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Population Pharmacokinetics and Pharmacodynamics of Ciprofloxacin Prophylaxis in Pediatric Acute Lymphoblastic Leukemia Patients

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Background. Ciprofloxacin is used as antimicrobial prophylaxis in pediatric acute lymphoblastic leukemia (ALL) to decrease infections with gram-negative bacteria. However, there are no clear guidelines concerning prophylactic dose.

Aims. To determine the pharmacokinetics and pharmacodynamics (PKPD) of ciprofloxacin prophylaxis in a pediatric ALL population. The effect of patient characteristics and antileukemic treatment on ciprofloxacin exposure, the area under the concentration time curve over minimal inhibitory concentration (AUC_{24}/MIC) ratios, and emergence of resistance were studied.

Methods. A total of 615 samples from 129 children (0–18 years) with ALL were collected in a multicenter prospective study. A population pharmacokinetic model was developed. Microbiological cultures were collected prior to and during prophylaxis. An AUC_{24}/MIC of ≥125 was defined as target ratio.

Results. A 1-compartment model with zero-order absorption and allometric scaling best described the data. No significant ($P < .01$) covariates remained after backward elimination and no effect of asparaginase or azoles were found. Ciprofloxacin AUC_{24} was 16.9 mg*h/L in the prednisone prophase versus 29.3 mg*h/L with concomitant chemotherapy. Overall, 100%, 81%, and 18% of patients at, respectively, MIC of 0.063, 0.125, and 0.25 mg/L achieved AUC_{24}/MIC ≥ 125. In 13% of the patients, resistant bacteria were found during prophylactic treatment.

Conclusion. Ciprofloxacin exposure shows an almost 2-fold change throughout the treatment of pediatric ALL. Depending on the appropriateness of 125 as target ratio, therapeutic drug monitoring or dose adjustments might be indicated for less susceptible bacteria starting from ≥ 0.125 mg/L to prevent the emergence of resistance and reach required targets for efficacy.

Keywords. acute lymphoblastic leukemia; pharmacokinetics; ciprofloxacin; minimal inhibitory concentration; pediatrics.

During the treatment of hematological malignancies, patients may receive antimicrobial prophylaxis to suppress gram-negative bacterial colonization and prevent infection in this immunosuppressed population [1]. Studies have shown the effectiveness of antimicrobial prophylaxis in pediatric acute leukemia and superiority of quinolones over other antibiotics [2–4]. However, there is no guideline concerning the prophylactic dose of antibiotics. Hence, in most situations therapeutic dose-levels are used [5, 6]. In contrast to beta-lactam antibiotics, quinolones have a fast and concentration-dependent killing with a more sustained postantibiotic effect against most gram-negative pathogens [7, 8]. Therefore, the area under the concentration time curve over the minimal inhibitory concentration (AUC_{24}/MIC) is used as pharmacodynamics/pharmacokinetics (PKPD) target for quinolones [6, 7, 9]. Studies showed higher probabilities of clinical and microbiologic cure rates with AUC_{24}/MIC > 125 [6, 7]. However, it also showed that AUC_{24}/MIC of >125 might not be achieved in all patients, especially with less susceptible bacteria [7, 9–11]. Emergence of resistance is another area of concern, especially in our patients receiving antibiotics for an extended period. De novo resistance develops in a gradual, stepwise manner, usually from the accumulation of mutations.

In this study the pharmacokinetics and pharmacodynamics of ciprofloxacin were evaluated in a large pediatric ALL population to determine the effects of patient characteristics and treatment on the ciprofloxacin plasma concentrations. The presence

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of gram-negative bacteria and susceptibility to ciprofloxacin was evaluated. Subsequently, Monte Carlo simulations were performed to evaluate dosing regimens and MIC values in relation to AUC_{24}/MIC ratios.

MATERIALS AND METHODS

Patients and Treatment

The study was designed as a prospective multicenter Dutch Childhood Oncology Group (DCOG) study performed in the 7 pediatric oncology centers in the Netherlands. Children aged 0–18 years with ALL were eligible for the study when treated according to the DCOG ALL-11 protocol (April 1, 2012—ongoing), or the Interfant-06 protocol (February 2006—August 2016), receiving ciprofloxacin as antimicrobial prophylaxis in a dose of 15 mg/kg twice daily (maximum 1000 mg/day). Patients with Down syndrome were excluded from the study due to possible altered pharmacokinetics [12–14]. One infant was treated according to the Interfant-06 protocol with samples in week 1 containing prednisolone. The DCOG ALL-11 and DCOG Interfant-06 protocols were institutional review board (IRB) approved (EudraCT: 2012–00006725 (ALL-11) & 2005–004599-19 (Interfant-06); Dutch Trial Registry nr. 3379).

Sample Collection and Analysis

For the PK analysis, ciprofloxacin steady state samples were collected between February 2012 and August 2016. Samples were collected >24 hours after first administration and following a single dose (trough, t = 1, t = 2, and t = 4 hours). Samples were collected during 3 treatment phases; week 1 [block A], 52 days after start treatment [block B], and additional trough samples between block A and B and during risk-group (medium risk group [MRG]) intensification phase [block C]. In block A, patients received prednisolone and during block B and C concomitant chemotherapy (Figure 1 and supplement). Samples were analyzed with liquid chromatography tandem mass spectrometry (LC-MS/MS) at the department of Hospital Pharmacy in the Academic University Medical Centers in Amsterdam, The Netherlands. (LC: Shimadzu LC-30 Nexera [Nishinokyo-Kuwabaracho, Japan]; MS: AB Sciex 5500 QTrap® [Framingham, MA, USA]; high-performance liquid chromatography column: Thermo Scientific™ Hypersil Gold™ 50 × 2.1 mm, 1.9 µm [Waltham, MA, USA]). Blood samples were collected in K2 EDTA tubes and centrifuged at room temperature within 2 hours after withdrawal. Supernatant (serum) was collected and stored at −80° Celsius prior to analysis.

Microbiology

Routine surveillance cultures were taken according to DCOG supportive care guidelines prior to start prophylaxis and during treatment. Rectal and throat swabs were collected during periods of intense chemotherapy either weekly (when hospitalized) or every 2–3 weeks (outpatient clinic), including additional patients treated according to the ALL-11 protocol (outside of PK-study). Ciprofloxacin susceptibility was tested with VITEK®-2 system (BioMérieux, Marcy-l'Étoile, France) at the department of Microbiology in the Erasmus MC, Rotterdam, The Netherlands. Results were presented as MIC ≤ 0.25, 0.5, 1 and > 2 mg/L (MIC >0.5 mg/L is considered resistant) [15]. The incidence of febrile neutropenia during treatment was evaluated using reported episodes of febrile neutropenia to the DCOG. Febrile neutropenia was defined as neutrophil count $<1.0*10^9$ L^{-1} with a single temperature of >38.3° Celsius or ≥38.0° Celsius an hour apart.

Pharmacokinetic Analysis

The total concentration time profiles of ciprofloxacin were analyzed using the nonlinear effects modeling approach implemented in nonlinear mixed effects modeling (NONMEM®) first-order conditional estimates (FOCE) with interaction (version 7.3; Globomax LLC, Ellicott City, MD, USA]). The data were initially fitted to a 1-compartment linear model with first-order absorption followed by more complex models.

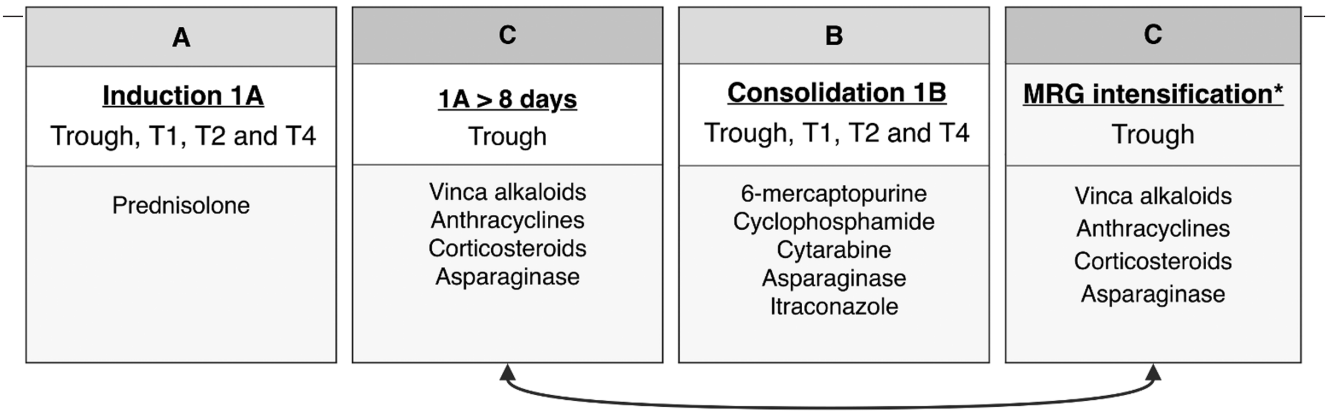

Figure 1. Treatment phases and sampling schedule. Overview of the treatment blocks and samples. T1, T2, and T4 are, respectively, 1, 2, and 4 hours after last administration of ciprofloxacin. Comedication according to protocol are stated per block. *Only medium risk patients. Abbreviation: MRG, medium risk group.

Improvement of the fit of the model was evaluated quantitatively by the precision of the estimated PK parameters and the change in the objective function values (OFV), and visually by goodness-of-fit plots (GoF) and visual predictive checks (VPC). A priori the parameters were normalized to a weight of 70 kilogram (kg) and allometrically scaled, with an exponent of 0.75 for clearance (CL) and 1 for apparent volume of distribution (V). A 3.84-point decrease in OFV for 1 degree of freedom was considered a significant improvement with a *P*-value of <.05. The evaluation of covariates was done through stepwise regression with iterative forward selection ($P < .05$) and backward elimination ($P < .01$) [16]. Continuous covariates were centered around the median. A proportional error model was used to describe the residual error in plasma concentrations. The robustness of the estimated model parameters was evaluated by a nonparametric bootstrap procedure (n = 1000). A visual predictive check was performed for internal validation of the model. Monte Carlo simulations were performed with the final model (n = 1000) for patients with body weights of 10–100 kg, and ciprofloxacin dose of 15 mg/kg with a maximum of 500 mg during treatment phases block A, B, and C. The area under the curve (AUC) was calculated for the different patients and dosages.

Statistical Analysis

The patient characteristics height, weight, age, albumin, creatinine, aspartate aminotransferase (ASAT), alanine aminotransferase (ALAT), bilirubin, and urea for different treatment phases were compared using 2-sided Mann-Whitney *U* test with $\alpha = 0.05$. The Pearson χ^2 test was used to compare sex, pharmaceutical formulation (tablet, capsule or oral liquid) and administration route (oral or via tube).

RESULTS

Patients and Samples

A total of 134 patients were enrolled in the study between October 2012 and August 2016. Five patients were excluded due to missing data. A total of 129 patients were included for the PK analysis; 646 samples were available for analysis. And 31 samples (4.8%) were excluded from the analysis, due to missing sampling data (n = 2; 0.3%), technical issues (eg, <250 uL plasma, n = 7; 1.1%), <lower limit of quantification of 0.02 mg/L (n = 10; 1.5%), or unrealistic concentrations due to sampling artifacts (n = 12; 2.0%). A total of 615 samples were used for the PK analysis. A detailed description of patient characteristics and samples is shown in Table 1. Observed differences between patients in treatment phases (mean [interquartile range]) were, albumin (38 [34–40] vs 33 [26–37] g/L; $P < .001$) and bilirubin (12 [6–14] vs 17 [9–18] umol/L; $P = .02$) for, respectively, block A versus B; urea (4.9 [3.8–6.2] vs 6.4 [4.5–7.3] mmol/L; $P = .02$) for block A versus C; and ASAT (57 [31–54] vs 55 [24–43] U/L; $P = .03$) and urea (4.8 [3.5–5.0] vs 6.4 [4.5–7.3] mmol/L; $P < .001$) for block B versus C.

Pharmacokinetic Model

Initially a 1-compartment model with first-order absorption was evaluated. The samples were a priori stratified in 3 treatment periods (block A, B, and C) and associated with CL and V. Compared to block A, CL and V were, respectively, 44% and 49% lower in block B and 31% and 33% lower in block C (decrease of 157 points in OFV; $P < .0001$). The association between treatment blocks and PK parameters greatly influenced the stability of the model and was therefore included in the structural model. Addition of a peripheral compartment model decreased

Table 1. Patient Characteristics

	All Patients median (range)	Block A median (range)	Block B median (range)	Block C median (range)
Patients (n)	129	91 [a]	76[a]	74[a]
Age (y)	5.6 (0.3–17.7)	5.6 (1.2–17.7)	5.0 (0.3–17.0)	6.2 (1.4–17.7)
Weight (kg)	21 (9–86)	20 (10–79)	21.5 (9–72)	25 (10–86)
Height (cm)	120 (78–190)	116 (81–188)	120 (78–184)	126 (79–190)
Female:male	39% vs 61%	38% vs 62%	39% vs 61%	39% vs 61%
Creatinine (umol/L)	28 (8–67)	28 (8–67)	28 (10–63)	28 (12–63)
GFR (ml/min/1.73 m^2)	179 (80–494)	162 (94–494)	181 (80–348)	176 (80–340)
ASAT (U/L)	37 (13–551)	37 (13–551)	37 (13–513)	37 (10–513)
ALAT (U/L)	62 (8–1321)	62 (8–1321)	62 (13–1321)	62 (13–1321)
Bilirubin (umol/L)	9 (2–158)	9 (2–64)	10 (2–158)	9 (2–64)
Urea (mmol/L)	4.5 (0.8–33)	4.5 (0.8–11.6)	4.5 (0.8–33)	4.9 (0.8–40)
Albumin (g/L)	37 (13–100)	37 (21–100)	36 (13–47)	37 (21–100)
Samples (n)	615	323	204	88
Samples per patient (n)	4 (1–13)	4 (1–13)	3 (1–4)	1 (1–3)
Dose ciprofloxacin (mg)	300 (75–500)	300 (75–500)	300 (75–500)	343 (80–500)
Azoles (%)	51%	3%	63%	38%

Abbreviations: ALAT, alanine aminotransferase; ALL, acute lymphoblastic leukemia; ASAT, aspartate aminotransferase; GFR, glomerular filtration rate.

[a]Patients with samples in block A, B, and C (n = 13); A and B (n = 18); A and C (n = 19); A (n = 23); B (n = 14); C (n = 11).

the OFV of 19.2 points ($P < .01$). However, the parameters of the second compartment could not be estimated precisely and resulted in a less stable model.

Different absorption models were evaluated; first-order absorption, zero-order absorption, lag time, and multi-compartment absorption models (up to 20 transit compartments). The absorption phase was best described with a zero-order absorption model. The final structural model was a 1-compartment model with zero-order absorption with allometric scaling and the association between treatment phase and CL and V. This model was used for the subsequent covariate analysis.

Covariate Analysis

The covariates were tested once at the time for improvement of the structural model. The age adjusted GFR decreased the OFV with 5.3 points ($P < .05$), bilirubin resulted in a 4.1-point decrease in OFV ($P < .05$), and ASAT with 4.8 points ($P < .05$). Although inter-individual variability on absorption rate (D) could not be adequately assessed, the covariate age could, and decreased the OFV with 5.7 points ($P < .05$). Age showed an exponential correlation with absorption rate, with increasing age resulting in extended time in the gut. The other covariates height, body surface area (BSA), sex, ALAT, albumin, and treatment center did not significantly improve the base model ($P > .05$). CL and exposure of patients (n = 14) who developed resistant micro-organisms during prophylaxis (MIC ≥ 0.5 mg/L) did not differ significantly from patients without (2.1-point decrease in OFV; $P > .05$). Neither pharmaceutical form nor administration route showed a significant effect. The covariates with a significant improvement were implemented in the PK model. However, none of the covariates were included in the final model after the more stringent backward elimination ($P < .01$).

The concomitant use of azoles was different between the blocks, whereas 3% of the patients received azoles in block A, 63% did in block B, and 38% in block C. Azoles as covariate did not improve the model with a decrease in OFV of .12 points. Additionally, concomitant use of asparaginase was evaluated in a subset of patients (n = 74) within block B and did not show a significant difference with a decrease of .53 points in OFV. The other chemotherapeutic drugs were received by all patients and could therefore not be compared within a single block.

The final model was a 1-compartment model with zero-order absorption with allometric scaling, an association between treatment phase and CL and V. The parameter estimates of the final model for block A were: CL 86 L/h/70 kg, V 695 L/70 kg. CL was reduced by 44% and 32%, and V was reduced by 49% and 34% in, respectively, block B and C compared to block A. The inter-individual variability was 27% for CL and 41% for V. For detailed PK estimates refer to Table 2. The ciprofloxacin protein binding showed a weak linear correlation over the concentration range with a coefficient of 0.16 ($P < .001$) (Suppl. Figure A). The median percentage of unbound ciprofloxacin was 63%. The AUC_{24} and unbound AUC_{24} ($fAUC_{24}$) are shown in Table 3. A steep decline was observed in patients achieving AUC_{24}/MIC ratios of ≥125 for MIC values of ≥0.25 mg/L, which was especially low in block A and C with, respectively, 1% and 18% of the patients (Table 3).

Model Validation

The nonparametric bootstrap procedure was performed to test the robustness of the model. A total 916 of the 1000 runs were successful. The results are shown in Table 2. The estimates of the final model are in accordance with the results from the 1000 bootstrap replicates. The plot of the prediction corrected visual predictive check shows the median and 90% confidence interval of the observed ciprofloxacin concentrations (Figure 2). The

Table 2. PK Parameters and Bootstrap

	NONMEM					Bootstrap		
Parameter	Estimate	RSE (%)	95% CI (lower)	95% CI (upper)	Shrink. (%)	Median	95% CI (lower)	95% CI (upper)
$\Theta_{CL/F}$ **(L/h/70 kg)**	86	5.5	76.6	95.0	...	88	79.1	97.4
$\Theta_{V/F}$ **(L/70 kg)**	695	8.9	574	816	...	692	594	821
$\Theta_{CL\ block\ B}$	0.56	6.5	.49	.63	...	0.58	.50	.66
$\Theta_{V\ block\ B}$	0.51	9.1	.42	.60	...	0.54	.44	.65
$\Theta_{CL\ block\ C}$	0.68	10.8	.54	.82	...	0.68	.56	.89
$\Theta_{V\ block\ C}$	0.66	16.7	.44	.87	...	0.67	.49	1.0
Θ_{D1}	0.62	25.0	.32	.92	...	0.65	.41	1.0
ω^2_{CL} **(%)**	26.6	25	19	34	22	41	29	53
ω^2_{V} **(%)**	39.2	17	33	48	24	50	33	67
σ^2_{prop}	0.46	4	.42	.49	7	0.40	.35	.45

The variables are as follows: ω^2, random effect parameter that represents interpatient variance for clearance (ω^2_{CL}) and distribution (ω^2_{V}); σ^2_{prop}, random effect parameter that represents proportional residual variance; $\Theta_{CL/F}$, population estimate for clearance including bioavailability; $\Theta_{V/F}$, population estimate of apparent volume of distribution including bioavailability; $\Theta_{CL\ block}$, population estimate for differences between block A and B or C on clearance; $\Theta_{V\ block}$, population estimate for differences between block A and B or C on distribution; Θ_{D1}, population estimate absorption rate constant.

Abbreviations: CI, confidence interval; NONMEM, nonlinear mixed effects modeling; PK, pharmacokinetics; RSE, relative standard error.

Table 3. AUC and AUC24/MIC Ratios

	Overall	Block A	Block B	Block C
Patients (n)	129	91	76	74
AUC_{24} mg*h/L (range)	22.3 (6.8–57.4)	16.9 (6.9–32.8)	29.3 (11.8–57.4)	24.8 (8.1–49.7)
$fAUC_{24}$ mg*h/L (range)	14.0 (4.3–36.2)	10.6 (4.3–20.7)	18.4 (7.4–36.2)	15.6 (5.1–31.3)
AUC_{24}/MIC at MIC 0.125 mg/L	178.4 (54.4–459.2)	135.2 (55.2–262.4)	234.4 (94.4–459.2)	198.4 (64.8–397.6)
AUC_{24}/MIC at MIC 0.25 mg/L	89.2 (27.2–229.6)	67.6 (27.6–131.2)	117.2 (47.2–229.6)	99.2 (32.4–198.8)
% of patients AUC_{24}/MIC ≥ 125				
	Overall	Block A	Block B	Block C
MIC 0.063	100%	97%	100%	99%
MIC 0.125	81%	65%	92%	87%
MIC 0.25	18%	1%	40%	18%
MIC 0.5	0%	0%	0%	0%

Abbreviations: AUC_{24}, 24-hour area under the curve; MIC, minimal inhibitory concentration.

model adequately predicts the time course of the ciprofloxacin plasma concentration (Figure 3).

PKPD Simulations

Monte Carlo simulations were performed to show the percentage of patients achieving the target AUC_{24}/MIC of 125 with the current dose over a range of MIC values (Figure 4). For the MIC values of 0.063, 0.125, 0.25, and 0.5 mg/L, respectively, 90%, 37%, 1%, and 0% (block A); 100%, 86%, 27%, and 0% (block B); and 99%, 74%, 13%, and 0% (block C) of patients achieved an AUC_{24}/MIC ratio of ≥125. The AUC was lower in patients with high body weight compared to low body weight. Note that the maximum dose is 500 mg/dose; hence patients with body weight >33.3 kg received a relative lower dose on a weight basis.

Microbiology

In sum, 251 rectal and throat surveillance cultures of 121 patients were collected and analyzed (including 67 patients from the PK analysis). MIC values were determined in case of positive bacteremia. Ciprofloxacin resistant gram-negative bacteria (MIC ≥ 0.5 mg/L) were identified in routine colonization rectal cultures in 26 out of 121 (21%) all with MIC > 2 mg/L. In 16 out of 121 (13%) patients, resistant gram-negative cultures emerged during ciprofloxacin prophylaxis, with a median of 34 days (range 5–279 days) after diagnosis, in 4 (3%) patients were

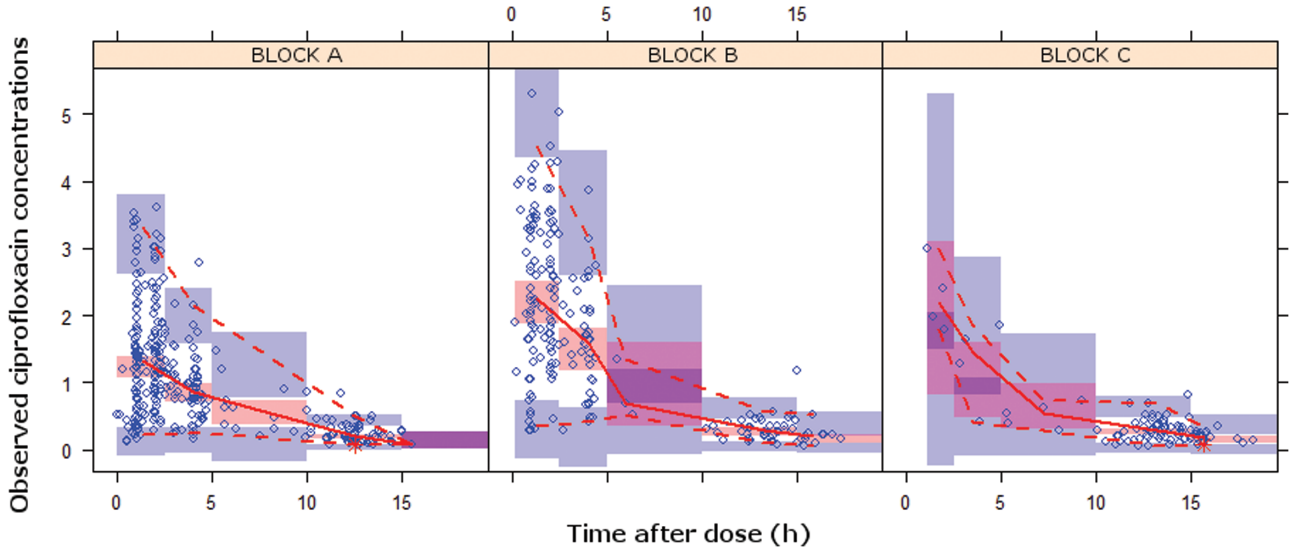

Figure 2. Visual predictive check. Visual predictive checks for each block. The fit of the predicted ciprofloxacin concentrations versus the observed concentrations of the final model. The predictions are in line with the observed data. The red solid line indicates the median observed concentrations and the surrounding opaque red area the simulation based 95% confidence interval for the median. The red dashed lines indicates the observed 5% and 95% percentiles, and the surrounding opaque blue areas show the simulated 95% confidence intervals for the corresponding predicted percentiles.

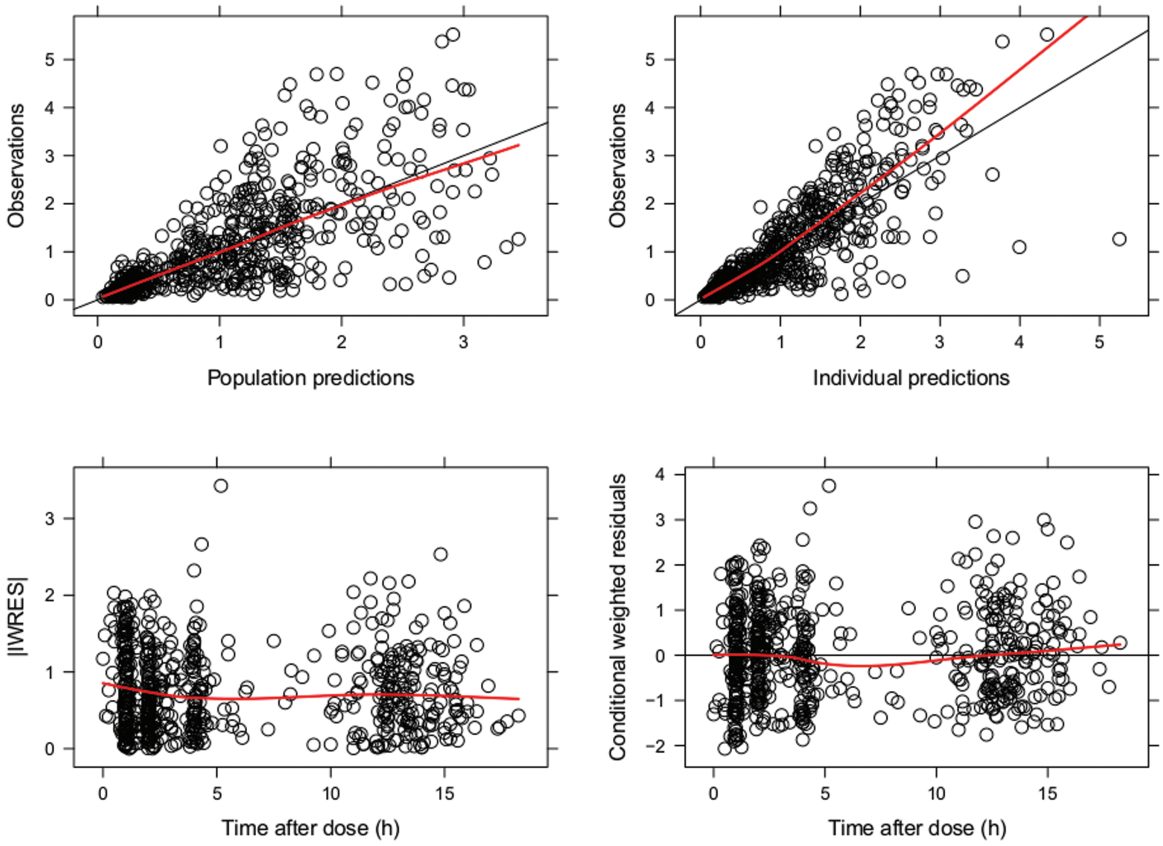

Figure 3. Goodness-of-fit plot. Goodness-of-fit plots final model. Predicted population concentrations versus observed concentrations of the final model (upper left); predicted individual concentrations versus observed concentrations of the final model (upper right). Individual weighted residuals versus individual predictions (lower left), conditional weighted residuals versus time after dose (h = time in hours) (lower right). Abbreviation: IWRES, iindividual weighted residuals.

colonized with resistant bacteria prior to prophylaxis. For 6 (5%) patients with resistant cultures, no data were available prior to prophylaxis and remain inconclusive. Resistance occurred most frequently in *Escherichia coli* (67%) and *Pseudomonas aeruginosa* (14%) (Table 4). A detailed overview of the cultures and MIC values is presented in Supplement Table A. The AUC of patients in block A who developed gram-negative bacteremia during prophylaxis (n = 12) was lower than patients without (n = 54; $P = .025$). However, no difference in AUC was observed in block B, C, or overall (see Figure 5).

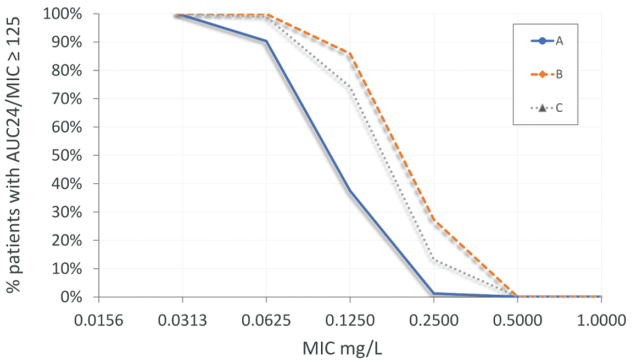

Figure 4. Patients with AUC_{24}/MIC ≥ 125 in block A, B, and C. The effect of treatment phase and patient weight on exposure and AUC_{24}/MIC ratio. Simulation (n = 1000) of patients with a weight of 10–100 kg and a dose of 15 mg/kg (max 500 mg) during different treatment phases (block A, B, and C). The x-axis shows different MIC values in mg/L, and the y-axis shows the percentage of patients exceeding the AUC_{24}/MIC threshold of 125. A steep decline is shown in patient exceeding the threshold ratio for MIC > 0.125 and >0.25. Abbreviation: AUC_{24}/MIC, 24-hour area under the curve/ minimal inhibitory concentration.

A total of 165 episodes of febrile neutropenia were reported to the DCOG in 85 of 108 patients during their ALL treatment; 74 (45%) of these episodes (64 patients) occurred in the first weeks of treatment. In 71 cases microbiological documentation was available, with 7 (10%) documented gram-negative blood or surveillance cultures (1 blood, 5 rectal, urinary tract or throat, and 1 unknown). Thirty-eight of these 71 episodes occurred in the first weeks of treatment including 3 (8%) of the documented gram-negative bacteremia.

DISCUSSION

Overall, a total of 81% of the studied patients achieved an AUC_{24}/MIC ratio of ≥125 for ciprofloxacin susceptible bacteria with MIC of ≤0.125 mg/L and 100% with MIC of ≤0.063 mg/L. However, the majority of patients did not achieve the target ratio

Table 4. Results of Micro-organism Selective Decontamination of Digestive Tract

Resistant micro-organisms	MIC (mg/L) resistant[a]	No Pat
Escherichia coli	≥ 0.5	14
Pseudomonas aeruginosa	≥ 0.5	3
Klebsiella pneumoniae	≥ 0.5	1
Citrobacter freundii	≥ 0.5	1
Enterobacter cloacae complex	≥ 0.5	1
Acinetobacter baumannii complex	≥ 1.0	1
During prophylaxis		13.22%

Abbreviation: EUCAST, European Committee on Antimicrobial Susceptibility Testing; MIC, minimal inhibitory concentration.
[a]According to EUCAST reference database 2019.

for a MIC value of ≥0.25 mg/L (99% and 60% in, respectively, block A and B), which is still considered susceptible. Low rates above the AUC_{24}/MIC target of 125 were also found in other studies for MIC values >0.25 mg/L [7, 9–11, 17]. Although the susceptible MIC values were classified as ≤0.25 mg/L, the exact MIC values are likely much lower. The EUCAST reference database showed MIC predominantly ≤0.064 mg/L with mean of .015 mg/L for wild-type *E. coli* [18]. At these MIC levels the AUC_{24}/MIC target of 125 is reached in all patients. Patients did not reach target AUC_{24}/MIC for our MIC cutoff of >2 mg/L.

The observed rate of gram-negative bacteremia throughout the ALL treatment in the subset of patients was 16%, comparable to the study by Alexander et al (21%) in pediatric acute leukemia patients with levofloxacin [4]. Although higher cure rates have been shown above an AUC_{24}/MIC of ≥125, it is unclear how this translates to prophylactic treatment. In addition to treatment efficacy, the emergence of resistance and specific surface site colonization should be considered [19]. The AUC_{24}/MIC should be sufficient to prevent loss in susceptibility and

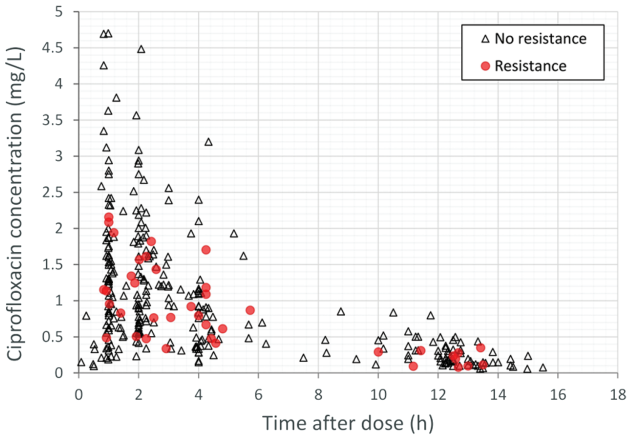

Figure 5. Concentration time curve for patient with and without ciprofloxacin resistant micro-organisms. Pooled concentration time curve of all observed ciprofloxacin concentrations. Samples of patients with resistant gram-negative cultures during treatment are highlighted in red. On the x-axis the time after ciprofloxacin dose, and on the y-axis the ciprofloxacin plasma concentration in mg/L.

emergence of resistance. In this study a correlation was found between exposure in week 1 (block A) and patients who developed resistant gram-negative bacteremia during ciprofloxacin prophylaxis. However, the AUC_{24}/MIC in these patients cannot be determined as the exact MIC value is not known.

The required AUC_{24}/MIC has been shown to differ between strains and fluorquinolones [20, 21]. Felsenstein et al observed a significant reduction in infections caused by gram-negative rods but a higher proportion of gram-positive bacterial and fungal infection with ciprofloxacin in pediatric AML patients [22]. Sung et al used levofloxacin with higher gram-positive sensitivity [2]. This might be something to take into account with regard to prophylaxis or treatment concerning gram-positive bacteremia.

This study showed an almost 2-fold change in ciprofloxacin clearance and exposure for different treatment phases. In the literature a wide range of CL can be found from 15.9 L/h/70 kg to 102.5 L/h/70 kg in a wide variety of pediatric patients (eg, severe malnutrition, cystic fibrosis), the CL and AUC in this study falls in the upper range [10, 23–26]. Ciprofloxacin is for 40–50% excreted in urine and 20–35% via biliary clearance or transintestinal elimination [27–29]. Most patients will have received hyperhydration and allopurinol/rasburicase (and sometimes diuretics) in week 1 to prevent tumor lysis syndrome, which could affect the estimation of CL. Other factors that might contribute to the difference in CL and AUC include kidney and liver function, transporters (eg, organic anion transporter [OAT3]), bioavailability, and drug interactions [27, 30, 31]. A significant effect of GFR, bilirubin, and ASAT ($P < .05$) was observed; however, it was not implemented in the final PK model after more stringent backward elimination ($P < .01$). All ciprofloxacin administrations were oral. Therefore, CL is the ratio of clearance and bioavailability, and changes in bioavailability (eg, due to binding of ciprofloxacin to multivalent cations in milk or tube feeding) are reflected in the CL.

The PK of ciprofloxacin was best described with a 1-compartment model with zero-order absorption. Other studies have established both 1- and 2-compartment models for ciprofloxacin [23, 32–34, 26]. A 2-compartment model was not supported by the data in our analysis with twice daily ciprofloxacin. Several models were tested to fit the absorption phase; however, all absorption models showed an underestimation of the individual predicted maximum concentration. Therefore, the model predicts a slightly lower ciprofloxacin exposure (AUC). This might be due to the limited data available during the absorption phase.

In conclusion, ciprofloxacin exposure shows a large difference throughout the treatment of pediatric ALL, with about twice the exposure during concomitant chemotherapy compared to the prednisone prophase. The current prophylactic treatment with ciprofloxacin seems to be adequate with limited emergence of resistance and few bacteremia. If the current AUC_{24}/MIC ratio of 125 is correct, the MIC cutoff of 0.25 mg/L might

be too high. The target at an MIC of 0.25 mg/L is achieved in only 18% of the patients overall. However, if current prophylactic therapy suffices even with MIC levels of 0.25 mg/L, the target AUC_{24}/MIC is higher than necessary. Therapeutic drug monitoring might be recommended with increasing MIC levels in order to achieve sufficient AUC_{24}/MIC levels or using the mutant selection window (see Firsov et al [2015] or Olofsson [2006]) [21, 21] to prevent the emergence of resistance and acquire efficacy targets.

Supplementary Data

Supplementary materials are available at *Clinical 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.

Notes

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