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Clindamycin Pharmacokinetics and Safety in Preterm and Term Infants

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Clindamycin may be active against methicillin-resistant *Staphylococcus aureus*, a common pathogen causing sepsis in infants, but optimal dosing in this population is unknown. We performed a multicenter, prospective pharmacokinetic (PK) and safety study of clindamycin in infants. We analyzed the data using a population PK analysis approach and included samples from two additional pediatric trials. Intravenous data were collected from 62 infants (135 plasma PK samples) with postnatal ages of <121 days (median [range] gestational age of 28 weeks [23 to 42] and postnatal age of 17 days [1 to 115]). In addition to body weight, postmenstrual age (PMA) and plasma protein concentrations (albumin and alpha-1 acid glycoprotein) were found to be significantly associated with clearance and volume of distribution, respectively. Clearance reached 50% of the adult value at PMA of 39.5 weeks. Simulated PMA-based intravenous dosing regimens administered every 8 h (≤32 weeks PMA, 5 mg/kg; 32 to 40 weeks PMA, 7 mg/kg; >40 to 60 weeks PMA, 9 mg/kg) resulted in an unbound, steady-state concentration at half the dosing interval greater than a MIC for *S. aureus* of 0.12 μg/ml in >90% of infants. There were no adverse events related to clindamycin use. (This study has been registered at ClinicalTrials.gov under registration no. NCT01728363.)

Gram-positive organisms account for 70% of late-onset sepsis in the neonatal intensive care unit (NICU), most commonly coagulase-negative staphylococci and *Staphylococcus aureus* (1). In the NICU, *S. aureus* infections are associated with severe pneumonia, septic shock, and high mortality in infants (~25%) (2, 3). In addition, a large fraction of *S. aureus* isolates in this setting are methicillin resistant (3).

Clindamycin is a lincosamide antibiotic approved by the U.S. Food and Drug Administration (FDA) for use in adults and children requiring treatment for staphylococcal, streptococcal, and anaerobic infections. Doses of 15 to 20 mg/kg/day are recommended for infants <1 month of age, and doses of 20 to 40 mg/kg/day are recommended for children 1 month to 16 years old (both administered in three or four divided doses) (4). The available data suggest that there are important age-dependent differences in clindamycin disposition, particularly in preterm infants, where pronounced physiological differences are expected (5, 6). Clindamycin is largely metabolized by CYP3A4 (7), and the ontogeny of this drug-metabolizing enzyme may contribute to pronounced differences in its clearance (CL). Furthermore, clindamycin is highly protein bound (78 to 94%) (8–10), primarily to alpha-1 acid glycoprotein (AAG), and ontogenic changes in this plasma protein during childhood and infancy may also alter clindamycin's distribution into tissues.

Despite the public health need for rigorous clinical trials to be performed in children during the first few months after birth, drug labeling changes frequently do not include neonatal data (11). Preterm infants, who are a particularly vulnerable subpopulation due to immaturity in their organ systems, are rarely studied, and thus optimal dosing and safety information is lacking. Due to

clindamycin's widespread use in infants (12), we performed a prospective, multicenter clinical trial to characterize its developmental pharmacokinetics (PK) and safety in preterm and term infants. Relative to our previous investigation (13), this trial provided more intense PK sampling in preterm and term infants, sought to account for the role of age-dependent AAG concentrations on clindamycin disposition, and collected detailed safety data in infants, which are currently lacking in the literature.

MATERIALS AND METHODS

Patient population. PK and safety data were collected as part of the Pharmacokinetics of Anti-Staphylococcal Antibiotics in Infants clinical trial (Staph Trio; NICHD-2012-STA01, ClinicalTrials.gov NCT01728363; IND 115,396). This was a multicenter (*n* = 8 enrolling under clindamycin), prospective, multiple-dose PK and safety study. Infants with a suspected systemic infection or receiving one of three antibiotic drugs of

interest per local standard of care (including clindamycin) were eligible for enrollment. For the clindamycin group, infants were <30 weeks' gestational age (GA) and <121 days' postnatal age (PNA). Infants who met any of the following criteria were excluded: allergic reactions to a study drug, urine output < 0.5 ml/kg/h, or serum creatinine >1.7 mg/dl. The study was reviewed and approved by the local institutional review board. Informed consent was obtained from the legal guardian of each study participant. The first and last infants were enrolled on 8 February 2013 and 28 February 2014, respectively.

We combined clindamycin data from Staph Trio with PK data collected after intravenous clindamycin administration in two additional clinical trials: (i) Pharmacokinetics of Understudied Drugs Administered to Children per Standard of Care (PTN POPS) and (2) Safety and Pharmacokinetics of Multiple-Dose Intravenous and Oral Clindamycin Pediatric Subjects With BMI ≥ 85th Percentile (CLIN01). Combining the data across all three trials allowed for development of a population PK model that describes clindamycin disposition after intravenous administration across pediatric age groups. The PTN POPS and CLIN01 studies are described in separate publications (13; M. Smith, D. Gonzalez, J. Goldman, R. Yogev, J. E. Sullivan, M. Reed, K. Anand, K. Martz, K. Berezny, P. B. Smith, M. Cohen-Wolkowicz, and K. Watt, presented at the Pediatric Academic Societies 2015 Annual Meeting, San Diego, CA, 25 to 28 April 2015). Briefly, PTN POPS (NICHD-2011-POP01, ClinicalTrials.gov NCT01431326; IND 113,645) was a multicenter ($n = 27$), prospective, PK and safety study. PTN POPS enrolled children (<21 years of age) who received a drug of interest (including clindamycin) per standard of care as administered by their treating caregiver. CLIN01 (NICHD-2012-CLN01, ClinicalTrials.gov NCT01744730; IND 115,396) was a prospective, multicenter ($n = 6$), open-label, multiple-dose PK and safety study of clindamycin in children 2 to <18 years of age with a body mass index (BMI) ≥ 85th percentile. Children with a suspected or confirmed infection or those receiving clindamycin per standard of care were eligible for the study.

Drug dosing and sample collection. In the Staph Trio trial, all infants received clindamycin 10 mg/kg intravenously every 6, 8, or 12 h unless they were prescribed clindamycin per standard of care, in which case dosing was at the discretion of the treating caregiver. The dosing interval used was based on PNA: <14 days, 10 mg/kg every 12 h; ≥14 to 45 days, 10 mg/kg every 8 h; and >45 to 120 days, 10 mg/kg every 6 h. Clindamycin was administered over 30 min. Predefined PK sample time collection windows based on dosing interval were noted in the protocol (see Table S1 in the supplemental material); however, samples collected outside these collection windows were also included in the analysis.

For the PTN POPS study, dosing information was collected for up to eight doses prior to the sampling dose (last dose before biological sample collection). Since PTN POPS used an opportunistic study design, the timing of blood sample collection was dependent on standard-of-care laboratory assessments, unless a parent/guardian provided consent to obtain PK sampling for research purposes only (13). In the CLIN01 trial, clindamycin was prescribed at a dose of 30 to 40 mg/kg/day (based on the total body weight [WT]) every 6 or 8 h. Predefined PK sampling times used were based on route of administration and dosing interval (Smith et al., Pediatric Academic Societies 2015 Annual Meeting).

Analytical methods. Whole blood was collected (200 μl) in an EDTA-K2 microtainer and processed immediately prior to freezing at the study sites. Plasma samples were stored at or below −70°C within 8 h of collection. PK samples were sent to the Pediatric Trials Network central laboratory (OpAns, LLC, Durham, NC) for storage and analysis. Clindamycin concentrations were quantified using a validated liquid chromatography-tandem mass spectrometry assay as previously described (13). The lower limit of quantification was 50 ng/ml. Accuracy and precision were within the FDA bioanalytical assay validation criteria (e.g., ±15%).

An enzyme-linked immunosorbent assay (Assaypro LLC, St. Charles, MO) was used for the measurement of AAG in plasma. The method was qualified over the range 0.125 to 4 μg/ml for human AAG in MIX Diluent (a buffered protein base supplied with the kit) representing 0.125 to 4

mg/ml corrected for dilution. Both calibration standards and quality control samples met assay validation criteria. Each study sample was diluted 1:1,000 into MIX Diluent and then processed in duplicate.

Population PK model development. Clindamycin plasma PK data collected after intravenous administration were analyzed with a nonlinear mixed effects modeling approach using the software NONMEM (version 7.2; Icon Solutions, Ellicott City, MD). The first-order conditional estimation method with interaction was used for all model runs. Run management was performed using Pirana (version 2.8.1) (14). Visual predictive checks and bootstrap methods were performed with Perl-speaks-NONMEM (PsN, version 3.6.2) (15). Data manipulation and visualization were performed using R (version 3.0.2; R Foundation for Statistical Computing, Vienna, Austria) and RStudio (version 0.97.551; RStudio, Boston, MA), with the packages lattice and ggplot2 used for the latter (16, 17).

As previously described, a one-compartment structural PK model was used (13). Interindividual variability was assessed for PK model parameters using an exponential relationship. The correlation between η parameters for CL and volume of distribution (V) was estimated according to equation 1:

$$\rho = \frac{\omega_{CL,V}}{\sqrt{\omega_{CL}^2 \cdot \omega_{V}^2}} \qquad (1)$$

where $\omega_{CL,V}$ denotes the off-diagonal element between CL and V, and ω_{CL}^2 and ω_V^2 are the variance estimates for the interindividual variability in CL and V, respectively. A proportional error model was used to estimate the residual variability for each study (Staph Trio, PTN POPS, and CLIN01) separately.

WT was assumed to be a significant covariate for CL and V and was included in the base model. The relationship between WT and PK parameters was characterized using a fixed exponent (0.75 and 1) allometric and linear relationship for CL and V parameters (scaled to a 70-kg standardized WT), respectively. Because postmenstrual age (PMA) was previously noted to be an important predictor of interindividual variability in clindamycin disposition in the pediatric population, this covariate was again tested. The following covariates were then also explored: aspartate aminotransferase (AST), alanine aminotransferase (ALT), serum creatinine, bilirubin (total and direct), serum albumin (ALB), AAG, obese status (BMI ≥ 95th percentile), ethnicity, and sex. PMA is defined as the sum of the GA (weeks) plus PNA in weeks (days/7).

The relationship between PMA and CL was characterized using a sigmoidal E_{MAX} maturation function as shown in equation 2:

$$F_{PMA} = \frac{PMA^{HILL}}{TM_{50}^{HILL} + PMA^{HILL}} \qquad (2)$$

where F_{PMA} denotes the fraction of the adult CL value, TM_{50} represents the value of PMA (weeks) when 50% adult CL is reached, and "HILL" is a slope parameter for the sigmoidal maturation model.

With the exception of WT and age, all other continuous covariates were normalized to the population median value as described in equation 3, whereas for dichotomous categorical covariates (e.g., obese status and sex) a relationship, as shown in equation 4, was used:

$$P_{ij} = \theta_{pop,j} \cdot \left(\frac{cov_i}{cov_m}\right)^{\theta_{cov}} \qquad (3)$$

$$P_{ij} = \theta_{pop,j} \cdot \theta_{cov}^{\,CATEGORICAL} \qquad (4)$$

where cov_i denotes the individual covariate value, cov_m is the population median covariate value, θ_{cov} is a parameter which represents the covariate effect, and "CATEGORICAL" is a categorical variable that can take on one of two values: zero or one.

A forward inclusion ($P < 0.05$ and change in objective function value > 3.8) and backward elimination ($P < 0.001$ and change in objective function value > 10.8) approach was used to assess the statistical significance of relevant covariates. Missing covariate values were imputed using the median value for the sample.

TABLE 1 Clinical data for preterm and term infants <121 days of age[a]

Characteristic	GA < 30 wk			GA ≥ 30 wk		
	PNA < 14 days (n = 16)	PNA ≥ 14–45 days (n = 16)	PNA > 45–120 days (n = 6)	PNA < 14 days (n = 9)	PNA ≥ 14–45 days (n = 5)	PNA > 45–120 days (n = 10)
GA (wk)	26.0 (22.9–29.7)	26.5 (23.0–28.9)	27.5 (24.0–29.0)	36.6 (31.1–40.0)	39.0 (37.0–39.7)	38.1 (30.0–42.0)
PNA (days)	4.9 (2.1–10.0)	22.5 (14.0–44.0)	58.9 (51.0–64.0)	6.3 (0.8–13.0)	16.1 (16.0–29.9)	78.5 (53.0–115.2)
Postmenstrual age (wk)	27.0 (23.6–30.0)	29.1 (25.7–34.3)	36.2 (31.3–37.1)	36.7 (32.0–41.4)	41.6 (39.3–42.0)	49.2 (37.6–56.3)
Wt (kg)	0.8 (0.5–1.2)	1.0 (0.6–2.6)	1.8 (1.4–3.0)	2.5 (1.2–3.8)	3.7 (2.4–4.4)	5.8 (1.9–8.8)
Serum creatinine (mg/dl)	1.0 (0.5–1.5)	0.5 (0.2–1.5)	0.3 (0.2–0.8)	0.4 (0.3–0.8)	0.3[b]	0.2 (0.2–0.3)
AST (U/liter)	21.0 (15.0–34.0)	24.5 (16.0–87.0)	109.0 (30.0–116.0)	NS	24.5 (21.0–28.0)	29*
ALT (U/liter)	6.0 (6.0–11.0)	15.5 (6.0–47.0)	41.0 (20.0–55.0)	NS	33.0 (11.0–55.0)	25*
Total bilirubin (mg/dl)	5.3 (2.3–7.7)	2.8 (0.5–8.2)	4.9 (3.5–7.9)	8.5*	1.4 (0.5–2.2)	0.5*
Albumin (g/dl)	2.3 (1.9–2.8)	2.3 (1.3–2.7)	2.2 (2.1–2.3)	NS	3.0 (2.1–3.7)	3.3 (2.6–4.0)
AAG (mg/ml)	1.2 (0.4–3.8)	1.0 (0.2–2.9)	1.3 (0.7–2.1)	2.2 (0.9–3.3)	2.1 (1.3–2.5)	2.1 (1.3–6.3)
No. of subjects (%)						
Male	10 (63)	6 (38)	5 (83)	5 (56)	2 (40)	9 (90)
Caucasian	13 (81)	15 (94)	3 (50)	6 (67)	5 (100)	10 (100)
Hispanic	4 (25)	2 (13)	1 (17)	1 (11)	2 (40)	3 (30)

[a] Values are medians (ranges) for continuous variables and no. (%) for categorical variables calculated based on values at the time of the first recorded dose. For categorical variables, the percentages were calculated as a function of the number of subjects in each study. GA, gestational age; PNA, postnatal age; Wt, total body weight; AST, aspartate aminotransferase; ALT, alanine aminotransferase; AAG, alpha-1 acid glycoprotein; NS, no subjects contributed data; *, one subject contributed data.

[b] Three subjects contributed data, but each had the same value.

Population PK model evaluation. During the population PK model-building process, the following tools or criteria were used to assess model robustness: successful minimization, standard diagnostic plots, plausibility and precision of parameter estimates, objective function and shrinkage values, and visual predictive checks. Parameter precision for the final population PK model was evaluated using nonparametric bootstrapping (1,000 replicates) to generate 95% confidence intervals for parameter estimates using the percentile method.

Dosing simulations. The final population PK model was used to simulate steady-state exposure in preterm and term infants following previously recommended (13) intravenous dosing regimens: ≤32 weeks PMA, 5 mg/kg every 8 h; >32 to 40 weeks PMA, 7 mg/kg every 8 h; and >40 to 60 weeks PMA, 9 mg/kg every 8 h. The steady-state area under the concentration versus time curve from 0 to 8 h ($AUC_{ss,0-8}$), maximal steady-state concentration ($C_{ss,max}$), and steady-state concentration at half the dosing interval ($C_{ss,50}$) were calculated according to equations 5 to 7:

$$AUC_{ss,0-8} = \frac{Dose}{CL} \quad (5)$$

$$C_{ss,max} = \frac{Dose}{(CL \cdot DUR)} \cdot \frac{[1 - EXP(-Ke \cdot DUR)]}{[1 - EXP(-Ke \cdot \tau)]} \quad (6)$$

$$C_{ss,50} = C_{ss,max} \cdot EXP(-Ke \cdot 3.5) \quad (7)$$

where Ke denotes the first-order elimination rate constant calculated as CL/V, "DUR" denotes the infusion duration (0.5 h for all dosing simulations), and τ is the dosing interval (8 h for all dosing simulations). Covariate values used in the simulations were the same as those in the study population used for model development. A total of 200 concentrations versus time profiles were simulated for each virtual patient. A maximum absolute dose of 900 mg every 8 h and infusion duration of 0.5 h were used in all dosing simulations.

Finally, the simulated unbound, steady-state concentration at half the dosing interval ($fC_{ss,50}$) was calculated for each virtual subject assuming a fraction unbound of 17% (9). The proportion of virtual participants with an $fC_{ss,50}$ greater than an MIC of 0.12 μg/ml (previously reported MIC_{90} for *S. aureus*) after the optimal dosing was calculated (18).

Safety. Safety was assessed from the time of informed consent through 72 h and 7 days after the last dose for adverse events and serious adverse events, respectively. For standard of care clindamycin dosing, the last dose

was defined as the sixth dose after enrollment. The safety data were reviewed on a quarterly basis by the Best Pharmaceuticals for Children Act data monitoring committee convened by the National Institute of Child Health and Human Development. An adverse event was defined as any untoward medical occurrence that took place during the conduct of the study trial regardless of whether it was drug related. A serious adverse event was an event that resulted in any of the following outcomes: death, life-threatening adverse event, persistent or significant incapacity or disruption in the ability to perform normal life functions, inpatient hospitalization or prolonging an existing hospitalization, or an important medical event that jeopardized the health of a study participant.

RESULTS

Patient characteristics. We enrolled 21 infants with a median (range) GA and PNA of 26 weeks (23 to 29) and 23 days (5 to 65), respectively. We collected 75 PK samples, of which eight scavenged (leftover samples from routine patient care) samples, two samples below the limit of quantification, and one sample with uncertain timing were not included in the analysis. The median (range) number of samples per infant was three (2 to 4). The median (range) clindamycin doses were 9.8 mg/kg/dose (4.3 to 13.0) and 28.9 mg/kg/day (10.0 to 39.5).

We combined the data from this prospective clinical trial with additional PK samples collected from preterm and term infants in PTN POPS, a separate opportunistic study (Table 1) (13). From this study, there were 41 infants with a <121-day PNA who contributed 71 PK samples (median [range] per subject of 2 [1 to 5]). The median (range) GA and PNA values were 33 weeks (22 to 42) and 16 days (1 to 115), respectively. The median (range) clindamycin dose was 5.1 mg/kg/dose (3.8 to 13.5) and 15.0 mg/kg/day (7.6 to 40.6).

Population PK model development and evaluation. The data across three trials (total $n = 220$ subjects; 420 PK samples) were pooled to develop a population PK model that characterizes clindamycin disposition across all pediatric age groups (see Table S2 in the supplemental material). CLIN01 included 89 plasma PK samples from 21 overweight or obese children. After accounting
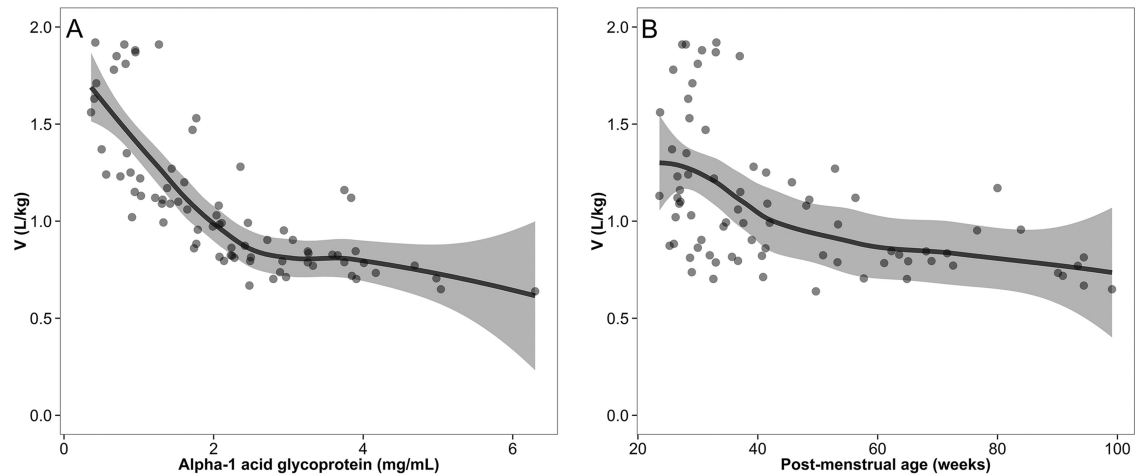
FIG 1 (A) Alpha-1 acid glycoprotein versus volume of distribution (V); (B) postmenstrual age versus V. The black line and shaded area denote the loess curve and an associated 95% confidence region.

for body size using WT, inclusion of PMA on CL and ALB and AAG on *V* further reduced the objective function value by 115.6, 18.5, and 9.2 points, respectively. Inclusion of serum creatinine on CL also significantly reduced the objective function value (11.6 points) but was not included in the final model because its retention in the model was largely a result of one influential individual (with a value of 3.4 mg/dl). No other covariates reached statistical significance.

For the final model, the typical values for CL and *V* can be expressed according to the following equations: CL (liters/h) = $13.8 \cdot (WT/70)^{0.75} \cdot [PMA^{2.83}/(39.5^{2.83} + PMA^{2.83})]$; *V* (liters) = $63.6 \cdot (WT/70) \cdot (ALB/3.3)^{-0.83} \cdot (AAG/2.4)^{-0.25}$ (see Table S3 in the supplemental material). There was an inverse relationship between AAG levels and weight-normalized *V* (Fig. 1). Eta shrinkage estimates for CL and *V* were 6.2 and 23.6%, respectively; epsilon shrinkage estimates for PTN POPS, Staph Trio, and CLIN01 were 25.8, 13.7, and 11.9%, respectively. Goodness-of-fit plots and a visual predictive check for all data included in the analysis are shown in Fig. S1 to S3 in the supplemental material. Empirical Bayesian estimates stratified by age are shown in Table 2. Clearance values increased with age, whereas *V* decreased with age due in part to increasing plasma protein concentrations.

Dosing simulations. PMA-based dosing ($\leq$32 weeks, 5 mg/kg; >32 to 40 weeks, 7 mg/kg; >40 to 60 weeks, 9 mg/kg; each regimen administered intravenously every 8 h) resulted in compara-

ble $AUC_{ss,0-8}$ (median [2.5th to 97.5th quantiles] 33.8 μg $\cdot$ h/ml [10.5 to 110]) and $C_{ss,max}$ (median [range] 7.9 μg/ml [3.4 to 18.3]) across all infant age categories (Fig. 2) (19). The $fC_{ss,50}$ was greater than the MIC for *S. aureus* of 0.12 μg/ml in >97% of virtual infants.

For infants >5 months to 1 year PNA, 12 mg/kg administered intravenously every 8 h resulted in a median (2.5th to 97.5th quantiles) simulated $AUC_{ss,0-8}$ and $C_{ss,max}$ of 41.2 μg $\cdot$ h/ml (13.0 to 137.0) and 14.1 μg/ml (9.2 to 26.7), respectively. The $fC_{ss,50}$ was >0.12 μg/ml for 94.3% of the virtual infants.

Safety. Nine (43%) infants experienced a total of 14 adverse events, none of which were deemed related to study drug. The 14 adverse events were as follows (*n* [%]): seizures (3 [21%]), anemia (2 [14%]), worsening necrotizing enterocolitis (NEC) (1 [7%]), worsening spontaneous bowel perforation (1 [7%]), respiratory acidosis (1 [7%]), hypotension (1 [7%]), abdominal wound dehiscence from NEC surgery (1 [7%]), diaper rash (1 [7%]), chronic lung disease (1 [7%]), neonatal feeding intolerance (1 [7%]), and grade I intraventricular hemorrhage (1 [7%]).

The three infants who experienced a seizure were 25 to 26 weeks' GA and <21 days' PNA and received a median clindamycin dose of ~10 mg/kg intravenously every 12 h. Based on their empirical Bayesian estimates and dosing, their predicted steady-state area under the concentration versus time curves from zero to 12 h ($AUC_{ss,0-12}$) were 17.9, 93.9, and 108.6 μg $\cdot$ h/ml; the $C_{ss,max}$

TABLE 2 Individual empirical Bayesian post hoc parameter estimates stratified by age

Parameter	Median (range)[a]				
	PMA $\leq$ 28 wk (*n* = 16)	PMA > 28–32 wk (*n* = 14)	PMA > 32–40 wk (*n* = 16)	PMA > 40–60 wk (*n* = 18)	PNA > 5 mo to 1 year (*n* = 15)
CL (liters/h)	0.11 (0.05–0.55)	0.23 (0.06–0.36)	0.50 (0.06–2.89)	1.37 (0.17–6.35)	1.90 (0.63–5.75)
CL (liters/h/kg)	0.14 (0.07–0.55)	0.19 (0.06–0.42)	0.24 (0.06–1.13)	0.28 (0.08–0.93)	0.28 (0.14–0.61)
CL (liters/h/70 kg)	3.31 (1.55–13.2)	4.91 (1.44–9.21)	7.37 (1.33–34.5)	10.0 (2.24–36.49)	10.97 (4.95–25.72)
V (liters)	1.15 (0.49–2.31)	1.00 (0.67–2.46)	2.72 (0.70–5.43)	4.56 (1.53–9.86)	6.12 (3.17–11.10)
V (liters/kg)	1.20 (0.87–2.26)	1.30 (0.74–1.88)	1.03 (0.70–2.12)	0.99 (0.64–1.27)	0.83 (0.70–1.17)
V (liters/kg/70 kg)	83.50 (61.17–158.51)	90.95 (51.59–130.92)	71.90 (49.14–147.90)	68.99 (44.68–88.84)	57.90 (49.10–81.79)
Half-life (h)	5.89 (2.42–12.90)	5.25 (2.34–8.87)	3.96 (1.30–8.83)	2.35 (0.94–6.44)	2.05 (1.26–3.47)

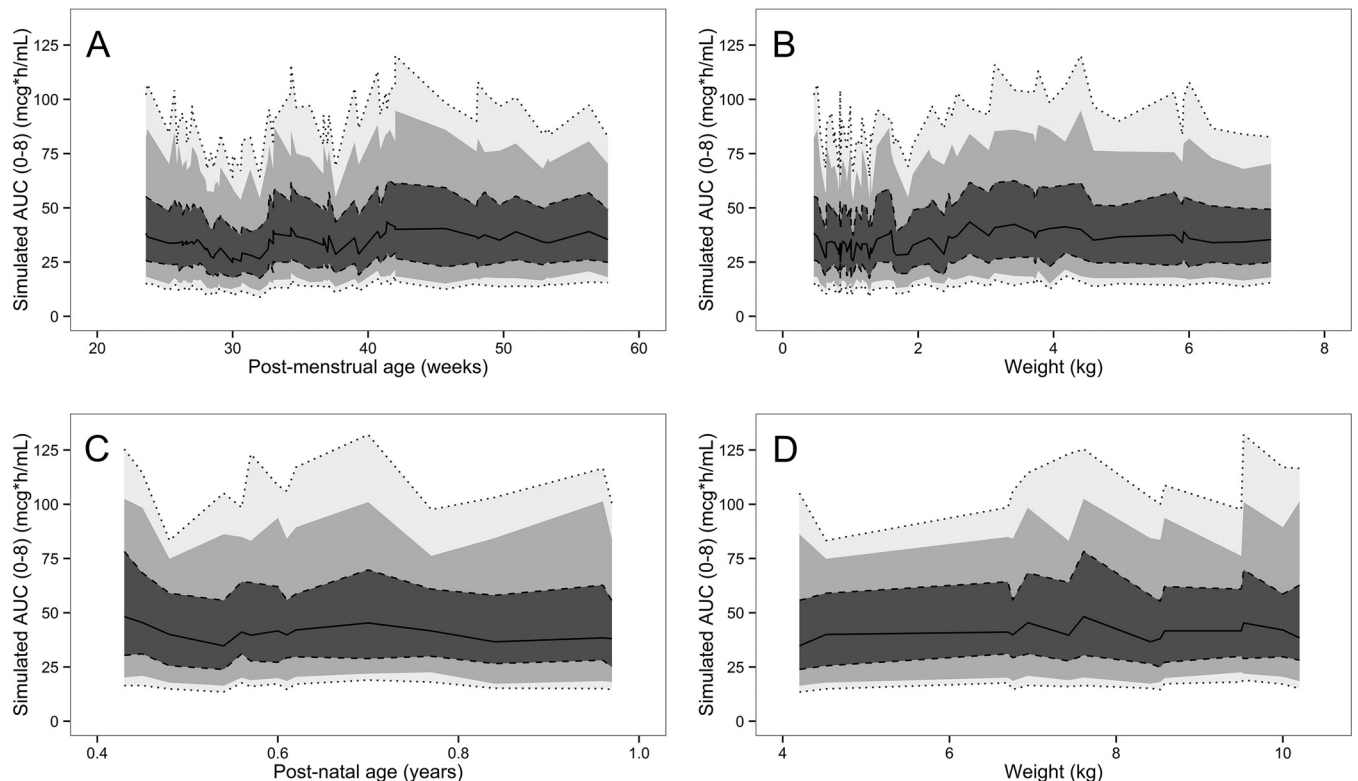[a] PMA, postmenstrual age; PNA, postnatal age; CL, clearance; *V*, volume of distribution.

FIG 2 Simulated steady-state area under the total clindamycin concentration versus time curve from 0 to 8 h ($AUC_{ss,0-8}$) after intravenous dosing to achieve exposure comparable to observed adult values after 600 mg intravenously every 8 h (mean [standard deviation], 31.8 μg · h/ml [6.7]) (19). (A and B) $AUC_{ss,0-8}$ versus postmenstrual age and total body weight after age-based dosing: ≤32 weeks' postmenstrual age, 5 mg/kg every 8 h; >32 to 40 weeks' postmenstrual age, 7 mg/kg every 8 h; and >40 to 60 weeks' postmenstrual age, 9 mg/kg every 8 h. (C and D) $AUC_{ss,0-8}$ versus postnatal age and total body weight after 12 mg/kg every 8 h for infants > 5 months to 1 year of age. The shaded regions denote the 90% (95th and 5th percentiles), 80% (90th and 10th percentiles), and 50% (75th and 25th percentiles) prediction intervals from lightest to darkest color intensity, respectively. The dashed black lines denote the 95th, 75th, 25th, and 5th percentiles, respectively. The solid black line is the median.

values were 5.2, 10.7, and 14.2 μg/ml. In four subjects who received clindamycin intravenous dosing every 12 h (5 to 10 mg/kg/dose) and did not experience a seizure, the median (range) $AUC_{ss,0-12}$ and $C_{ss,max}$ were 42.2 μg · h/ml (28.8 to 57.3) and 6.7 μg/ml (4.1 to 9.1), respectively.

DISCUSSION

As previously described (13), we used a one-compartment structural PK model to find that after correcting for body size using WT, PMA was the most significant covariate that accounts for maturation in infants. Using a sigmoid E_{MAX} maturation function, maturation reached 50% adult CL values at 39.5 weeks' PMA, comparable to other CYP3A4 substrates (e.g., 39.7 weeks with lopinavir) (20, 21). The population estimates for CL and *V* were 13.8 liters/h and 63.6 liters (scaled to a 70-kg standardized adult WT), respectively, which were comparable to reported adult values of 15.2 liters/h and 66.2 liters, respectively (22).

In addition to body size and age (PMA), plasma protein concentrations (AAG and ALB) significantly explained interindividual variability in *V*. Clindamycin binds primarily to AAG, and changes in the concentrations of this protein would be expected to alter its fraction unbound in infants (8–10, 23) A reduction in *V* with age was observed in part due to increased AAG concentrations, which is consistent with a previous investigation that predicted 50% adult concentrations at birth (24). A trend toward

lower ALB levels in infants was also observed (~40% lower in infants <28 weeks versus >40 to 60 weeks PMA), but a substantial fraction of subjects were lacking an available measurement.

We compared our individual clindamycin PK estimates with two previous studies in infants (5, 6). One study that enrolled 40 preterm and term infants (GA, 28 to 40 weeks; PNA, 2 to 27 days; WT, 1 to 9.6 kg) and administered intravenous clindamycin (15 to 20 mg/kg/day) noted increases in CL with PNA (0.29 liter/h for preterm and <28 days PNA, 0.68 liter/h for term and <28 days PNA, and 1.59 liter/h for >4 weeks of age) (5). Although not statistically significant, the authors noted that *V* was three times higher in preterm infants (relative to term infants < 28 days and infants > 4 weeks of age) (5). A second study enrolled 12 newborn infants (GA, 26 to 39 weeks; PNA, 1 to 24 days; WT, 0.8 to 2.6 kg) and reported a mean (range) weight-normalized *V* and CL of 0.56 liter/kg (0.15 to 1.1) and 0.06 liter/h/kg (0.02 to 0.13), respectively (6). These estimates of CL and *V* are in agreement with the values observed in our study, whereby preterm infants had the lowest CL and highest *V* estimates.

The treatment regimens simulated in our study were within the range of recommended doses in the package insert but were further stratified based on the PMA of the infant. The regimens we simulated resulted in comparable simulated exposure relative to adult estimates (19). The exposures were comparable even when plotted as a function of weight and varying AAG and ALB concen-

trations. Furthermore, a high percentage of infants (>94%) up to 1 year of age had simulated concentrations above an MIC of 0.12 μg/ml across all dosing regimens, which suggests that these doses will yield a therapeutic benefit.

Clindamycin was generally well tolerated in our study. None of the adverse events reported were deemed related to study drug. The most common adverse events (seizures, anemia, and worsening NEC) may be due to the inherent disease processes in this vulnerable population. Although seizures are possibly due to high concentrations of clindamycin, the extent of central nervous system penetration of clindamycin in children is unknown, and in adults the cerebrospinal fluid/plasma ratio is low, generally 1 to 3% (25). Two of the three infants who experienced seizures had a predicted exposure in the upper range of all infants enrolled in the infant PK study. For one of the infants, the seizure occurred ∼3 days after the last clindamycin dose. A follow-up study to evaluate clindamycin safety in preterm and term infants is needed.

Combining clindamycin data collected across multiple PK studies allowed us to characterize the disposition of this drug as a function of age. We used a flexible study design, which collected PK and safety data for three antistaphylococcal antibiotics (including clindamycin) and then merged these data with two other data sets. The final population PK model then allowed us to identify important covariates that explain interindividual variability and explore clindamycin dosing. A few limitations of our approach should be noted. First, we combined data across three clinical trials with different study designs and patient populations, which may introduce additional variability. As a result, in our model we estimated separate residual variability parameters for each study. Second, in the opportunistic study, a substantial proportion of the subjects were missing laboratory data (e.g., ALB), which limited our ability to evaluate the significance of some covariates. However, a measurement of AAG, clindamycin's predominant binding protein, was available for 98% of subjects across all three studies.

Conclusion In conclusion, a one-compartment population PK model accounting for size-based differences using WT, maturation in drug CL using PMA, and differences in protein binding using AAG and ALB concentrations characterized clindamycin disposition in preterm and term infants. In preterm infants, clindamycin should be dosed using WT and PMA to achieve therapeutic exposures.

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