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Ampicillin Dosing in Premature Infants for Early-onset Sepsis: Exposure-driven Efficacy, Safety, and Stewardship

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Abstract

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Objective: Define optimal ampicillin dosing for empiric early-onset sepsis (EOS) therapy in preterm neonates.

Study design: We simulated ampicillin concentrations in newborns (birthweight<1500g; gestational age 22–27 weeks), summarizing three 48-hour regimens: high 100mg/kg Q8hr, medium 100mg/kg Q12hr, and standard 50mg/kg Q12hr. Concentration data were analyzed for concentration above minimum inhibitory concentration (MIC), below neurotoxicity threshold (C_{max}≤140mcg/mL), and duration limited to 48 hours.

Results: Among 34,689 newborns, all dosing regimens provided concentrations above MIC through 48 hours, but C_{max} exceeded the neurotoxicity threshold. With the 4-dose standard regimen, >90% maintained concentrations >MIC beyond 48 hours. With the 2-dose regimen, newborns maintained the mean concentration >MIC within the 48-hour culture window and below neurotoxicity level. Infants 22–24 weeks' gestation had higher drug concentrations and more prolonged exposure duration than 25–27 weeks' gestation.

Conclusions: For EOS in preterm infants, two ampicillin doses (50mg/kg) provided optimal bactericidal exposures, while minimizing potential toxicity.

Keywords

early onset sepsis; antimicrobial stewardship; ampicillin

Ampicillin is the most commonly prescribed medication in the neonatal intensive care unit (NICU) [1], where it is primarily used along with an aminoglycoside as part of the empiric coverage for early-onset sepsis (EOS) [2, 3]. Recent United States cohort studies report that more than 75% of very low birth weight (VLBW; <1500 grams) infants received antibiotics in the first 3 days after birth [2, 4]. Despite its common use, ampicillin dosing is highly variable and ranges from 100–400 mg/kg/day. The most common dose regimen in clinical practice is 100 mg/kg/dose Q12 hours (Q12h) [5]. The Food and Drug Administration (FDA) ampicillin label and the American Academy of Pediatrics (AAP) group B *Streptococcus* (GBS) guidance recommends a lower standard dose, 50 mg/kg/dose Q12hr for preterm infants ≤34 weeks' gestation age (GA) [5, 6]. The AAP guidance recommends treating infants with GBS meningitis using a 3-fold higher regimen (100 mg/kg/dose Q8hr), regardless of GA [7]. In a recent United States survey, only 26% of level 3–4 NICUs reported using the standard 50 mg/kg dose regimen [8].

Optimal dosing should consider efficacy, safety, and stewardship. Beta-lactam antibiotics, such as ampicillin, follow time-dependent pharmacodynamics. Bactericidal effects typically require drug concentrations to be above the minimum inhibitory concentration (MIC) of common pathogens [9]. For preterm infants with serious infections, many suggest maintaining concentration above the MIC for the entire dosing interval (*f*T >MIC = 100%) [10]. This conservative metric accounts for the immunodeficiency of preterm infants, as well as the variability in drug exposure found in neonatal PK studies. In adults, high ampicillin concentrations have been associated with neurotoxicity, including seizures [11]. High concentrations are not necessary in newborns since common EOS pathogens have low MIC susceptibility breakpoints. In preterm infants, ampicillin concentrations remain

bactericidal for 2–3 days after the last dose; stewardship practices encourage limiting this unnecessary duration exposure [12].

Pharmacokinetic (PK) model-based simulation is a robust methodology to explore dose-exposure relationships, particularly when there is large variation in dosing practice and when dose-escalation studies would be difficult. We performed a simulation study to evaluate ampicillin exposures in a large retrospective cohort of VLBW infants. We aimed to define the optimal ampicillin dosing strategy for empiric EOS evaluations using exposure-based metrics for efficacy, safety, and stewardship. This is the first study to consider all three metrics simultaneously.

Methods

We created a large retrospective cohort of VLBW infants receiving care among the >300 Pediatrix Medical Group NICUs between 1997 and 2016, with covariate data obtained from the Pediatrix Medical Group Clinical Data Warehouse [13] using the following inclusion criteria: GA 22–27 weeks, postnatal age <7 days, birth weight (BW) <1500g, and receipt of ampicillin on day 0–1 of age. The study was approved by the Duke University Institutional Review Board as exempt research. Initial simulation analysis and complete methodology have been published [12].

Pharmacokinetic model-based simulated exposure

We used the ampicillin population-based PK model for neonates developed by Tremoulet et al. [5] since it most closely matched our target population. This model was derived from 143 ampicillin concentrations obtained from 73 neonates, including 21 neonates born at ≤34 weeks' GA (range 24–34 weeks) and postnatal age ≤7 days (median 1 day). Ampicillin volume of distribution (Vd) varied with weight and clearance (CL) varied with weight, postmenstrual age, and serum creatinine. Monte Carlo simulations using NONMEM 7.3 (Icon, Dublin, Ireland) with this population PK model were used to simulate ampicillin concentrations following three different dose regimens used in clinical care and/or recommended by either AAP and FDA guidance [5–7]: standard dose (defined as 50 mg/kg/dose Q12 hr), medium dose (defined as 100 mg/kg/dose Q12 hr), and high dose (defined as 100 mg/kg/dose Q8 hr).

For all dosing regimens, simulated infants received their first dose on day of birth and all simulated doses were administered intravenously over 20 minutes. Ampicillin was continued every 8–12 hours to provide 48 hours of therapeutic coverage. This 48-hour duration was chosen to represent the typical blood culture incubation window in clinical practice. The 4-dose, Q12hr regimens (standard and medium) provided the last dose at 36 hours and the 6-dose, Q8hr regimen (high dose) provided the last dose at 40 hours. Concentrations were summarized at 6-hour intervals from start of therapy through the 48-hour culture incubation time and up to 96 hours after discontinuing therapy. Maximum concentration (C_{max}) at steady-state and minimum concentrations after discontinuing therapy were also evaluated. Shorter courses were explored to limit ampicillin exposure after 48 hours.

Dose-exposure evaluation and pharmacodynamic exposure metrics

Ampicillin exposure was evaluated relative to the MIC susceptible interpretative breakpoints tables obtained from the United States Committee on Antimicrobial Susceptibility Testing (USCAST) [14] and European Committee on Antimicrobial Susceptibility Testing (EUCAST) [15] for the most common EOS pathogens, including GBS (MIC 0.25 mcg/mL), other *Streptococccus sp.* (MIC 0.5 mcg/mL), *Listeria monocytogenes (*MIC 1 mcg/mL*)*, and *E. coli* (MIC 8 mcg/mL). Bactericidal activity for beta-lactams is defined by the fraction of dosing interval time in which the free drug concentration remains above the MIC (*f*T>MIC) [9]. Ampicillin has low protein binding [6]; therefore, the total drug concentrations were used.

Ampicillin exposures were evaluated relative to three pre-specified targets for efficacy, safety, and antimicrobial stewardship. For efficacy, bactericidal activity was defined as the *f*T>MIC 100%) meaning that the ampicillin concentration was above the MIC for 100% of the dosing interval using the MIC susceptibility breakpoints 0.25, 1, and 8 mcg/mL for common EOS pathogens. For safety, we aimed to limit steady-state C_{max} to ≤140 mcg/mL, a concentration far above the MIC of common pathogens and a neurotoxicity and seizure threshold proposed in adults [16]. For stewardship, we aimed to limit therapeutic exposure to 48 hours. To determine duration of therapeutics exposure, we evaluated ampicillin concentrations after the last dose, including minimum concentration at 48, 60, 72, 84, and 96 hours after initiation of therapy. Shorter courses were explored to minimize concentrations beyond the 48-hour culture incubation window.

Statistical analysis

R version 3.5.0 (https://www.r-project.org/) was used for statistical computation and graphical visualization. Data were evaluated for the entire cohort, as well as in two groups stratified by GA (22–24 and 25–27 weeks). For three ampicillin dosing regimens, the mean and 95% confidence interval (CI) of ampicillin concentration were computed at 6-hour interval time points from start of antibiotics through 96 hours. Visual curve plots of the plasma concentration profiles were generated. Probability of target attainment (PTA) of infants achieving concentration over MIC was analyzed over time for different MIC susceptibility breakpoints. For duration of efficacy, we used the last time point at which ≥90% of infants had ampicillin concentrations above the MIC. For shorter course regimens, percent target attainment for efficacy was assessed for *f*T>MIC metric of 100, 75, and 50% of dosing interval.

Results

We used a population PK model to simulate ampicillin concentrations during 48-hour EOS evaluations in a cohort of 34,689 premature neonates born at a median (interquartile range) GA 26 (24–27) weeks and BW 790 (0.655–0.938) grams (Table 1). Neonates born at 22–24 weeks' GA had smaller BW, slower apparent ampicillin clearance, and a median predicted elimination half-life that was 1 hour longer than neonates born at 25–27 weeks' GA (Table 1). Table 2 summarizes the minimum and steady-state maximum ampicillin concentrations

for the standard, medium and high dose regimens (50–100 mg/kg/dose administered Q8–12 hours) commonly used during empiric 48-hour EOS evaluations.

All dose regimens achieved bactericidal ampicillin concentrations that were far above the MIC susceptibility breakpoints 0.25, 1, and 8 mcg/mL to cover GBS, other *Streptococcus sp. /Listeria*, and *E. coli,* respectively (Table 2 provides data by GA groups). At the end of the 48-hour culture incubation window, the mean (95% Cl) ampicillin concentrations for the entire cohort were 59.3 (19.4, 119), 119 (38.9, 239), and 221 (89.1, 413) mcg/mL in the standard-, medium-, and high-dose regimens, respectively. The bactericidal exposure target (*f*T>MIC 100%) was predictively achieved in 100% of infants through 48 hours (Figure 1). Even though the last dose was administered at 36–40 hours of age, the median ampicillin concentrations remained above the MIC for common pathogens through 72 hours (Table 2, Figure 1). The most premature neonates, 22–24 weeks' GA, accumulated more ampicillin with repeated dosing and at 48 hours, had concentrations 23% higher than neonates born at 25–27 weeks' GA (Table 2).

From a safety perspective, the steady-state C_{max} was far above the MIC and rarely below the neurotoxicity exposure metric. Only 5.4% (1869/34689) of infants receiving standard, 50 mg/kg, 4-dose regimen had $C_{max} \leq 140$ mcg/mL. The mean (95% CI) steady-state C_{max} for the entire cohort was 170 (133, 213), 349 (268, 463), and 446 (314, 628) mcg/mL for the standard-, medium-, and high-dose regimens, respectively (Table 2 provides data in GA groups). During a 48-hour course, neonates receiving this standard regimen had concentrations above the neurotoxicity exposure metric for a mean of 6.2 hours compared to 32 and 41 hours, for the 100 mg/kg medium- and high-dose regimens. Neonates receiving the medium- and high-dose regimens had 48-hour trough concentrations that still exceeded the neurotoxicity metric in 30% and 85% of neonates, respectively.

From a stewardship perspective and desire to avoid prolonged exposure, we evaluated concentrations after the last dose to determine total duration of therapeutic exposure. At the end of the 48-hour course (4 doses), 100% of infants in the standard 50 mg/kg Q12hr regimen still had concentrations >8 mcg/mL (MIC breakpoint *E. coli*) (Figure 1). After discontinuing therapy, the PTA for ampicillin concentration >MIC decreased over time based on the MIC susceptibility breakpoint. More than 90% of neonates maintained concentrations above the MIC for a total of 54 hours for MIC 8 mcg/mL (*E. coli*), 72 hours for MIC 1 mcg/mL (*Streptococcus sp. /Listeria*), and 78 hours for MIC 0.25 mcg/mL (GBS) (Figure 1). Infants born at 22–24 weeks' GA sustained higher post-discontinuation exposures with mean concentrations at 72 hours that were 62% higher than neonates 25–27 weeks' GA (Table 2).

The prolonged exposure after discontinuation led us to evaluate shorter courses. Ampicillin concentrations using a short 2-dose course, 50mg/kg at time 0 and 12 hours after blood culture, limited antibiotic exposure beyond 48 hours (Table 2). Ampicillin concentrations were below the neurotoxicity exposure metric for an average of 46.6 of the 48-hour course. At 48 hours, the mean concentration was 6.3 mcg/mL. More than 90% of neonates had concentrations above a MIC of 8, 1, and 0.25 mcg/mL through 42, 54, and 66 hours, respectively (Figure 1). For common gram-positive pathogens (MIC ≤1 mcg/mL), this

regimen achieved the bactericidal metric *f*T>MIC for 100% and 75% of dosing interval over 48 hours in 90% and 100% of infants, respectively. For *E. coli* (MIC 8 mcg/mL), this regimen achieved the bactericidal metric *f*T>MIC for 100%, 75%, and 50% of the dosing interval in 28, 79, and 100% of infants, respectively.

Figure 2 shows mean ampicillin concentrations with standard 50 mg/kg dosing regimens with an overlay of all three exposure metrics. Exposures with the 2-dose regimen were above the MIC breakpoint of common pathogens, below the neurotoxicity exposure metric, and within the 48-hour culture incubation window.

Discussion

Simulated ampicillin exposures in this large VLBW cohort allowed us to define optimal dosing for empiric EOS therapy by incorporating efficacy, safety, and stewardship exposure-based metrics. A short, 2-dose course of ampicillin (50 mg/kg Q12h) provided bactericidal exposure against common EOS pathogens, limited high concentrations to minimize risk of toxicity, and limited the duration of therapeutic exposure to 48 hours. This short-course regimen acknowledges the time-dependent pharmacodynamics of ampicillin, the low MIC for common EOS gram-positive pathogens, and the long duration of post-discontinuation antibiotic exposure [17]. The previous 50 mg/kg dose recommendation for infants born ≤34 weeks' gestation [5] is now affirmed for younger VLBW infants. The 100 mg/kg dose regimens are not recommended since they resulted in high ampicillin concentrations above the proposed threshold and prolonged the post-discontinuation exposure time.

Ampicillin is a time-dependent antibiotic; therefore, higher ampicillin exposures may not offer therapeutic benefit. Maximal bactericidal activity is conferred by maintaining the concentration above the MIC with small doses, long infusion times, and/or short dosing intervals [9]. The low MICs of common gram-positive EOS pathogens allow low ampicillin concentrations to be effective. Most gram-negative pathogens in neonatal units are resistant to ampicillin; consequently, additional antibiotics should be used to cover these organisms.

The therapeutic serum concentration for meningitis is not well defined. Past studies of meningitis report serum exposures less than 100 mcg/mL to be effective; therefore, very high concentrations may increase the risk of toxicity without further benefit. The ampicillin serum:cerebrospinal fluid (CSF) exposure ratio estimate of 10–20% suggests that serum exposures of 50–100 mcg/mL would achieve CSF exposure (5–10 mcg/mL) more than adequate for most *Streptococcus sp.* and *Listeria* with MIC<1 mcg/mL [18]. For neonatal meningitis, doses of 40–70 mg/kg provided serum concentrations of 4–122 mcg/mL and CSF concentrations of 1–28 mcg/mL. In these neonates, CSF concentrations were 11–65% of serum exposures and all above the GBS susceptibility breakpoint MIC 0.25 mcg/mL [19, 20]. In a study of infants and children with *H. influenzae* meningitis receiving ampicillin 50 mg/kg dosing, serum concentrations of 1.5–74 mcg/mL were associated with CSF concentrations of 0.5–14 mcg/mL [21]. Very preterm infants likely have higher CSF exposure given immaturity of their central nervous system, blood-brain barrier system, and drug transport channels. As a result, the standard 50 mg/kg dose may be adequate to achieve

exposure effective for meningitis, especially in VLBW neonates. More studies are needed to define ampicillin dosing for meningitis in these very preterm infants.

The magnitude of ampicillin exposure was notable, particularly for the 100 mg/kg medium and high dose regimens that are commonly used in clinical practice. Ampicillin concentrations were more than double the toxicity threshold for most of the 48-hour dosing period. These high concentrations were consistent with exposures previously reported in term and preterm infants receiving 100 mg/kg dosing [5, 22, 23]. Some of the high exposure likely reflects prematurity and its associated slow drug clearance and long half-life [23]. Previous studies of ampicillin dosing did not address these high exposures. However, high concentrations are unlikely beneficial since the bactericidal activity of ampicillin is time-dependent and the MIC of common pathogens is very low. For the standard 50 mg/kg dose regimen, ampicillin concentrations were briefly above the neurotoxicity exposure threshold and this could be minimized by infusion times longer than the 20 minutes used in this simulation. Shorter infusion times are not advised.

The impact of these very high ampicillin concentrations is unknown. Very premature infants may be particularly vulnerable to medication toxicity due to high drug exposures, delayed drug clearance, and their immature kidneys and central nervous system [23, 24]. High ampicillin concentrations present significant drug elimination burden to the kidney. At high concentrations, beta-lactam antibiotics can interact with ɣ-aminobutyric acid neurotransmitters and lead to neurotoxicity and seizures [16, 23, 24]. In a simulation study, infants with ampicillin concentrations above this same neurotoxicity exposure target had a 1.76-fold increased odds of seizures [11]. In very preterm infants, seizures can be difficult to detect since they may not be associated with tonic-clonic movements. The incidence of seizures among very preterm infants receiving ampicillin is unknown and safety has largely been assessed using observational studies rather than controlled trials. Ampicillin has also been associated with prolonged bleeding times and nephritis; however, the exposure metrics for these effects have not been defined [25–27]. Further evaluation of potential toxicity associated with high ampicillin exposures is warranted.

From a stewardship perspective, bactericidal ampicillin concentrations beyond the 48-hour culture incubation window are unnecessary. In VLBW infants with negative cultures, limiting antibiotic exposures in the first week after birth may be particularly prudent. Longer antibiotic courses have been associated with changes in the microbiome and later-onset morbidities and mortality [28–31]. With current microbial Bactek culture systems, 94% of blood cultures drawn in the setting of EOS evaluations were positive by 36 hours [32]. Clinicians who are hesitant to stop antibiotics by 48 hours, given the clinical instability of a preterm infant, can be reassured by the post-discontinuation antibiotic exposure that provides an additional 2–3 days of therapeutic coverage for most gram-positive pathogens [12]. The short course, 2-dose regimen is a reasonable consideration for EOS evaluations. Dose recommendations that consider exposure duration can limit unnecessary antibiotic exposure in the NICU.

This study also demonstrates the importance of PK studies and dose adjustment in premature VLBW infants. The FDA and AAP guidance for ampicillin in premature infants relies on

a 34-week gestational age cut off and, therefore, does not account for differences in drug clearance with more significant prematurity. In this study, the most premature infants born at 22–24 weeks' gestation had higher drug concentrations and longer exposure duration compared to infants born at 25–27 weeks' gestation. The AAP dose recommendations for GBS meningitis are the same for both preterm and term infants, but premature infants will have much higher exposures than term infants. Further studies are needed to evaluate the safety of high exposures and support dose recommendations specifically for these very premature infants.

This study has several strengths. Monte Carlo simulation is a robust strategy to explore dose-exposure relationships in large cohorts of premature infants in whom dose-finding studies are difficult. We used a population PK model informed by ampicillin concentrations in a cohort that included very premature infants and near-term newborns. We chose a very conservative efficacy target by maintaining concentrations above the MIC for 100% of the dosing interval and using a broad range of MIC breakpoints up to an MIC 8 mcg/mL for *E. coli*. Bactericidal exposure is likely even longer than reported in these simulations for two reasons: maintaining concentrations above MIC for 50–75% of the dosing interval is an acceptable efficacy metric and empiric coverage for *E. coli* typically requires alternative antibiotics since ampicillin resistance exceeds 80%.

The main limitation of this study is the use of simulated ampicillin concentrations. The absence of patient-level, concentration data is an acknowledged weakness. These simulated concentrations during therapy were consistent with concentrations observed in prior PK studies with preterm infants [5, 22, 23]. The use of serum creatinine in the PK model can be difficult in newborns since early creatinine values are often higher and typically represent maternal creatinine. Clearance may be biased by the elevated creatinine in our population. The creatinine values were appropriate for the degree of prematurity of this cohort. Regardless of creatinine, the first 48-hours after birth is a period of delayed renal drug clearance in most newborns. A follow-up prospective study is planned to confirm ampicillin exposures especially in the most premature infants and after discontinuation of therapy. Contemporary studies of ampicillin exposure in the CSF of premature infants are also needed.

In conclusion, this study defined empiric ampicillin dosing for VLBW premature infants at risk for EOS. A short-course ampicillin regimen (2 doses, 50 mg/kg Q12hr) provides bactericidal exposure, minimizes the risk of potential toxicity, and promotes stewardship by limiting empiric exposure to 48 hours. A prospective study is planned to confirm ampicillin exposures and explore the potential early and late effects of shortened therapy. The safety and justification of high ampicillin exposures with the 100 mg/kg dosing needs further evaluation.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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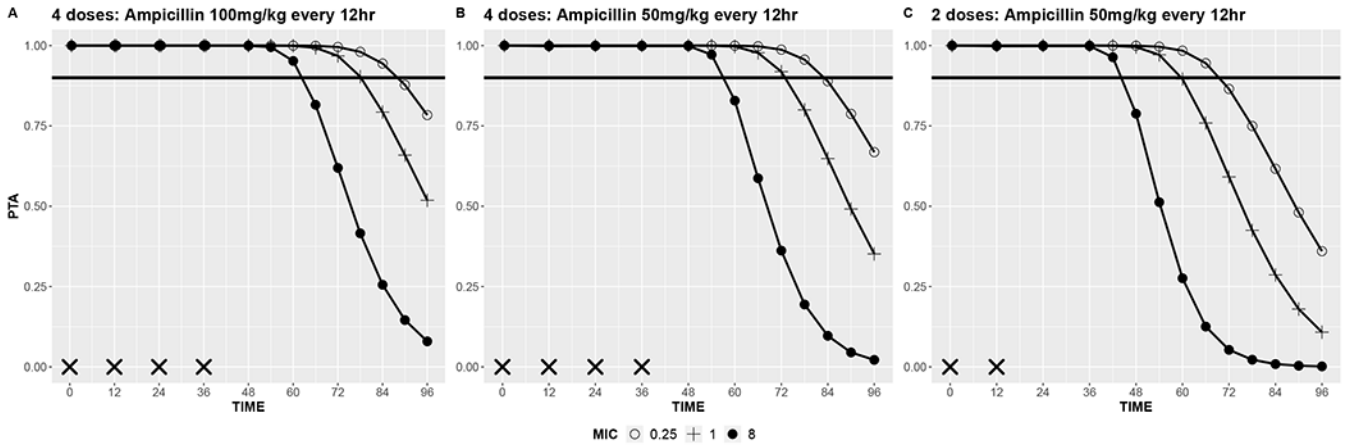

Figure 1. Probability of therapeutic target attainment over time from therapy initiation

Among VLBW neonates receiving different ampicillin regimens, graphs represent the probability that neonates will reach the desired therapeutic target attainment (PTA) with ampicillin concentration above the MIC for 100% of dosing time interval (*f*T>MIC =100%) over time from start of therapy and for different MIC breakpoints of 0.25 mcg/mL for GBS, 1 mcg/mL for *Streptococcus sp.* and *Listeria*, and 8 mcg/mL for *E. coli*. Black line represents 90% target attainment. X marks time of doses administered.

GBS, group B *Streptococcus*; hr, hour; MIC, minimum inhibitory concentration; PTA, probability of target attainment; VLBW, very low birth weight

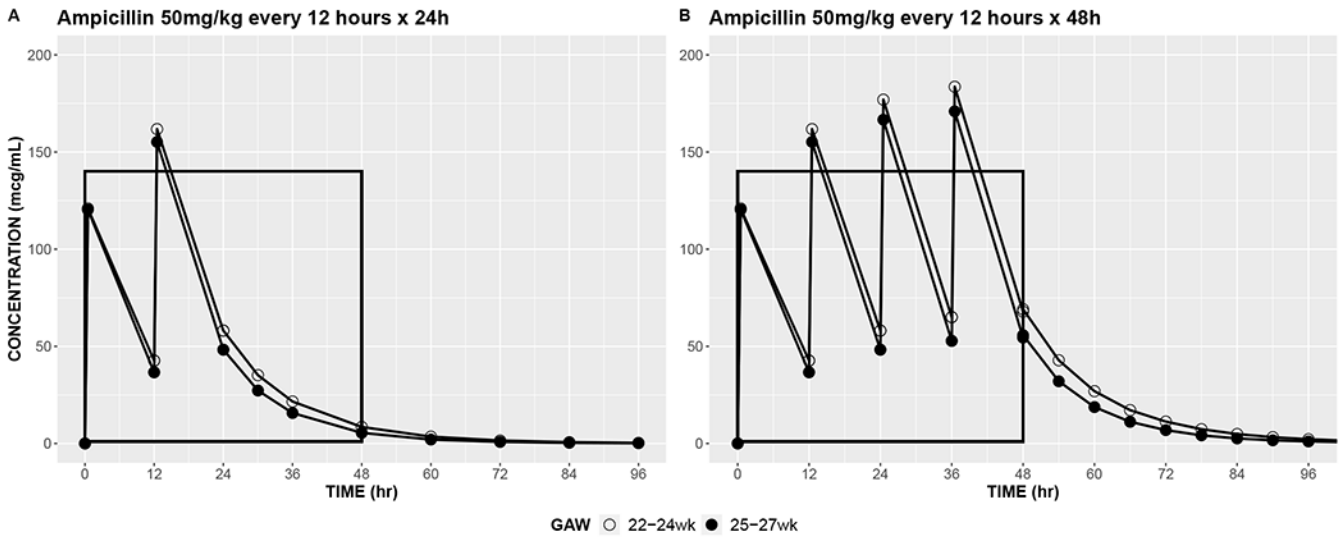

Figure 2. Mean predicted concentration versus time curve of ampicillin 50mg/kg/dose.

Mean predicted concentration versus time curve of ampicillin 50mg/kg/dose for 2 (A), and 4 (B) doses for VLBW neonates in two gestational age groups. Concentrations inside the black box are within the concentration metrics, accounting for efficacy (>MIC 1 mcg/mL), safety (≤140 mcg/mL), and stewardship ending at 48-hour culture incubation window. MIC, minimum inhibitory concentration; VLBW, very low birth weight

Table 1.

Demographic data of simulated VLBW population for ampicillin exposure by gestational age groups

	Total cohort[a]	**22-24 weeks' gestation**	**25-27 weeks' gestation**
Sample size	34,689	9,378	25,311
Gestational age (weeks)	26 [24-27]	24 [23-24]	26 [25-27]
Birth weight (kg)	0.790 [0.655-0.938]	0.630 [0.560-0.697]	0.860 [0.743-0.986]
Postnatal age (days)	1 [1-1]	1 [1-1]	1 [1-1]
Serum creatinine (mg/dL)	0.90 [0.71-1.0]	0.90 [0.7-1.0]	0.89 [0.72-1.0]
Volume[b] (L/kg)	0.32 [0.261-0.374]	0.25 [0.223-0.278]	0.34 [0.297-0.393]
Clearance[b] (L/hr/kg)	0.032 [0.024-0.042]	0.023 [0.018-0.028]	0.036 [0.028-0.045]
Half-life (hours)	6.9 [5.8-8.3]	7.6 [6.4-9.0]	6.6 [5.6-7.9]

[a]Numbers represent median with interquartile range in brackets.

[b]Ampicillin population PK model [5] derived volume (V) and clearance (CL): $V = 0.399 * WTKG$ and $CL = 0.078 * WTKG * (0.6/SCR)^{0.428} * (PMA/37)^{1.34}$

CL, clearance; PMA, post menstrual age; SCR, serum creatinine; V, volume; VLBW, very low birth weight; WTKG, weight in Kg

Table 2.

Ampicillin exposures among VLBW premature infants exposed to empiric dosing regimens designed to provide coverage over 48-hour culture incubation window

Dosing regimens	**Maximum concentration** [a,b] **(mcg/mL)**		**Minimum concentration at time from 1st dose (mcg/mL)** [a,b]					
			48 hours into therapy		**60 hours into therapy**		**72 hours into therapy**	
Gestational age	**22-24wk**	**25-27wk**	**22-24wk**	**25-27wk**	**22-24wk**	**25-27wk**	**22-24wk**	**25-27wk**
High dose 300 mg/kg/day 100 mg/kg Q8hr 6 doses	474 (334, 661)	434 (309, 605)	252 (109, 456)	211 (85.4, 391)	97.2 (19.4, 244)	69.9 (11.2, 187)	40.4 (3.60, 135)	25.4 (1.48, 92.3)
Medium dose 200 mg/kg/day 100 mg/kg Q12hr 4 doses	367 (281, 484)	342 (265, 447)	138 (51.5, 266)	112 (36.7, 223)	53.9 (9.38, 140)	37.5 (4.83, 107)	22.5 (1.73, 76.8)	13.7 (0.648, 52.4)
Standard dose 100 mg/kg/day 50 mg/kg Q12hr 4 doses	184 (140, 242)	171 (133, 223)	69.1 (25.7, 133)	55.8 (18.4, 111)	26.9 (4.69, 69.8)	18.7 (2.42, 53.3)	11.2 (0.867, 38.4)	6.9 (0.324, 26.2)
Short course 50 mg/kg Q12hr 2 doses	162 (137, 188)	155 (131, 181)	8.48 (0.679, 27.2)	5.46 (0.271, 19.7)	3.50 (0.113, 14.2)	2.02 (0.034, 9.35)	1.51 (0.019, 7.48)	0.786 (0.004, 4.44)

[a] Numbers represent mean (95% confidence interval) of simulated ampicillin concentrations.

[b] Infusion time for ampicillin was 20 minutes.

VLBW, very low birth weight; wk, week