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Publication Date

DOI

Peer reviewed

ORIGINAL ARTICLE

Prolonged Post-Discontinuation Antibiotic Exposure in Very Low Birth Weight Neonates at Risk for Early-Onset Sepsis

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Background. Premature, very low birth weight (VLBW) neonates are at risk for early-onset sepsis and receive ampicillin and gentamicin post-birth. Antimicrobial stewardship supports short-course antibiotics, but how long antibiotic concentrations remain therapeutic post-last dose is unknown.

Methods. Using Monte Carlo simulations (NONMEM 7.3), we analyzed antibiotic exposures in a retrospective cohort of 34 689 neonates (<1500 g, 22-27 weeks of gestation). Therapeutic exposure for ampicillin and gentamicin was evaluated relative to the minimum inhibitory concentration (MIC) for common pathogens (MIC 0.25-8 mcg/mL for group B s*treptococcus* [GBS] and *Escherichia coli*). Post-discontinuation antibiotic exposure (PDAE) was defined as the time from the last dose to time when concentration decreased below MIC.

Results. Neonates had a median (range) gestational age of 26 (22-27) weeks and BW, 790 g (400-1497) . All ampicillin dosing regimens (50-100 mg/kg every 8-12 hours for 2-6 doses) achieved therapeutic exposures > MIC range. After the last dose, the PDAE mean (95% confidence interval [CI]) ranged from 34 to 50 hours (17–79) for *E. coli* (MIC 8) and 82 to 104 hours (95% CI: 39-122) for GBS (MIC 0.25); longer PDAE occurred with higher dose, shorter interval, and longer course. Short-course ampicillin (2 doses, 50 mg/kg every 12 hours) provided PDAE 34 hours for *E. coli* and 82 hours for GBS. Single-dose 5 mg/kg gentamicin provided PDAE > MIC 2 for 26 hours.

Conclusions. In VLBW neonates, ampicillin exposure remains therapeutic long after the last dose. Short-course ampicillin provided therapeutic exposures throughout the typical blood culture incubation period.

Key words. ampicillin; antimicrobial stewardship; early-onset sepsis; gentamicin; Monte Carlo simulation; neonatal sepsis; neonate; pharmacokinetics.

Early-onset sepsis (EOS) is a potentially life-threatening systemic bacterial infection occurring in 0.5% of newborns within the first 72 hours after birth. In a recent multistate report of 1484 EOS cases, 11% died and 6% of survivors had sequelae at discharge [1]. Group B *streptococcus* (GBS), *Escherichia coli*, and *Viridans streptococci* were the most common pathogens, accounting for 80% of cases. Extremely preterm and very low birth weight (VLBW, birth weight < 1500 g) infants experience a higher incidence of EOS and EOS-attributed mortality that is consistently reported to be at least an order of magnitude higher relative to term infants [1]. Premature VLBW infants who are considered critically ill often exhibit cardiopulmonary

insufficiency that can be attributed to premature lung development, sepsis, or both. As a result, most of the VLBW infants receive empiric antibiotics for at least 48 hours after birth, while blood culture results are pending. Even with negative cultures, clinicians are often hesitant to discontinue empiric antibiotics resulting in prolonged courses of antibiotics of ≥5 days [2]. This prolonged antibiotic exposure in the first week after birth has been associated with an increased risk of infectious and non-infectious morbidities and mortality as well as changes in the infant's microbiome [3, 4].

Antimicrobial stewardship efforts are increasing in neonatal intensive care units (NICUs). Rates of prolonged early antibiotic courses, defined as those initiated within the first 72 hours of life and continued for ≥5 days, have declined to 30%–40% of VLBW neonates [2]. Based on one systematic review, a reduction in antimicrobial utilization through antimicrobial stewardship programs in children's hospitals did not negatively impact patient outcomes [5]. In light of antimicrobial stewardship programs that support the use of short courses of antibiotics, prompt discontinuation of therapy is prudent once an infection is no longer suspected [6].

When a robust and precise population-based pharmacokinetic model is available in the specific patient population, Monte Carlo simulation is a powerful methodology that provides an opportunity to improve our understanding of the relationship between drug exposure (which is based on drug dosing) and clinical outcomes, encompassing both efficacy and safety. This approach has been applied to the dosing of antimicrobial drugs in neonates, in whom the pharmacodynamic thresholds for therapeutic efficacy are thought to be similar across different neonatal age groups [7, 8].

Traditionally, studies of antibiotic dosing regimens have not considered exposures after discontinuation of therapy. We hypothesized that VLBW infants receiving empiric antibiotics shortly after birth would have prolonged antibiotic exposures after discontinuation due to lower drug clearance. Therefore, this new concept of post-discontinuation antibiotic exposure (PDAE) warranted further exploration in our effort to promote antimicrobial stewardship in this high-risk population. We used Monte Carlo simulation methodology to characterize PDAE of the most common empiric antibiotics, ampicillin and gentamicin, administered shortly after birth among preterm VLBW neonates (<28 weeks of gestation and <1500 g BW) at risk for EOS.

METHODS

Design
We performed a pharmacokinetic-pharmacodynamic simulation study using data from infants cared for in the Pediatrix Medical Group NICUs. The Pediatrix Medical Group Clinical Data Warehouse contains data obtained from admission notes, daily progress notes, and discharge summaries, including demographic data, medications, laboratory results, and diagnoses [9]. This study was approved by the Duke University Institutional Review Board as exempt research.

Subject Selection
Using the Pediatrix Medical Group Clinical Data Warehouse, we created a virtual population of infants who met the following criteria: preterm neonates with gestational age (GA) <28 weeks, postnatal age (PNA) <7 days, VLBW ≤1500 g, and receipt of ampicillin and gentamicin on day 0–1 of age. Demographic data, pertinent covariates (including BW, postmenstrual age, and serum creatinine), antibiotic utilization, and culture results were extracted.

Model Selection
A PubMed search for ampicillin and gentamicin population-based pharmacokinetic models in neonates was performed [10–17]. From the search results, the population-based pharmacokinetic models used in our simulation study were selected based on the demographic characteristics of neonates in the

model that most closely fit our target study population: preterm neonates with GA < 28 weeks, PNA < 7 days, and BW ≤ 1500 g (Supplementary Table 1) as well as model robustness and sample sizes included in the original studies. The models with the closest match to our study population were the ampicillin model by Tremoulet et al [16] and the gentamicin model by DiCenzo et al [10].

Monte Carlo Simulations
Simulations were performed using the final population-based pharmacokinetic models to determine the antibiotic exposures during the antibiotic course and the distribution of PDAE after the last dose of antibiotics. Pharmacokinetic parameters, including volume of distribution, clearance, half-life, and elimination rate constant (k), were calculated for each patient. Simulations (ie, one per subject, N = 34 689) were performed using NONMEM 7.3 (Icon, Dublin, Ireland) to generate concentration time profiles for the most commonly used dosing regimens of ampicillin 50–100 mg/kg/dose every 8–12 hours for 24–48 hour courses (ie, 2-6 doses) and 1 dose of 5 mg/kg gentamicin. Concentrations were predicted every 6 hours during therapy and up to 4 days after antibiotic discontinuation (PDAE). Interindividual variability and residual error were integrated into the simulations based on the data from selected models. For gentamicin, we evaluated concentration over time, as well as maximum concentration (C_{max}) and area under the curve over 24 hours (AUC_{24}). Total, rather than free, drug concentration was used in this study, due to low protein binding of ampicillin and gentamicin reported in preterm neonates [18].

PDAE definitions were defined as specific to the pharmacodynamics properties of each drug. For ampicillin, the PDAE was defined as the duration of time between the last dose and the time ampicillin concentrations fell below the minimum inhibitory concentration (MIC); this definition ensures that the ampicillin concentration was above the MIC for 100% of the dosing interval. For gentamicin, the PDAE was defined in 2 ways: (1) the duration of time between the single dose administered and the time at which the concentration decreased below the MIC susceptibility breakpoint of 2 mcg/mL for *E. coli* and (2) the duration of time between the dose of gentamicin and the time at which the AUC_{24} decreased below 100 mcg-h/L, which has been proposed as a therapeutic target for *E. coli* [10, 19, 20].

The susceptible interpretative breakpoints were obtained from the United States Committee on Antimicrobial Susceptibility Testing (USCAST; http://www.uscast.org) and European Committee on Antimicrobial Susceptibility Testing (EUCAST; http://www.eucast.org), which had concordant MIC values, except for *Listeria monocytogenes* with breakpoint obtained from EUCAST. For ampicillin, the MIC susceptible breakpoint values that were evaluated ranged from 0.25 to 8 mcg/mL to cover the most common EOS pathogens, GBS, and *E. coli*, respectively, as well as to cover the range of

MIC susceptibility breakpoints for less common organisms, including *L. monocytogenes* (MIC 1), *V. streptococci* (MIC 0.5), and *Enterococcus* (MIC 8). For gentamicin, the susceptibility breakpoint MIC of 2 mcg/mL was used for *E. coli*.

Pharmacokinetic Analysis

R version 3.5.0 was used for statistical computation and graphical visualization. Elimination curves were plotted using a decay equation, $C = C_o * e^{(-kt)}$, with elimination constant k calculated for each patient from simulation-derived volume of distribution and clearance. The mean and 95% confidence interval (CI) of drug concentration was computed every 6 hours for up to 4 days after the last dose in order to generate visual curve plots of the plasma concentration profiles after a various dosing regimen of ampicillin and 1 dose of gentamicin. The AUC at 24-hour interval for gentamicin was calculated using the trapezoidal rule.

RESULTS

Our study population consisted of 34 689 one-day-old preterm neonates born at a median of 26 weeks' gestation who met the study criteria and were included in our simulations (Table 1). Applying the published population-based pharmacokinetic models in our study population, the median volume of distribution and clearance for simulated subjects were 0.32 L/kg and 0.032 L/kg/h for ampicillin, and 0.39 L/kg and 0.025 L/kg/h for gentamicin, respectively, which are consistent with reported values in the literature [15, 21]. The concentration profiles of ampicillin (at different doses, dose intervals, and duration) and gentamicin (one 5 mg/kg dose), simulated up to 4 days post-antibiotic discontinuation, are depicted in Figure 1.

Ampicillin

During therapy, all evaluated ampicillin dosing regimens provided therapeutic exposure above 8 mcg/mL (ie, MIC breakpoint for *E. coli*). After the last 2–6 doses, the mean (95% CI)

duration of PDAE for ampicillin ranged from 34 to 50 hours (17-79) for *E. coli* MIC 8 mcg/mL and 82 to 104 hours (95% CI: 39-122) for GBS MIC 0.25 mcg/mL (Table 2 and Figure 1A–F), respectively. The PDAE was longest for GBS, due to its low MIC breakpoint. An ampicillin dose increase from 50 to 100 mg/kg or dosing interval decrease from every 12 to 8 hours was associated with an increase in the duration of PDAE. A short course of ampicillin 50 mg/kg every 12 hours × 2 doses achieved a modest mean PDAE of 34 hours for *E. coli* at a MIC of 8 mcg/mL and 82 hours for GBS at a MIC of 0.25 mcg/mL.

Gentamicin

A single 5 mg/kg dose of gentamicin provided concentrations above 2 mcg/mL (MIC breakpoint for *E. coli*) for a mean PDAE of 26 hours (95% CI: 16-41; Figure 1G). Other therapeutic exposure targets unique to gentamicin include C_{max} and AUC_{24} [7]. The mean steady-state peak concentration was 10 mcg/mL (95% CI: 6.4-15), resulting in a peak-to-MIC ratio of 5 based on an *E. coli* MIC breakpoint of 2 mcg/mL. The mean AUC_{24} exposure was 123 mcg-h/mL (95% CI: 88-165; Figure 2), and 89% of all infants achieved $AUC_{24} > 100$ mcg-h/L throughout the first 24 hours. If we used the therapeutic target of AUC_{24} at or above 100 mcg-h/mL, then the PDAE using endpoint $AUC_{24} < 100$ was 24 to 30 hours.

DISCUSSION

In this study of simulated drug exposures, we demonstrated that VLBW neonates receiving common clinical dosing regimens of ampicillin and gentamicin after birth continue to have therapeutic exposure of ampicillin against common EOS pathogens from 1.5 to 3.5 days after the last dose of a 2-dose, 50mg/kg every 12-hour regimen. Even at a high MIC of 8 mcg/mL, the PDAE at the 2.5% is 17 hours. Prolonged exposure after discontinuing therapy is unnecessary, unlikely to be recognized by clinicians, and potentially harmful. This PDAE concept provides an exposure metric to reevaluate dosing regimens and a new antimicrobial stewardship opportunity for this highly vulnerable population. Additionally, PDAE awareness may help clinicians use shorter empiric antibiotic courses when cultures are negative.

Clinical trials and drug dosing evaluation in neonates are difficult. When robust and precise population pharmacokinetic models exist, then Monte Carlo simulations of large neonatal cohorts provide an ethical and cost-effective opportunity to evaluate novel dosing considerations. We innovatively created this PDAE metric as a method to identify unnecessary antibiotic exposures, reevaluate dosing regimens, and improve antimicrobial stewardship. The prolonged ampicillin PDAE after the traditional 48-hour dosing period was much longer than clinicians would predict and can be explained by both the magnitude of per kilogram dosing and delayed drug clearance. These PDAE simulations demonstrate

Table 1. Demographic Data of Simulated Population

Drug	Ampicillin[16,a,b]	Gentamicin[10,a,c]
Sample size	34,689	
GA (wk)	26 (22–27)	
BW (kg)	0.790 (0.400-1.497)	
Postnatal age (d)	1 (1)	
PMA (wk)	26 (22-27)	
SCR (mg/dL)	0.90 (0.05-4.7)[d]	
Volume (L/kg)	0.32 (0.16-0.60)	0.39 (0.09-1.28)
CL (L/h/kg)	0.032 (0.007-0.159)	0.025 (0.006-0.080)

Abbreviations: BW, birth weight; CL, clearance; GA, gestational age; N/A, not applicable or available; PMA, post-menstrual age; SCR, serum creatinine; WTKG, weight in kg; V, volume of distribution
[a]Numbers, except for sample size, represent median with range in parentheses.
[b]Ampicillin model: V = 0.399 * WTKG and CL = 0.078 * WTKG * (0.6/SCR)[0.428] * (PMA/37)[1.34].
[c]Gentamicin model: CL = (0.00504 + [0.00108*GA]) *BW; median V and CL values with respective ranges for GA < 28 weeks were used.
[d]At baseline from start of antibiotic therapy, most of the subjects (82%) had SCR < 1 mg/dL, 16% with 1 to 2 mg/dL, and <1% with >2 mg/dL.
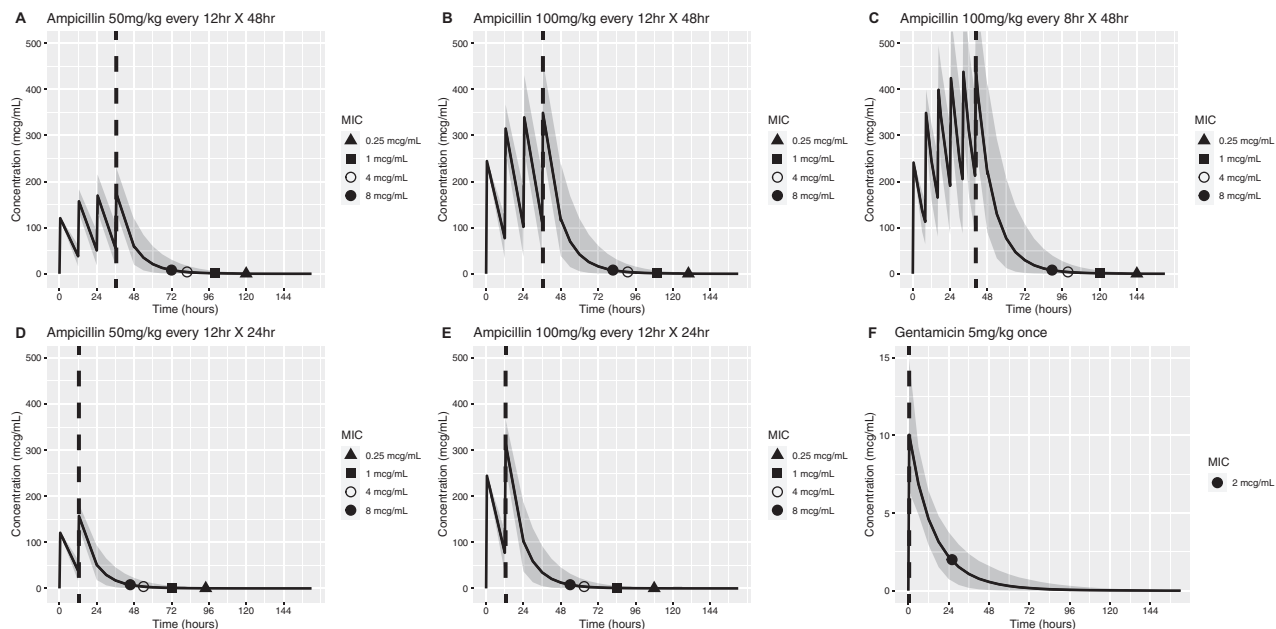
Figure 1. Simulated plasma concentration profiles of ampicillin and gentamicin relative to susceptibility breakpoints of common pathogens. Blue solid line denotes mean drug concentration; shaded area, 95% CI; red dashed line, time at last antibiotic dose; shape symbols indicate time points at which mean antibiotic concentrations decay to susceptibility breakpoint MIC for different bacteria post-antibiotic discontinuation. PDAE represents the time between the red line and symbol. (A–C) represent drug exposure during standard 48-h ampicillin dosing regimens; (D) and (E) represent drug exposure after proposed shortened, 2-dose ampicillin regimens; (F) represents gentamicin exposure after a single, high-dose, extended interval regimen. MIC susceptibility breakpoints for ampicillin range from 0.25 mcg/mL for GBS to 8 mcg/mL for *Escherichia coli*. Ampicillin MIC susceptible breakpoints for less common organisms include *Listeria monocytogenes* (MIC 1), *Viridans streptococci* (MIC 0.5), and *Enterococcus* (MIC 8). For gentamicin, the susceptibility breakpoint MIC of 2 mcg/mL was used for *E. coli*. Abbreviations: CI, confidence interval; GBS, group B *streptococcus*; MIC, minimum inhibitory concentration; PDAE, post-discontinuation empiric antibiotic exposure.

that a shorter 2-dose ampicillin course, with the last dose 12 hours after a blood culture, would still provide therapeutic ampicillin exposure during the traditional 48-hour blood culture incubation window to rule out bacteremia. Efforts to minimize ongoing PDAE could potentially mitigate the risk of microbiome alteration, development of antimicrobial resistance, and drug toxicity. The clinical impact of the shorter ampicillin courses and limiting PDAE requires further exploration.

VLBW preterm infants with negative cultures at birth are vulnerable to prolonged antibiotic exposures. Prolonged early courses of antibiotics (≥5 days) in preterm neonates with negative blood cultures at birth, while common in clinical practice, are associated with increased risk of late-onset infections, necrotizing enterocolitis, changes in microbiome, and mortality [2]. Additionally, antibiotic use can negatively add selective pressure on the intestinal microbiota for up to 1 year [22, 23].

Table 2. Ampicillin PDAE Among Very Low Birth Weight Infants by Susceptibility Breakpoints of Common Bacterial Pathogens[a,b]

| Organism | Susceptible MIC (mcg/mL) | 2 Doses[c] | | 4 Doses[c] | | 6 Doses |
		50 mg/kg Q12 h	100 mg/kg Q12 h	50 mg/kg Q12 h	100 mg/kg Q12 h	100 mg/kg Q8 h
Escherichia coli[d]	8	34 ± 9.4 (17, 54)	42 ± 11 (22, 66)	36 ± 11 (18, 60)	46 ± 13 (22, 72)	50 ± 14 (24, 79)
	4	42 ± 11 (22, 66)	51 ± 13 (26, 78)	46 ± 12 (23, 72)	55 ± 15 (26, 84)	60 ± 16 (27, 91)
Listeria monocytogenes	1	60 ± 15 (30, 90)	72 ± 18 (34, 103)	64 ± 17 (30, 97)	74 ± 19 (35, 109)	80 ± 20 (36, 116)
Group B *Streptococcus*[e]	0.25	82 ± 19 (39, 114)	96 ± 21 (42, 126)	84 ± 21 (39, 120)	94 ± 21 (43, 126)	104 ± 20 (44, 122)

Abbreviations: MIC, minimum inhibitory concentration in mcg/mL; PDAE, post-discontinuation empiric antibiotic exposure; Q8, every 8 h; Q12, every 12 h.

[a]Numbers represent mean ± standard deviation (95% confidence interval) for the duration of therapeutic exposure (hours) from the last dose of ampicillin up to the MIC of bacterial pathogens commonly isolated in early-onset sepsis.

[b]Infusion time for ampicillin was 15–30 min.

[c]Last dose was 12 h for 2 doses, 36 h for 4 doses, and 40 h for 6 doses.

[d]MIC of 8 mcg/mL is also the breakpoint for *Enterococcus* spp.

[e]MIC of 0.25 mcg/mL is also the breakpoint for Streptococci groups A, B, C, and G; *Viridans streptococci* have MIC breakpoint of 0.5 mcg/mL.
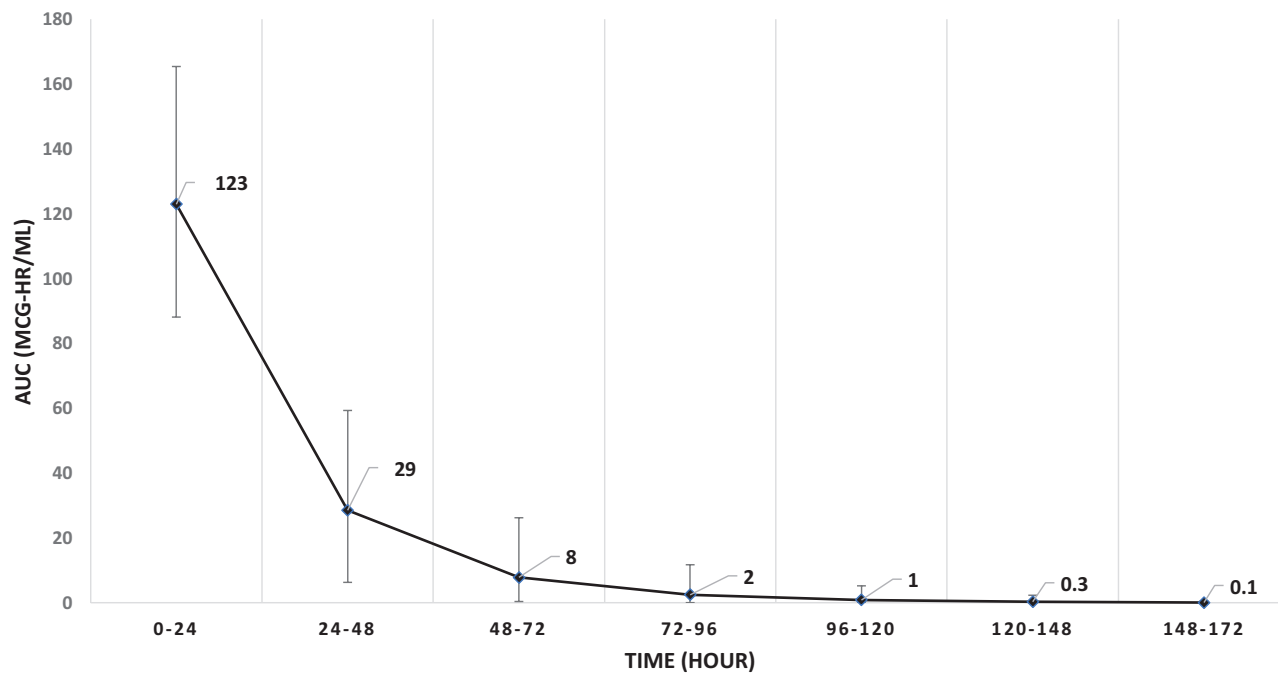
Figure 2. AUC profile after 1-dose gentamicin. AUC profile after 1 dose of gentamicin 5 mg/kg at 24-h interval. Black line represents mean and bar, 95% confidence interval. Abbreviation: AUC, area under the curve.

Minimizing antibiotic exposure in these VLBW infants during their first week of life may decrease their risk of developing infectious and noninfectious morbidities and mortality and preserve the antibiotic armamentarium as they are likely to remain hospitalized for treatment of their underlying medical conditions [3, 4]. Minimization of antibiotic administration and consequent exposure can be achieved by accounting for PDAE in our dosage regimens and encouraging the use of the shortest duration of empiric antibiotics.

From an antimicrobial stewardship perspective, clinician's awareness of PDAE could help minimize antibiotic exposures in critically ill premature infants with negative cultures. Their cardiopulmonary instability and small blood-volume cultures can make it difficult for clinicians to stop antibiotics even when cultures are negative. A recent study reported that 30%–40% of VLBW infants with negative cultures continue to receive antibiotics for 5 days or longer [2]. Awareness of the ongoing therapeutic PDAE of ampicillin after a 48-hour course could encourage clinicians to comfortably and prudently discontinue antibiotics at least by 48 hours for this challenging population. Molecular diagnostics to provide a more timely and reliable method for detecting bacteremia, although not yet available in most hospitals, could further limit empiric coverage to the shortest possible duration [24–28].

Interpretation and utility of PDAE depend on the pharmacodynamic properties of the antimicrobial drug. For time-dependent antimicrobials like ampicillin, the PDAE relates directly to the time at which the drug concentration decreases below the MIC [8]. For VLBW preterm neonates, a conservative approach to the pharmacodynamics of time-dependent antibiotics typically relies on maintaining exposures above the MIC for 100% of the dosing interval. The PDAE may be even longer if shorter exposures, 50%–75% of the dosing interval, were effective. In contrast, the pharmacodynamics of gentamicin is different and leads to distinct PDAE interpretation.

Gentamicin PDAE, although more difficult to interpret, was not prolonged. The high gentamicin dose with extended interval regimen reflects its pharmacodynamic properties, specifically, the concentration-dependent killing based on the peak-to-MIC ratio >5 and the post-antibiotic effect, which is characterized by ongoing growth suppression after the drug concentration falls below the MIC of an offending organism [8, 29, 30]. Our study confirmed therapeutic gentamicin exposures after a single 5 mg/kg dose based on the peak-to-MIC ratio of 5 for an *E. coli* MIC breakpoint of 2 mcg/mL [31]. The duration of therapeutic exposure must then account for the time the concentration is above the MIC (PDAE of 26 hours for *E. coli* with MIC 2 mcg/mL) followed by the post-antibiotic effect, which has been estimated in other studies to continue for at least another 7.5 hours [32, 33]. As such, the total antibacterial protective time after a 5 mg/kg gentamicin dose is predicted to be at least 33 hours. PDAE could also target the alternative $AUC_{24} >$ 100 mcg-h/mL efficacy metric, which in this study is predicted to be at least 24–30 hours and includes (or does not include) the post-antibiotic effect.

This novel PDAE metric may be a particularly important dosing consideration for neonates. In the NICU, drug dosing is often off-label and may not be supported by rigorous pharmacokinetic and safety studies. Preterm infants are at risk for higher or prolonged drug exposures since they often exhibit delayed drug clearance, due to immature renal function and inefficient drug metabolism. Renal drug clearance is particularly prolonged shortly after birth, a time when most of the VLBW infants receive many medications for their cardiopulmonary morbidities and risk for EOS. For drugs with high renal elimination such as ampicillin and gentamicin, different degrees of renal function will also impact their PDAE (ie, increased PDAE with decreased renal function). Notably, the use of the Pediatrix Medical Group Clinical Data Warehouse that contains a large dataset reflective of authentic patients provides a robust and clinically meaningful distribution of PDAE results. PDAE likely provides an important exposure metric for other antibiotics and for patients of all ages with delayed drug clearance.

There were 2 main limitations of this study. First, while we selected the most robust models that employed population-based pharmacokinetic modeling, the selected models also enrolled older infants by GA and PNA. Nonetheless, the selected models were the closest match to our target study population. Second, we did not assess actual antibiotic concentrations in our subjects, since this is the first-ever attempt to evaluate the presence and extent of PDAE. Notably, the use of a powerful pharmacologic tool to evaluate PDAE with simulated exposures allowed us to mitigate any risks to this vulnerable population. Also, we employed a large national database that identified more than 30 000 subjects for our study, consequently allowing us to minimize the number of simulations per subject, which increased the power of our study and maximized the accuracy of our prediction. Future studies are necessary to confirm PDAE (via pharmacokinetic sampling after antibiotic discontinuation) and to ascertain the safety and effectiveness of dosing practices that account for PDAE.

CONCLUSIONS

PDAE is an innovative metric designed to identify opportunities to reevaluate dose-exposure relationships, enhance antimicrobial stewardship, and minimize unnecessary antibiotic exposure. With the typical ampicillin dosing, simulated exposures demonstrate that premature VLBW neonates had therapeutic exposure for EOS pathogens long after discontinuation of therapy. A short 2-dose course of ampicillin, 50 mg/kg every 12 hours, appears to provide adequate antibacterial coverage pending blood culture results when the PDAE metric of 34 hours was accounted for. Exposure-driven dosing may enhance antimicrobial stewardship and potentially limit morbidities

that have been associated with prolonged antibiotic exposure. Prospective studies are necessary to confirm the relationship between PDAE and clinical outcomes.

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