloxacin	12%[72,75] and 12%[76,77]
Nenova 2001, Bulgaria[78]	No	No	1	HM	70 (36, 33)	1994–2000	Ciprofloxacin (20 patients), pefloxacin, enoxacin, or norfloxacin	5%[79] and 6%[33]
Bucaneve 2005, Italy[2]	Yes	Yes	22 in 760	HM and lymphoma	760 (373, 363)	2001–2003	Levofloxacin	20%[13] and 20%[14]
Vehreschild 2012, Germany[31]	Yes	Yes	0	Auto-HSCT	66 (34, 32)	2006–2008	Moxifloxacin	4%[32] and 27%[33,41]
Laoprasopwattana 2013, Thailand[34]	Yes	Yes	0	AML children	71 (34, 37)	2008–2009	Ciprofloxacin	20% (swabs from the same study)

AL: acute leukaemia; ALL: acute lymphoblastic leukaemia; AML: acute myelogenous leukaemia; Auto-HSCT: autologous stem cell transplant; HM: haematological malignancy; HSCT: haematopoietic stem cell transplant.

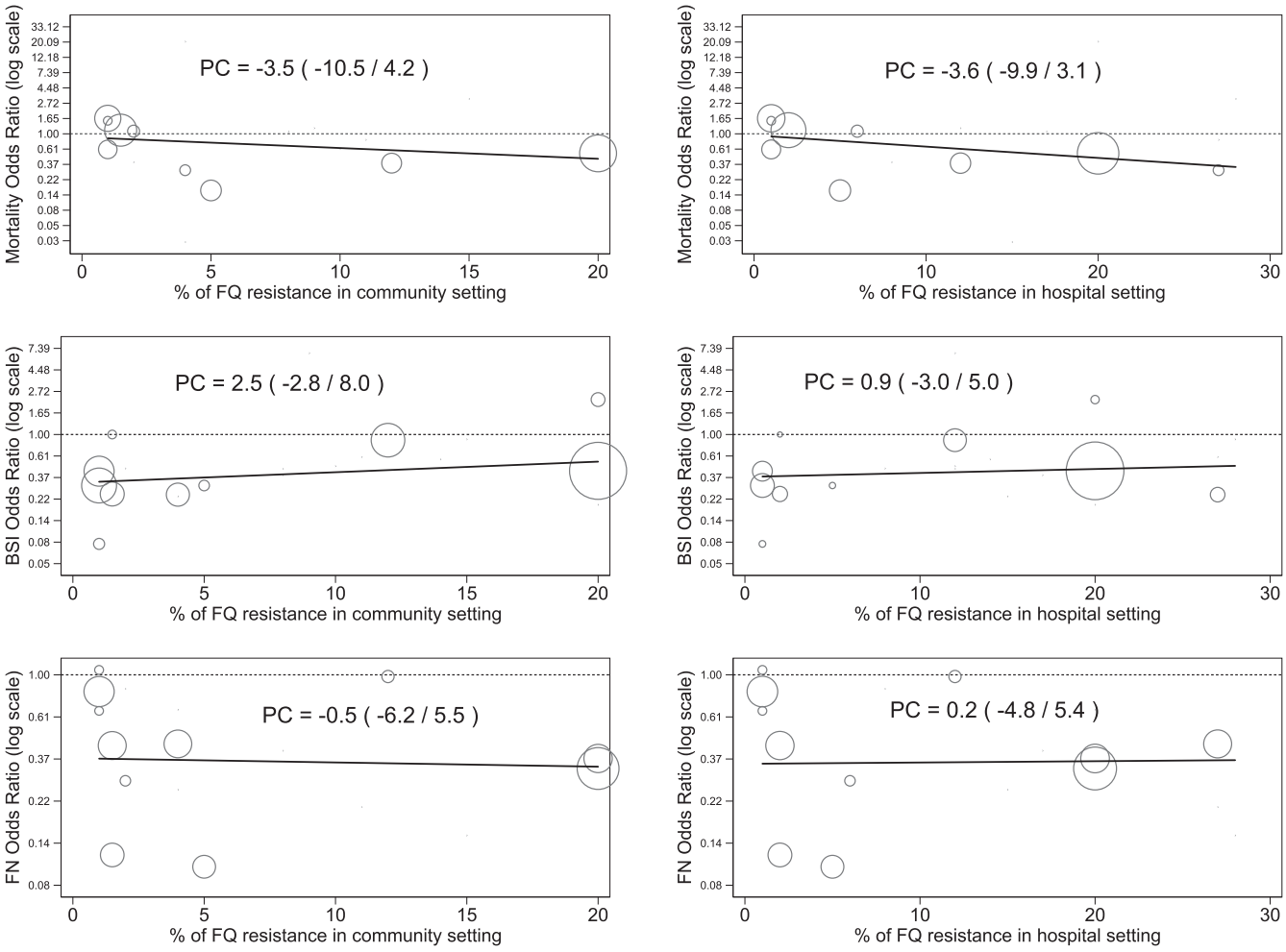

Figure 4 Line graph of the fitted values estimated from meta-regression of all randomised controlled studies on the impact of the background FQ resistance in the community (left) and in the hospital (right) setting on the efficacy of FQ prophylaxis on the three endpoints (overall mortality, rate of bloodstream infections and rate of fever during neutropenia) plotted against the % of FQ resistance, together with the estimates from each study represented by circles. The circle size depends on the weight given to each study in the random-effects model. FQ, fluoroquinolones; BSI, bloodstream infection; FN, episodes of fever during neutropenia. PC, percent change in OR when FQ increases of 1 unit, in brackets the 95% confidence interval. PC > 0 means that a 1% increase in the prevalence of background FQ resistance reduces the efficacy of FQ prophylaxis by PC %; Dashed line (OR = 1): no effect of prophylaxis.

plot asymmetry was not strong enough to suspect the presence of a significant publication bias and the small-study effect was absent.

Meta-regression for the impact of FQ resistance on the efficacy of FQ prophylaxis (studies 1987–2014)

The data from all RCTs on FQ prophylaxis vs. placebo/no treatment published between 1987 and 2014 and from observational studies published after 2005 were included in the meta-regression (PRISMA flow diagram of studies included in meta-regressions is reported in Figure S2 and PRISMA checklist in Table S2 of supplementary material). In 5 observational discontinuation studies, data from the first cohort (receiving FQ prophylaxis) were compared to that from the discontinuation cohort (no prophylaxis).[48,51,52,54,57]

Overall, 11 RCTs were included in the meta-regression (Table 3), of which 2 were published in 2009 and 2013, and 9 between 1987 and 2005. The forests plot of the effect of FQ prophylaxis on the mortality, rate of BSI and rate of fever episodes during neutropenia in these RCT are shown in Figures S3, S4 and S5. The corresponding background resistance rates to FQ were established, as explained in the materials and methods, and it varied from < 1% to 20% for community setting[13,31,32,34,49,60–62,65,67,69–75,78,79] and from 1% to 28% for hospital setting.[14,33,34,37,41,45,50,56,59,63,64,66,68,70,76,77] All FQ resistance rates considered for the meta-regression, and their respective references, are reported in Tables 1 and 3.[32,36,40,44,45,50,53,55,58]

There was no significant effect of the background rate of FQ resistance on the efficacy of FQ prophylaxis in reducing the rates of the overall mortality, BSI and FN in the meta-regressions performed for both RCT and for observational studies (Figs. 4 and S6, respectively), both considering community and hospital settings (Table S3).

Second objective: impact of FQ prophylaxis on antibiotic resistance

Resistance to FQ

As shown in Table 4, three studies (one RCT and two observational studies) and one meta-analysis addressed the impact of FQ prophylaxis on subsequent colonisation with FQ-resistant strains. In the Thai RCT with a 20% background FQ resistance, the prevalence of FQ-resistant bacteria in surveillance swab after two weeks of FQ prophylaxis increased from 23% to 97% for *E. coli* and from 29% to 86% for *K. pneumoniae*.[34] Also in a study from Belgium, a decrease followed by an increase in colonisation with FQ-resistant bacteria was noted after, respectively, discontinuation and restarting FQ prophylaxis.[57] On the contrary, in an observational prospective study from Japan, in which rectal swabs were performed before and after levofloxacin prophylaxis, a decrease in the percentage of patients colonised with Gram-negative bacteria was noted (36% vs. 10%) without an increase in FQ-resistance (16% vs. 19%).[80] Finally, no significant increase in the colonisation with FQ-resistant bacteria (7.6% vs. 11%, p = 0.249) was reported in the meta-analysis focusing specifically on resistance, but data were derived from only 3 studies published between 1987 and 1992 which included 161 patients.[23]

The possible impact on the rate of FQ-resistant BSI was addressed in two RCTs, 14 observational studies and one meta-analysis (Table 4),[23,31,34,35,38,39,42,43,46–48,51,52,54,57,58,80–82] and only 3 observational studies (2 from the same centre) reported an increase in FQ resistant infections during prophylaxis,[38,42,43] mainly in Gram-negative BSI.[42,43]

Finally, there was no increase in the rate of infections caused by FQ resistant strains in the meta-analysis (rate of 4% both in patients with or without FQ prophylaxis).[23]

Colonisation and infection with MDR strains

Eleven studies reported the influence of FQ prophylaxis on either colonisation (n = 3) or infection (n = 8) with MDR bacteria (Table 4). One RCT and one observational study screened patients for ESBL colonisation by surveillance rectal swabs taken before and after prophylaxis and no increase in the rate of ESBL-producing *E. coli* was found,[34,80] while an observational discontinuation study showed a halved rate of faecal carriage of ESBL during the no-prophylaxis phase (not statistically significant).[57]

The data from 8 observational studies focusing on the influence of FQ prophylaxis on the rate of infections with MDR bacteria were discordant. Increase in MDR infections was reported in 3 (vancomycin resistant enterococci in 2 studies from the same institution, ESBL-producers in 1),[38,42,43] while it was not evident, or only relative, in the other 5 studies.[46,48,52,54,81]

Guidelines on antibiotic prophylaxis during neutropenia

Seven national and international guidelines have been published between 2007 and 2013 and additional one in 2016.[1,24–30] Five of 6 guidelines recommending FQ prophylaxis, did so for high risk patients with expected neutropenia lasting 7 days or longer. On the contrary, concerned about the worldwide spread of antibiotic resistance, the Australian guidelines[25] did not recommend FQ in low risk patients and gave a low level (grade C) of recommendation for high risk patients with an exception of outpatient HSCT recipients and patients on palliative management with persistent bone marrow failure[25]; while European Society for Medical Oncology (ESMO) guidelines discouraged any antimicrobial prophylaxis.[30] The detailed description of these guidelines is available in Table S2.

Discussion

This literature review from 2006 to 2014, aimed at evaluating the efficacy of FQ prophylaxis in the last decade and its impact on the increase in bacterial resistance, yielded mainly observational single-centre experiences.

As far as efficacy was concerned, neither any of the studies nor their pooled analysis, showed a favourable impact on mortality (Figure 1). Among 3 previous meta-analyses, which included all RCT starting from 1973, only one documented a reduction in overall mortality in the FQ prophylaxis arm.[20] On the contrary, in terms of rates of BSI, several studies, and their pooled analysis demonstrated lower rate of BSI during FQ prophylaxis (Figure 2). Also two previous meta-analyses showed a significant reduction.[20,22] However, the clinical cost/effectiveness of FQ prophylaxis in preventing BSI depends on the rate of BSI, since the NNT would be significantly higher in populations with low rate of BSI. Of note, the number needed to treat to prevent 1 BSI was twice as high in studies published after 2005 compared to previous RCT (15 vs. 7, data not shown for RCT before 2005). Finally, although few studies reported a significant reduction of the episodes of fever during neutropenia in the FQ prophylaxis group,[34,43,54] pooled data (Fig. 3) and previous meta-analyses reported a statistically significant reduction.[20,22] Thus, FQ prophylaxis might reduce the need for empirical antibiotic treatment, and consequently exposure to other broad spectrum agents. However, since most of the patients on FQ prophylaxis still develop fever during neutropenia,[83] this benefit might be of little clinical relevance, while other strategies, such as early discontinuation or de-escalation of empirical therapy when appropriate, could be more effective in limiting the exposure to broad spectrum antibiotics.[84]

Assuming that the protection provided by FQ would be reduced in case of high level of circulation of FQ-resistant strains, two meta-regressions using data on background FQ resistance from hospital and community settings were performed. No direct correlation between lower efficacy of FQ prophylaxis in settings of higher background FQ resistance could be demonstrated, for the maximum prevalence of FQ resistance in the community of 20% and in the hospital setting of 28%. However, it must be kept in mind that these results cannot be extrapolated to populations with higher FQ resistance rates or in which MDR pathogens are routinely isolated.

When dealing with the possible role of FQ prophylaxis on the emergence of resistant pathogens, shortage of data was the main issue. The effect on the incidence of BSIs due to FQ-resistant pathogens was limited, with most of the studies reported only a relative increase in the prevalence of FQ resistance among the isolated Gram-negatives. Interestingly, an American study in a group of patients showed

Table 4 The impact of FQ prophylaxis on resistance in studies published between 2006 and 2014.

Study, country	Study type	Type of patients	Number of patients (episodes of neutropenia)	Years of observation and type of prophylaxis	Resistance to fluoroquinolones (FQ) during FQ prophylaxis		Multidrug resistance (MDR) during FQ prophylaxis	
					Increase in colonisation with FQ resistant bacteria	Increase in FQ-resistant BSI	Increase in colonisation with MDR bacteria	Increase in infections by MDR bacteria
Laoprasopwattana 2013, Thailand[34]	Randomised controlled	ALL or lymphoma children	95 randomised but 71 neutropenic and included	2008–2009 randomised ciprofloxacin 20 mg/kg/day oral (max 750 mg bid) vs. placebo	Yes *E.coli* FQ-resistant Week 0 17% vs 22%, Week 1 95% vs 25%, Week 2 97% vs 23%; *K. pneumoniae* FQ-resistant Week 0 26% vs 36%, Week 1 100% vs 44%, Week 2 86% vs 29%	No 0% vs. 0%	No Surveillance swabs pre- and post-prophylaxis, respectively *E. coli* 10% vs 13% *K. pneumoniae* 21% vs 21%	ND
Vehreschild 2012, Germany[31]	Randomised controlled	ASCT	66	2006–2008 randomised moxifloxacin 400 mg/day vs. placebo	ND	No 2 of 3 breakthrough BSI in moxifloxacin arm were FQ susceptible	ND	ND
Halim 2007, Canada[35]	Retrospective observational	AML outpatients vs. inpatients	294 (634)	1998–2001: none (inpatients) 2001–2004: ciprofloxacin (outpatients)	ND	No Only relative increase in FQ-resistant *E. coli* from 14% (2/14) to 100% (2/2)	ND	ND
Craig 2007, USA[38]	Retrospective within prospective trial on empirical therapy	HM	543	1999–2002: none 2002–2004: levofloxacin (+ 8 month cycling of antibiotic for empirical therapy)	ND	Yes Increase of FQ-resistant streptococci (0.9 x 1000 PD vs. 0, $p < 0.01$) but no change in Gram-	ND	Yes Increase in VRE (0.1 vs. 1 x 1000 PD, $p < 0.05$) and a trend for MRSA (0.3 vs. 1 x 1000 PD, $p = 0.11$)
Wolska 2012, Poland[39]	Retrospective observational	ASCT	104	2005–2007: none 2007–2008: ciprofloxacin	ND	No 1 FQ-resistant Gram- BSI in each group	ND	ND
Cumpston 2013, USA (continuation of Craig 2007)[42]	Retrospective within prospective trial on empirical therapy	HM	1145	1999: none 2002–2004: levofloxacin (+ 8 month cycling) 2005–2009: levofloxacin (+ 3 month cycling)	ND	Yes Increase of FQ-resistant Gram- (0.1 vs. 0.5 vs. 1.1 x 1000 patient-days, $p = 0.033$)	ND	Yes Increase in VRE bacteraemia ($p = 0.005$) and a trend for more MRSA ($p = 0.08$)
Chong 2014, Japan[80]	Prospective observational	HM patients	68	2011–2013: levofloxacin (no controls)	No Rectal swab before and after prophylaxis: decrease in Gram- colonisation (36% vs. 10%) but no increase in FQ-resistant *E. coli* (16% vs. 19%)	ND	No No increase in ESBL+ faecal colonisation (10% vs. 10%)	ND

(*continued*)

Table 4 (*continued*)

Study, country	Study type	Type of patients	Number of patients (episodes of neutropenia)	Years of observation and type of prophylaxis	Resistance to fluoroquinolones (FQ) during FQ prophylaxis		Multidrug resistance (MDR) during FQ prophylaxis	
					Increase in colonisation with FQ resistant bacteria	Increase in FQ-resistant BSI	Increase in colonisation with MDR bacteria	Increase in infections by MDR bacteria
Garnica 2014, Brasil[43]	Retrospective observational, from a prospectively collected database	HM	220 (329)	2005: none 2005–2009: ciprofloxacin	ND	Yes Increase in overall FQ-resistant BSI (3.02 vs. 6.77 x 1000 PD p = 0.03) and FQ-resistant Enterobacteriaceae (0.38 vs. 2.12, p = 0.06)	ND	Yes Increase in ESBL producing bacteria in the haematology 0.52/1000 patient/days vs. 1.59, p = 0.08
Macesic 2014, Australia[81]	Retrospective observational	Allo-HSCT	508	2001–2005: none 2006–2010: ciprofloxacin	ND	No Only relative increase in FQ resistance in Gram- strains causing infections from 16% to 35% (p = 0.001)	ND	Yes ESBL increased from 31% to 50% (p = 0.011); MDR increased from 11% (2001–2004) to 22% (2007–2010)
Yeh 2014, Taiwan[46]	Retrospective observational	AML and ALL children	113 (600)	2005–2009: none 2010–2012: ciprofloxacin 300 mg/m2 bid	ND	No Data for the whole institution: decrease in FQ-resistant Gram- during prophylaxis: *E. coli* 21 to 19% (p < 0.01), *Pseudomonas* 33% to 28% (p < 0.01), *K. pneumoniae* 17% to 10% (p < 0.01), *Serratia* 41% to 30% (p < 0.01)	ND	No No change in MDR infection rate
Felsenstein 2015, USA[47]	Retrospective observational	AML children	34 (153)	2008–2010: none 2010–2012: ciprofloxacin	ND	No FQ-resistant Gram- 2/12 vs. 2/3	ND	ND
Miles-Jay 2015, US[82]	Longitudinal retrospective observational	Allo-HSCT	2306 HSCT, 280 with Gram- BSI	2003–2012: levofloxacin (no controls)	ND	No FQ-resistant Gram- BSI stable over time 0.23 x 1000 PD in 2003, 0.81 x 1000 PD in 2009, 0.19 x 1000 PD in 2012	ND	ND
Saito 2008, Japan[48]	Observational discontinuation	HM	807	2001–2003: levofloxacin (liberal = 56%) 2003–2005: levofloxacin (restricted to HSCT recipients = 28.8%)	ND	No Only a related decrease among Enterobacteriaceae causing BSI Pre: 75% Discontinuation: 17%, p = 0.007	ND	No Pre: 0 Discontinuation: 2 BSI due to MDR *Pseudomonas*
Kanda 2010, Japan[51]	Observational discontinuation	HSCT	129	2000–2004: levofloxacin or ciprofloxacin or tosufloxacin 2004–2008: discontinuation (none)	ND	No Pre: 6/6 MDI Discontinuation: 2/6, p = 0.06	ND	ND

(*continued*)

Table 4 (*continued*)

Study, country	Study type	Type of patients	Number of patients (episodes of neutropenia)	Years of observation and type of prophylaxis	Resistance to fluoroquinolones (FQ) during FQ prophylaxis		Multidrug resistance (MDR) during FQ prophylaxis	
					Increase in colonisation with FQ resistant bacteria	Increase in FQ-resistant BSI	Increase in colonisation with MDR bacteria	Increase in infections by MDR bacteria
Chong 2011, Japan[52]	Observational discontinuation	Allo-HSCT	1981	2003–2005: levofloxacin 2006–2009: discontinuation	ND	No; no change in Gram+ (60%)	ND	No Pre: 0% Discontinuation: 48% *E. coli*, 13% *K. pneumoniae* ESBL
Sohn 2012, Korea[54]	Observational discontinuation	ASCT	277	2001–2005: ciprofloxacin 2004–2008: none (other HM protocol)	ND	No, only a relative decrease from 5/5 *E. coli* to 0/1	ND	No 1 ESBL vs. 0 in controls
Verlinden 2014, Belgium[57]	Observational discontinuation	HM	112 (154), 154 stool surveillance samples available	2009: ciprofloxacin 2009–2010: discontinuation (8 months) 2010–2011: ciprofloxacin	Yes Pre: 27% (14/51) Discontinuation: 6.7% (3/45) Post: 41% (24/58), both differences $p < 0.05$	No, only a relative increase Pre: 3/51 (3/3 *E.coli*) Discontinuation: 1/45 (1/10 *E.coli*) Post: 5/58 (5/5 *E.coli*)	No (trend only) Pre: 16% (8/51) ESBL faecal carriage Discontinuation: 8% (4/45) Post: 17% (10/58)	ND
Gafter-Gvili 2007[23]	Meta-analysis	RCT	2712 patients, 8 studies from 1987 to 2005 on FQ vs. placebo	FQ vs. placebo	No No increase in colonisation by FQ-resistant bacteria: 7.6% vs. 11%, $p = 0.24$ (3 studies, 161 patients, years of publication: 1987 – 1992)	No Rate of FQ-R infections among study patients - 4% vs. 3.8%, NS Higher rate of FQ-R infections among MDI – 30% vs. 16%, <0.0001	ND	ND

ALL: acute lymphoblastic leukaemia; allo-HSCT: allogeneic HSCT; AML: acute myelogenous leukaemia; ASCT: autologous stem cell transplant; BSI: bloodstream infection; ESBL: extended spectrum beta-lactamase; HM: haematological malignancy; HSCT: haematopoietic stem cell transplant; MDI: microbiologically documented infections; MRSA: methicillin-resistant *Staphylococcus aureus*; ND: no data; NS: not significant statistically, VRE: vancomycin-resistant enterococci.

significant variations of rate of FQ resistance in the years 2003–2012 despite a constant use of levofloxacin prophylaxis.[82] In terms of colonisation with FQ-resistant strains, data varied from no effect to a definite increase in one study,[34] while the specific meta-analysis reported a non-significant increase in colonisation with FQ-R bacteria.[23] Although it is intuitive that use of FQ would increase colonisation with FQ resistant strains, insufficient data and confounding factors associated with evolving local hospital epidemiology hamper quantifying the extent of this risk.

The emergence of MDR and ESBL-producers was not studied frequently and the data were contrasting. While most studies reported no effect, others reported an increase in infections caused by vancomycin resistant enterococci or ESBL-producing Gram-negative rods. Importantly, no data were available on the impact of FQ prophylaxis in patients already colonised with MDR bacteria, in whom FQ might reduce the number of susceptible pathogens and promote selection and growth of MDR strains. Consequently, there might be an increased risk of subsequent infection due to a MDR strain or its horizontal transfer to other patients and possible changes in local epidemiology. Thus, FQ prophylaxis might be potentially even deleterious in a setting where colonisation with resistant bacteria is routinely present, since it may select these strains and the mortality in neutropenic patients in case of BSI due to MDR Gram-negatives can reach 40%–60%.[85,86] Data on this issue are urgently needed.

In addition to potential selection of resistant strains in already colonised patients, other harmful effect associated with FQ use should be considered. They include the increased risk of infection due to *C. difficile*, which is already high in patients with haematological malignancies[87] and recently raised concerns about neurological and musculoskeletal side effects. Indeed, based on pharmacovigilance reports, the issue of FQ toxicity has been raised recently by the U.S. Food and Drug Administration (FDA), which released a warning against unnecessary use of FQs, because of the association with disabling and potentially permanent serious side effects that involve tendons, muscles, joints, nerves, and the central nervous system (http://www.fda.gov/Drugs/DrugSafety/ucm511530.htm). Therefore, the decision of using FQ prophylaxis should be taken responsibly in light of the abundant literature on the harms associated with the extensive use of antibiotics, the indications stemming from our analyses, and the recent warnings on FQ-related toxicity.

Last but not least, ethical issues of withdrawing FQ prophylaxis should be considered, since it is still recommended by most of the guidelines. Interestingly, based on the same data from the literature, only the Australian and ESMO guidelines put the extensive use of FQ in the context of increasing antibiotic resistance, and, considering no benefit on mortality, advised against the routine use of FQ prophylaxis during neutropenia.[25,30]

Although this review found no data contradicting the ECIL 1 recommendation on FQ prophylaxis administered in order to prevent infections in neutropenic patients, two main caveats need to be considered. First, antibiotic pressure has been invariably linked to an increase in bacterial resistance which has already an important negative impact worldwide. Second, the potential benefit of lower rate of BSI is limited, has no evident impact on mortality and, most importantly, was demonstrated only in settings with low or moderate resistance rates and, as such, cannot be held applicable to regions with a high prevalence of resistant pathogens. Therefore, local antibiotic policies on FQ use should be in line with national antimicrobial stewardship programs and based on local epidemiological data, although no clear cut off guaranteeing the efficacy of FQ prophylaxis could be provided.[88] The worldwide problem of a global crisis in terms of antimicrobial resistance and spread of MDR pathogens, calls for changes in the way we look at indications that were apparently consolidated and for new responsibilities of every specialist concerning proper use of antibiotics.[89,90]

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Conflict of interests

All the authors: none to declare.

Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.jinf.2017.10.009.

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