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Impact of ciprofloxacin prophylaxis on blood stream infection during early treatment phase of pediatric acute lymphoblastic leukemia: An observational cohort study

Fenna Scharloo [a], Tom F.W. Wolfs [b], Tjomme van der Bruggen [c], Inge M. van der Sluis [d], Wim J.E. Tissing [d,e], Angelica M.M. de Vrankrijker [b,*]

[a] Faculty of Medicine, University Medical Center Utrecht, Utrecht, the Netherlands
[b] Department of Pediatric Infectious Diseases and Immunology, Wilhelmina Children's Hospital, University Medical Center Utrecht, Utrecht, the Netherlands
[c] Department of Medical Microbiology, University Medical Center Utrecht, Utrecht, the Netherlands
[d] Princess Máxima Center for Pediatric Oncology, Utrecht, the Netherlands
[e] Department of Pediatric Oncology, University of Groningen, University Medical Center Groningen, Groningen, the Netherlands

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ABSTRACT

Purpose: Data on the efficacy of antibiotic prophylaxis in children with acute lymphoblastic leukemia (ALL) is scarce and recent guidelines advise against its use. This study is conducted to evaluate if the use of ciprofloxacin prophylaxis is associated with a decrease in blood stream infection (BSI) incidence in children with newly diagnosed ALL.

Methods: This was a retrospective, observational cohort study. Patients were newly diagnosed with ALL between 2020 and 2021 (prophylaxis group) or 2021–2022 (no prophylaxis group). Primary outcome was occurrence of BSI caused by Gram-negative pathogens or *Staphylococcus aureus* during induction or consolidation I. Secondary outcomes were Pediatric Intensive Care Unit (PICU) admission, mortality, ciprofloxacin resistance and *Clostridioides difficile*-associated diarrhea (CDAD).

Results: Two hundred patients were included (prophylaxis group n=94, no prophylaxis group n=106). Ciprofloxacin prophylaxis was associated with significantly lower BSI-incidence (HR 0.37; 95 % CI 0.15–0.94) There was no significant difference for BSI-related PICU admission (OR 0.37; 95 % CI 0.04–3.61), BSI-related mortality (1.1 % vs 0 %), all-cause mortality (OR 0.55; 95 % CI 0.10–3.10), and short-term resistance rates (16.0 % vs 13.0, OR 1.2; 95 % CI, 0.57–2.74) or CDAD (0 % vs 0.9 %) between the prophylaxis group and no prophylaxis group.

Conclusion: The use of ciprofloxacin prophylaxis was associated with a significantly lower incidence of BSI. While this finding shows the beneficial effect of ciprofloxacin prophylaxis in the first treatment phase of ALL, RCTs with a large sample size are needed, particularly to assess the effect on ciprofloxacin resistance.

1. Introduction

Bloodstream infections (BSI) are an important cause of treatment-related morbidity and mortality in children with acute lymphoblastic leukemia (ALL) [1,2]. The high rate of BSI in this group is related to the effects of intensive chemotherapy, including prolonged neutropenia and mucositis, and the necessity of central venous catheters [3]. An approach to managing these infections is to administer antibiotic prophylaxis. Fluoroquinolone prophylaxis in patients receiving chemotherapy or undergoing hematopoietic stem cell transplantation reduces BSI and infection-related mortality, in studies in predominantly adult patients [4]. Nevertheless, prophylaxis is also associated with antimicrobial resistance and *Clostridioides difficile* associated diarrhea (CDAD) [5]. For the ALL population, few studies are conducted and high level evidence is scarce [6]. Recent guidelines advised against administration of antibiotic prophylaxis in pediatric ALL patients, citing lack of robust supporting data and concern about antibiotic resistance [5,7]. Accordingly, the standard use of ciprofloxacin prophylaxis in all Dutch pediatric ALL patients was discontinued from July 2021. We aimed to evaluate the occurrence of BSI during the first treatment phases of ALL and, to some extent, the possible harms of ciprofloxacin, before and after this policy change.

* Correspondence to: Wilhelmina Children's Hospital, Lundlaan 6, Utrecht 3584 EA, the Netherlands.
E-mail address: a.m.m.devrankrijker@umcutrecht.nl (A.M.M. de Vrankrijker).

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2. Methods

This was a retrospective, observational cohort study at the Princess Maxima Center for pediatric oncology, which provides care for all pediatric cancer patients in the Netherlands and diagnoses approximately 110 new ALL patients every year.

2.1. Patients

Patients aged <21 years, newly diagnosed with ALL between 1 July 2020 and 30 June 2022 and treated according to the ALLtogether1 protocol [8] were included after informed consent. No exclusion criteria applied. The biobank and data access committee gave permission for use and analysis of the data for publication.

Two patient groups were compared: the prophylaxis group included patients diagnosed between 1 July 2020 and 30 June 2021 who received antibiotic prophylaxis during induction (day 1-day 29) and consolidation 1 (day 30-day 71). Ciprofloxacin prophylaxis was prescribed irrespective of bacterial colonization data (dosing regimen 15 mg/kg/dose BID PO, with a maximum of 1000 mg per day). Patients remained in the study in case of (temporary) discontinuation of ciprofloxacin use, to best reflect clinical practice.

The no prophylaxis group included patients diagnosed between 1 July 2021 and 30 June 2022 who did not receive ciprofloxacin prophylaxis (due to the policy change).

2.2. Data collection

Patient data and microbiological results were collected retrospectively using the electronic medical record and microbiology database. Per patient, age, sex, Down syndrome, immunophenotype, NCI risk group and induction therapy were registered. For each patient with a BSI, causative pathogen and resistance pattern, day of occurrence, symptoms and outcome were noted. Only BSIs caused by Gram-negative bacteria or *Staphylococcus aureus* were included as these are highly virulent pathogens and mostly ciprofloxacin susceptible [9].

Surveillance stool culture data (Gram-negative bacilli and *S. aureus*) was gathered to assess the emergence of resistance to ciprofloxacin. Therefore, the prevalence of ciprofloxacin resistant pathogens in stool cultures during the first 14 days and during the whole follow-up period (71 days) was determined.

Additionally, data about the incidence of CDAD was obtained. CDAD was only tested upon clinical suspicion and was performed using the Xpert *C. difficile* assay (Cepheid) on feces.

2.3. Standard of care

All patients were treated according to the ALLTogether1 protocol. For induction therapy, patients received 3 or 4 drug induction with dexamethasone, vincristine, Pegasparaginase, with or without daunorubin for high and low risk patients respectively. For detailed information regarding therapy, see supplemental Figures S1-S2. During the two-year study period, some changes were made in the ALLtogether1 protocol to lower toxicity, starting March 2021 (Figure S2). Regarding induction, the dexamethasone dose of 6 mg/m2/day was capped at 10 mg/day. Additionally, the administration of daunorubicin to Down patients in case of poor response on day 15 was discontinued. In consolidation 1, changes entailed not using Pegasparaginase during consolidation 1 and postponing the second cyclophosphamide to the end of consolidation 1. In addition, more strict starting criteria were added for every cytarabine course. Supportive care guidelines did not change. Empirical therapy consisted of ceftazidime intravenously. In case of known colonization with third generation cephalosporin resistant (e.g. extended spectrum beta-lactamase or AmpC beta-lactamase positive) microorganisms, meropenem was used as empirical therapy.

Blood cultures were performed in case of fever. In the event of a negative blood culture but persistent fever (>72 hours), new blood cultures were performed.

2.4. Definitions

Fever was defined as two measurements of body temperature of >38 °C or one of 38.5 °C. Bloodstream infection was defined as a positive blood culture with clinical signs of infection corresponding with the cultured microorganism. If the same microorganism was cultured in blood multiple times <7 days apart it was considered as the same BSI. BSI-related mortality was defined as death following BSI in the absence of other likely causes of death.

2.5. Outcomes

The primary outcome of this study was the incidence of BSI caused by Gram-negative bacteria or *S. aureus*. Secondary outcomes were incidence of BSI-related pediatric intensive care unit (PICU) admission, all-cause mortality, and BSI-related mortality.

Additionally, other secondary outcomes were incidence of ciprofloxacin resistant pathogens in stool cultures and incidence of CDAD.

Follow-up was 71 days, comprising the ALL treatment phases induction and consolidation 1.

2.6. Statistical analysis

Continuous and ordinal outcomes were compared between groups using the non-parametric Mann-Whitney U test, Pearson's Chi Square was used for categorical variables. Fisher's exact test was used to compare proportions. Logistic regression was performed to assess association between ciprofloxacin use and clinical outcomes. Cox proportional hazards model was used to compare cause specific hazards for BSI and ciprofloxacin use. An additional analysis was performed in which we adjusted for age, sex, immunophenotype of ALL, induction treatment and Down syndrome. All analyses were done using IBM SPSS version 29.

3. Results

A total of 200 patients (prophylaxis group n=94, no prophylaxis group n=106) were newly diagnosed with ALL and treated according to the ALLTogether1 during the study period, all patients were included in the study. There were no significant differences in baseline characteristics between both groups (Table 1).

Table 1
Baseline characteristics.

No (%) of patients			
	Ciprofloxacin prophylaxis (n=94)	No antibacterial prophylaxis (n=106)	*P*
Age at ALL diagnosis, median [IQR]	5.0 [3.0–12.0]	6.0 [4.0–12.0]	0.33¥
Male sex	46 (48.9)	56 (52.8)	0.58§
Down syndrome	3 (3.2)	6 (5.7)	0.51*
Immunophenotype			0.60§
T-ALL	12 (12.8)	11 (10.4)	
B-cell precursor ALL	82 (87.2)	95 (89.6)	
NCI risk group[a]			0.86§
NCI SR	46 (58.2)	53 (59.6)	
NCI HR	33 (41.8)	36 (40.4)	
Induction treatment[b]			0.62§
3 drug	49 (52.1)	59 (55.7)	
4 drug	45 (47.9)	47 (44.3)	

¥Mann-Whitney U test *Fisher's exact test §Pearson Chi Square.
[a]NCI: National Cancer Institute. The NCI risk group is only applicable to non-Down B-cell precursor ALL. NCI SR: NCI standard risk. NCI HR: NCI high risk.
[b]3 drug induction: dexamethasone, Pegasparaginase and Vincristine. 4 drug induction: 3 drug induction plus daunorubicin.

During the study period, 23 patients had a BSI caused by Gram-negative bacteria or *S. aureus*; 6 patients in the prophylaxis group (6.4 %) and 17 patients in the no prophylaxis group (16.0 %) (Table 2). Ciprofloxacin prophylaxis was associated with a significantly lower BSI-incidence (OR 0.36; 95 % CI 0.13–0.95, *p* 0.03).

Blood culture isolates in the prophylaxis group were Gram-negative strains (3) (*Escherichia coli, Klebsiella pneumoniae, Enterobacter cloacae complex*), *S. aureus* (2) and polymicrobial (*E. coli* and *K. pneumonia*) (1)). In the no prophylaxis group, isolated pathogens were Gram-negative strains (11) (*E. coli* (4), *Pseudomonas aeruginosa* (3), *K. pneumoniae* (1), *E. cloacae complex* (1), *Acinetobacter baumannii* (1), *Hafnia alvei* (1)), *S. aureus* (4) or polymicrobial (*E. coli* and *S. aureus* (2)). BSIs in the no prophylaxis group were mostly caused by ciprofloxacin susceptible pathogens (89.5 % (17/19)), whereas in the ciprofloxacin prophylaxis group, only 28.6 % (2/7) were susceptible.

All patients were admitted to the hospital. The accompanying symptoms included fever only (65.2 % (15/23)), sepsis (17.4 % (4/23)), septic shock (8.7 % (2/23)), endocarditis (4.3 % (1/23)) and myositis (4.3 % (1/23)). There was no significant association between prophylaxis use and PICU-admission (OR 0.37; 95 % CI 0.04–3.61 *p* 0.39), or all-cause mortality (OR 0.55; 95 % CI 0.10–3.10, *p* 0.67). One patient died due to BSI (prophylaxis group (1.1 %)). This patient, a two-year-old girl with B-cell precursor ALL, that received ciprofloxacin prophylaxis, had a BSI with *E. cloacae complex* (AmpC producer, ciprofloxacin resistant). The patient was colonized with a ciprofloxacin resistant *E. cloacae complex*. The patients' death was due to multiple organ failure caused by severe sepsis and hemophagocytic lymphohistiocytosis. In this patient, due to known colonization with an AmpC producer, the empiric antibiotic regimen for neutropenic fever was adjusted to meropenem (instead of ceftazidime). Ciprofloxacin resistance was not associated with carbapenem resistance.

A time-to-event analysis showed a hazard ratio for occurrence of BSI of 0.37 (95 % CI 0.15–0.94, *p* 0.04) for patients on ciprofloxacin prophylaxis. Adjusting for age, ALL phenotype, induction treatment, Down syndrome or sex did not significantly change the model (Fig. 1).

At treatment start, stool surveillance cultures showed no difference in number of patients colonized with ciprofloxacin resistant bacteria in the prophylaxis group compared to the no prophylaxis group: 5.3 % (5/94) vs. 4.7 % (5/106), OR 1.14; 95 % CI 0.32–4.05) *p* 1.00. Ten weeks after treatment start, there was an increase in patients colonized with a ciprofloxacin resistant bacteria, similar for the prophylaxis group and the no prophylaxis group: 16.0 % (15/94) vs. 13.2 % (14/106), OR 1.21; 95 % CI 0.57–2.74: *p* 0.58.

CDAD was tested in 5.3 % (5/94) (prophylaxis group) and 7.5 % (8/106) (no prophylaxis group). None of the five tested patients in the prophylaxis group was positive for *C. difficile* whereas one of eight tested patients in the no prophylaxis was positive.

Table 2
BSI characteristics.

No (%) of patients			
	Ciprofloxacin prophylaxis (n=94)	No antibacterial prophylaxis (n=106)	*P*
BSI-no. of patients (%)	6 (6.4)	17 (16.0)	0.02[§]
time to BSI-median no. of days [IQR]	46.0 [22.5–70.3]	14.0 [9.0–33.5]	0.03[#]
Total number of isolates (Gram-negative bacilli or *S. aureus*) from BSI episodes	7	19	
S. aureus	2	6	
Gram-negative bacteria	5	13	
No. of ciprofloxacin susceptible isolates from BSI episodes (% of all isolates)	2/7 (28.6)	17/19 (89.5)	0.006*
S. aureus	2/2 (100.0)	6/6 (100.0)	
Gram-negative bacilli	0/5 (0.0)	11/13 (84.6)	
PICU admission due to BSI	1 (1.1)	3 (2.8)	0.62*
BSI mortality	1 (1.1)	0 (0.0)	n/a
All-cause mortality	2 (2.1)	4 (3.8)	0.67*

Three BSIs were polymicrobial, one BSI was caused by two Gram-negative bacteria (prophylaxis group), two BSIs were caused by a combination of *S. aureus* and Gram-negative bacteria. None of the patients had multiple BSIs.
[§]Pearson Chi-Square test [#]Mann-Whitney U test *Fisher's exact test.

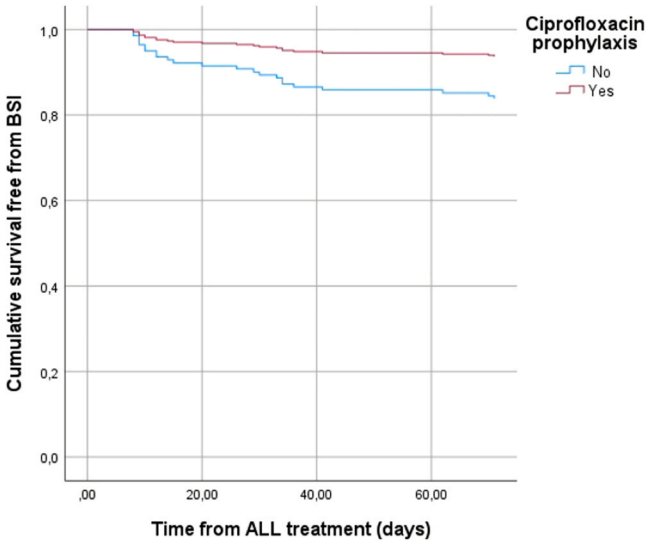

Fig. 1. Cox proportional hazards analysis for time to bacteremia during the first 71 days of treatment. Patients receiving ciprofloxacin prophylaxis had a lower risk of BSI with Gram-negative bacilli or *S. aureus* (hazard ratio 0.37; 95 % CI 0.15–0.94, *p* 0.04).

4. Discussion

In this study of 200 pediatric ALL patients, receiving ciprofloxacin during the induction and consolidation I phases was associated with a significantly lower BSI-incidence with Gram-negative bacteria or *S. aureus*, as compared to patients without prophylaxis.

The data observed in our study are in accordance with those from studies in adults [4], and a recent meta-analysis on quinolone prophylaxis in pediatric acute leukemia, including both AML and ALL [10]. The latter showed that the use of quinolone prophylaxis in acute leukemia significantly reduced the incidence of BSI (OR 0.31 (95 % CI, 0.22–0.43, p <0.001), based on data from 919 patients.

However, there are few studies conducted specifically in newly onset ALL patients using fluoroquinolones prophylaxis. To our knowledge, two pediatric RCTs are available; Widjajanto et al., which showed a trend towards a higher incidence of sepsis and toxicity death rate in the ciprofloxacin group. Of note, the ciprofloxacin group had a lower nadir white blood cell count, and the overall death rate during induction was 13 % [11]. The second RCT, by Laoprasopwattana et al., did not demonstrate a lower risk of BSI for ciprofloxacin prophylaxis users [12]. Consequently, these trials do not support the use of ciprofloxacin prophylaxis. However, these trials are conducted in Thailand and Indonesia, limiting generalizability to a high-resource setting, lower toxicity death rate and lower background rates of ciprofloxacin resistance. For comparison, in the Netherlands, 13 % of *E. coli* isolates demonstrate fluoroquinolone resistance while in Thailand and Indonesia, isolated E. coli are fluoroquinolone resistant in 50 % and 70 %, respectively [13,14].

Other available studies concern a cohort study by Wolf et al., including 344 patients, which showed a significantly lower incidence of BSI in the group receiving levofloxacin, compared to no prophylaxis, and a retrospective study by Yeh et al. [15,16]. The latter showed a lower BSI-incidence per chemotherapy course for patients receiving

ciprofloxacin compared to no prophylaxis, but also simultaneously introduced antifungal prophylaxis.

Like most previous studies, we did not find a difference in mortality. While this could mean that there is no effect of fluoroquinolone prophylaxis on mortality, this could also be due to the limited sample-size and low baseline risk of BSI-mortality. The fact that present studies are not powered to answer this question is difficult, since the guideline considers this as the most important endpoint [7].

In our study, one patient died due to BSI, caused *by E. cloacae complex*. This patient was on ciprofloxacin prophylaxis, while being colonized with a ciprofloxacin resistant, *E. cloacae complex (AmpC producer)*. However, as the empiric antibiotic regimen for neutropenic fever in this patient was therefore adjusted to meropenem, there was no delay in start of appropriate antibiotic therapy.

The recent advice against routine administration of antibiotic prophylaxis for newly diagnosed pediatric ALL patients was primarily based on the absence of a significant decrease in mortality, and a decreased but high incidence of BSI in the most important pediatric trial. This pediatric trial by Alexander et al., including AML and relapsed ALL, reported a significantly lower BSI-incidence in patients receiving prophylaxis. However, when comparing incidence rates, the BSI-incidence in the control group (~40 %) was higher than in other studies, while the BSI-incidence in the prophylaxis group was comparable to the typical BSI incidence of 20 %, making these numbers less comparable to other populations with lower BSI-incidence[7,17].

Concern of increasing antibiotic resistance was another reason for advising against routine prophylaxis [7]. In our cohort, we could only study resistance during a limited follow-up. Moreover, we only studied the effect in this patient group, without considering the possible effects on the whole institution. We found an increase in colonization with ciprofloxacin resistant Gram-negative bacteria over time. This finding was similar for the prophylaxis and no prophylaxis group (16 % vs 13 %), which suggests that other factors might be of additional influence on ciprofloxacin resistance, for instance hospitalization or use of broad-spectrum antibiotics. Some previous studies have shown higher levels of ciprofloxacin resistance in rectal swabs from patients using ciprofloxacin [12,18]. Studies with a prolonged follow-up time and considering factors like hospitalisations and use of broad-spectrum antibiotics are warranted to evaluate the long-term effects.

After careful evaluation of the available evidence, the use of ciprofloxacin prophylaxis in all Dutch pediatric ALL patients was reinstated as of October 2022. Acknowledging that the evidence on which the decision is based is limited, the authors believe that a probable lower incidence of BSI outweighs the possible negative effects, as BSI is also a proxy for other complications, such as intensive care unit admission [7].

This study has several limitations. An important limitation of this study is its retrospective observational design, the two compared groups were not treated simultaneously. The absence of prophylaxis in the second group could have elicited a prolonged duration of antibiotic therapy in case of neutropenic fever, Nevertheless, this would in fact protect the no prophylaxis group from BSI. Moreover, the protocol for antibiotic therapy in neutropenic fever did not change during the study period. Secondly, because the studied groups were not diagnosed simultaneously, changes in ALL treatment strategy were possible. For this reason, we chose to compare only patients treated according to the ALLTogether1 protocol to minimize differences, instead of including more patients from different protocols. As the ALLTogether1 protocol was adapted to reduce toxicity (starting March 2021), it is possible that this could have influenced the occurrence and outcome of BSIs. However, the less intensive treatment would have favored the no prophylaxis group (diagnosis from July 2021) and would likely have led to a lower BSI-incidence. Thirdly, the follow-up time to study the influence on ciprofloxacin resistance was limited, as previously discussed. Finally, the duration of neutropenia could not be studied. Alternatively, we aimed to assess the level of immunosuppression by comparing the use of daunorubicin (using a four-drug induction instead of a three-drug induction).

These results support RCTs with a prolonged follow-up time to further evaluate the effect of ciprofloxacin prophylaxis on BSI and, in particular, effects on development of resistance.

In conclusion, in newly diagnosed pediatric ALL patients, ciprofloxacin prophylaxis was associated with a significantly lower BSI-incidence, compared to patients not receiving prophylaxis. While this finding shows the beneficial effect of ciprofloxacin prophylaxis in the first treatment phase of ALL, RCTs with a large sample size are needed, particularly to assess the effect on ciprofloxacin resistance.

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CRediT authorship contribution statement

Wim J.E. Tissing: Writing – review & editing. **Inge M. van der Sluis:** Writing – review & editing. **Tjomme van der Bruggen:** Writing – review & editing, Writing – original draft, Methodology, Conceptualization. **Tom F. W. Wolfs:** Writing – review & editing, Writing – original draft, Supervision, Methodology, Conceptualization. **Fenna Scharloo:** Writing – review & editing, Writing – original draft, Methodology, Formal analysis. **Angelica M.M. de Vrankrijker:** Writing – review & editing, Writing – original draft, Supervision, Formal analysis, Conceptualization.

Author contributions

FS, TW, TB, AM designed the study and wrote the manuscript. **FS** and **AM** did the statistical analysis. All authors reviewed the manuscript.

Additional contributions

We would like to thank dr. Peter M van de Ven, PhD for assisting with the data analysis (Julius Center for Health Sciences and Primary Care, Department of Data Science and Biostatistics, University Medical Centre Utrecht, Utrecht, Netherlands).

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.ejcped.2024.100167.

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