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REVIEW ARTICLE

Effectiveness of Quinolone Prophylaxis in Pediatric Acute Leukemia and Hematopoietic Stem Cell Transplantation: A Systematic Review and Meta-analysis

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The effectiveness of quinolone prophylaxis in high-risk hematological pediatric patients is controversial. A systematic review was performed according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines, including studies that involved children and young adults undergoing chemotherapy for acute leukemia or hematopoietic stem cell transplantation (HSCT) who received quinolone prophylaxis compared with no prophylaxis. A meta-analysis was performed on bloodstream infections and neutropenic fever. Data regarding the impact of prophylaxis on overall survival, antibiotic exposure, antibiotic-related adverse effects, antibiotic resistance, *Clostridium difficile* infections, fungal infections, length of hospitalization, and costs were reviewed in the descriptive analysis. Sixteen studies were included in the qualitative analysis, and 10 of them met the criteria for quantitative analysis. Quinolone prophylaxis was effective in reducing the rate of bloodstream infections and neutropenic fever in pediatric acute leukemia compared with no prophylaxis, but it had no significant effect in HSCT recipients. Prophylaxis was associated with a higher rate of bacterial resistance to fluoroquinolones and higher antibiotic exposure.

Keywords. acute leukemia; meta-analysis; pediatric; quinolone prophylaxis; stem cell transplantation.

Infective complications represent the leading cause of morbidity and mortality among pediatric patients with cancer receiving intensive chemotherapy and undergoing hematopoietic stem cell transplantation (HSCT) [1]. Particularly, the presence of a central line, the relatively high frequency of blood draws and transfusions, the intestinal mucositis, and the therapy-induced neutropenia expose these patients to a higher risk of bloodstream infections (BSIs) [2, 3]. BSIs lead to longer hospitalizations with a consequent increase in health care costs, extensive exposure to antibiotics, more systemic complications, and higher mortality [4]. Antibiotic prophylaxis (PPX) represents a potential preventive strategy for BSI, and several prophylactic regimens have been historically proposed for cancer patients consisting of oral absorbable and nonabsorbable compounds as well as intravenous antibiotics. However, oral nonabsorbable antibiotics have been generally abandoned for poor tolerance and compliance, whereas most of the oral absorbable antibiotics, such as trimethoprim-sulfamethoxazole, have failed to demonstrate a significant difference in mortality [5]. In this context, quinolones have been historically commonly used as prophylactic agents, given their broad spectrum of antimicrobial activity, their capacity to preserve the anaerobic flora, their good tolerability, and their low myelosuppression [5–7]. In a meta-analysis of studies published before 2010 including adult patients with hematological and nonhematological malignancies undergoing chemotherapy, antibiotic prophylaxis was associated with reduced all-cause mortality, fewer febrile episodes, and gram-negative bacillus BSI, most significantly when assessing prophylaxis with quinolones [5]. However, a meta-analysis of studies published during 2006–2014 did not confirm a reduction in mortality on fluoroquinolone prophylaxis but still showed lower rates of BSI and of episodes of fever during neutropenia [8, 9]. The most recent meta-analysis, comprising adult and pediatric studies, found that levofloxacin PPX during intensive chemotherapy for acute leukemia significantly reduced febrile neutropenia, bacteremia, and microbiologically documented infection rates, but did not improve the death rate [10]. While the effectiveness of PPX in adult patients has been addressed in several studies, data regarding pediatric patients are limited [11]. A narrative review by Calitri and colleagues raised questions about antibacterial prophylaxis in children with leukemia, highlighting the lack of strong evidence for its use in the pediatric population [12].

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Moreover, new evidence demonstrated the association of extended-spectrum antibiotic use with the emergence of multidrug-resistant bacteria and gut dysbiosis [13, 14], further suggesting a clear risk-benefit assessment. Among pediatric cancers, patients with acute leukemia (AL) or receiving HSCT are at higher risk of developing BSI due to long-lasting neutropenia combined with a higher presence of mucositis [15]. The current guideline does not recommend routine antibacterial PPX for pediatric patients with AL receiving intensive chemotherapy or with neutropenia during the pre-engraftment stage of HSCT based on the low level of evidence [11]. Moreover, the possible benefits should be weighed against potential harm, including *Clostridium difficile* infection (CDI) risk, drug-related side effects, and association with colonization or infection with fluoroquinolone- or multidrug-resistant strains [8, 16]. Recent data also highlighted the detrimental role of antibiotic prophylaxis on the gut microbiota, which results in a disruption of eubiosis associated with bacterial dominance and a higher rate of immune-mediated complications [14, 17]. We here conducted a systematic review and meta-analysis of the available studies comparing quinolone PPX vs no PPX in pediatric patients with AL undergoing HSCT.

METHODS

Literature Search

This systematic review and meta-analysis was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [18]. Electronic databases, including PubMed, TRIP, and CINAHL, were searched up to January 20, 2022. The search strategy and the search string used to perform the browsing are reported in the Supplementary Data. The search was restricted to English-language studies involving children and young adults (age >30 days and <23 years) receiving chemotherapy for AL or undergoing HSCT who received a quinolone-based antibacterial PPX compared with no PPX. Two reviewers (D.L. and N.A.) independently identified potentially eligible studies by title/abstract screening. The same authors assessed the full texts of potentially relevant studies for inclusion and consulted the references of previously published primary and secondary papers, including reviews and meta-analyses, to manually search for additional relevant papers. Any disagreement regarding eligibility and inclusion in the systematic review was resolved through discussion and consensus between the 2 authors. If consensus was not reached, the opinion of a third author (E.M.), who acted as the final arbiter, was requested. Investigators and corresponding authors were contacted to obtain additional information about studies with incomplete data.

Data Extraction and Meta-analysis

We used the same methodology for data extraction, performed independently by the same 2 reviewers (D.L. and N.A.) under the supervision of a third author (E.M.). Data were summed and analyzed using Microsoft Office Excel for Mac 2022 (Microsoft, Redmond, WA, USA) and Stata 13 (StataCorp, College Station, TX, USA). Only papers reporting outcomes related to the total number of patients were included in the quantitative synthesis. Subsequently, we performed a meta-analysis considering the primary outcome, incidence of BSI and neutropenic fever (NF), considering the number of patients with at least 1 episode of BSI/NF. Primary outcomes were selected in consideration of the main aim of prophylactic antibiotic treatments. Secondary outcomes, in order, were overall survival, antibiotic exposure, antibiotic-related adverse effects, antibiotic resistance, *Clostridium difficile* infections, fungal infections, length of hospitalization, and health care costs. BSIs have been defined as any infection caused by a recognized pathogen that was isolated from ≥1 blood culture in the context of a compatible clinical illness. Even if there is no consensus yet, febrile neutropenia has been consistently defined as a core body temperature ≥38.3°C or ≥38°C for ≥1 hour in the context of neutropenia, defined as an absolute neutrophil count (ANC) ≤500/mmc [19, 20]. We analyzed statistical heterogeneity to determine the feasibility of summing the results of the different studies considered eligible for the meta-analysis. We assessed heterogeneity by graphic funnel plots and by calculating the I^2 statistic, which represents the percentage of the variance in effect estimates that is caused by heterogeneity rather than by sampling bias (chance). An I^2 statistic >40% was considered significantly heterogeneous. When the number of studies was <5 or studies were substantially heterogeneous, we used a random-effects model in accordance with the Cochrane Handbook for Systematic Reviews of Interventions [21]. We followed the method of DerSimonian and Laird [22] to compute the random effects estimates for the corresponding statistics. We chose to use forest plots to graphically show effect estimates with 95% CIs for individual trials and pooled results. We carried out the meta-analysis using RevMan, version 5.3 (https://revman.cochrane.org). Sensitivity analyses were also performed by removing studies separately based on the chosen criteria, namely, quality of the study, type of study, and type of country in which the study was performed.

Quality Assessment

Quality assessment was performed independently by 2 authors (D.L. and N.A.), and any disagreement was resolved through discussion and consensus between the 2 authors. We used the Cochrane Tool for Quality Assessment for evaluating RCTs and the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement to assess the quality of the observational studies included in the meta-analysis. The Cochrane tool allows for the analysis of 7 types of bias: sequence generation and allocation concealment (both within the domain of selection bias or allocation bias), blinding of participants and personnel (performance bias), blinding of

outcome assessors (detection bias), incomplete outcome data (attrition bias), selective reporting (reporting bias), and an auxiliary domain, "other bias" [23]. For each type of bias, it was possible to assign a value of "high," "low," or "unclear" risk of bias when it was not specified whether a specific type of bias was present. Each bias judgment aids in assigning a global assessment to every RCT (good, fair, or poor) according to the Agency for Healthcare Research and Quality standards [24]. The STROBE statement is a 22-item tool specifically designed to evaluate the quality of cohort studies [25]. Items are associated with different sections of an article, such as title and abstract (item 1), introduction (items 2 and 3), methods (items 4–12), results (items 13–17), discussion (items 18–21), and other information (item 22 for funding). Eighteen items are identical for 3 different study designs, whereas 4 items (items 6, 12, 14, and 15) are differentially intended for a specific study type (ie, cohort or case–control study). The STROBE statement does not provide scoring stratification. As a general rule, the higher the score, the higher the quality of the study. Thus, we created 3 score thresholds corresponding to 3 levels of quality: 0–14 was considered low quality; 15–25, intermediate quality; 26–33, high quality.

RESULTS

Literature Search and Population

The literature search strategy identified a total of 3447 references (2062 in PubMed, 1385 in CINAHL) (Figure 1). A total of 3199 records were excluded according to the full title, and the duplicates were removed. The resulting 248 records were assessed by full text: 136 studies were excluded because they concerned adult patients, 33 because they did not compare quinolone PPX with no PPX, and 5 because quinolones were not used in a PPX setting. Reviews (41), meta-analyses (3), guidelines and recommendations (10), and complementary articles and editorials (4) were excluded as well. Of the 16 studies included in the qualitative synthesis, 7 were excluded [26–32]. Detailed reasons for exclusion are reported in Supplementary Table 1 and Figure 1. The total number of patients included in the quantitative synthesis was 2254. Among the 9 studies selected for the meta-analysis, 6 were retrospective single-center studies [33–38] and 3 were prospective studies [39–41], 2 of which were randomized [40, 41]; 1 was also multicentric [41]. Two studies included only patients with acute lymphoblastic leukemia (ALL) [39, 40], 1 only patients with acute myeloid leukemia (AML) [37], 2 both ALL and AML patients [33, 42], 1 only patients undergoing autologous HSCT (auto-HSCT) [35], 2 both auto- and allogenic HSCT (allo-HSCT) [34, 36], and 1 all groups of patients [41]. Two of the 6 studies on ALL patients studied relapsed ALL (rALL) [33, 41]. Detailed data on AL patients in the studies included in the meta-analysis are reported in Table 1. Levofloxacin (LVX) [33, 39, 41] and ciprofloxacin (CPFX) [37, 39, 40, 42] were both used in the AL setting, whereas HSCT studies investigated only the use of LVX PPX [34–36, 41]. The quality of the included studies in the meta-analysis was assessed as described in Methods and reported in Table 2.

Bloodstream Infections

Nine studies were included in the meta-analysis for the impact of quinolone PPX on BSI [33–37, 39–41, 43]. Among these, 6 studies were conducted in patients with AL [33, 37, 39–41, 43] and 4 in the HSCT setting [34–36, 41]. One study included both AL and HSCT patients but considered separately the incidence of BSI in patients with AL and those undergoing HSCT [34]. Analyzing the data together, the incidence of BSI was significantly lower in the PPX groups compared with non-PPX (273 of 1106 vs 368 of 1148), with an odds ratio (OR) of 0.50 (95% CI, 0.30–0.84; $P = .008$). Heterogeneity among the studies was 88% (Figure 2).

Dissecting the analysis between patients with AL and those receiving HSCT, the results were different. In the AL group, the incidence of BSI was still significantly lower in PPX compared with non-PPX (79 of 386 vs 199 of 533), with an OR of 0.31 (95% CI, 0.22–0.43; $P < .001$). Heterogeneity was lower in this subanalysis (35%) (Figure 3).

Analyzing the studies reporting outcomes for patients receiving HSCT, the incidence of BSI was comparable between the 2 groups (194 of 720 vs 169 of 615), with an OR of 0.82 (95% CI, 0.47–1.41; $P = .46$). Heterogeneity among these studies was higher, reaching 75% (Figure 4).

We then performed a sensitivity analysis for the quality of studies and type of studies, and the data were comparable (Supplementary Figures 1, 2, and 3). A sensitivity analysis for countries' incomes was performed as well, showing no effect on the incidence of BSI (Supplementary Figure 4).

Six papers on children with AL did not meet the inclusion criteria and were not included in the quantitative synthesis. McCormick et al. retrospectively compared the incidence of BSI for each hospital admission in which no PPX or quinolone PPX was used. They reported a BSI incidence of 26.2% and 8.9% in the non-PPX and PPX groups, respectively [26]. Felsenstein et al. compared the incidence of BSI in 153 chemotherapy courses for AML in pediatric patients receiving or not receiving CPFX PPX. They found no statistically significant difference in the 2 groups (odds ratio, 1.1; 95% CI, 0.6–2.1; $P = .80$) [27]. In a paper by Yousef et al., the incidence of culture-positive bacteremia per delayed intensification (DI) chemotherapy cycle in children with ALL was retrospectively analyzed [28]. The authors found a reduction in the rate of positive blood cultures from 22% in the control population to 9% in the study group in which PPX with CPFX was administered ($P = .028$). Widjajanto et al. analyze the role of CPFX PPX in the frequency of bacterial infection and toxic death during

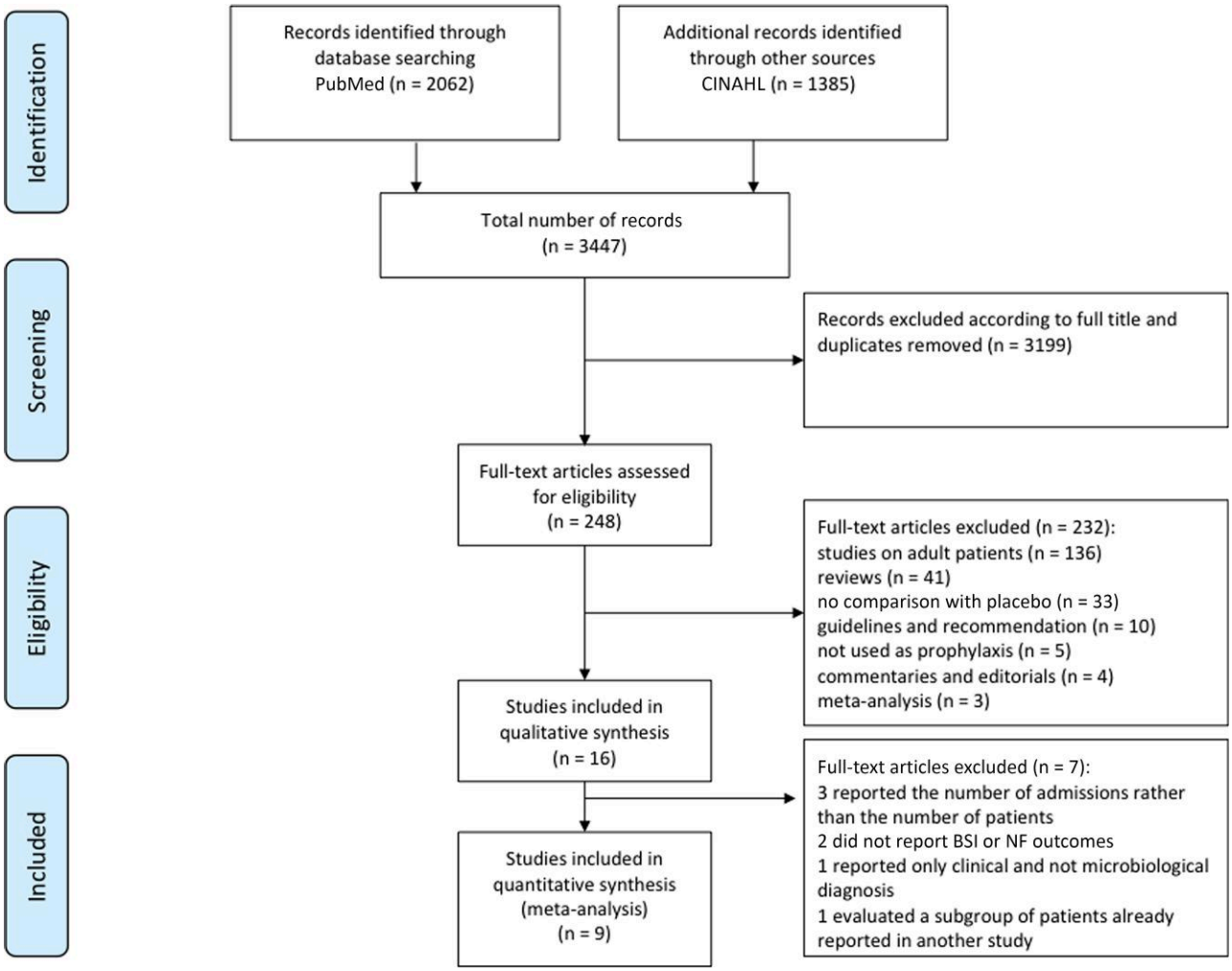

Figure 1. PRISMA flow diagram of the search strategy and included studies. The relevant number of papers at each point is given. Abbreviation: BSI, bloodstream infection; NF, neutropenic fever; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

induction treatment of childhood ALL in a middle/low-income country; this study was excluded from the meta-analysis because it did not consider the microbiological diagnosis. The authors found that the CPFX arm had a modestly greater risk for clinical sepsis compared with the placebo group (50.0% vs 38.5%; $P = .22$) [31]. Interestingly, fluoroquinolone PPX seems to reduce infections due to gram-negative bacteria having a small influence on gram-positive BSI both in AL [27, 28, 37, 41] and HSCT settings [35, 36, 41].

Neutropenic Fever

Four of the 9 studies included in the meta-analysis reported the incidence of neutropenic fever (NF) among patients receiving fluoroquinolone PPX or placebo [39–41, 43]. All studies included patients with AL. Alexander et al. reported the overall number of patients with at least 1 episode of neutropenic fever, without considering separately patients with AL and those undergoing HSCT [41]. Overall, the incidence of NF was significantly lower in the PPX group than in the control group (191 of 300 vs 351 of 459), with an OR of 0.44 (95% CI, 0.31–0.62; $P < .001$). Heterogeneity was 37% (Figure 5).

Removing the study by Alexander et al. and considering only papers including patients with AL exclusively, the incidence of NF was still significantly lower in the PPX group than in the control group (36 of 83 vs 144 of 207), with an OR of 0.31 (95% CI, 0.16–0.59; $P < .001$). Heterogeneity was 22% (Figure 6). We then performed a sensitivity analysis by type of study, and the data were comparable (Supplementary Figure 5).

The paper by Yeh et al. reported the incidence of NF in AML patients but was excluded because it reported an outcome related to the number of chemotherapy courses rather than the number of patients [37]. The frequencies of NF were reduced significantly during the PPX period, namely, in induction from 99% to 78%, in high-dose chemotherapy from 94% to 64%, and in modest-

Table 1. Characteristics of AL Patients Included in the Meta-analysis

Study	Population	Chemotherapy Phase and/or Criteria for FLQ PPX
Alexander et al. [41]	rALL, any AML (de novo, relapsed, or secondary AML, AL of ambiguous lineage treated with standard AML therapy)	2 consecutive cycles of intensive chemotherapy, defined as regimens that are predicted to cause neutropenia (ANC <200/mm^3) for >7 d
Davis et al. [33]	rALL, AML, other AL who received AML-type chemotherapy	Phase not specified—chemotherapy expected to lead to prolonged severe neutropenia (ANC <200/mm^3)
Laoprasopwattana et al. [40]	ALL, lymphoma—not specified if newly diagnosed and/or relapse	Either induction or consolidation
Wolf et al. [39]	Newly diagnosed ALL	Induction
Yeh et al. [43]	Newly diagnosed ALL, newly diagnosed nonacute promyelocytic leukemia AML	Induction, consolidation, or reinduction (ALL); induction, postremission high dose and modest dose (AML)—expected prolonged neutropenia (ANC ≤500/mm^3 for >7 d)
Yeh et al. [37]	Newly diagnosed AML (no Down syndrome, acute promyelocytic leukemia, or therapy-related AML)	Induction, postremission high dose, postremission modest dose

Abbreviations: AL, acute leukemia; ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; ANC, absolute neutrophil count; FLQ, fluoroquinolone; PPX, prophylaxis; rALL, relapsed ALL.

dose chemotherapy from 58% to 27% (all $P < .001$). However, a lower cumulative incidence of NF using Kaplan–Meier analysis was observed only in induction ($P = .037$) or modest-dose chemotherapy ($P < .001$) during the PPX period. Widjajanto et al. [31] found that patients who received CPFX PPX had more fever compared with those who did not receive PPX (50.0% vs 32.7%), even if significance was not achieved [31].

Overall Survival

Clinical outcomes were described in 8 studies reporting variable parameters and results [27, 28, 33–35, 37, 41, 43]; outcome results are summarized in Table 3. Data regarding mortality were reported too heterogeneously to allow for a meta-analysis. In the acute leukemia setting, overall mortality was not associated with CPFX PPX in the univariate analysis of the study by Felsenstein et al. [27], whereas it was reduced after the introduction of quinolone PPX in 2 other studies [33, 42]. When infection-related mortality was specifically analyzed, no difference was reported with FLQ PPX in 2 studies [28, 33], while it was significantly reduced in the 2 subsequent studies by Yeh et al. [37, 43]. Notably, in these last 2 papers, antifungal PPX was associated with quinolone PPX, possibly biasing these results. Regarding HSCT, no difference in survival outcomes was reported by studies investigating survival and mortality [34, 35, 41]. Gardner et al. reported a significantly higher rate of acute graft-vs-host disease in the PPX group [34].

Antibiotic Exposure

The impact of fluoroquinolone PPX on antimicrobial exposure, namely, the number of days on which a specific antimicrobial was administered, was analyzed by 7 studies, including both leukemia and HSCT settings [27, 34–37, 39, 41]; the results are summarized in Table 4. Among children with AL, 2 studies reported a significantly greater exposure to antimicrobials used for PPX with a concomitant significantly lower exposure to antibiotics and/or antifungal agents administered for the empirical therapy of infections in the fluoroquinolone group compared with the control group [37, 39]. Similarly, in the study by Felsenstein et al., PPX with CPFX significantly decreased the duration of antibiotic treatment both overall and specifically of aminoglycoside therapy, primarily because of fewer gram-negative infections in the PPX group [27]. In the transplantation setting, LVX PPX significantly reduced the duration of empiric antibiotic administration [34, 35]. Lopes et al. described a marked increase in the use of LVX during the PPX period; conversely, the use of systemic treatment antibiotics was similar before and after the introduction of LVX PPX [36]. Finally, in the research by Alexander et al., in children with AL and undergoing HSCT, total duration of exposure and any exposure to aminoglycosides, third- and fourth-generation cephalosporins, and antibiotics commonly used for empirical therapy for fever and neutropenia were lower in the LVX group compared with the no PPX group [41].

Antibiotic Resistance

Eight of the included studies reported data on the impact of fluoroquinolone PPX on the development of antibiotic resistance in colonizing microorganisms and/or in bacteria isolated from blood [29, 32, 33, 36, 37, 40, 41, 43]; the results are summarized in Table 5. Among patients with AL receiving fluoroquinolone PPX, 3 studies found an increased incidence of gram-negative bacteria resistant to fluoroquinolone in intestinal microflora [29, 40] and isolated from blood [33]. Similarly, in the study by Margolis et al., the prevalence of topoisomerase point mutations, known to confer fluoroquinolone resistance, increased during induction chemotherapy for ALL in participants receiving LVX but not those receiving no PPX [32]. Conversely, in the 2 works of Yeh et al., CPFX [43] and amikacin [37] resistance to the most common gram-negative bacilli at the study

Table 2. Summary of Studies Included in the Meta-analysis

First Authors	Year	Study Design	Type of Patients	Total Patients	PPX Group	No PPX Group	Type of PPX	Quality Assessment
Alexander et al. [41]	2018	Randomized, open-label, multicenter	rALL, AML auto-HSCT, allo-HSCT	195, 418	96, 210	99, 208	Levofloxacin	Good quality[b]
Davis et al. [33]	2022	Retrospective, single center	rALL, AML	135	72	63	Levofloxacin	High quality[a]
Gardner et al. [34]	2021	Retrospective, single center	Auto/allo-HSCT	443	227	216	Levofloxacin	High quality[a]
Hafez et al. [35]		Retrospective, single center	Auto-HSCT	96	50	46	Levofloxacin	Intermediate quality[a]
Laoprasopwattana et al. [40]	2013	Randomized, open-label, single center	ALL	95	45	50	Ciprofloxacin	Fair quality[b]
Lopes et al. [36]	2014	Retrospective, single center	Auto/allo-HSCT	378	233	145	Levofloxacin	Low quality[a]
Wolf et al. [39]	2017	Prospective, observational, single center	ALL	253	80	173	Levofloxacin (69), ciprofloxacin (11)	High quality[a]
Yeh et al. [37]	2021	Retrospective, single center	AML	90	28	62	Ciprofloxacin	High quality[a]
Yeh et al. [43]	2014	Retrospective, single center	ALL, AML	151	65	86	Ciprofloxacin	Intermediate quality[a]

Quality assessment was carried out as specified in the Methods.

Abbreviations: AL, acute leukemia; ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; auto, autologous; allo, allogeneic; HSCT, hematopoietic stem cell transplantation; PPX, prophylaxis; rALL, relapsed ALL.

[a]Quality assessed using the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement for prospective cohorts.

[b]Quality assessed using the Cochrane Tool for Quality Assessment for randomized controlled trials.

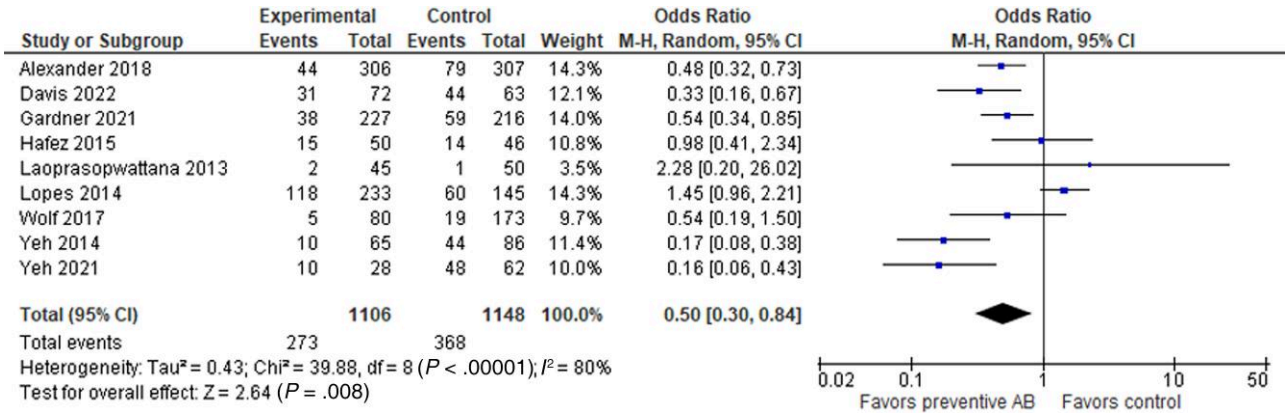

Figure 2. Forest plot showing the association between the use of quinolone PPX and the incidence of BSI in pediatric patients with AL or receiving HSCT. Abbreviations: AB, antibiotics; AL, acute leukemia; BSI, bloodstream infection; HSCT, hematopoietic stem cell transplantation; PPX, prophylaxis.

institution was significantly reduced during the PPX period, with a concomitant rising of cefuroxime and imipenem resistance [37]. Among patients undergoing HSCT, a significant increase in quinolone resistance throughout LVX PPX compared with the pre-PPX period was demonstrated in 1 study [36]. Finally, Alexander et al. found that the proportion of selected intestinal organisms with newly detected resistance to LVX, cefepime, and imipenem from baseline to follow-up was low, reaching a maximum of 9.3% for LVX resistance among patients with AL receiving PPX, and not significantly different between the LVX PPX and control groups for both patients with AL and those undergoing HSCT [41].

Antibiotic-Related Adverse Effects

Quinolones have been commonly associated with several side effects, mainly consisting of gastrointestinal symptoms, such as dyspepsia, nausea and vomiting, and central nervous system reactions such as dizziness, insomnia, headache, and musculoskeletal adverse events [44, 45]. Details of the main side effects associated with quinolone prophylaxis are listed in Table 6. The study of

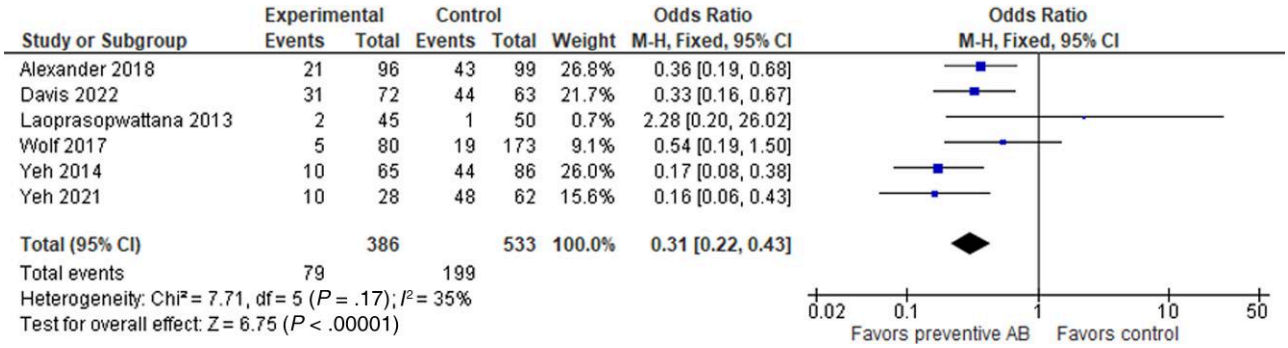

Figure 3. Forest plot showing the association between the use of quinolone PPX and the incidence of BSI in pediatric patients with AL. Abbreviations: AB, antibiotics; AL, acute leukemia; BSI, bloodstream infection; PPX, prophylaxis.

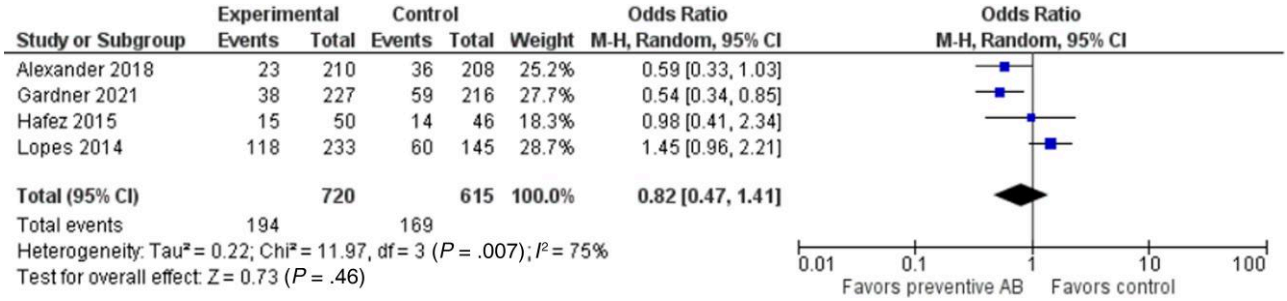

Figure 4. Forest plot showing the association between the use of quinolone PPX and the incidence of BSI in pediatric patients with HSCT. Abbreviations: AB, antibiotics; BSI, bloodstream infection; HSCT, hematopoietic stem cell transplantation; PPX, prophylaxis.

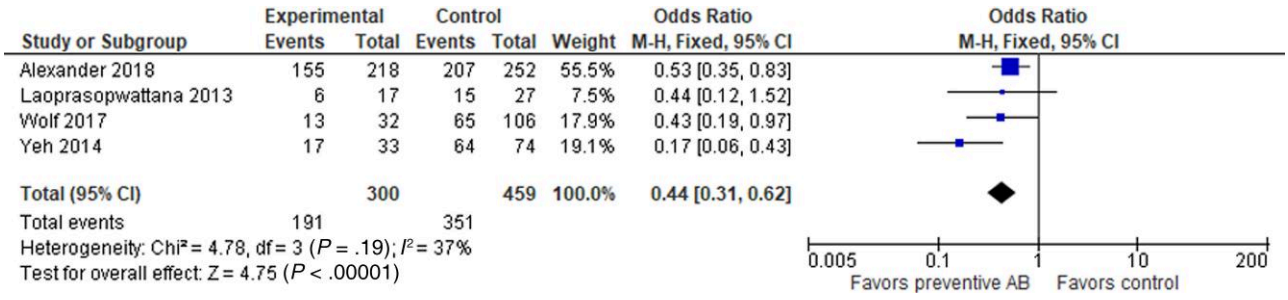

Figure 5. Forest plot showing the association between the use of quinolone PPX and the incidence of NF in pediatric patients with AL and HSCT. Abbreviations: AB, antibiotics; AL, acute leukemia; HSCT, hematopoietic stem cell transplantation; NF, neutropenic fever; PPX, prophylaxis.

Karol et al. specifically investigated the association between fluoroquinolone during induction therapy for ALL and the development of neuropathic pain and vincristine-induced neuropathy, reporting no significant association between antibiotic exposure and neurotoxicity [30]. Rare skin allergic reactions associated with quinolones were reported in 2 studies [27, 40]. Three studies evaluated musculoskeletal side effects in the 2 cohorts and did not find any differences [26, 27, 40]. Gardner et al. investigated the impact of PPX with LVX on cardiac function by evaluating baseline and follow-up electrocardiogram (ECG) and reporting no difference in terms of QTc prolongation between the 2 groups (21/93 vs 16/106; $P = .20$) [34]. In the 2 studies evaluating the impact of combined antibacterial and antifungal PPX, increased liver enzyme levels were reported in patients receiving PPX, but this side effect was mainly related to micafungin and voriconazole administration [37, 43].

Fungal Infections

The detrimental role of quinolones on intestinal flora has been reported to be associated with fungal overgrowth and

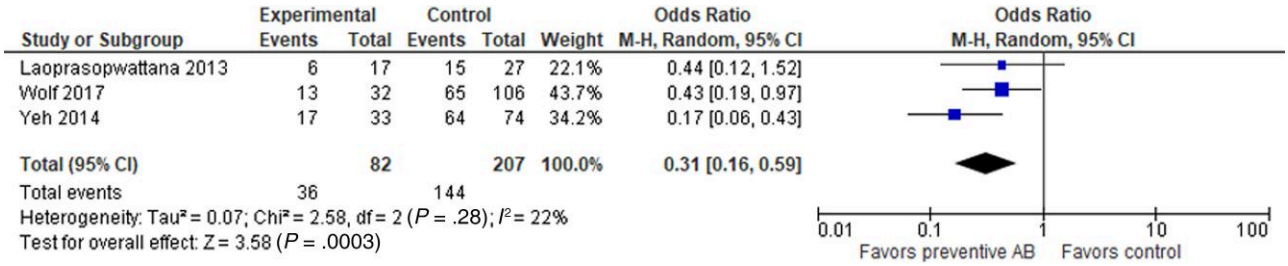

Figure 6. Forest plot showing the association between the use of quinolone PPX and the incidence of NF in pediatric patients with AL. Abbreviations: AB, antibiotics; AL, acute leukemia; NF, neutropenic fever; PPX, prophylaxis.

Table 3. Summary of Outcome Results of Studies Included in the Systematic Review

Study	Patients	FLQ Prophylaxis	Outcome Results
Felsenstein et al. [27]	AML	Ciprofloxacin	No association between all-cause mortality and PPX, expressed as number of chemotherapy cycles treated with PPX (OR, 0.99; $P = .96$) and total days of PPX exposure (OR, 1.1; $P = .85$).
Yousef et al. [28]	ALL	Ciprofloxacin	No infection-related deaths in either the controls or the PPX patients. PPX group experienced a greater induction failure rate (31.0% vs 25.0%; 95% CI, 0.58–3.12; $P = .48$) and higher toxic death rate (18.9% vs 5.8%; 95% CI, 0.92–13.80; $P = .05$).
Davis et al. [33]	ALL, AML	Levofloxacin	Death during PPX was significantly reduced (RR, 0.58; 95% CI, 0.36–0.95; $P = .04$) but not bacterial infection–associated death (RR, 0.38; 95% CI, 0.05–2.79; $P = .63$).
Yeh et al. [42]	ALL, AML	Ciprofloxacin + voriconazole or micafungin	In AML patients, overall mortality rate in the pre-PPX and PPX periods was 25% and 7%, EFS rate was 50 and 55%, and OS rate was 60% and 68%, respectively, a median of 7 months after the completion of intensive chemotherapy. Infection-related deaths during PPX were significantly reduced (7/24 vs 0/14; $P = .03$). In ALL patients, overall mortality rate in the pre-PPX and PPX periods was 6.5% and 2%, EFS rate was 78% and 87%, and OS rate was 86% and 98%, respectively, a median of 21 months after the completion of intensive chemotherapy. Infection-related deaths during PPX were not significantly reduced (1/62 vs 0/51; $P = .55$).
Yeh et al. [37]	AML	Ciprofloxacin + voriconazole or micafungin	Infection-related deaths decreased from 21% (13/62 patients) during the pre-PPX period to 4% (1/28 patients) in the PPX period. 5-year OS rate increased from 54.8% (42.5% to 67.1%) to 78.6% (63.3% to 93.9%), and 5-year EFS rate increased from 51.6% (39.3% to 63.9%) to 70.6% (53.4% to 87.8%) with the introduction of PPX.
Alexander et al. [41]	rALL, AML auto-HSCT, allo-HSCT	Levofloxacin	No infection-related deaths.
Gardner et al. [34]	Auto/allo-HSCT	Levofloxacin	Higher rate of graft-vs-host disease by day 100 in the PPX group (11.7% vs 4.2%, $P = .01$). No difference in mortality in the first 100 days (4% vs 8%; $P = .16$) and in the first 12 months post-transplant (18.1% vs 23.6%; $P = .16$) in PPX group and non-PPX group. No difference in nonrelapse mortality in the first 12 months post-transplant (11.5% vs 14%; $P = .48$) in PPX group and non-PPX group.
Hafez et al. [35]	Auto-HSCT	Levofloxacin	No difference in infection-related mortality between PPX group and control group (0/50 vs 2/46; $P = .227$).

Abbreviations: ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; auto, autologous; allo, allogeneic; FLQ, fluoroquinolone; HSCT, hematopoietic stem cell transplantation; OR, odds ratio; PPX, prophylaxis; rALL, relapsed ALL; RR, relative risk.

ultimately with fungal infections [46]. Six studies investigated the modification of fungal infection rate in patients receiving and not receiving PPX with fluoroquinolones [27, 28, 34, 37, 41, 43]; details are reported in Table 7. In the study of Felsenstein et al., after the introduction of CPFX PPX, fungemia occurred significantly more frequently ($P = .01$) [27]. An opposite trend was described in the study by Yousef et al., in which all 3 fungal septicemias occurred in the control group, while no episode was reported in the PPX group [28]. Of note, a significant decrease in invasive fungal infection rate was also reported in the 2 studies by Yeh et al., but it has to be considered that the intervention adopted in the study included a combined antibacterial and antifungal PPX with CPFX and micafungin or voriconazole [37, 43]. In patients with AL and undergoing HSCT randomized to receive LVX or no PPX, there were no significant differences in invasive fungal disease (2.9% vs 2.0%; risk difference, −1.0%; 95% CI, −3.4% to 1.5%; $P = .41$) [41]. In the transplanted patients in the study of

Table 4. Summary of Antibiotic Exposure Results of Studies Included in the Systematic Review

Study	Patients	FLQ Prophylaxis	Antibiotic Exposure
Yeh et al. [36]	AML	Ciprofloxacin + voriconazole or micafungin	Patients receiving PPX had greater exposure to ciprofloxacin, vancomycin, and voriconazole and lower exposure to carbapenem, amikacin, amphotericin B, and caspofungin compared with those receiving no prophylaxis (all $P < .001$).
Wolf et al. [38]	ALL	Levofloxacin, ciprofloxacin	Antibiotic exposure and cumulative antibiotic exposure were greater in patients receiving any PPX ($P < .001$). Patients receiving levofloxacin PPX had less exposure to cefepime/ceftazidime, vancomycin, meropenem, or aminoglycosides when compared with those receiving no PPX (all $P < .01$) or other PPX (all $P < .05$).
Felsenstein et al. [27]	AML	Ciprofloxacin	Longer exposure to treatment antibiotics overall in the control group (PPX: median [IQR], 15 [5–21] days; no PPX: median [IQR], 19 [12–30.5] days; $P < .01$). Ciprofloxacin PPX did not impact duration of meropenem use per CC (PPX: median [IQR], 10 [4.2–19] days; no PPX: median [IQR], 11 [3.5–22.5] days; $P = .62$) or duration of vancomycin use per CC (PPX: median [IQR], 2 [2–9] days; no PPX: median [IQR], 4 [4–8] days; $P = .43$). However, it decreased duration of aminoglycoside use per CC (PPX: median [IQR], 0 [0–0] days; no PPX: median [IQR], 2 [0–4] days; $P < .01$).
Hafez et al. [35]	Auto-HSCT	Levofloxacin	The median duration of empiric antibiotic use in the PPX group was 11 days compared with 14 days in the control group ($P < .001$). The frequency of empirical antifungal use was higher in the control group compared with the PPX group (98% vs 46%; $P < .001$).
Gardner et al. [34]	Auto/allo-HSCT	Levofloxacin	Higher average number of antibiotic days (mean, 47 vs 35 days; $P < .0019$) and greater meropenem (mean, 4.2 vs 2.5 days; $P = .02$), metronidazole (mean, 1.4 vs 0.25 days; $P < .001$), and cefepime use (mean, 19.6 vs 14.9 days; $P < .001$) in the control group than in the PPX group.
Lopes et al. [36]	Auto/allo-HSCT	Levofloxacin	Increase in the use of levofloxacin in the PPX period from 19.4 to 166.6 DDD per 1000 patient-days. Slight increase in meropenem use from 4.59 to 5.33 DDD per 1000 patient-days and decrease in cefepime use from 3.75 to 3.32 DDD per 1000 patient-days in the PPX period.
Alexander et al. [41]	rALL, AML auto-HSCT, allo-HSCT	Levofloxacin	The mean antibiotic exposure days per 30 patient-days was 1.2 vs 2.3 (adjusted RR, 0.49; 95% CI, 0.33–0.73; $P = .001$) for aminoglycosides, 5.3 vs 7.1 (adjusted RR, 0.74; 95% CI, 0.60–0.92; $P = .006$) for third- and fourth-generation cephalosporins, 9.6 vs 13.1 (adjusted RR, 0.72; 95% CI, 0.63–0.83; $P < .001$) for antibiotics commonly used empirically for fever and neutropenia (defined as imipenem, meropenem, cefepime, ceftazidime, or piperacillin-tazobactam), and 5.3 vs 6.1 (adjusted RR, 0.87; 95% CI, 0.7–1.06; $P = .17$) for gram-positive agents (defined as vancomycin, linezolid, daptomycin, or quinupristin/dalfopristin) in LVX group and no PPX group, respectively.

Abbreviations: ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; auto, autologous; allo, allogeneic; CC, chemotherapy cycle; DDD, defined daily dose; FLQ, fluoroquinolone; HSCT, hematopoietic stem cell transplantation; IQR, interquartile range; LVX, levofloxacin; PPX, prophylaxis; rALL, relapsed ALL; RR, relative risk.

Gardner et al., there was no significant difference between the PPX and control groups regarding fungal infection rate (1/227 [0.4%] vs 4/216 [2%]; $P = .21$) [34].

Clostridium difficile Infections

The impact of antibiotic PPX on *Clostridium difficile* infection rate was evaluated in 3 studies [33, 39, 41]. In the post hoc analyses of the RCT by Alexander et al., patients receiving levofloxacin were less likely to have a positive test result for *Clostridium difficile* (7.8% vs 14.0%; $P = .02$) [41]. One study showed a significant reduction in cumulative incidence of *Clostridium difficile* infection in patients receiving PPX with LVX compared with those receiving no PPX during induction therapy for newly diagnosed pediatric ALL (from 9.8% to 0%; adjusted odds ratio, 0.03; 95% CI, 0.01–0.24; $P < .001$ on multivariate logistic regression analysis) [39]. Another paper in the leukemia setting performed only a descriptive analysis regarding *Clostridium difficile* infections, showing no difference between the 2 groups (19.0% vs 19.4%) [33].

Length of Hospitalization

The impact of antibiotic PPX on the duration of hospitalization was assessed in only 2 studies concerning the HSCT setting [28, 35]. The duration of hospitalization was significantly shorter in patients receiving PPX, from 28 to 24 days in 1 study ($P < .01$) [35] and from 10 to 6 days in a second study ($P = .001$) [28].

Health Care Costs

Two studies on AL reported a decrease in health care costs with the administration of PPX [26, 43]. A multicenter retrospective study evaluated epidemiologic data regarding LVX use as prophylaxis in children with AML and specifically evaluated the cost-effectiveness of this strategy by using a decision analysis model. Cost-effectiveness was defined as cost per bacteremia episode, intensive care unit (ICU) admission, and avoidance of death in children undergoing LVX PPX compared with no PPX. PPX decreased the absolute risk of bacteremia by 17%, with a cost of $1464 compared with no PPX, thus resulting in a PPX cost of $8491 per bacteremia episode prevented. This

Table 5. Summary of Antibiotic Resistance Results of Studies Included in the Systematic Review

Study	Patients	FLQ Prophylaxis	Sample	Antibiotic Resistance
Tunyapanit et al. [29]	ALL and lymphoma	Ciprofloxacin	Rectal swab cultures	The percentage of ciprofloxacin susceptibility of *E. coli* and *K. pneumoniae* before intervention and at the third week of the study decreased in PPX group (83.9% vs 4.5%) and improved in the placebo group (70.6% vs 100%). After the study, the MIC50s of ciprofloxacin were significantly higher in the PPX group than in the placebo group. Although the susceptibility rates to ceftazidime were not different between the PPX and placebo groups after the study, the MIC50s were significantly higher in the PPX group compared to the placebo group; moreover, the MIC50s significantly increased in PPX group (from 0.12 μg/mL before intervention to 0.19–0.38 μg/mL after 1–3 weeks), but significantly decreased in placebo group (from 0.12 μg/mL to 0.12–0.09 μg/mL; all $P < .01$).
Laoprasopwattana et al. [40]	ALL and lymphoma	Ciprofloxacin	Rectal swab cultures	In the first and second weeks after intervention, ciprofloxacin susceptibility was lower in PPX group compared with placebo group, in both *E. coli* (first week 5.1% vs 75.0%, second week, 2.9% vs 77.3%, all $P < .001$) and *K. pneumoniae* (first week 0% vs 65.5%; $P = .002$).
Davis et al. [33]	AML, rALL	Levofloxacin	Blood cultures	Incidence of bacteremia due to gram-negative rods nonsusceptible to levofloxacin increased during the PPX period (RR, 3.38; $P < .001$).
Yeh et al. [42]	ALL, AML	Ciprofloxacin + voriconazole or micafungin	Not specified	During the PPX period, a reduction was observed in the ciprofloxacin resistance of *E. coli* (from 21% to 19%), *K. pneumoniae* (from 17% to 10%), *P. aeruginosa* (from 33% to 28%), and *S. marcescens* (from 41% to 30%; all $P < .01$). Ciprofloxacin resistance of *A. baumannii, E. cloacae, P. mirabilis, Salmonella* spp. did not change.
Yeh et al. [37]	AML	Ciprofloxacin + voriconazole or micafungin	Not specified	During the PPX period, cefuroxime susceptibility of *E. coli* or *K. pneumonia* decreased ($P = .027$, $P = .01$, respectively); imipenem susceptibility of *E. cloacae* or *A. baumannii* decreased ($P = .009$, and $P = .002$, respectively). Amikacin susceptibility of *E. coli*, *K. pneumoniae*, *E. cloacae*, *P. aeruginosa*, *C. freundii* improved during the PPX period ($P = .042$, $P = .001$, $P = .007$, $P = .003$, $P = .001$, respectively). Ampicillin/sulbactam, linezolid, teicoplanin, and vancomycin resistance of *Enterococcus* spp. decreased during the PPX period ($P = .001$, $P = .027$, $P = .001$, $P = .001$, respectively). Values are presented as the median number of infection episodes from any site of the body per year.
Margolis et al. [32]	ALL	Levofloxacin	Fecal samples	Prevalence of topoisomerase point mutations increased from baseline to follow-up (completion of induction and completion of consolidation therapy) in the PPX group (10.4%; 95% CI, 3.2%–25.4%; after induction; vs 3.7%; 95% CI, 0.2–22.5; at baseline) but not in the no-PPX group (0% vs 0%; $P < .0001$). Acquisition of specific fluoroquinolone resistance genes was too infrequent for any effect of PPX to be detected; the estimated prevalence remained low, reaching a maximum of 10.4% after the completion of induction in participants who received LVX, and increasing to 15.1% after the 8-week consolidation phase of chemotherapy, when the fluoroquinolone pressure had been removed. A significant increase in the relative abundance of aminoglycoside and multidrug resistance genes was seen regardless of PPX. Vancomycin resistance genes and β-lactam resistance genes did not change significantly.
Lopes et al. [36]	Auto/allo-HSCT	Levofloxacin	Different samples	An increase in quinolone resistance during the PPX period compared with pre-PPX was observed for all bacteria isolated (46.0% vs 76.5%; $P = .0002$) and for gram-negatives (21.4% vs 60.7%; $P = .0163$) and gram-positives (55.6% vs 82.9%; $P = .0025$) separately. Considering the single species, that is, Enterobacteriaceae, *E. coli*, *P. aeruginosa*, and coagulase-negative staphylococci, the increase in resistance was not statistically significant.
Alexander et al. [41]	rALL, AML auto-HSCT, allo-HSCT	Levofloxacin	Fecal samples	In the AL setting, newly detected resistance to levofloxacin among *S. mitis*, *E. coli*, *K. pneumoniae*, and *P. aeruginosa* in follow-up specimens was 9.3% vs 8.9% in the PPX and placebo groups, respectively. Newly detected resistance to cefepime was 2.3% vs 8.9% and resistance to imipenem was 0% vs 6.7% in the PPX and placebo groups. In the HSCT setting, newly detected resistance to levofloxacin among the same species in follow-up specimens was 1.7% vs 0.8% in the

Table 5. Continued

Study	Patients	FLQ Prophylaxis	Sample	Antibiotic Resistance
				PPX and placebo groups, respectively. Newly detected resistance to cefepime was 2.5% vs 2.5% and resistance to imipenem was 0.9% vs 0% in the PPX and placebo groups. The overall proportion of newly detected resistance to any of the selected pathogens was low and not significantly different between the levofloxacin prophylaxis and control groups for patients with acute leukemia (5 of 43 vs 7 of 45; $P = .59$) or patients undergoing HSCT (4 of 118 vs 4 of 120; $P = .98$).

Abbreviations: ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; auto, autologous; allo, allogeneic; FLQ, fluoroquinolone; HSCT, hematopoietic stem cell transplantation; MIC, minimal inhibitory concentration; PPX, prophylaxis; rALL, relapsed ALL; RR, relative risk.

approach was determined to be cost-effective, considering that an episode of bacteremia added an average hospital cost of $119.478. The percentage of ICU admission and mortality reduction due to PPX was lower, resulting in lower cost-effectiveness of PPX regarding these outcomes. PPX also decreased ICU admission risk by 2.1% with a cost of $81 609 per ICU admission avoided compared with an average added hospital cost of $94 181 per ICU admission. Finally, PPX reduced mortality attributed to bacteremia risk by 0.7%, costing $220 457 per death avoided. A probabilistic and sensitivity analysis was also performed to evaluate model uncertainty, and PPX remained cost-effective in 94.6% of simulations [26]. Another study on AL evaluated the total costs of antibiotics and antifungal agents in patients receiving and not receiving PPX, comparing the preprophylaxis and prophylaxis periods. A significant reduction of antimicrobial costs during the PPX period was observed in both ALL and AML patients [43].

DISCUSSION

Antibiotic PPX represents an important approach to reducing bacterial infections and their consequences. Among these, quinolones have been widely used as prophylactic agents in pediatric patients, mainly due to the observed efficacy in adults [47]. Other prophylactic regimens have been proposed in the literature; however, quinolones have been more commonly used in current practice [9, 48]. Notably, the use of antibiotic PPX may be associated with several drawbacks, such as toxicity or emergence of antibiotic-resistant bacterial strains, and thus a balance between risks and benefits should be considered. However, this fine-tuning is difficult as data in the pediatric setting are scarce and heterogenous, and recommendation, therefore, relies on a low level of evidence [11].

To our knowledge, this is the first meta-analysis on the effectiveness of quinolone PPX in pediatric patients with AL or undergoing HSCT. Our data suggest that quinolone PPX is effective at reducing the number of BSIs in pediatric leukemia patients but does not seem to be as effective in the HSCT setting. Moreover, PPX seems to reduce the incidence of NF in the AL setting. However, these results should be interpreted specifically in the AL setting. AL studies are heterogeneous, comprising different pathologies—that is, ALL and AML—within which exist different classes of risk and corresponding chemotherapy protocols, as well as different phases of chemotherapy. Moreover, the newly diagnosed acute leukemia setting is different from the relapse or refractory setting. Most of the included studies analyzed the use of FLQ PPX during a period of intensive chemotherapy, expected to lead to prolonged neutropenia (Table 1). Due to the small number and heterogeneity between studies, it was not possible to carry out subgroup analysis in the AL setting. Unfortunately, the data regarding mortality are heterogeneous, and we could not include them in the quantitative synthesis. Thus, it is not possible to draw meaningful conclusions regarding the impact of quinolone PPX on mortality. This should be a major focus of future research to understand if the observed reduced incidence of infectious complications translates into improved survival for the patients.

The occurrence of side effects is a frequent concern in the pediatric population, also considering that antibacterial agents used for treatment and prophylaxis are often not licensed in children. Interestingly, the safety profile of LVX was confirmed in all the reported studies, showing no differences in drug-related adverse events in patients undergoing or not undergoing prophylaxis.

A reduction in the length of hospitalization and health care costs was reported in patients undergoing PPX [26, 28, 35, 43]. These results need to be confirmed in larger cohorts but are certainly of interest. First, prophylaxis can prevent febrile episodes, potentially leading to a reduced length of hospital stay, with a relevant positive effect on the quality of life of patients and caregivers. Moreover, shorter hospitalization can contribute to the potential cost-effectiveness of the prophylaxis approach.

Although studies reported variable results, an increase in fluoroquinolone resistance was generally reported in patients undergoing PPX [41]. Interestingly, this increase seems to be related to the acquisition of topoisomerase mutations known to confer resistance to fluoroquinolones [32]. Furthermore, the emergence of new antibiotic resistance in bacterial

Table 6. Summary of Side Effects Associated With Quinolone Prophylaxis

Study	Patients	FLQ Prophylaxis	Side Effects
Karol et al. [30]	ALL	Ciprofloxacin, levofloxacin	No significant correlation between fluoroquinolone exposure during the induction phase for ALL and vincristine-induced peripheral neurotoxicity (neuropathic pain, neuropathy, combined pain/neuropathy; hazard ratio, 0.8; 95% CI, 0.5–1.04; $P = 0.08$) and high-grade neuropathy (hazard ratio, 1.1; 95% CI, 0.4–2.2; $P = 0.87$). The lack of association was maintained adjusting for race and age and after restriction to early onset symptoms. Considering specific drug, no significant increase in neuropathy or neuropathic pain was shown when comparing levofloxacin with ciprofloxacin or no fluoroquinolone.
Laoprasopwattana et al. [40]	ALL and lymphoma	Ciprofloxacin	Similar numbers of patients in the ciprofloxacin (45) and placebo (50) groups developed minor side effects, including skin rash (2 vs 0), nausea/vomiting (12 vs 11), diarrhea (0 vs 1), abdominal pain (2 vs 5), and arthralgia/arthritis (1 vs 1; $P = .05$). Only 1 skin rash in a patient presented a definite association with the drug (subsequently discontinued), whereas all other adverse events were associated with chemotherapy or the underlying disease.
Felsenstein et al. [27]	AML	Ciprofloxacin	1/64 patients receiving prophylaxis developed an allergic skin rash attributed to ciprofloxacin with discontinuation. No musculoskeletal side effects in any patient who received prophylaxis.
Yousef et al. [28]	ALL	Ciprofloxacin	No musculoskeletal side effects were noted in the placebo group or PPX group.
Alexander et al. [1]	rALL, AML auto-HSCT, allo-HSCT	Levofloxacin	No significant differences in musculoskeletal side effects at 2 months (11.4% vs 16.3%; risk difference, 4.8%; 95% CI, −1.6% to 11.2%; $P = .15$) or 12 months (10.1% vs 14.4%; risk difference, 4.3%; 95% CI, −3.4% to 12.0%; $P = .28$) between the levofloxacin and control groups.
Gardner et al. [34]	Auto/allo-HSCT	Levofloxacin	No difference in terms of cardiac function evaluated by QTc prolongation at ECG. 17/216 patients (7.9%) in the no prophylaxis group had a prolonged QTc interval at baseline, compared with 15/227 patients (6.6%) in the prophylaxis group ($P = .46$). At follow-up ECG, a prolonged QTc interval was found in 21 patients in the no prophylaxis group and 16 in the prophylaxis group ($P = .20$).
Yeh et al. [58]	ALL, AML	Ciprofloxacin + voriconazole or micafungin	Hepatotoxiciy with elevated transaminase levels (related to micafungin and voriconazole)
Yeh et al. [37]	AML	Ciprofloxacin + voriconazole or micafungin	Hepatotoxiciy with elevated transaminase levels (related to micafungin and voriconazole)

Abbreviations: ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; auto, autologous; allo, allogeneic; ECG, electrocardiogram; FLQ, fluoroquinolone; HSCT, hematopoietic stem cell transplantation; IFI, invasive fungal infection; PPX, prophylaxis; rALL, relapsed ALL.

microflora was noted in some studies, reporting an increase in ceftazidime and cefuroxime resistance [29, 37]. This effect is particularly relevant for patients, potentially affecting the efficacy of fourth-grade cephalosporins as first-line antibiotic therapy in acute leukemia and HSCT settings [11]. The emergence of multidrug-resistant gram-negative bacteria has also been reported in adults undergoing quinolone prophylaxis, representing a major threat in neutropenic patients [8]. However, it must be considered that data on antibiotic susceptibility are highly dependent on local epidemiology, which may represent a bias in interpreting the results. Surveillance of bacterial resistance and colonization is mandatory to guide the appropriate clinical management of these patients.

Regarding *Clostridium difficile* infections or antibiotic exposure, some inconsistencies between the studies are reported, suggesting a nonsignificant role for quinolone PPX.

Gut microbiota modifications were studied by Margolis et al., focusing on resistome modifications after PPX and providing evidence that LVX can increase the risk of colonization with resistant bacteria. Nonetheless, considering that new important evidence reported a detrimental role of antibiotic-mediated dysbiosis [49–51], this should be addressed in future studies, with a particular focus on understanding the modifications associated with adverse effects such as antibiotic-associated diarrhea, risk of BSI with resistant bacteria, *Clostridium difficile* infections, and NF [52].

Finally, the occurrence of breakthrough infections has not been reported in the included studies, and specific analyses have not been systematically performed [39]. An increase in breakthrough infections with resistant organisms in patients receiving prophylaxis could represent a relevant concern for clinicians considering the poor outcomes of MDR infections [53, 54]. The possible emergence of potentially severe breakthrough infections in this category of patients certainly needs to be considered in future studies.

This meta-analysis presents several limitations. Patients receiving allo-HSCT were few and often mixed with autologous transplantation, and the AL population included in this study is heterogeneous. Infectious risk in these different categories is significantly different, depending on various factors. The incidence of bacterial infections is higher in patients with AML than ALL and is also higher in the induction therapy phase than in the consolidation phase [38, 39]. Moreover, this risk is significantly

Table 7. Summary of Fungal Infection Results of Studies Included in the Systematic Review

Study	Patients	FLQ Prophylaxis	Fungal Infections
Felsenstein et al. [27]	AML	Ciprofloxacin	Fungemia occurred more frequently in the PPX group (5 vs 0 episodes in the PPX and no PPX groups; $P = .01$). Fungi isolated from blood were *A. versicolor* (1), *C. krusei*, (2), *C. lipolytica* (1), *C. parapsilosis* (1). No difference in all proven, probable, and possible IFIs considered combined between the PPX and no PPX groups.
Yousef et al. [28]	ALL	Ciprofloxacin	Fungemia occurred only in the no PPX group (0 vs 3 episodes in the PPX and no PPX groups). All isolates were *Candida* spp.
Yeh et al. [58]	ALL, AML	Ciprofloxacin + voriconazole or micafungin	All episodes of IFI (fungi isolated body fluid culture or histology of infected tissue) occurred in the no PPX period (22 vs 0 episodes in the PPX and no PPX groups). *Candida* species were the leading pathogens (15/22 episodes, 68%), followed by *Aspergillus* species (6/22 episodes, 27%). 12 episodes occurred in patients with AML, due to *C. glabrata* (2), *C. albicans* (1), *C. tropicalis* (1), *Aspergillus* spp. (5), *Rhodotorula* spp. (1), other (2). 10 episodes occurred in patients with ALL, due to *C. albicans* (2), *C. tropicalis* (4), *C. parapsilosis* (1), *Aspergillus* spp. (1), other (2).
Yeh et al. [37]	AML	Ciprofloxacin + voriconazole or micafungin	All episodes of IFI occurred in the no PPX period (17 vs 0 episodes in the PPX and no PPX groups; $P = .003$), due to *Aspergillus* spp. (9*), *Candida* spp. (6*), other (2). *Two microorganisms were isolated concomitantly
Alexander et al. [41]	rALL, AML auto-HSCT, allo-HSCT	Levofloxacin	No differences in invasive fungal disease (9/306 [2.9%] vs 6/307 [2.0%] patients in the PPX and no PPX groups; risk difference, −1.0%; 95% CI, −3.4% to 1.5%; $P = .41$).
Gardner et al. [34]	Auto/allo-HSCT	Levofloxacin	No difference in fungal infection rate (1/227 [0.4%] vs 4/216 [2%] patients in the PPX and no PPX groups; risk difference; $P = .21$)

Abbreviations: ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; auto, autologous; allo, allogeneic; FLQ, fluoroquinolone; HSCT, hematopoietic stem cell transplantation; IFI, invasive fungal infection; PPX, prophylaxis; rALL, relapsed ALL.

higher in relapsed patients [9]. Among the meta-analyzed studies on AL patients, in all cases PPX was prescribed during a period of intensive chemotherapy, differently but quite consistently defined, namely, during induction for ALL [39, 40] or during regimens that are predicted to cause prolonged neutropenia [32, 33, 41, 42]. Moreover, 4 of 6 studies included patients with AML [33, 37, 41, 42] and 2 of 6 included patients with rALL [33, 41]. Future studies should focus on the benefit of PPX in these specific subpopulations to better define its clinical impact. Local epidemiology and resistance patterns change year by year. The results of LVX PPX in adult patients seem to change based on the time span considered [7, 8]. From the results of this meta-analysis, including patients from January 2005 [42] to February 2021 [33], temporal changes cannot be clearly seen because of the small number and different designs of the analyzed studies. Future evaluations could show temporal changes in PPX effectiveness and downsides. The effect of prophylaxis seems to be different in lower-income countries than in higher-income countries. Among the included studies, 3 [35, 36, 40] were performed in low- and middle-income countries according to the most recent World Bank and Organisation for Economic Co-operation and Development classification [55]. We performed a sensitivity analysis on this topic, and we found no effect of prophylaxis in reducing the incidence of BSI. Nevertheless, we observed that none of these papers reached statistical significance in the end points that we considered for the quantitative synthesis and that none of them was rated as high or good quality. It is therefore certainly an issue to be considered in future studies to generalize the present results for countries with lower income.

CONCLUSIONS

To our knowledge, this is the first meta-analysis on the effectiveness of quinolone PPX in pediatric patients with leukemia or undergoing HSCT. Our results seem to confirm the positive effect of quinolone PPX on reduction of the risk of infections during chemotherapy courses for ALs. No significant effect was reported in HSCT setting. The main limitation of our study is the impossibility of defining the effect of PPX on the different risk classes of AL and the phase of treatment. Further larger randomized studies will help better define its exact effectiveness and indications. Moreover, future studies on the impact of antibiotic PPX on the gut microbiota are highly awaited [56, 57].

Supplementary Data

Supplementary materials are available at *Open Forum Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

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Patient consent. This work does not include factors necessitating patient consent due to design of the study.

Ethical approval. The study was conducted in accordance with the Declaration of Helsinki. Ethical review and approval were waived for this study due to the design of the study.

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