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Oral and Intravenous Amoxicillin Dosing Recommendations in Neonates: A Pooled Population Pharmacokinetic Study

Fleur M. Keij,[1,2,a] Stef Schouwenburg,[3,4,a] René F. Kornelisse,[1] Tim Preijers,[3,4] Fatima Mir,[5] Pieter Degraeuwe,[6] Leo M. Stolk,[7] Arianne van Driel,[8] Sandra Kenter,[2] Jacqueline van der Sluijs,[9] Jojanneke Heidema,[10] Paul C. P. den Butter,[11] Irwin K. M. Reiss,[1] Karel Allegaert,[3,12,13] Gerdien A. Tramper-Stranders,[1,2] Birgit C. P. Koch,[3,4,a] and Robert B. Flint[1,3,4,a]

[1]Department of Paediatrics, Division of Neonatology, Erasmus University Medical Centre–Sophia Children's Hospital, Rotterdam, The Netherlands; [2]Department of Paediatrics, Franciscus Gasthuis & Vlietland, Rotterdam, The Netherlands; [3]Department of Hospital Pharmacy, Erasmus University Medical Centre, Rotterdam, The Netherlands; [4]Rotterdam Clinical Pharmacometrics Group, Erasmus University Medical Centre, Rotterdam, The Netherlands; [5]Section of Paediatric Infectious Disease, Paediatrics and Child Health, Aga Khan University, Karachi, Pakistan; [6]Department of Paediatrics, Division of Neonatology, Maastricht University Medical Centre, Maastricht, The Netherlands; [7]Department of Clinical Pharmacy, Maastricht University Medical Centre, The Netherlands; [8]Department of Paediatrics, IJsselland Hospital, Capelle a/d IJssel, The Netherlands; [9]Department of Paediatrics, Division of Neonatology, Maxima Medical Centre, Veldhoven, The Netherlands; [10]Department of Paediatrics, St. Antonius Hospital, Nieuwegein, The Netherlands; [11]Department of Paediatrics, Ikazia Hospital, Rotterdam, The Netherlands; [12]Department of Development and Regeneration, KU Leuven, Leuven, Belgium; and [13]Department of Pharmaceutical and Pharmacological Sciences, KU Leuven, Leuven, Belgium

Background. There is a lack of evidence on oral amoxicillin pharmacokinetics and exposure in neonates with possible serious bacterial infection (pSBI). We aimed to describe amoxicillin disposition following oral and intravenous administration and to provide dosing recommendations for preterm and term neonates treated for pSBI.

Methods. In this pooled-population pharmacokinetic study, 3 datasets were combined for nonlinear mixed-effects modeling. In order to evaluate amoxicillin exposure following oral and intravenous administration, pharmacokinetic profiles for different dosing regimens were simulated with the developed population pharmacokinetic model. A target of 50% time of the free fraction above the minimal inhibitory concentration (MIC) with an MIC_{ECOFF} of 8 mg/L (to cover gram-negative bacteria such as *Escherichia coli*) was used.

Results. The cohort consisted of 261 (79 oral, 182 intravenous) neonates with a median (range) gestational age of 35.8 weeks (range, 24.9–42.4) and bodyweight of 2.6 kg (range, 0.5–5). A 1-compartment model with first-order absorption best described amoxicillin pharmacokinetics. Clearance (L/h/kg) in neonates born after 30 weeks' gestation increased with increasing postnatal age (PNA day 10, 1.25-fold; PNA day 20, 1.43-fold vs PNA day 3). Oral bioavailability was 87%. We found that a twice-daily regimen of 50 mg/kg/day is superior to a 3- or 4-times daily schedule in the first week of life for both oral and intravenous administration.

Conclusions. This pooledpopulation pharmacokinetic description of intravenous and oral amoxicillin in neonates provides age-specific dosing recommendations. We conclude that neonates treated with oral amoxicillin in the first weeks of life reach adequate amoxicillin levels following a twice-daily dosing regimen. Oral amoxicillin therapy could therefore be an adequate, cost-effective, and more patient-friendly alternative for neonates worldwide.

Keywords. amoxicillin; absorption; pharmacokinetics; neonates.

Worldwide, many neonates receive antibiotics because of possible serious bacterial infection (pSBI) [1]. Causative pathogens differ based on timing of infection onset in relation to birth and geographic distribution. Early-onset infections (<72 hours after birth) are caused by both gram-positive (ie, group B *Streptococcus* [GBS]) and gram-negative pathogens (ie, *Escherichia coli*) [2]. Late-onset infections (>72 hours after birth) are commonly caused by environmentally encountered pathogens, especially in hospitalized neonates (ie, coagulase-negative staphylococcus, *Staphylococcus aureus*, gram-negative bacilli, and Candida species). Therefore, empiric antibiotic therapy needs to target both gram-positive and gram-negative bacteria [3, 4].

Amoxicillin is a beta-lactam antibiotic that belongs to the aminopenicillins. Amoxicillin is easily deactivated by beta-

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[a]F. M. K., S. S., B. C. P. K., and R. B. F. contributed equally to this work.

Correspondence: Robert B. Flint, Department of Hospital Pharmacy, Department of Paediatrics, Division of Neonatology, Erasmus University Medical Centre, Postal Box 2040, Rotterdam, CA 3000, The Netherlands (r.flint@erasmusmc.nl). Fleur M. Keij, Department of Neonatology, Erasmus MC-Sophia Children's Hospital, Postal Box 2040, Rotterdam, CA 3000, The Netherlands (f.keij@erasmusmc.nl).

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lactamase. Therefore, it can be combined with a beta-lactamase inhibitor (eg, clavulanic acid) to restore efficacy against beta-lactamase–producing bacteria. Its pharmacokinetic–pharmacodynamic mode of action depends on the time (T) the free drug concentration (fC) exceeds the minimal inhibitory concentration (MIC) of the targeted pathogen (fT > MIC). An adequate %fT > MIC ensures bacterial killing, whereas a suboptimal %fT > MIC allows for the development of antibiotic resistance. For neonates, although still debated, a target exposure of 40%–50%fT > MIC is currently advised [5–7]. However, in recent clinical trials, higher targets have been evaluated, especially when severe sepsis is suspected and/or in an intensive care setting.

Amoxicillin is widely used to treat respiratory tract infections and uncomplicated urinary tract infections. It can be administered both orally and intravenously. In neonatology, amoxicillin combined with an aminoglycoside is commonly used in cases of suspected sepsis. There is a high demand for evidence of the neonatal bioavailability of oral amoxicillin in both high-income countries (HICs) and low- and middle-income countries (LMICs). In LMICs, oral dosing recommendations have already been implemented by the World Health Organization (WHO) in case hospital referral is not possible, despite the lack of pharmacokinetic evidence [8]. Oral antibiotics allow adequate community-based treatment of neonates with pSBI in settings with minimal resources and lack of additional diagnostics. In HICs, antimicrobials are generally administered intravenously in neonates, given concerns about adequate exposure following oral administration. Yet, oral treatment allows for earlier discharge, which could positively impact quality of life and reduce healthcare costs [9]. However, as robust data on oral absorption and pharmacokinetic target attainment in neonates are lacking, broad implementation of oral amoxicillin use in neonatal care is hampered.

We aimed to describe the disposition of amoxicillin following oral and intravenous administration in preterm and term neonates. Our second aim was to provide dosing recommendations that are based on target attainment for oral and intravenous treatment of amoxicillin in neonates.

METHODS

Study Design and Participants

This was a pooled population pharmacokinetic study in which we combined 3 datasets that reported plasma concentrations of amoxicillin in neonates following oral and intravenous administration [10–14]. For each patient, the following demographic and clinical characteristics were recorded or calculated: gestational age (GA), postnatal age (PNA), postmenstrual age (PMA), small for gestational age (SGA) [15], current bodyweight, and sex.

The first dataset was part of the RAIN (Reduction of intravenous Antibiotics In Neonates) study, a multicenter, randomized, controlled trial in which the noninferiority of intravenous-to-oral switch therapy in neonates with a probable bacterial infection was or has been? evaluated [9]. Neonates with a PMA of ≥35 weeks, PNA of 0–28 days, and a bodyweight of ≥2 kg who received a full course of antibiotic treatment because of a "probable bacterial infection" were eligible.

The second dataset consisted of data from the SATT (Simplified Antibiotic Therapy Trial), a large, open-label, randomized, clinical trial in Karachi, Pakistan, in which a parenteral regimen of penicillin and gentamicin was compared with 2 simplified regimens that included oral amoxicillin [10, 14]. This trial was conducted in young infants with 1 or more signs of bacterial infection. Patients with a PNA of 0–59 days could be included if they had 1 or more signs of severe infection and the family refused to have the patient admitted to the hospital.

The third dataset, "Maastricht" by Pullen et al, was a pharmacokinetic study that aimed to define the appropriate intravenous amoxicillin dosage regimen for neonates in the first week of life and thereafter [11, 12]. Neonates with pSBI were treated according to the guidelines of the Neonatal Formulary (amoxicillin + gentamicin) and could be included if their PNA was ≤9 days [16].

Additional information on sample management and analysis for each study is provided in Supplementary Appendix *A*.

Outcomes

The European Committee on Antimicrobial Susceptibility Testing (EUCAST) epidemiological cufoff values (MIC_{ECOFF}) were used to define the pharmacodynamic target [17]. The MIC_{ECOFF} describes the highest MIC for microorganisms without phenotypically detectable acquired resistance mechanisms. The MIC_{ECOFF} for *E. coli* is higher than for GBS (MIC 8 mg/L vs 0.25 mg/L, respectively); therefore, the MIC_{ECOFF} for *E. coli* was chosen as the target [17]. The percentage of time (T) of the free fraction (f) above the MIC was targeted at 50%. A range of MICs has been used to assess target attainment of the current WHO oral amoxicillin dosing regimens [5].

Statistical Analyses

Population pharmacokinetic analysis was performed using the nonlinear mixed-effects modeling approach (NONMEM, version 7.4, ICON, Ellicott City, MD). During the development and evaluation stage of the model, Perl-speaks-NONMEM version 4.2.0, Pirana software version 3.0.0 (Certara, Princeton, NJ), and R version 4.1.2 (R Foundation for Statistical Computing, Vienna, Austria) were used for pharmacokinetic data exploration. We checked the combined dataset for inconsistencies. Missing data were omitted from the modeling procedures. The model development was performed stepwise as

follows: (1) selection of structural model, (2) selection of error model, (3) covariate analysis, and (4) internal validation. Thirteen amoxicillin plasma concentrations were above the upper limit of quantification, and 5 were below the lower limit of quantification; these were not excluded from the dataset. Continuous covariates were centered on the median and were modeled as exponential and power relationships. Categorical covariates were modeled as proportional models. Covariate analysis was performed using stepwise forward inclusion and backward elimination. Details on model development are provided in Supplementary Appendix *B*.

Evaluation of Different Dosing Regimens Using Simulations

To evaluate amoxicillin exposure following oral and intravenous administration, pharmacokinetic profiles for different dosing regimens were simulated with the developed population pharmacokinetic model. As target exposure in the neonatal population varies, dosages and intervals were chosen based on national and international guidelines and the available literature (Supplementary Table 3). The following dosages were simulated: 20, 30, 50, 60, 75, 100, and 150 mg/kg/day, with dosing intervals of 6, 8, or 12 hours. Dosages were evaluated based on mean target attainment and the percentage of simulated patients who achieved ≥50% $fT > MIC$ during the second 24 hours of treatment (time window, 24–48 hours) when exposure is mostly stabilized and reaches steady state. A threshold of 90% of cases ≥50% $fT > MIC$ was used to define adequate treatment. Age categories were established based on the combined dataset and clinical convenience. For each age category, simulations were performed with 3 hypothetical patients representing the lowest, median, and highest age per category. More details on the dosage simulations are provided in Supplementary Table 2.

Additionally, dosage simulations were performed to evaluate the efficacy of internationally recognized oral dosing regimens (100 mg/kg/day every 12 hours PNA <7 days and 150 mg/kg/day every 8 hours PNA >7 days) for a range of MICs [18, 19]. These simulations were performed with a covariate distribution using the data from the combined dataset (RAIN study, SATT trial, Pullen).

RESULTS

A total of 938 amoxicillin plasma concentrations (123 oral, 815 intravenous) were obtained from 261 preterm and term neonates (79 oral, 182 intravenous; all unique patients) and used for this pharmacokinetic analysis. Seven patients (13 oral samples) switched from intravenous to oral amoxicillin. The median GA of the total population was 35.8 weeks (range, 24.9–42.4). The median current bodyweight was 2.6 kg (range, 0.5–5.0). Amoxicillin concentrations ranged from 0.8 mg/L to 251.4 mg/L for patients receiving intravenous amoxicillin and from 0.6 mg/L to 72.9 mg/L for patients receiving oral amoxicillin (concentrations not corrected for dose). Baseline characteristics that are subdivided per dataset are summarized in Table 1. Covariate density for GA (weeks), GA (days), and weight (kg) are visualized in Supplementary Figure 1.

Final Population Pharmacokinetic Model

Oral and intravenous amoxicillin plasma concentrations were best described by a 1-compartment model with first-order absorption, bioavailability, and interindividual variability on clearance. A mixed error model was used to describe the residual variability. Detailed results and model development regarding the pharmacokinetic analysis and the final model are described in Supplementary Figures 2–9.

We tested the following covariates: current bodyweight, sex, PNA, GA, PMA, study center, and SGA. Amoxicillin oral bioavailability was estimated at 87%. We estimated a relatively low absorption rate constant of 0.085 $hours^{-1}$ (relative standard error, 24.3%). GA and PNA were found to best describe maturation of amoxicillin clearance ($P < .001$, −100 points in objective function value [OFV] and $P < .001$, −123 points in OFV, respectively); these covariates were therefore implemented in the final pharmacokinetic model. All pharmacokinetic parameter estimates of the final model are provided in Table 2. Figure 1 illustrates the impact of GA and PNA on mean amoxicillin clearance, indicating rapid nonlinear maturation of amoxicillin clearance with increasing GA and PNA.

Target attainment of the different oral amoxicillin dosing regimens per age category are visualized in Figure 2*A* (PNA, 0–7 days) and Figure 2*B* (PNA, 7–28 days) with corresponding mean target attainment percentages listed in Supplementary Tables 4*A* and 4*B*.

Dosage Simulations

The simulations illustrate that the lowest oral dosage for PNA of <7 days to achieve a target attainment of $fT > MIC$ of 50% for an MIC of 8 mg/L, 24–48 hours after start of oral therapy is 50 mg/kg/day, independent of dosage interval (6, 8, and 12 hours), for both GA range 34–36 + 6 and 37–41 weeks. For PNA 7–28 days, 50 mg/kg/day and 60 mg/kg/day are sufficient to reach target attainment for both GA range 34–36 + 6 and 37–41 weeks, respectively, independent of dosage interval (6, 8, and 12 hours). For oral regimens, <50 mg/kg/day as a twice-daily regimen (higher dose per administration) resulted in a higher target attainment compared with a 3- or 4-times daily dosing regimen 24–48 hours after the start of oral therapy.

Target attainment following intravenous amoxicillin for age ranges (GA, PNA) is shown in Supplementary Figure 10 and Supplementary Tables 6*A* and 6*B*. For age range GA 25–27 + 6 and 28–31 + 6 weeks, 30 mg/kg/d resulted in adequate exposure, irrespective of dosing interval and PNA. The remaining age ranges GA 32–36 + 6 and 37–41 weeks achieved adequate exposure with

Table 1. Baseline Characteristics

Characteristic	All Patients (n = 261)	Reduction of intravenous Antibiotics In Neonates Study (n = 39)	Maastricht (n = 182)	Simplified Antibiotic Therapy Trial (n = 40)	*P* Value
Female sex, no. (%)	112 (42.9)	10 (25.6)	85 (46.7)	17 (42.5)	.136
Median gestational age, wk [IQR]	37.4 [31.7–39.86]	40.4 [39.1–41]	33.6 [30.4–39.3]	38.0 [37.0–38.0]	.045
Median postnatal age,[a] d [IQR]	1 [0–4]	2.9 [2–3]	1 [0–2]	13.5 [3–36.3]	<.0001
Median postmenstrual age, wk [IQR]	38.29 [31.9–40.71]	40.6 [39.4–41.2]	34.4 [30.9–39.9]	39.7 [38.4–43.2]	.62
Median body weight, kg [IQR]	2.6 [1.6–3.5]	3.6 [3.3–4.0]	2.1 [1.4–3.3]	2.8 [2.2–3.6]	.008
No. of plasma concentrations	938	65	815	58	
Route of administration	Oral and intravenous	Oral	Intravenous	Oral	
Median amoxicillin dosage per administration, mg/kg/dose (range)	iv: 50 (9.4–112.9) oral: 78.9 (23.4–100)	24.9 (23.4–51.0)	50 (9.4–112.9)	90.9 (78.9–100.0)	<.0001
Comedication		Amoxicillin + clavulanic acid (4:1) in all patients	Indomethacin	Unknown	

One-way analysis of variance was used for continuous data.

Abbreviation: IQR, interquartile range.

[a]Postnatal age during therapy.

Table 2. Parameter Estimates of the Final Model and Corresponding Bootstrap Estimates

Parameter	Parameter Estimate, Shrinkage [%] (Relative Standard Error %)	Bootstrap Estimates (95% Confidence Interval)
Fixed effects		
Ka (h^{-1})	0.085 (25)	0.091 (.06–.11)
$CL_A\ (L/h) = TVCL \times \left(\frac{BW}{70}\right)^{0.75} \times \left(\frac{PNA}{6.8}\right)^{\theta_{PNA}} \times \left(\frac{GA}{35.8}\right)^{\theta_{GA}}$		
TVCL (L/h)	3.22 (3)	3.22 (3.09–3.35)
$V_A\ (L) = TVV1 \times \left(\frac{BW}{70}\right)^{1.00}$		
TVV1 (L)	43 (2)	43 (41.61–44.32)
F (%)	0.873 (16)	0.832 (.72–1.02)
Covariate relationships		
θ_{PNA}	0.357 (8)	0.359 (.30–.41)
θ_{GA}	2.37 (6)	2.37 (2.13–2.61)
Interindividual variability		
Clearance (%)	26.7 [21]	26.7 (.05–.09)
Residual variability		
Proportional error	0.132 (10)	0.133 (.11–.15)
Additive error (mg/L)	4.48 (12)	4.38 (3.59–5.37)

Final parameter estimates were within the 95% confidence interval of the bootstrap, indicating a low model bias. Current bodyweight is scaled to 70 kg. Both postnatal age and gestational age are scaled to dataset median.

Abbreviations: BW, bodyweight; CL_A, clearance of amoxicillin; F, bioavailability; GA, gestational age; Ka, absorption constant; PNA, postnatal age; TVCL, the typical value for clearance (L/h); TVV1, the typical value for distribution volume; V_A, distribution volume of amoxicillin.

a dosage of 50 mg/kg/d irrespective of dosing interval (6, 8, and 12 hours) and PNA. However, the mean percentage of simulated patients per age range that achieved 50% T > MIC was slightly higher when dosing every 6 hours instead of every 8 or 12 hours.

The differences in concentration–time profiles relating to the route of administration (oral vs intravenous) are visualized in Supplementary Figure 11 for a single dose of amoxicillin of 25 mg/kg (RAIN study dosing regimen). Figure 3 illustrates the oral exposure in relation to a range of MIC values following the internationally recognized dosing regimens 100 mg/kg/day every 12 hours (PNA <7 days) and 150 mg/kg/day every 8 hours (PNA >7 days), demonstrating that both dosing regimens achieved sufficient exposure in the first 24 hours art (>50% *f*T > MIC) up to an MIC of 16 mg/L.

International Dosing Regimen Evaluation

An overview of model-based dosing recommendations for both oral and intravenous amoxicillin treatment, subdivided per age category, is presented in Table 3. The selection of dosing recommendations was based on the mean percentage of simulated patients per age category who achieved 50% T > MIC (see Supplementary Tables 5*A* and 5*B*, Supplementary Tables 7*A* and 7*B*). We took into consideration the delayed absorption following oral administration that resulted in a twice-daily

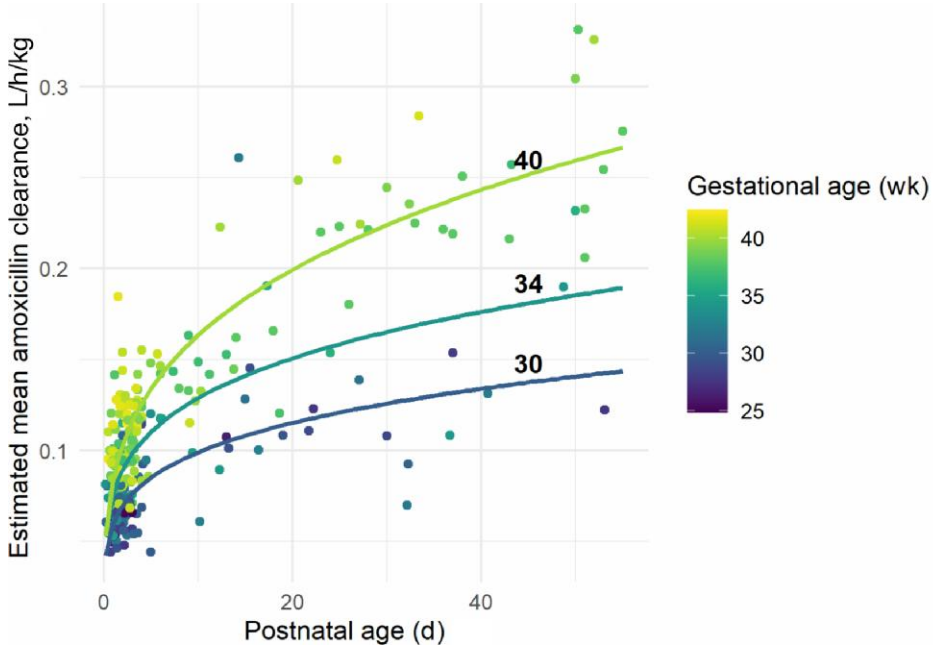

Figure 1. Nonlinear impact of gestational age and postnatal age on amoxicillin clearance. Dots represent the mean estimated individual clearance values, with colors representing the gestational age of the patient. Solid lines represent gestational age categories observed in the pooled dataset.

dosing recommendation. For intravenous administration, we chose a 3-times daily regimen for children with a PNA >7 days, as this leads to slightly better exposure and lower peak concentrations compared with a twice-daily regimen. GA and PNA have a major impact on amoxicillin exposure in neonates. Consequently, dosing regimens need to be adjusted based on these maturational indicators, irrespective of the route of administration.

DISCUSSION

In this pooledpopulation pharmacokinetic study, we successfully described the disposition of amoxicillin after oral and intravenous administration in both preterm and term neonates. Amoxicillin clearance displays a rapid intra- and extra-uterine maturation, which was best captured by GA and PNA. The estimated oral amoxicillin bioavailability in neonates (GA ≥34.0 weeks) was 87%, although absorption was slower compared with older children and adults [20]. The high oral bioavailability encourages an early switch to oral administration in neonates, which has been reported to lead to equal efficacy and safety profiles [9]. We provide oral and intravenous dosing regimens for amoxicillin that warrant a fT/MIC of >50% in more than 90% of the treated neonates.

The combination of GA and PNA as the most important covariates for clearance reflects intra-uterine and extra-uterine maturation of renal function in neonates. At a GA of 30 weeks, clearance (L/h/kg) was 1.25-fold and 1.43-fold higher for a PNA of 10 days and 20 days, respectively, compared with neonates at 3 days GA. This aligns with previously reported glomerular filtration rate maturation and pharmacokinetic descriptions of renally cleared drugs in neonates [21, 22]. The 87% oral bioavailability of amoxicillin in neonates is comparable to that in adults (70%–90%) [23]. Absorption of amoxicillin occurs through both passive diffusion and PEPT1-mediated active transport in the gut [24]. It is thought that the oral absorption rate of PEPT1 substrates is constant across the pediatric age range [25]. However, animal studies have shown that prenatal PEPT1 expression reached maximal levels in the first weeks of life, which subsequently decreased to adult levels after the first year of life [26]. This could explain why, in contrast to previously published oral amoxicillin models in adults, a model with saturable or nonlinear absorption did not allow a better description of our combined dataset of neonates [20].

We evaluated target attainment of the currently recommended international dosing regimens and demonstrated that a twice-daily oral regimen is superior to a 3- or 4-times daily regimen in terms of exposure for all neonatal age categories. This can be explained by the delayed absorption that leads to a gradual increase in plasma concentration. A twice-daily schedule is very suitable as it can easily be integrated into feeding schedules and reduces the risk of missed administrations. For neonates with a GA ≥34 weeks in the first week of life, the recommended dosing schedule for oral administration is identical to that of

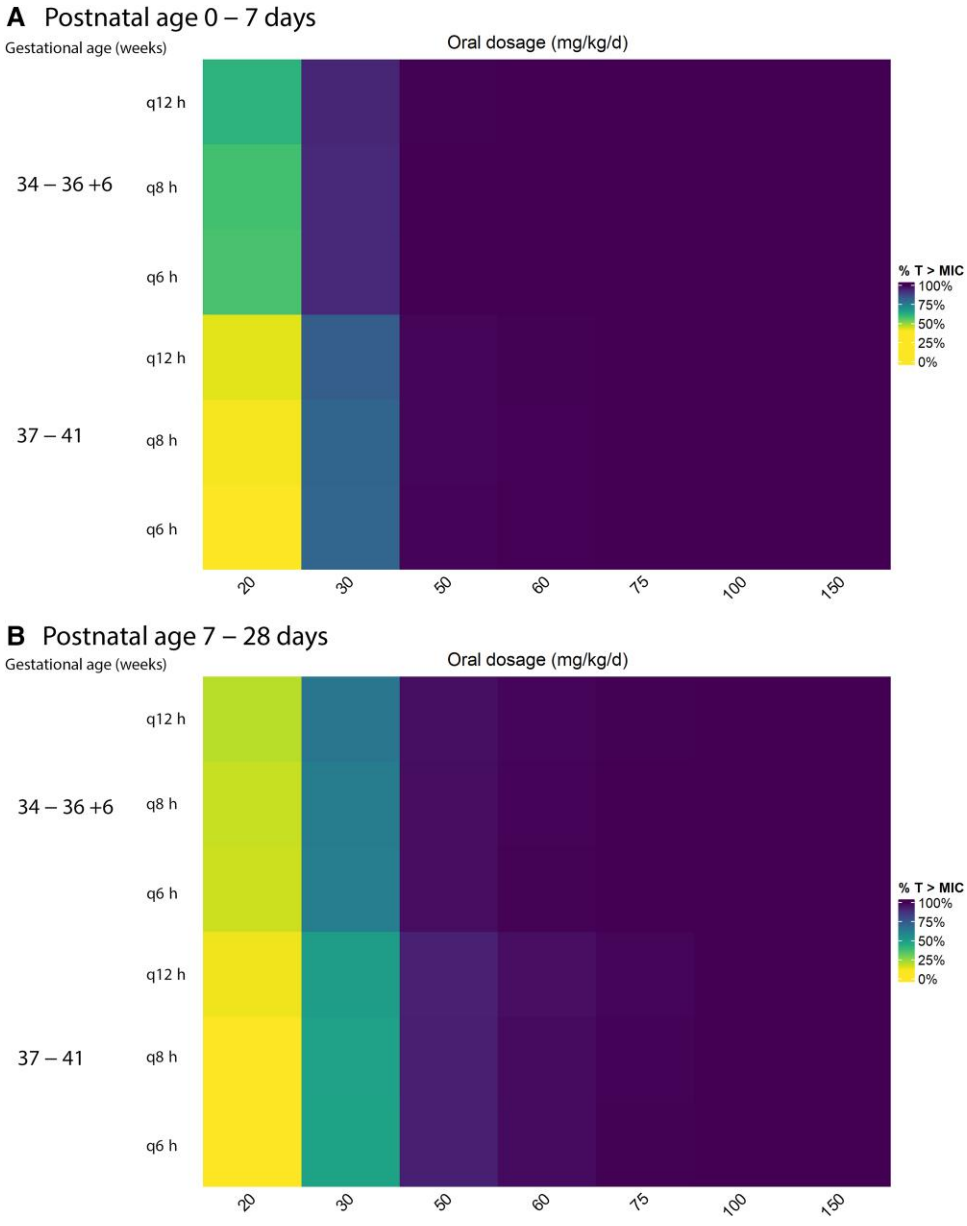

Figure 2. Exposure to oral amoxicillin (24–48 hours after start) for different dosing regimens in simulated patients (gestational age (GA) range, 34–36 + 6 weeks, and GA range, 37–41 weeks; corresponding current weight was estimated based on real patients). The color intensity of a square represents the mean percentage of target attainment (% $fT >$ MIC) of approximately 2500 simulations. Rows show dosing interval: q12 h, 2 times daily; q8 h, 3 times daily; q6 h, 4 times daily. Columns show dosage in mg/kg/day. *A,* Postnatal age (PNA) range, 0–7 days. *B,* PNA range 7–28 days. Abbreviations: MIC, minimal inhibitory concentration; q, every; T, time.

intravenous administration. Higher daily dosages are, however, recommended in term neonates for infections that occur beyond day 7 after birth (PNA, 7–28 days) compared with the first week of life (PNA, 0–7 days), irrespective of the route of administration.

To further simplify the implementation of our oral dosing schedule, we created ready-to-use dosing charts for the 2 available amoxicillin suspensions listed on the WHO Model List of Essential Medicines (125 mg/5 mL and 250 mg/5 mL). These can be found in Supplementary Tables 8 and 9.

One strength of this study is that we combined 3 datasets from different hospitals. Here, we showed that pharmacokinetic–pharmacodynamic research is possible in neonates while reducing the burden for the individual participant by pooling previously reported data for a more real-world statistical approach. Blood sampling in neonates is deemed unethical and hampered by blood volume restrictions due to their low circulating blood volume. Therefore, pharmacokinetic studies should be encouraged to use opportunistic sampling strategies. Pooling data from different studies also supports

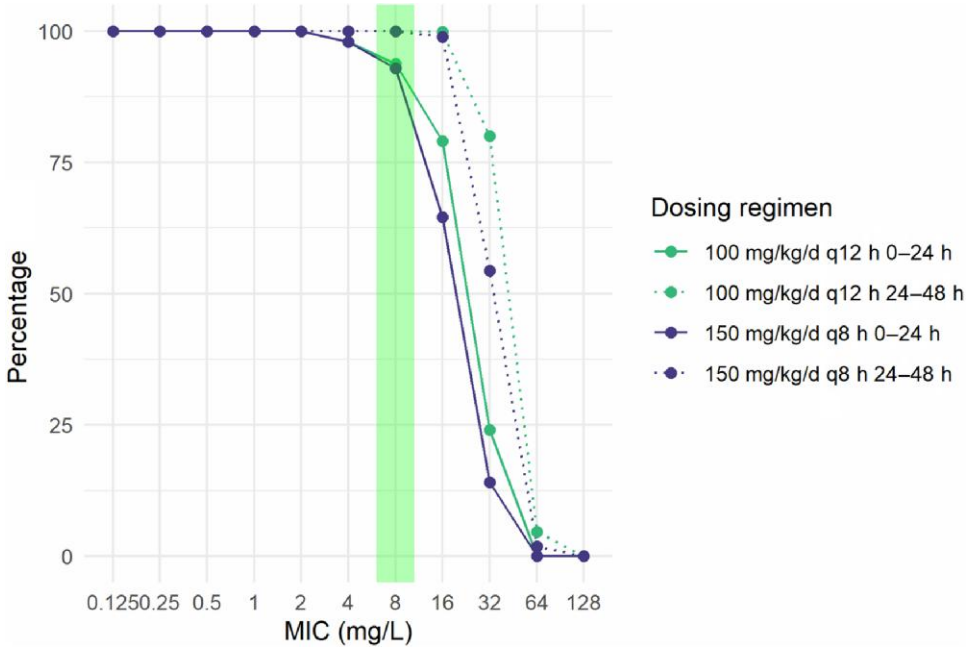

Figure 3. Percentage of target attainment in a typical patient for oral amoxicillin 100 mg/kg/day q12 h (typical patient postnatal age <7 days) and 150 mg/kg/day q8 h (typical patient >7 days) for a range of MICs during the first day (0–24 hours) and second day (24–48 hours) of treatment. Green highlighted section: primary outcome MIC of 8 mg/L. Abbreviations: MIC, minimal inhibitory concentration; q, every; q8 h; 3 times daily; q12 h; 2 times daily.

Table 3. Oral and Intravenous Dosage Recommendations for Amoxicillin Based on Gestational Age and Postnatal Age Based on Simulations

	Postnatal Age, day	
Gestational Age, week	0–7	7–28
Oral dosage recommendation[a]		
34–36 + 6	50 mg/kg/day every 12 h	50 mg/kg/day every 12 h
37–41	50 mg/kg/day every 12 h	60 mg/kg/day every 12 h
Intravenous dosage recommendation[b]		
25–27 + 6	20 mg/kg/day every 12 h	30 mg/kg/day every 8 h
28–31 + 6	30 mg/kg/day every 12 h	50 mg/kg/day every 8 h
32–36 + 6	50 mg/kg/day every 12 h	60 mg/kg/day every 8 h
37–41	50 mg/kg/day every 12 h	75 mg/kg/day every 8 h

Abbreviation: GA, gestational age; MIC, minimal inhibitory concentration; PNA, postnatal age.

[a]Dosage simulations were performed for which the highest age per category (ie, for the upper left category: GA, 36+6 weeks, and PNA, 7 days) achieved 50% $fT >$ minimal inhibitory concentration (MIC; 8 mg/L) in 90% of cases.

[b]Dosage simulations were performed for the highest age per category (ie, for the upper left category: GA, 27+6 weeks, and PNA, 7 days) achieved 50% $fT >$ MIC (8 mg/L) in 90% of cases.

generalizability of the findings as it limits the impact of local laboratory deviations on the pharmacokinetic description. Second, we simulated several dosing regimens that enabled translation to ready-to-use dosing recommendations that are adjustable for country-specific pathogen MIC distribution and resistance rates. When culture results are not available or are negative or if MICs are unknown, one needs to rely on the epidemiological data, which differs substantially between countries and hospital settings. Finally, we provide dosing recommendations for both intravenous and oral administration of amoxicillin in term and preterm neonates. These can be used in both HICs and LIMCs. As stated earlier, oral antibiotic use in neonates is still uncommon in HICs as pharmacokinetic evidence and dosing recommendations are not yet available. Our findings promote the reliable use of oral treatment in neonates and provide clinicians with guidance on how to consider this new treatment strategy when prolonged antibiotic therapy is indicated. This will facilitate home-based treatment and thereby prevent or minimize parent–child separation, which will have a positive impact on quality of life of parents and their newborns. Furthermore, it offers many advantages such as a potential reduction in costs related to prolonged hospitalization, promotes healthcare accessibility with reliable oral antibiotic therapy in settings where hospitalization is difficult, and protects neonates against other hospital-related risks. However, it must be stressed that in case of suspected sepsis, therapy should always be initiated intravenously to rapidly reach therapeutic levels. The same holds true for central nervous system infections for which oral treatment is not indicated.

Although this study confirms the potential of oral amoxicillin use in neonates, several limitations need to be addressed. First, our pharmacodynamic target was defined as >50% fT

> MIC. This target percentage is under debate; the EUCAST recommends 30%–40% fT > MIC for amoxicillin, and slightly higher percentages are recommended in neonates as they are viewed as immunocompromised compared with older children and adults [17]. Moreover, higher concentrations might be needed in settings where multidrug-resistance rates are high or the pathogen distribution differs from those described here. A second limitation of our data is that the number of tested covariates was limited. This was mainly due to the fact that each separate dataset recorded different variables and that only a few overlapped. Feeding status could be an important covariate when evaluating oral use. However, even if relevant, it would be challenging to consider a neonate's feeding status when administering antibiotics, which is intensive and often on a neonate's demand. A second important covariate is the coadministration of other drugs, that is, nephrotoxic drugs that could potentially influence the amoxicillin plasma concentration [21]. We did, however, test the study center as a covariate in the model (eg, 1 center coadministered clavulanic acid, and the others did not), thereby indirectly correcting for differences with regard to comedication between the 3 datasets. Finally, none of the 3 included centers measured free concentrations; therefore, measured concentrations could be an overestimation of the free concentration. We chose to not correct for protein binding, as it is limited in neonates (10%–14%) compared with adults and only gradually increases with age. Moreover, it would require larger blood samples, which could negatively impact the feasibility of our study [27].

In conclusion, this pharmacokinetic description of oral and intravenous amoxicillin highlights the potential of oral amoxicillin treatment in neonates treated for a pSBI. Given the large impact of GA and PNA on amoxicillin exposure, both should be considered when dosing in the first 28 days of life. The high oral bioavailability of 87% and reported maintained efficacy further confirm the noninferiority of oral compared with intravenous treatment in neonates. Finally, we provide ready-to-use dosing recommendations that can be adjusted based on the clinical characteristics of and the setting for the individual patient. Future research and implementation should focus on the proper indication for oral amoxicillin therapy (patient, type of infection, duration) and on the potential long-term impact of oral amoxicillin on the developing neonate.

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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Potential conflicts of interest. F. M. K. reports an ESPR travel grant. R. F. K. reports participation on a data and safety monitoring board or advisory board for the PROTEA study (Protecting late-moderate preterm infants from respiratory tract infections and wheeze in their first year of life by using bacterial lysates). B. C. P. K. reports grants or contracts from ZonMw, the Dutch government, and the AIDS Foundation and a leadership or fiduciary role with EPASG, EC ESCMID, Council IATDMCT, and UEMS Pharmacology. J. H. reports payment or honoraria for teaching the Dutch pediatric antibiotics course for pediatric trainees and pediatricians. All remaining authors: No reported conflicts of interest.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

Will individual participant data be available (including data dictionaries)?	yes
What data in particular will be shared?	Individual participant data
What other documents will be available	-
When will data be available? (start and end dates)	Immediately following publication. No end date
With whom?	Researchers who provide a methodological sound proposal
For what types of analyses?	To achieve aims in the approved proposal
By what mechanism will data be made available?	Proposals should be directed to dr. R. B. Flint (r.flint@erasmusmc.nl) To gain access, data requestors will need to sign a data access agreement.

Data sharing. Individual participant data will me made available immediately following publication. Researchers need to provide a methodological sound proposal. Proposals should be directed to dr. R. B. Flint (r.flint@erasmusmc.nl). Once approved, researchers will need to sign a data access agreement in order for the data to be made available.

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