JPPT | Simulation Trial

Dosing Recommendations for Ampicillin and Ceftriaxone in the Treatment of Pediatric Community-Acquired Pneumonia Using Monte Carlo- and Physiologic-Based Pharmacokinetic Simulations

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OBJECTIVE Since 2011, Ampicillin (AMP) has been recommended as the parenteral antibiotic of choice for pediatric community-acquired pneumonia (CAP), but ceftriaxone (CRO) is recommended for unvaccinated children and those with complicated CAP. Using penicillin and CRO susceptibility data for pneumococcus, we evaluated the adequacy of currently recommended doses of AMP and CRO.

METHODS With nonlinear mixed-effects modeling v7.3, Monte Carlo simulations (MCS, N = 10,000) for AMP and CRO were conducted for 6 virtual patients aged 3 months, 1, 2, 5, 10, and 15 years. PK-Sim v9.0 was used to develop physiologic-based pharmacokinetic (PBPK) models for AMP (N = 4000) and CRO (N = 3000). The probability of target attainment (PTA) was determined for both serum and lung (epithelial lining fluid [ELF]) exposure to achieve free drug concentrations above the minimum inhibitory concentration (%*f*T>MIC) for pneumococci at 30% to 50% of the dosing interval.

RESULTS We performed simulations based on susceptibility data from 21 pneumococci isolated from children with CAP and found all 21 (100%) to be susceptible to AMP and CRO using Clinical & Laboratory Standard Institute/US Food and Drug Administration breakpoints, where susceptible, intermediate, and resistant strains of *Streptococcus pneumoniae* were ≤1, 2, and ≥4 mg/L for CRO and ≤2, 4, and ≥8 mg/L for AMP (extrapolated from penicillin), respectively (where intermediate and resistant were considered nonsusceptible); and 18 (85.7%) were susceptible to AMP, and 19 (90.5%) to CRO using the European Committee on Antimicrobial Susceptibility Testing/European Medicines Agency breakpoints, where susceptible and nonsusceptible strains were as follows: 0.5 and 2 mg/L for CRO and 0.5 and 1 mg/L for AMP. Both the serum and ELF, antibiotic regimens achieved >99% PTA at 30% to 50% *f*T>MIC using MCS and PBPK.

CONCLUSION In the pneumococcal conjugate era, standard doses of AMP and CRO appear to provide the appropriate serum and ELF exposure for clinical and microbiologic success for >98% of children with pediatric CAP. The required dose to achieve the desired outcomes may change if beta-lactam resistance in pneumococcus increases.

ABBREVIATIONS AMP, ampicillin; CAP, community-acquired pneumonia; CLSI, Clinical & Laboratory Standard Institute; CRO, ceftriaxone; ELF, epithelial lining fluid; EUCAST, European Committee on Antimicrobial Susceptibility Testing; IDSA, Infectious Diseases Society of America; MCS, Monte Carlo simulation; MIC, minimum inhibitory concentration; NONMEM, nonlinear mixed-effects modeling; PBPK, physiologic-based pharmacokinetic; PCV, pneumococcal conjugate vaccines; PIDS, Pediatric Infectious Diseases Society; PMPSSG, Pediatric Multicenter Pneumococcal Surveillance Study Group; PTA, probability of target attainment; %*f*t>MIC, percent fraction of time above the MIC

KEYWORDS beta-lactams; children; Monte Carlo simulation; pharmacodynamic; physiologic-based pharmacokinetic simulation; pneumococcal vaccine; *Streptococcus pneumoniae*

J Pediatr Pharmacol Ther 2025;30(3):352–361

DOI: 10.5863/JPPT-24-00069

Introduction

Community-acquired pneumonia (CAP), occurring in 155 million children annually, continues to be a leading cause of childhood death worldwide.[1] Even in a developed country, such as the United States, CAP is a leading cause of hospitalization in children and cost the health care system approximately $1 billion in 2009.[2] The most common pathogen implicated in childhood CAP is *Streptococcus pneumoniae,* which is responsible for up to 44% of cases.[1] With extensive clinical use of ampicillin (AMP) for almost 50 years, providing clinical and microbiologic efficacy with a favorable adverse event profile, 2011 guidelines from the Pediatric Infectious Diseases Society (PIDS) and Infectious Diseases Society of America (IDSA) recommended AMP as the first-line treatment for pediatric CAP, with penicillin G as an equivalent option. For complicated CAP or those with a high risk of penicillin resistance, ceftriaxone (CRO) was recommended. Oral switch therapy was recommended for recovering children using high-dose amoxicillin therapy because it was believed necessary for penicillin-nonsusceptible strains that were prevalent before the widespread use of pneumococcal conjugate vaccines (PCVs).[1] The time-dependent pharmacodynamic property of beta-lactams in pneumococcal infections is optimized when free drug concentrations are above the minimum inhibitory concentration (%*f*T>MIC) for at least 30% to 50% of the dosing interval.[3,4]

PCVs have been approved by the US Food and Drug Administration for the prevention of CAP for children in the US, the PCV 7-valent in 2000 and PCV 13-valent in 2010. The use of PCV-13 has significantly decreased the incidence of documented CAP, particularly cases requiring hospitalization and those that are considered complicated.[5,6] In addition, the resistance to beta-lactam antibiotics for pneumococcal strains isolated from community-acquired infections has significantly decreased with the widespread use of PCV-13 immunization.[7] PCV-20 vaccine with protection against serotypes 1, 3, 4, 5, 6A, 6B, 7F, 8, 9V, 10A, 11A, 12F, 14, 15B, 18C, 19A, 19F, 22F, 23F, and 33F was licensed by the US Food and Drug Administration in April 2023.[8,9]

Table 1. Demographic Data of Simulated Subjects

N	Age, yr	Weight, kg	Serum Creatinine, mg/dL
1	0.25	6	0.24
2	1	9.55	0.28
3	2	12.7	0.3
4	5	18	0.38
5	10	32	0.53
6	15	52	0.59

Currently, the attainment of optimal pharmacodynamic parameters in the era of PCV vaccination, with increasing antibiotic susceptibility, using guideline-recommended beta-lactam dosing regimens has not been evaluated. To this end, we aimed to evaluate, by modeling, the probability of target attainment (PTA) of 2 different beta-lactam antibiotics recommended by the pediatric CAP guidelines in achieving optimal %*f*T>MIC within the serum and epithelial lining fluid (ELF) against *S. pneumoniae.*

Methods

Monte Carlo simulations (MCS) were conducted using nonlinear mixed-effects modeling (NONMEM) v7.3 via Pirana using 6 virtual subjects (ages 3 months,1, 2, 5, 10, and 15 years; Table 1). Individual subject weight was obtained by averaging the male and female weights at the 50th percentile from the Centers for Disease Control and Prevention Clinical Growth Chart for the respective age.[10] Normal age-based serum creatinine values were obtained from published literature.[11]

Simulations (N = 10,000) were conducted to determine the PTA after the administration of 2 guideline-recommended beta-lactam regimens (AMP 150 mg/kg/day every 6 hours, CRO 50 mg/kg/day every 24 hours).[2] The target PTA of 90% was selected for these simulations and based on free, nonprotein-bound concentrations in the plasma and in ELF at concentrations above the MIC ranging from 30% to 50% of the dosing interval at steady state (which represented the onset of bacteriostatic activity for most beta-lactams).[12] Antibiotic concentrations were derived using pharmacokinetic parameters from published literature (Table 2).[13–18]

Simulations were also conducted using PK-Sim to develop physiologic-based pharmacokinetic (PBPK) models, evaluating 4 virtual subjects (1, 2, 5, and 10 years; Table 1). Individual subject demographics provided by Bayer for PK-Sim were based on the 1997 National Health and Nutrition Examination Survey of White Americans. Weight was obtained by averaging the male and female weights at the 50th percentile from the Centers for Disease Control and Prevention Clinical Growth Chart for the respective age.[10] Glomerular filtration rate was obtained by PK-Sim from published clinical pharmacokinetic

Table 2. Antibiotic Pharmacokinetic Parameters

PK Parameter	Ampicillin	Ceftriaxone
Clearance, L/hr/kg	0.293 (SD 0.084)[14]	0.0384 (SD 0.0072)[15]
Volume of distribution, L/kg	0.3 (SD 0.08)[14]	0.26[15]
Protein binding, %	20[17]	80.48,[18] 95[17]
Epithelial Lining Fluid:Plasma Ratio	0.53[13]	1[16]

data, and an age-based formula was used to estimate glomerular filtration rate.[19] Physico-chemistry properties of both antibiotics were required for PK-Sim simulations and obtained from published literature and databases. These included, but were not limited to, molecular weight, lipophilicity, plasma albumin binding fraction, pKa values, and solubility. When determining the ELF concentrations, the ELF-to-plasma ratio was obtained from published literature.[20] A concentration versus time curve graph was digitized from the Nahata 1999[14] paper to produce an observed data set to assess the validity of the AMP model (Figure 1a). For CRO, however, an observed data set to compare our simulated model with was not readily available and, therefore, was created using the intermittent short-infusion equation and PK parameters provided in the Nahata 1986[15] paper to also estimate fraction unbound using the regression equation from Fukumoto 2009[18] (Figure 1b).

Intermittent short-infusion

$$MD = \frac{Cpssmax\ (Cl)\cdot(tin)\cdot(1 - e^{-k\tau})}{(1 - e^{-ktin})\ e^{-ktmax}}$$

$tmax = 0$ *and starts from the end of infusion*

$$LD = (C_{max,ss})(V)$$

Simulations (N = 4000 and 3000 for AMP and CRO, respectively) were conducted using PK-Sim v9.0 to determine the PTA of 2 guideline-recommended beta-lactam regimens (AMP 150 mg/kg/day every 6 hours, CRO 50 mg/kg/day every 24 hours).[2] The target PTA and MIC used were the same as previously described for the MCS modeling. Antibiotic concentrations were derived using pharmacokinetic parameters from published literature (Table 2).[13–18]

The following CLSI breakpoints were used for nonmeningitis infections: susceptible, intermediate, and resistant strains of *S. pneumoniae* were ≤1, 2, and ≥4 mg/L for CRO and ≤2, 4, and ≥8 mg/L for AMP (extrapolated from penicillin), respectively (where intermediate and resistant were considered nonsusceptible).[21] Additionally, EUCAST breakpoints used for susceptible and nonsusceptible strains were as follows: 0.5 and 2 mg/L for CRO and 0.5 and 1 mg/L for AMP.[22] The MIC data used in our study were based on 2018 surveillance from a program spanning almost 3 decades by the US Pediatric Multicenter Pneumococcal Surveillance Study Group (PMPSSG) focusing on isolates of *S. pneumoniae* from lower respiratory tract infections after PCV-13 vaccination from 2007–2018.[23,24] Each virtual patient was stochastically assigned an MIC based on the frequency distribution of PMPSSG susceptibility data from 2018.

Results

The CRO regimen achieved 100% PTA in the serum for 30% to 50% *f*T>MIC at both CLSI and EUCAST susceptible breakpoints and 2018 PMPSSG susceptibility data (Figure 3a and b and Tables 3 and 4, respectively) for both simulation methods (NONMEM and PK Sim). AMP regimen achieved >99% PTA in the serum for 30% to 50% *f*T>MIC at both CLSI and EUCAST susceptible breakpoints and 100% PTA in the serum for 30% to 50% represented in the assigned MIC based on 2018 PMPSSG susceptibility data (Figure 3a and b and Tables 3 and 4, respectively) for both simulation methods. CRO achieved 100% PTA in the serum even at both its CLSI "resistant" and EUCAST "nonsusceptible" breakpoints (i.e., 4 and 2 mg/L, respectively; Figure 3).

Serum and Epithelial Lining Fluid Data. Compared with serum, the PTA in the ELF was lower for AMP. As expected, given ELF penetration of 100% (Table 2), CRO achieved 100% PTA for 30% to 50% *f*T>MIC in both serum and ELF, even at the CLSI and EUCAST nonsusceptible breakpoints. At 30% to 40% *f*T>MIC in the ELF, 100% PTA was achieved at both CLSI and EUCAST susceptible MIC values, and at 30% *f*T>MIC, 100% PTA was achieved at the nonsusceptible breakpoint for AMP in the MCS. Whereas in the PK-Sim simulation, for the goal of achieving 30% *f*T>MIC in the ELF, 100% PTA was achieved at susceptible MIC values.

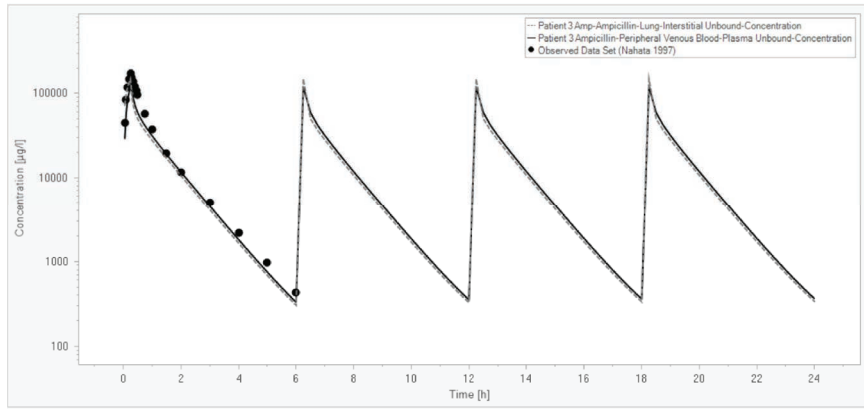
AMP and CRO both displayed good PTA profiles. Overall, the PTA was higher when using a more easily achieved lower %*f*T>MIC in both serum and ELF (30% vs 50%). In the serum, 100% PTA was achieved for AMP administered every 6 hours at 30%, 40%, and 50% *f*T>MIC when MIC was 8, 4, and 1 mg/L, respectively, for the MCS antibiotic concentrations (Figure 3a). One hundred percent PTA in serum was achieved for AMP administered every 6 hours at 30%, 40%, and 50% *f*T>MIC when MIC was 4, 1, and 0.5 mg/L, respectively, for the PK-Sim antibiotic concentrations (Figure 3b). The ELF data demonstrated 100% PTA achievement for AMP administered every 6 hours at 30%, 40%, and 50% *f*T>MIC when MIC was 4, 2, and 1 mg/L, respectively, for the MCS antibiotic concentrations (Figure 3a). One hundred percent PTA in ELF was achieved for AMP administered every 6 hours at 30%, 40%, and 50% *f*T>MIC when MIC was 4, 1, and 0.5 mg/L, respectively, for the PK-Sim antibiotic concentrations (Figure 3b). Given that the susceptible breakpoint for CRO is 1 (CLSI) and 0.5 (EUCAST) mg/L, 100% PTA was retained in both serum and ELF when MIC was ≤4 mg/L even at 50% *f*T>MIC for both simulation methods (Figure 3a and b).

Susceptibility Data. Compared with the pre–PCV-13 from 1993–2001, the susceptibility of *S. pneumoniae* to penicillin and CRO improved post–PCV-13 vaccination from 2007–2018 (Figure 2).[23,24] If this susceptibility trend continues to hold true, the currently recommended PCV-20 will further improve susceptibility to penicillin and CRO. The data on susceptibility impact by PCV-20 have not been published.

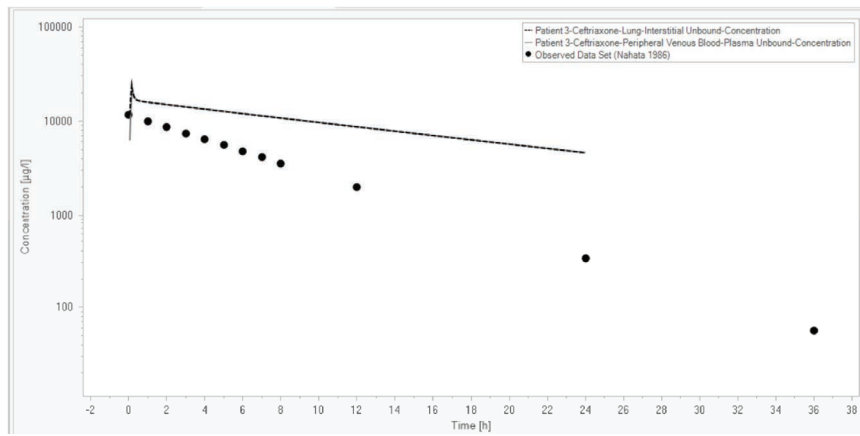
When using the PMPSSG susceptibility data obtained during the PCV-13 period, for AMP, 100% PTA was seen

Figure 1. PK-Sim Models (Concentration [mcg] vs Time [h]). **(a)** Ampicillin. **(b)** Ceftriaxone.

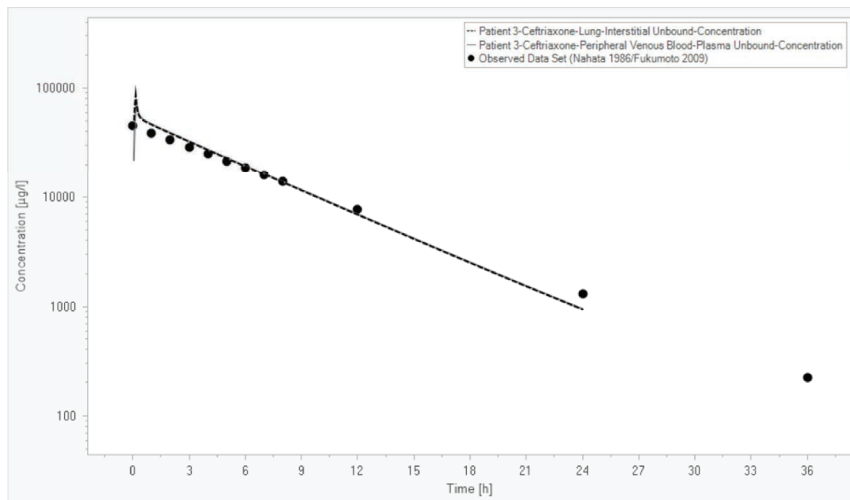
(a)



(b) Using protein fraction unbound (fu) = 0.05

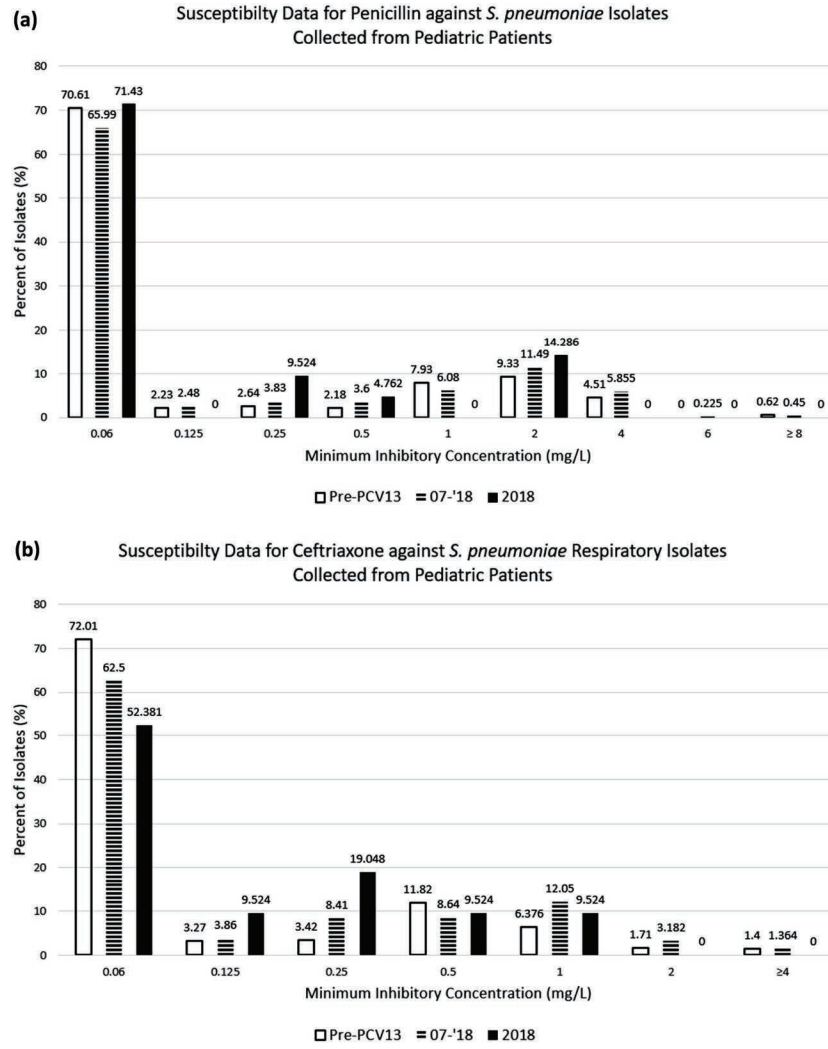


Using protein fraction unbound (fu) = 0.1952



at 30% to 50% *f*T>MIC when each patient was stochastically assigned an MIC based on the 2018 PMPSSG susceptibility data for both the MCS and PK-Sim serum antibiotic concentrations (Tables 3 and 4). For CRO, 100% PTA was seen at 30% to 50% *f*T>MIC when each patient was stochastically assigned an MIC based on the 2018

Figure 2. Susceptibility data for penicillin **(a)** and ceftriaxone **(b)** against *S. pneumoniae* respiratory isolates collected from pediatric patients from the Pre-PCV-13 Period (1993–2001) and post-PCV-13 period (2007–2018) minimum inhibitory concentration (MIC) vs percent of isolates.



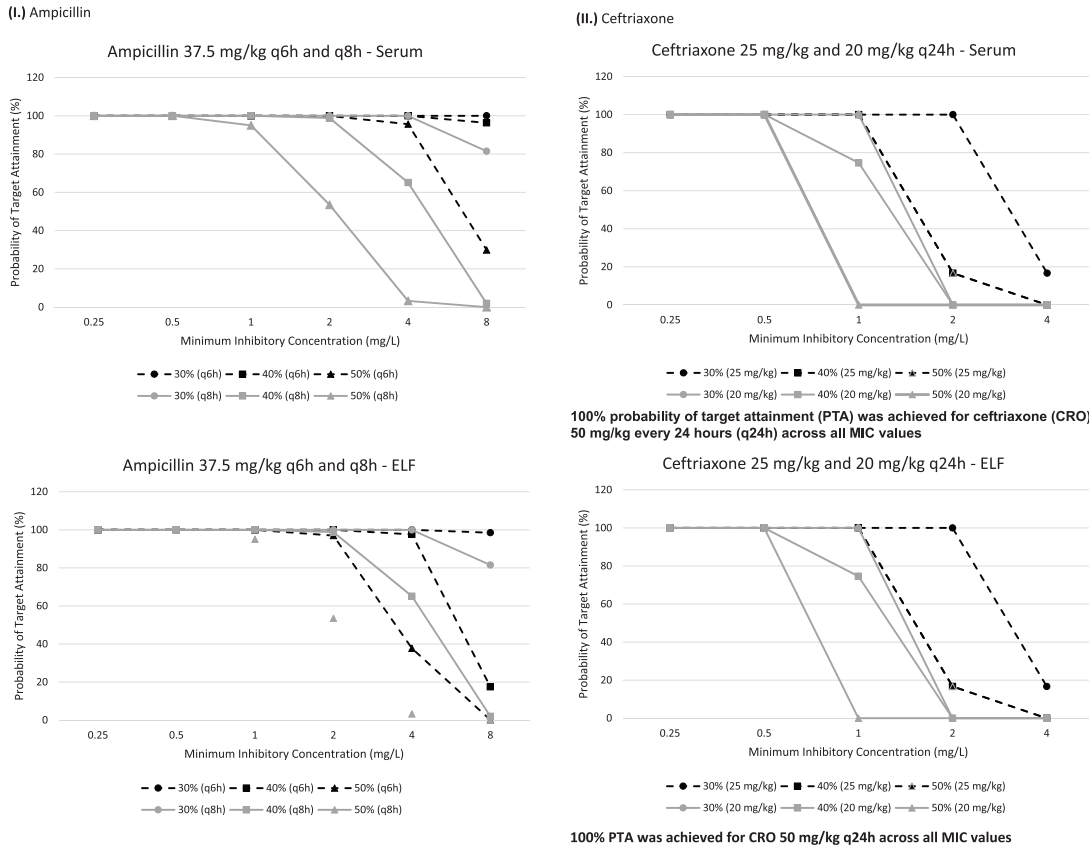
PMPSSG susceptibility data for both the simulation's serum and ELF antibiotic concentrations (Table 3a and b).

In addition to similar PTA profiles produced by both the MCS and PBPK simulations (Tables 3 and 4), the PK-Sim models were visually comparable to observed data. Both the digitized concentration versus time graph and the observed data set derived from the intermittent short-infusion equation (for AMP and CRO, respectively) matched the simulated curve, providing validity upon visualization (Figure 1a and b).

Discussion

While a wide range of antibiotics can easily be evaluated *in vitro* for antibacterial effect against *S. pneumoniae*, selecting the best antibiotic and dose effective for pneumonia is based on achieving sufficient antibiotic exposure at the site of infection. The rate of eradication of the pathogen at the site of infection varies between antibiotic classes with respect to the antibiotic concentration and the time the antibiotic is present at the site of infection. Pharmacodynamics is the term used to describe the concept of the different observed bacterial eradication rates as a function of dosing and, therefore, exposure. Some antibiotics kill the pathogens more rapidly at higher exposures, often in direct proportion to increasing antibiotic concentrations (e.g., aminoglycosides). Other antibiotics just require a specific amount of time at the site of infection in

Figure 3a. (NONMEM) Probability of target attainment of beta-lactams against *S. pneumoniae* using Clinical & Laboratory Standard Institute (CLSI)* and European Committee on Antimicrobial Susceptibility Testing (EUCAST)† breakpoints in the serum and epithelial lining fluid (ELF).



x-axis represents the percent fraction of time above the minimum inhibitory concentration.

* For susceptible and non-susceptible (intermediate and resistant isolates), minimum inhibitory concentration (MIC) = 2, 4, and 8 mg/L, respectively, for ampicillin.
* For susceptible and non-susceptible (intermediate and resistant isolates), MIC = 1, 2, and 4 mg/L, respectively, for ceftriaxone.
† For susceptible and non-susceptible, MIC = 0.5 and 1, respectively, for ampicillin.
† For susceptible and non-susceptible, MIC = 0.5 and 2, respectively, for ceftriaxone.

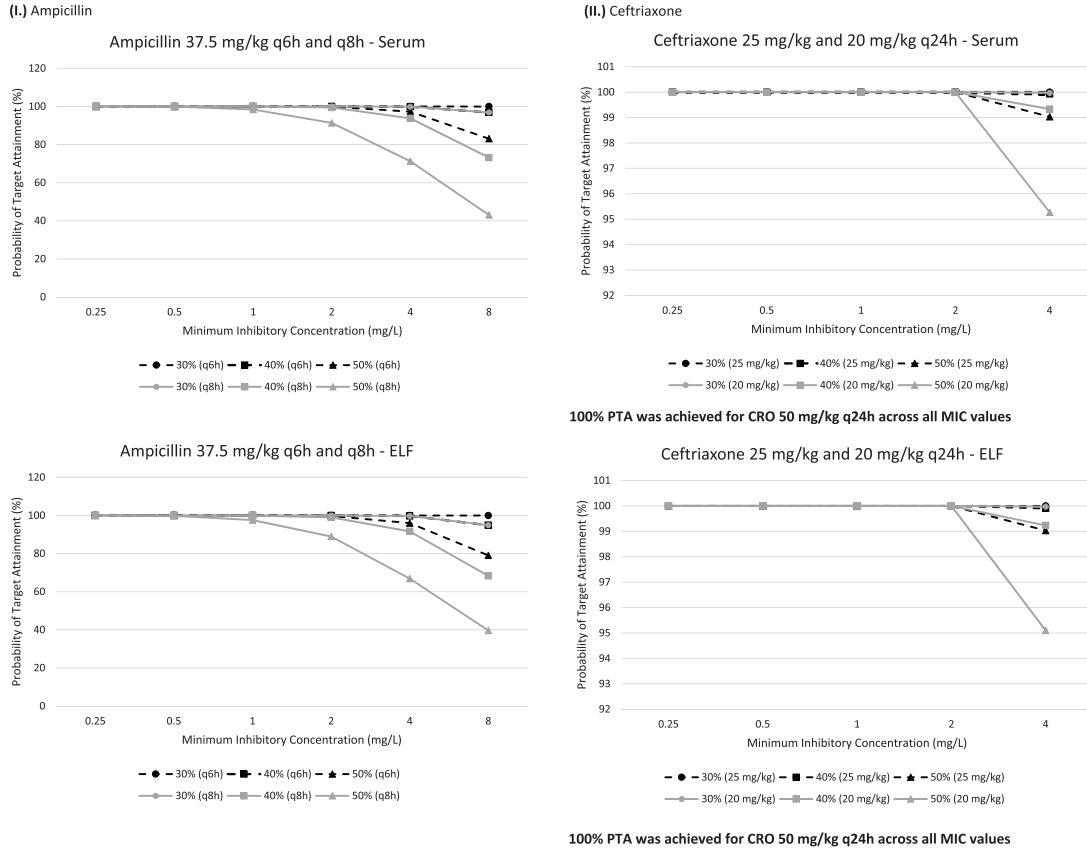
concentrations of free, unbound antibiotic above the MIC to kill the pathogen (e.g., beta-lactams), described as %*f*T>MIC. In this scenario, higher concentrations do not enhance rapid killing, nor does prolonged exposure beyond that required for inhibition.

The best empiric antibiotic dose is the one that is sufficient to cure the specific infection in most children. Achieving the antibiotic exposure associated with a cure in 90% to 95% of those infected is a standard target for otherwise healthy patients with non-central nervous system infections. In special circumstances, such as a neutropenic host, where failure may lead to death, 98% to 99% would be a more appropriate target to achieve. Higher doses may be appropriate and well tolerated for some classes of antibiotics (beta-lactams); however, for others (aminoglycosides), higher doses should be avoided as they can be associated with increased side effects.

Using available data for susceptibility of pneumococcus to beta-lactams and population pharmacokinetics of AMP and CRO during the creation of the PIDS/IDSA Pediatric CAP Guidelines, efforts were made to incorporate pharmacodynamic dosing concepts into the actual recommendations, rather than merely citing literature on doses previously used in clinical trials.[2] A full explanation of the rationale behind pharmacodynamic dosing was not presented in the guidelines. We now present a more complete explanation of the way in which pharmacodynamics, MCS, and PK-Sim PBPK modeling can be used to determine the most appropriate dose to recommend to health care providers based on the current susceptibilities of clinical isolates collected from pediatric patients.

We report the first MCS of the pharmacodynamics of PIDS/IDSA guideline-recommended beta-lactam

Figure 3b. (PK-Sim) PTA of beta-lactams against *S. pneumoniae* using CLSI* and EUCAST† breakpoints in the serum and ELF.



x-axis represents the %fT>MIC.

* For susceptible and nonsusceptible (intermediate and resistant isolates), MIC = 2, 4, and 8 mg/L, respectively, for ampicillin.
* For susceptible and nonsusceptible (intermediate and resistant isolates), MIC = 1, 2, and 4 mg/L, respectively, for ceftriaxone.
† For susceptible and nonsusceptible, MIC = 0.5 and 1, respectively, for ampicillin.
† For susceptible and nonsusceptible, MIC = 0.5 and 2, respectively, for ceftriaxone.

regimens for pediatric CAP in the serum and ELF before and after the era of conjugate pneumococcal vaccination with PCV-13. Using the PMPSSG penicillin and CRO susceptibility data for *S. pneumoniae* strains before and after the advent of PCV-13, we observed that a vast majority of strains had MIC values well below even the EUCAST breakpoints for susceptibility both before and after widespread use of PCV-13 (77.6% [N = 500 of 644] and 75.9% [N = 337 of 444] for penicillin; 90.5% [N = 582 of 643] and 83.4% [N = 367 of 440] for CRO, respectively), a trend that we believe will continue in the era of PCV-20 vaccine.[23,24]

Our data demonstrated that guideline-recommended regimens for both AMP and CRO for pediatric CAP are pharmacodynamically effective against recent *S. pneumoniae* strains because they achieved desirable pharmacodynamic parameters, including the concentrations via MCS and PK-Sim that displayed good PTA profiles in both serum and ELF. These findings support the first-line use of beta-lactams for the treatment of community-acquired pediatric CAP.[25–27] Furthermore, adherence to guideline recommendations has not been associated with adverse events, and the use of narrow-spectrum antibiotics (i.e., penicillins), as compared with vancomycin and broad-spectrum antibiotics previously used for penicillin-resistant pneumococci, resulted in shorter hospital stay.[2,28–30]

Of note, in our study, we evaluated standard doses on the lower end of the dosing range from guideline recommendations from 2011 and additional doses below the recommendations. As these doses have shown sufficient pharmacodynamic attainment in our analyses, higher doses are not likely to be necessary for the treatment of routine pediatric CAP, given the current susceptibility profiles of pneumococcus. In fact, most *S. pneumoniae* clinical isolates modeled in our study displayed MICs well below the CLSI and EUCAST susceptible breakpoints for penicillin, AMP, and CRO

Table 3. Probability of Target Attainment from NONMEM of Beta-Lactam Regimens Against *Streptococcus pneumoniae* with Antibiotic Concentrations Using 2018 MIC PMPSSG Susceptibility Data With Random Assignment of Minimum Inhibitory Concentration for Patients in the Serum and Epithelial Lining Fluid

%*f*T>MIC	Concentration Site	Probability Target Attainment (%)*		
		Ampicillin 37.5 mg/kg every 6h	Ampicillin 37.5 mg/kg every 8h	Ceftriaxone 20 mg/kg every 24h†
30	Serum	100	100	100
	ELF	100	100	100
40	Serum	100	99.85	97.6
	ELF	100	95.67	97.61
50	Serum	100	92.72	90.36
	ELF	99.6	85.97	90.36

%ft>MIC, percent fraction of time above the minimum inhibitory concentration; ELF, epithelial lining fluid; MIC, minimum inhibitory concentration; NONMEM, nonlinear mixed-effects modeling; PMPSSG, Pediatric Multicenter Pneumococcal Surveillance Study Group

* Patients 1–6

† 100% probability of target attainment was achieved for ceftriaxone 25 mg/kg and 50 mg/kg q24h

Table 4. Probability of Target Attainment from PK-Sim of Beta-Lactam Regimens Against *Streptococcus pneumoniae* with Antibiotic Concentrations Using 2018 MIC PMPSSG Susceptibility Data With Random Assignment of Minimum Inhibitory Concentration for Patients in the Serum and Epithelial Lining Fluid

%*f*T>MIC	Concentration Site	Probability Target Attainment, %		
		AMP 37.5 mg/kg every 6h*	AMP 37.5 mg/kg every 8h*	CRO 20 mg/kg every 24h†‡§
30	Serum	100	100	100
	ELF	100	100	100
40	Serum	100	99.95	100
	ELF	100	99.85	100
50	Serum	100	98.98	100
	ELF	100	98.73	100

%ft>MIC, percent fraction of time above the minimum inhibitory concentration; AMP, ampicillin, CRO, ceftriaxone, ELF, epithelial lining fluid; MIC, minimum inhibitory concentration; PMPSSG, Pediatric Multicenter Pneumococcal Surveillance Study Group

* Patients 2–5 only

† Patients 2–4 only

‡ Using protein fraction unbound (fu) = 0.05 and 0.1952

§ 100% probability of target attainment was achieved for CRO 25 mg/kg and 50 mg/kg q24h

both before and after the pneumococcal conjugate vaccine use was widespread.

There are several limitations to our analysis. The pharmacokinetic parameters used in our simulations often originated from older, small studies with varying methodologies. In addition, some parameters were extrapolated from adult data because no pediatric data were available. This analysis was only preliminary, and prospective, controlled studies need to be conducted to confirm findings. Analyzing these regimens in the context of more resistant *S. pneumoniae* strains and in subjects, real or simulated, with altered pharmacokinetics (i.e., critically ill and renally impaired or those with augmented renal clearance) may also be warranted. Additionally, the use of breakpoints, which are an interpretation of the MIC, may underestimate the ability of a beta-lactam antibiotic to successfully treat an infection, as higher doses of AMP and CRO may achieve the required target exposure for pneumococci with higher MICs, even for strains labeled as nonsusceptible.

PBPK modeling is an area that holds the potential to further validate dosing recommendations in populations with scarce clinical data. PK-Sim is a whole-body PBPK modeling tool that can be used to predict human drug concentrations based on the physiologic properties of a drug and preclinical data in patients of various ethnicities, ages, and disease states. One of the major advantages of PK-Sim is that enzyme synthesis and degradation can be modeled to predict concentrations of parent drugs and metabolites at any given time.

These models allow the integration of data that are not traditionally used in PK modeling, which include drug properties, physiological changes, and biological parameters that can differ between populations of individuals. Generated PBPK models for both AMP and CRO yielded similar PTA to those generated by the MCS with >98% PTA at 30%, 40%, and 50% *f*T>MIC in both serum and ELF. We originally developed models for penicillin G and amoxicillin, but these were not included because of a lack of observed pediatric data to validate the use of the model.

However, PK-Sim comes with its own limitations. The program itself requires ample clinical trial data to validate PBPK models that are able to simulate concentrations adequately. For this reason, models for penicillin G and amoxicillin were omitted. Current published literature with the mention of PK-Sim in the methodology mentions the scaling of adult PBPK models to develop a pediatric model, possibly due to a lack of clinical trial data. In this study, physiologic drug properties and pharmacokinetic parameters were collected from various databases as well as published literature, which were then input into PK-Sim for simulation. As this is a preliminary analysis, a dedicated study collecting the physiologic properties of the drug, pharmacokinetic parameters of the intended study population, and observed concentration data are needed to confirm simulated concentrations and help rationalize the difference in PTAs observed. Alternatively, an adult PBPK model could be used to develop a pediatric model, which could then be further assessed for validity by comparing simulated concentrations to observed concentrations from the available scientific literature on the drug of choice.

Conclusion

Using MCS, pharmacodynamic-based dosing of beta-lactams achieves appropriate antibiotic concentrations in the serum and ELF for the treatment of CAP caused by *S. pneumoniae*. Simulated antibiotic concentrations using PK-Sim further confirm these results for both AMP and CRO, highlighting the potential of PBPK modeling in aiding decisions for dose-finding studies or guideline recommendations for various populations.

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Disclosure. The authors declare no conflicts or financial interest in any product or service mentioned in the manuscript, including grants, equipment, medications, employment, gifts, and honoraria. The authors had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. All authors attest to meeting the four criteria recommended by the ICMJE for authorship of this manuscript.

Acknowledgments. This research was supported by Grant Number R01 HD095547 to JSB from the Eunice Kennedy Shriver National Institute of Child Health and Human Development. The content is solely the responsibility of the authors and does not necessarily represent the official views of the Eunice Kennedy Shriver National Institute of Child Health and Human Development, or the National Institutes of Health. Preliminary results were presented at the Annual Meeting of the American Society for Clinical Pharmacology & Therapeutics, Virtually, on March 16–18, 2022.

Submitted. June 26, 2024

Accepted. August 27, 2024

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