Fluoroquinolones in Children With Fever and Neutropenia

A Systematic Review of Prospective Trials

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Background: There has been reluctance to use fluoroquinolones in children because of arthropathy in animal models; experience in pediatric fever and neutropenia (FN) has been limited. Our primary objective was to describe the effectiveness and safety of fluoroquinolones as empiric therapy for children with FN.

Methods: We conducted electronic searches of Ovid Medline, EMBASE, the Cochrane Central Register of Controlled Trials, and limited studies to prospective pediatric trials in which any type of fluoroquinolone was administered as empiric therapy for FN.

Results: Of the 7281 reviewed articles, 10 were included in the meta-analysis that encompassed 740 episodes of FN. All studies consisted of low-risk FN episodes. The risk of treatment failure was 17% among those given ciprofloxacin monotherapy (n = 5 studies), 17% among those given nonciprofloxacin fluoroquinolone monotherapy (n = 2 studies), and 24% among those given fluoroquinolone combination therapy (n = 3 studies; $P = 0.80$). There were no cases of infectious deaths reported. Rates of sepsis and adverse events were very low.

Conclusion: Experience with fluoroquinolones demonstrates excellent outcomes and short-term safety, although reported studies have been restricted to low-risk patients. Fluoroquinolones can be comfortably adopted for low-risk FN, although experience in high-risk FN is uncertain in pediatrics.

Key Words: children, fever, neutropenia, fluoroquinolones, systematic review

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Fluoroquinolones are important antibiotics, which have garnered much interest because of their broad antimicrobial spectrum, systemic bactericidal activity, good tolerability, bioavailability as an oral agent, and lack of myelosuppression.[1] The original fluoroquinolones had a primary spectrum of activity against gram-negative organisms, although more recently developed products also have activity against some gram-positive and atypical organisms. Fluoroquinolones are particularly useful antibiotics for empiric therapy for FN because their spectrum of activity includes *Pseudomonas aeruginosa*.

However, use of fluoroquinolones has been curtailed in pediatric settings because of the concern of fluoroquinolone-induced cartilage and joint toxicity.[2] The original studies that raised such concerns were conducted in juvenile canines; cartilage damage in weight-bearing joints was observed.[3] Consequently, labeling precautions were applied regarding the use of fluoroquinolones in children. Nevertheless, given the excellent activity profile of fluoroquinolones, there has been increasing use of fluoroquinolones in pediatrics, with resultant reassuring data about the low incidence of arthropathy and excellent general safety profile in children.[4,5]

Given the emerging comfort with fluoroquinolone use in children, we assumed that there would be a concomitant increase in use of this class of antibiotics for empiric therapy for pediatric FN. However, there has not been a systematic description of the effectiveness and safety of fluoroquinolones in pediatric FN. To provide more data for evidence-based recommendations, we sought to synthesize all existing prospective trials focused on fluoroquinolone use in empiric pediatric FN management. Consequently, our objective was to describe the effectiveness and safety of fluoroquinolones as empiric therapy in pediatric FN.

MATERIALS AND METHODS

Data Sources and Searches

Using the Strengthening the Reporting of Observational Studies in Epidemiology guidelines for reporting observational studies,[6] we developed a protocol for this systematic review. We conducted electronic searches of OVID Medline (1980 to March 7, 2011), EMBASE (1980 to March 7, 2011), and the Cochrane Central Register of Controlled Trials (until the first quarter of 2011). Appendix, Supplemental Digital Content 1, http://links.lww.com/INF/B59, illustrates the search strategy that included the Medical Subject Headings and text words "fever" and "neutropenia." The search was limited to studies conducted after 1980 and those published in the English language.

Study Selection

We defined eligibility criteria a priori. Inclusion criteria were: (1) the study examined any infection outcome of a homogeneous initial empiric regimen, (2) the population consisted of children, or results were abstractable for the pediatric subgroup (age defined by each study but in general <18 years), and (3) the study was conducted prospectively (to avoid bias associated with retrospective studies). The exclusion criteria were as follows: (1) conference proceeding only, (2) not published in English language, (3) not a study (for example, a commentary or a review), (4) retrospective,

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(5) population did not consist of children or data not abstractable for children, (6) cohort did not consist of patients with initial presentation of FN (ie, enrolled ≥24 hours after initial empiric treatment), (7) antibiotic treatment not for initial empiric therapy, (8) heterogeneous empiric therapy regimens, (9) pharmacokinetic study, (10) no infection outcomes reported, and (11) duplicate publication. Among this set of studies, those that described any fluoroquinolone use, either as monotherapy or in combination, were then selected.

One reviewer (L.S.) evaluated the titles and abstracts of publications identified by the search strategy, and any publication that could be potentially relevant was retrieved in full. Two independent reviewers (L.S. and A.M.) assessed full publications for eligibility; reviewers were not blinded to study authors or outcomes. Final inclusion of studies into the meta-analysis was by agreement of both reviewers. Agreement between reviewers was evaluated using the kappa statistic. Strength of agreement as evaluated by the kappa statistic was defined as slight (0.00–0.20), fair (0.21–0.40), moderate (0.41–0.60), substantial (0.61–0.80), or almost perfect (0.81–1.00).[7]

Data Extraction and Quality Assessment

Two reviewers (L.S. and A.M.) extracted data from included trials using a standardized data collection form. Antibiotic regimens were fully described; fluoroquinolone strategies were classified as ciprofloxacin monotherapy, other fluoroquinolone monotherapy, and fluoroquinolone combination therapy. Many studies administered a single dose of 1 or 2 nonquinolone antibiotics and then initiated fluoroquinolones. For the purpose of this classification, the single antibiotic dose preceding fluoroquinolone administration was ignored. For example, if a regimen administered 1 dose of ceftazidime and then continued treatment with ciprofloxacin, then this regimen was classified as ciprofloxacin monotherapy even though another antibiotic was given once.

The primary outcome measure was treatment failure at 30 days when antibiotic modification was included as a criterion for failure. Even though the trials used heterogeneous definitions of treatment failure, most definitions included persistence, recurrence or worsening of fever/infecting organisms, new infections, any modification of antibiotics, readmission, or death during study drug treatment. Secondary outcome measures were as follows: 30-day overall mortality and infection-related mortality, treatment failure when antibiotic modification was excluded in the failure definition, fever duration, recurrent infection (reappearance of infection or fever after initial resolution), sepsis, secondary infection (occurrence of new infection during treatment), adverse events leading to antibiotic discontinuation, and readmission to hospital. In particular, musculoskeletal adverse events were recorded when available.

Study quality was assessed using a modified version of an instrument previously developed to describe quality in studies of prognosis,[8] as pragmatic effectiveness rather than comparative efficacy was being assessed. This quality assessment instrument examines 4 potential sources of bias: study participation, study attrition, confounding variables, and measurement of outcomes. Each element was rated as having low, medium, or high risk of bias for each study.

Data Synthesis and Analysis

This meta-analysis combined data at the study level and not at the individual patient level. All descriptive outcomes were presented as percentages, with the exception of duration of fever, which was described using the mean. For fever duration, we made the following assumptions to facilitate data synthesis: the mean can be approximated by the median and the range contains 6 standard deviations. Given the anticipation of heterogeneity between studies, a random effects model[9] was used for all analyses. Because these outcomes were single percentages and not within-study comparisons, we did not test for publication bias because publication bias is not relevant in this context.

There were 6 randomized controlled trials that compared oral or step-down antibiotics with a fluoroquinolone versus intravenous or step-down antibiotics with a nonfluoroquinolone.[10–15] We compared the risk of treatment failure between the 2 groups, and the difference between the 2 groups was expressed as a rate ratio; a ratio less than 1 favored fluoroquinolone therapy. All effects were weighted by the inverse variance.

The meta-analysis was performed using Review Manager (RevMan) (Version 5.1.0; The Cochrane Collaboration, Oxford, England). Agreement was calculated using the SAS statistical program (SAS-PC, version 9.1; SAS Institute Inc., Cary, NC). Statistical significance comparing subgroups was only calculated if there were at least 2 studies in at least 2 subgroups; significance was defined as $P < 0.05$.

RESULTS

Figure, Supplemental Digital Content 2, http://links.lww.com/INF/B57, illustrates the flow diagram of trial identification and selection. A total of 7281 titles and abstracts were reviewed, and 380 full articles were retrieved. Of these, 66 articles satisfied predefined inclusion criteria. Reasons for excluding 314 articles are provided in Figure, Supplemental Digital Content 2, http://links.lww.com/INF/B57. The reviewers had almost perfect agreement on articles for inclusion ($\kappa = 0.98$; 95% CI: 0.96–1.00).

Of the 66 studies,10 included a fluoroquinolone and were thus included in this analysis.[10–19] These studies encompassed 740 FN episodes. Of these 10 studies, 5 consisted of ciprofloxacin monotherapy[12–16] (although only 1 of these administered only ciprofloxacin and did not administer 1 dose of another nonquinolone antibiotic before starting ciprofloxacin[19]), 2 consisted of other fluoroquinolone monotherapy (ofloxacin and gatifloxacin),[17,18] and 3 consisted of combination fluoroquinolones.[10] For these 10 studies, the number of studies that demonstrated low risk of bias was as follows: 9 for study participation, 8 for study attrition, 1 for confounding, and 5 for measurement of outcomes.

Clinical characteristics of these 10 studies are presented in Table 1. Six studies were randomized controlled trials, and 4 were prospective nonrandomized studies. All these studies consisted of low-risk (for poor FN outcomes) patients only. However, the specific definition of low risk varied between studies. Eight studies administered fluoroquinolones either as initial outpatient or as step-down outpatient therapy.

Table, Supplemental Digital Content 3, http://links.lww.com/INF/B58, demonstrates treatment outcomes subdivided by ciprofloxacin monotherapy, other fluoroquinolone monotherapy, or combination fluoroquinolone therapy. The risk of treatment failure when modification of antimicrobials was included as a criterion for failure was less than 25% in all groups. Figure 1 illustrates the Forest plot for treatment failure; no significant difference was seen between fluoroquinolone subgroups ($P = 0.80$). Table, Supplemental Digital Content 3, http://links.lww.com/INF/B58, also illustrates that most failure is due to modification of antibiotics because the risk of treatment failure when modification is excluded from the definition of failure was about 5% to 7%. No cases of mortality and more specifically infection-related mortality were reported. The rate of adverse events leading to antibiotic discontinuation was extremely low, although this figure was only based on 3 studies. Two of the 740 patients were reported to have arthralgias but arthritis, serious arthropathy, or tendinopathy were not reported. However, only 2 studies explicitly described a follow-up period for arthropathies

TABLE 1. Characteristics of Prospective Studies of Initial Empiric Regimens that Included a Fluoroquinolone for Pediatric Fever and Neutropenia

Author	Year	RCT	Setting	Route	FN risk group	Drug(s)	FN episodes	Mean or Median* Age in Years	FUO (%)	L&L† (%)	ANC < 100‡ (%)
Ciprofloxacin Monotherapy											
Aquino[16]	2000	N	sdOut	sdPO	Low	Ceftazidime then Ciprofloxacin	45	6.5	87	69	40
Mullen[12]	1999	Y	Out	sdPO	Low	Ceftazidime then Ciprofloxacin	40	9.8	82	NR	65
Paganini[14]	2001	Y	sdOut	sdPO	Low	Ceftriaxone, Amikacin then Ciprofloxacin	48	5*	31	42	23
Paganini[13]	2003	Y	Out	sdPO	Low	Ceftriaxone, Amikacin then Ciprofloxacin	88	8.2*	25	56	50
Petrilli[15]	2000	Y	Out	PO	Low	Ciprofloxacin	68	10.3*	41	6	NR
Other Fluoroquinolone Monotherapy											
Malik[17]	1997	N	Out	PO	Low	Ofloxacin	91	9.2	84	48	27
Petrilli[18]	2007	N	Out	PO	Low	Gatifloxacin	201	10.8	51	15	NR
Combination Fluoroquinolone											
Cagol[10]	2009	Y	In	PO	Low	Ciprofloxacin, Amoxicillin-clavulanate	43	7.9	88	9	NR
Gupta[11]	2009	Y	Out	PO	Low	Ofloxacin, Amoxicillin-clavulanate	62	8.3*	27	31	21
Shrestha[19]	2009	N	In	PO	Low	Ofloxacin, Amoxicillin-clavulanate	54	7.2	83	74	0

FUO indicates fever of unknown origin; L&L, leukemia and lymphoma; ANC, absolute neutrophil count; NR, not reported; RCT, randomized controlled trial; FN, fever and neutropenia; In, inpatient; Out, outpatient; sdOut, step-down outpatient; PO, oral therapy; sdPO, step-down oral therapy. Step-down therapy refers to treatments which begin as an inpatient or with intravenous therapy and then transition to outpatient or oral therapy respectively.

*Denotes that the number listed is the median value. Absence of * denotes that this value is the mean.

†Percentage of patients with leukemia or lymphoma.

‡Percentage of patients with absolute neutrophil count < 100 per microliter at presentation.

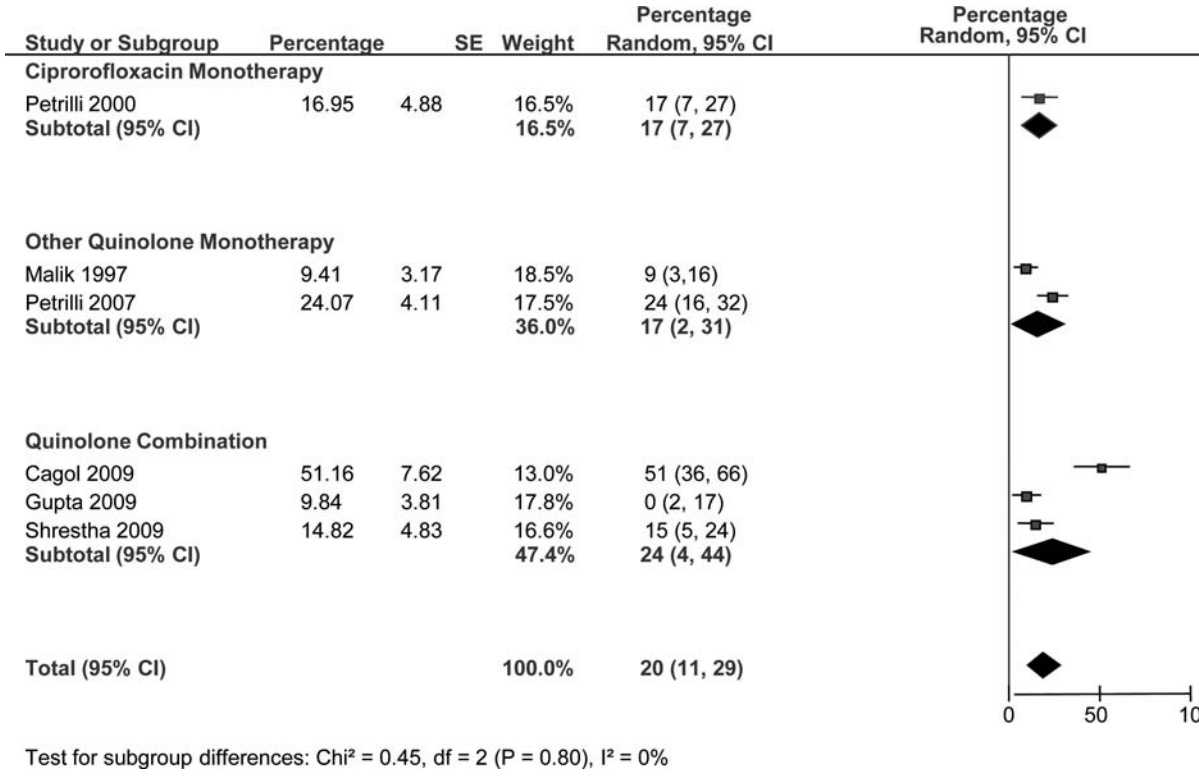

FIGURE 1. Forest plot of treatment failure including antibiotic modification by fluoroquinolone treatment group. Squares indicate percentages with horizontal lines representing 95% CIs. Diamonds represent overall percentages from the meta-analysis with corresponding 95% CIs.

which exceeded the observation period for FN outcomes. These follow-up periods were 3 and 6 months, and monitoring was conducted using surveillance knee radiographs.[15,18] No differences in secondary outcomes were seen between the 3 subgroups (data not shown).

We also compared fluoroquinolone versus nonfluoroquinolone antibiotics among the 6 randomized controlled trials. We found no difference in treatment failure when antibiotic modification was included as a criterion for failure (rate ratio: 1.02, 95% CI: 0.72–1.45; $P = 0.92$) and when modification was excluded as a criterion for failure (rate ratio: 1.79, 95% CI: 0.72–4.42; $P = 0.21$).

DISCUSSION

We have shown that there is a moderate amount of published literature describing fluoroquinolones for empiric therapy for FN in children, and among the 10 studies, treatment outcomes are excellent with high rates of success and no cases of mortality among the 740 patients examined. Our results are strengthened by the analysis of randomized trials that showed similar rates of treatment failure among fluoroquinolone and nonfluoroquinolone antibiotics. However, it should be emphasized that to date, all published studies have been in the low-risk population, in whom only a small proportion of patients would be expected to have occult serious bacterial infections. These results suggest that fluoroquinolones can be confidently used in low-risk children with FN as long as the local antimicrobial resistance patterns support their use.

To better understand how to interpret the rates of treatment failure among children who received fluoroquinolones as empiric therapy, it would be useful to evaluate these rates among children who received other antibiotics in similar studies of pediatric FN. Among children with FN who received empiric treatment with antipseudomonal penicillin monotherapy, carbapenem monotherapy, and antipseudomonal cephalosporin monotherapy regimens, the rates of treatment failure when modification was included as a criterion for failure were 34% (95% CI: 27%–41%), 35% (95% CI: 24%–45%), and 41% (95% CI: 36%–46%), respectively.[20,21] Consequently, the results of fluoroquinolone empiric therapy compare favorably to these regimens.

Our study also has shown some marked limitations of the literature. First, fluoroquinolones have not been described when used as empiric therapy in high-risk children with FN. This issue might be particularly problematic if high-risk patients are receiving fluoroquinolone prophylaxis or in settings where prophylaxis is routinely given to other patients. Second, there is no published experience with levofloxacin in pediatric FN even though this agent is particularly attractive given its broad spectrum of activity, availability of pediatric dosing guidelines, and in some jurisdictions, availability of an oral liquid levofloxacin formulation. Third, although the FN guidelines from the Infectious Disease Society of America[22] specifies ciprofloxacin and amoxillin-clavulinic acid as an appropriate combination for low-risk FN management in adults, there is very little published data with regard to use of this combination in children. Notably, all combination studies of a fluoroquinolone and amoxicillin-clavulinic acid that report data specifically in children originated from low-income countries, although there was a combined adult and pediatric study originating from the United States, in which pediatric data were not abstractable.[23] Consequently, we do not know whether the number of daily antibiotic administrations for ciprofloxacin and amoxicillin-clavulinic acid (ie, 5 administrations per day) is a problem in young children. Fourth, there is no published experience with parenteral fluoroquinolones in children with FN. Finally, there are only 2 studies that have explicitly monitored for late arthropathies in children receiving fluoroquinolones for FN; thus, future research is warranted.

In considering the use of fluoroquinolone antibiotics, it is important to consider the potential impact of its use on resistant microorganisms. Studies have suggested that fluoroquinolone use may be associated with an increased risk of multidrug-resistant organisms and increased resistance to fluoroquinolones specifically.[24–26]

One limitation of our meta-analysis was the variability in definition of our primary outcome, treatment failure, across all studies. This composite endpoint encompassed multiple outcomes in most of the evaluated studies, resulting in significant heterogeneity. Optimally, we would have examined the components of treatment failure separately and indeed, we did do that where possible. Unfortunately, studies did not describe components of treatment failure consistently. Second, we restricted our review to studies published in the English language. A previous review found that restriction of systematic reviews to English, when compared with the inclusion of other languages, does not bias results,[27] although it may lead to increased sparseness of information. Third, many studies administered a single dose of another antibiotic and then initiated fluoroquinolone treatment. It is possible that the single dose of antibiotic that preceded the quinolone was in fact sufficient to treat these low-risk children, and thus, the true efficacy of the fluoroquinolone monotherapy is not reflected by these studies. Finally, we restricted this review to the use of fluoroquinolones as initial empiric therapy for pediatric FN. Consequently, our analysis did not address the use of fluoroquinolones as prophylaxis, modification of empiric FN therapy, or definitive treatment of infection in children with cancer.

Another limitation of our review is that, in general, these studies have only collected short-term toxicities; long-term toxicities such as arthritis may not be well captured. In another report, arthralgia based on parental report may in fact be higher in children treated with levofloxacin compared with nonfluoroquinolone antibiotics, although recall bias is a problem with this report.[4]

In summary, fluoroquinolones as empiric therapy for pediatric FN appear to be efficacious and safe at least in terms of short-term toxicities, although all published studies to date have included only low-risk patients. Further research should focus on describing the outcomes of other commonly available fluoroquinolone antibiotics, such as levofloxacin, and describing comparative efficacy and safety of fluoroquinolones and combination approaches in high-risk pediatric FN.

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