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Paradoxical Antibiotic Effect of Ampicillin: Use of a Population Pharmacokinetic Model to Evaluate a Clinical Correlate of the Eagle Effect in Infants with Bacteremia

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Keywords

Enterococcus ; group B streptococcus; *Escherichia coli* ; exposure; dosing

Hospitalized infants frequently receive antibiotics to treat invasive bacterial infections.[1] Ampicillin is the most commonly used medication in hospitalized infants, with nearly 70% of infants admitted to a neonatal intensive care unit (NICU) receiving at least one dose.[1,2] High doses of ampicillin are often used to obtain drug concentrations sufficient to penetrate the central nervous system in the event that meningitis is present.[3]

However, for some antibiotics, a paradoxical relationship has been observed between antibiotic concentration and bacterial killing. This phenomenon was first described in 1948 when penicillin was found to kill fewer colonies of streptococci *in vitro* when the dose was increased beyond a threshold concentration (the “Eagle effect”).[4] Since then, paradoxical antibiotic effects have been best described for beta-lactam antibiotics in the setting of Gram-positive organisms[5,6] but have also been observed with aminoglycosides for Gram-negative organisms,[7] quinolones for *Escherichia coli,*[8] dicloxacillin for *Staphylocccus aureus*[9] and ampicillin, ciprofloxacin, vancomycin and daptomycin for enterococcal infections.[10] In vitro studies evaluating for a paradoxical antibiotic effect for ampicillin with *E. coli* have been less clear with only a few isolates demonstrating decreased killing at high ampicillin

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concentrations.[11] The clinical importance of paradoxical antibiotic effects is unclear, but clinical failures thought to be due to this phenomenon have been reported.[12]

If ampicillin does exert a paradoxical effect in infants, the use of high doses of ampicillin may unexpectedly lead to treatment failures and worse outcomes for infants treated with ampicillin. To the best of our knowledge, the possibility of a paradoxical antibiotic effect leading to treatment failure in infants with sepsis has not been evaluated. We sought to examine the relationship between dosing, pharmacokinetic (PK), and pharmacodynamic parameters of ampicillin and infant outcomes following bacteremia to identify evidence suggesting a clinical correlate of the paradoxical effect. We hypothesized that high ampicillin doses and exposures would be associated with worse outcomes, providing evidence of a paradoxical antibiotic effect.

Methods

Study Population

We identified all infants ≤28 days of age discharged from 348 neonatal intensive care units (NICUs) managed by the Pediatrix Medical Group from 1997–2012 with a monomicrobial positive blood culture for *E. coli*, *Streptococcus agalactiae* (GBS), or *Enterococcus* species who were included in a prior study that used an established ampicillin PK model to simulate ampicillin exposures.[13] Included infants were 21–41 weeks gestational age and 500–5400 g birth weight with most recent serum creatinine of 0.2–2.5 mg/dL prior to the first dose of ampicillin that were started on ampicillin prior to 25 days of age and completed prior to 60 days of age. Specific ampicillin minimum inhibitory concentrations (MICs) for each infection were not available, but ampicillin resistance for *E. coli* infections was available as a yes/no result. *E. coli* infections with recorded resistance to ampicillin were excluded. For infants with >1 infection, only the first infection was included in the analysis. Information recorded included demographics, maternal history, and, on a daily basis, laboratory results, microbiology results, diagnoses, and procedures.[14] This study was approved by the Duke University Institutional Review Board with a waiver of informed consent.

Definitions

The duration of bacteremia was calculated as the number of days from the first to the last positive blood culture. Prolonged bacteremia was defined as ≥3 days between the first and last positive blood cultures with the same organism. Relative to the day of first positive culture, the following definitions were used: inotropic support as any exposure to dopamine, dobutamine, epinephrine, norepinephrine, or milrinone; mechanical ventilation as exposure to any invasive mechanical ventilation; and oxygen supplementation as the administration of any fraction of inspired oxygen >21%. Small-for-gestational-age status was defined as previously described.[15]

Dosing regimens were evaluated as mg/kg/dose and mg/kg/day. Four categories of dosing were defined: low dose, short interval (<75 mg/kg/dose every 6 or 8 hours); low dose, long interval (<75mg/kg/dose every 12 hours); high dose, short interval (≥75 mg/kg/dose every 6 or 8 hours); and high dose, long interval (≥75 mg/kg/dose every 12 or 24 hours). Using

a 1-compartment, intermittent infusion, population PK model, we simulated the minimum and maximum daily serum concentration of ampicillin at steady-state (C_{minss} and C_{maxss}, respectively) and the area-under-the-concentration time curve from 0 to 24 hours (AUC_{24}) using an established population PK model.[13,16] Between-subject variability in clearance was also included in the simulation. Drug exposure metrics of interest were: AUC^{24}, C_{minss}, C_{maxss}, and the time above the MIC (T>MIC) defined as the proportion of the dosing interval with the serum concentration above the MIC. The total, rather than free, drug concentration was used in this study due to low protein binding of ampicillin (~10%) reported in neonates.[17] Because MICs for each infection were not available, we used the Clinical Laboratory Standards Institute breakpoints for each organism as a surrogate for the ampicillin MIC. There were no changes made to the breakpoints or their interpretations during the study period.[18] For *E. coli*, the breakpoint used was 8 μg/mL; for GBS, 0.25 μg/mL; and for *Enterococcus sp.*, 8 μg/mL.[19] The T>MIC was estimated using the available PK parameters and reported as the percent of the dosing interval for which the ampicillin concentration was greater than the breakpoint.

Statistical analysis

We compared the odds of death within 7 and 30 days from the first positive blood culture for dose, daily dose, T>MIC and PK parameters using a separate logistic regression model for each parameter adjusted for gestational age group (≤25 weeks, 26–28 weeks, 29–32 weeks, 33–36 weeks and ≥37 weeks), small for gestational age status, postnatal age, and inotrope and ventilator use on the day of the first positive blood culture. Random effects were used to adjust for differences due to NICU site. Logistic regression and Poisson models adjusted for gestational age group, small for gestational age status, and postnatal age were used to calculate the odds of prolonged bacteremia and the marginal effect on the duration of bacteremia[20], respectively, for dose, T>MIC and the PK parameters of interest. Doses, daily doses, T>MIC, AUC_{24}, C_{maxss} and C_{minss} categories for comparison were all chosen *a priori* (Table 2). In a post-hoc analysis, we compared the median duration of bacteremia for infants with a T>MIC ≥50% of the dosing interval to those with a T>MIC <50% of the dosing interval using a Wilcoxon rank-sum test.[21,22]

We used Stata 14.0 (StataCorp, College Station, Texas) to perform all statistical analyses. $P<0.05$ was considered statistically significant.

Results

We identified 1272 infants meeting inclusion criteria (Table 1). GBS was the most common organism (776/1273, 61%) causing bacteremia in our cohort. Most infants (834/1273, 66%) received ampicillin at high doses with a long dosing interval; 897/1273 (70%) received ≥100 mg/kg/dose and 1026/1273 (81%) had a dosing interval of every 12 hours. There were no infants in our cohort who received ampicillin at dosing intervals other than every 6, 8, or 12 hours. The median gestational age was 38 weeks (5^{th}, 95^{th} percentiles 25, 40); the median birth weight was 2926 g (735, 4050). Most infants (1165/1273, 92%) had early onset sepsis with a median postnatal age at time of the first positive blood culture of 0 days (5^{th}, 95^{th} percentiles 0, 6). The high dose/short dosing interval dosing strategy was used more

frequently with increasing gestational ages, ranging from 3% of infants <25 weeks to 16% of infants ≥37 weeks gestational age.

The odds of death at 7 or 30 days were not different across of any of the doses or daily doses evaluated (Table 2). The odds of death at 7 days was increased both for C_{maxss} < 150 μg/mL and > 300 μg/mL compared to the reference of 150–300 μg/mL but did not show a threshold above which the odds of death increased. The duration of bacteremia was similarly decreased at C_{maxss} both <150 μg/mL and >300 μg/mL compared to the reference of 150–300 μg/mL with no threshold above which the duration of bacteremia was increased. The odds of prolonged bacteremia was lowest at the lowest dose category and the lowest daily dose category but not associated with the AUC_{24}, C_{maxss} or C_{minss}.

A T>MIC of ≥50% was associated with a decreased duration of bacteremia of 0.19 days (−0.31, −0.07) and decreased odds of prolonged bacteremia, adjusted odds ratio=0.17 (0.07, 0.38). Infants with a T>MIC ≥50% had a shorter duration of bacteremia than those with a T>MIC <50%, median 1 day (5^{th}, 95^{th} percentiles: 1, 1) and 1 day (1, 3), P<0.001. The proportion of patients achieving a T>MIC ≥50% was greatest for patients receiving a high dose with a short dosing interval (86% vs. 67–74% for other dosing patterns). Most of the infants receiving the high dose-short dosing interval dosing pattern were ≥37 weeks gestational age. Most infants (>60%) in all gestational age groups received a high dose, long dosing interval pattern of administration.

Discussion

We did not find evidence that a paradoxical antibiotic effect is likely to contribute to mortality when ampicillin is used for the treatment of *E. coli*, GBS, and *Enterococcus* bacteremia in this large cohort of infants. It is possible that lower doses of ampicillin are associated with a reduced odds of prolonged bacteremia.

Paradoxical antibiotic effects, also called optimum dosage effects or the Eagle effect, occur when high concentrations of antibiotic paradoxically result in less bacterial killing than lower concentrations.[4,5] Most studies describing this phenomenon have been *in vitro*, and the clinical significance of paradoxical antibiotic effects is unclear. However, paradoxical antibiotic effects have been observed in animal models of systemic infection, suggesting that a clinical correlate exists. Rabbits infected with nontoxigenic *Corynebacterium diphtheria* had fewer viable bacteria detected in cardiac valve vegetations when treated with ten-fold lower ampicillin doses.[23] Cloxacillin was similarly more effective at lower doses when used to treat rats with *S. aureus* endocarditis.[24] There are 2 cases reported in humans in which a paradoxical antibiotic effect was suspected after a reduction in the dose of penicillin improved the patient's condition: one was an 83 year old male with alpha-hemolytic streptococcal endocarditis[12] and the other was a 19 month old with non-hemolytic streptococcal endocarditis.[25] These cases were reported in 1985 and 1986.[12,25] The lack of additional reports in more than 30 years may reflect the tendency to increase the dose of antibiotic, or add or change to an alternate antibiotic class in the setting of clinical failure rather than decreasing the dose. That is, a lack of awareness among clinicians that a decreased dose may be more effective than the current dose prevents detection of this

phenomenon. We found that the lowest dose and daily dose categories were associated with a decreased odds of prolonged bacteremia compared to higher doses and daily doses. The corresponding analysis did not find that dose or daily dose were associated with the duration of bacteremia. While it is possible that the former finding represents a clinical correlate of the Eagle effect, we were unable to validate this finding using an alternative measure of bacteremia duration. There were no findings to suggest a paradoxical antibiotic effect when we considered mortality at 7 or 30 days.

Although we failed to observe convincing evidence of a paradoxical antibiotic effect in our cohort, we did note that infants with ampicillin concentrations greater than the MIC for at least 50% of the dosing interval had a decreased odds of prolonged bacteremia and a shorter duration of bacteremia compared with those who had <50% of the dosing interval above the MIC. These findings prompted us to compare the duration of bacteremia for patients with T>MIC for ≥50% and <50% of the dosing interval. Our initial findings that a T>MIC for ≥50% of the dosing interval is associated with an improvement in bacterial clearance compared to a shorter time above the MIC were confirmed. We chose 50% of the dosing interval as the cutpoint to assess because this fraction of the dosing interval has previously been described as providing bactericidal efficacy.[22]

The need for an adequate T>MIC target has previously been demonstrated in animals. Significantly more mice infected with *Streptococcus pneumoniae* or beta-hemolytic *Streptococcus* survived when penicillin was administered in multiple doses rather than as a single large dose.[26] The improved survival was thought to be due to a longer “penicillin time” which equates to the T>MIC for the organisms during treatment with penicillin. Similarly, rabbits infected with *S. pneumoniae*, beta-hemolytic *Streptococcus* or *Treponema pallidum* had improved survival when penicillin was administered at shorter intervals.[26] Later studies in mice with *Streptococcus pyogenes* myositis demonstrated that “the primary determinant of penicillin activity is the aggregate time, …, for which it [the penicillin concentration] remains at effective levels at the focus of infection.”[27]

The importance of adequate time with the antibiotic concentration above the MIC has also been demonstrated in adults and children. Patients with *Bacteroides fragilis* group infections treated with cefoxitin were more likely to experience clinical cure with a greater time above the MIC.[21,28] A study of 107 adults with sepsis who were treated with either cefepime or ceftazidime found that patients with a T>MIC ≥80% were significantly more likely to have bacteriologic eradication (96% vs 43%, respectively) and clinical cure (83% vs 29%, respectively) than patients with a T>MIC <80%.[29] Because of the ease of sampling from the middle ear space, otitis media has also been used as a platform for the study of antibiotic efficacy *in vivo*. A combined analysis of several prior studies[30–32] of otitis media found that T>MIC was highly correlated with antibiotic efficacy; T>MICs of 40–50% resulted in bacteriologic eradication in 80–85% of patients.[33] Microbiologic efficacy is the most commonly studied endpoint in pharmacodynamics studies, however, other clinical endpoints are also important. Pediatric cystic fibrosis patients had a greater increase in the forced expiratory volume in 1 minute (FEV1) when the T>MIC was >65% than when it was ≤65% of the dosing interval.[34]

The Food and Drug Administration (FDA) allows efficacy data derived in adults to be used for the extrapolation of efficacy to infants and children for many antimicrobials.[35] Studies evaluating the efficacy of other beta-lactam antibiotics have used a T>MIC of 40–50% as a threshold above which the antibiotic is likely to be effective.[36–39] We were able to demonstrate that, similar to adults and older children, the T>MIC is a key factor contributing to antimicrobial efficacy in infants with bacteremia when ampicillin is used. It is also likely that this is the case for other beta-lactam antibiotics. Our findings suggest that extrapolating beta-lactam efficacy data from adults to infants is a reasonable strategy.

This study is unique in the large number of young infants with PK measurements represented. A limitation of this analysis is that ampicillin PK parameters were not estimated directly in our study population but were predicted using a population PK model based on a similar patient population. The use of estimated parameters and drug exposures rather than measured concentrations introduces potential error in the assessment of efficacy based on these parameters. However, the ability to recruit a sufficient number of infants for this purpose is quite difficult; prior PK studies of ampicillin in infants have had 3–39 patients included.[40–43] Population PK modeling has been suggested as a novel method to overcome this challenge in the assessment of clinical pharmacology's impact on patient care.[44] Additionally, due to the infrequent occurrence of death and prolonged bacteremia, we were unable to stratify our analysis by organism. Important differences may exist when ampicillin is used for treatment of *E. coli* vs. GBS vs. *Enterococcus* species that we were not able to assess with our dataset. Our analysis did not account for the use of antibiotics in addition to ampicillin. It is possible that some patients may have received additional antibiotics which could have affected mortality or the duration of bacteremia. *E. coli* and GBS are typically treated with ampicillin monotherapy so the number treated with combination therapy is expected to be low. It is possible that our finding that the lowest ampicillin doses reduced the odds of prolonged bacteremia was due to unmeasured confounding such that sicker infants were more likely to receive higher doses of ampicillin and also more likely to experience a prolonged bacteremia episode. We attempted to address this by controlling for postnatal age and use of inotropes and mechanical ventilation but additional confounding may remain that we were unable to account for in our analysis. Lastly, the actual MIC value for each isolate was not available requiring us to use the CLSI breakpoint criteria to determine the T>MIC for each patient. However, these breakpoints would be expected to be much higher than the actual MIC for the majority of isolates leading to an underestimation of the true relationship between efficacy and T>MIC and a bias toward the null. Since we still appreciated a difference with increased T>MIC, it is likely that the actual difference is even more significant than we were able to calculate. We did not assess the relative safety of dosing strategies for ampicillin administration so our results should be not construed to indicate that high doses administered at short intervals is the preferred dosing strategy for infants, only that this dosing strategy is unlikely to be associated with decreased efficacy. The safety of ampicillin in infants has been described elsewhere.[13,45,46]

It is unlikely that a paradoxical antibiotic effect will have a clinical correlate when ampicillin is used for the treatment of *E. coli*, GBS, and *Enterococcus* bacteremia. On post-hoc analysis, maintaining a T>MIC ≥50% of the dosing interval was associated with decreased duration of bacteremia and a decreased odds of prolonged bacteremia.

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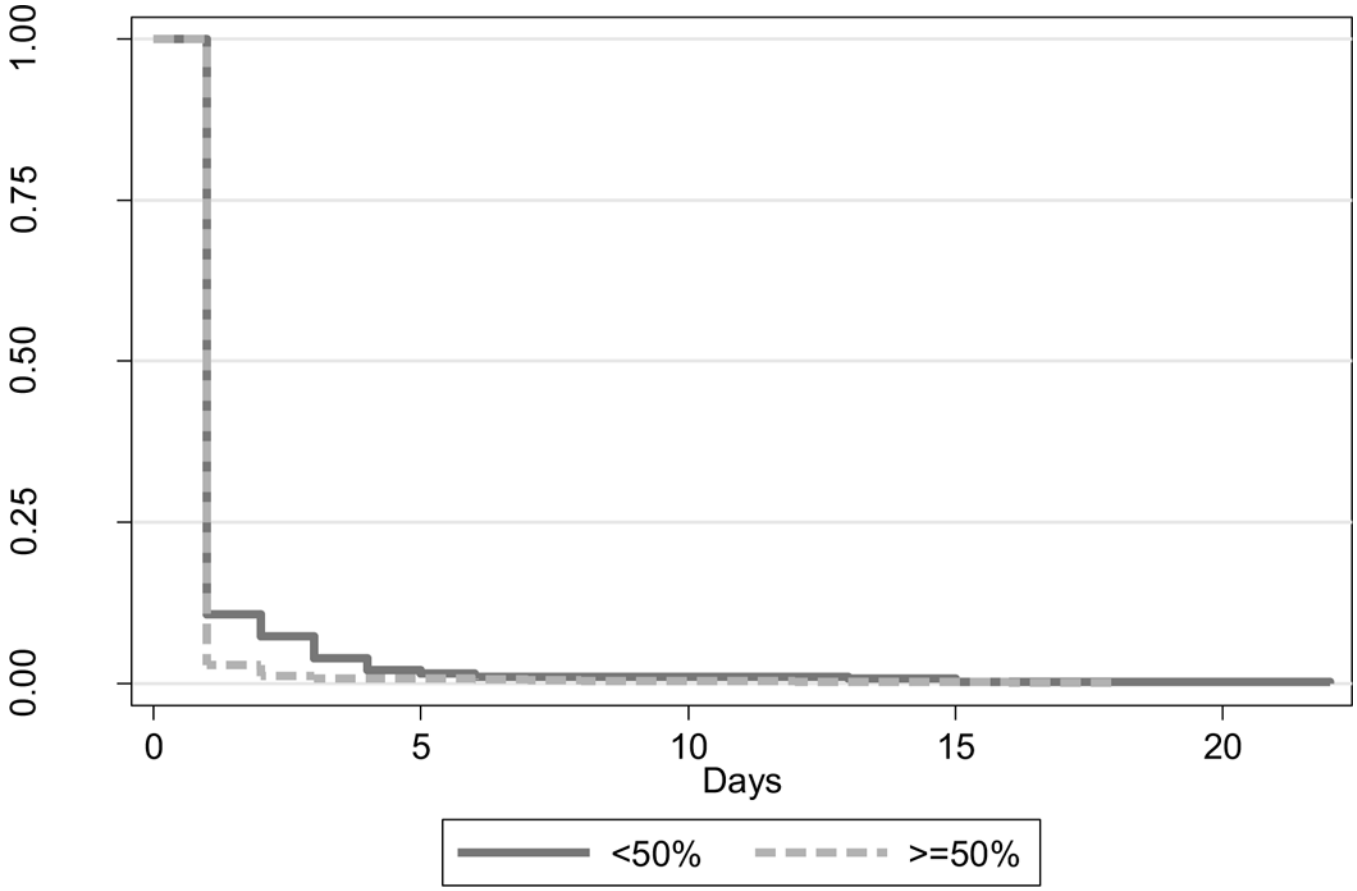

Figure 1.
Proportion of infants with ongoing bacteremia with ampicillin concentrations greater than the minimum inhibitory concentration for <50% and ≥50% of the dosing interval.

Table 1.

Infant characteristics.

	N=1273 (%)
Gestational age, weeks	
<25	94 (7)
26–28	100 (8)
29–32	157 (12)
33–36	192 (15)
>36	730 (57)
Birth weight, g	
<1000	137 (11)
1000–1499	137 (11)
1500–2499	198 (16)
2500–3499	526 (41)
>3500	274 (21)
Race/ethnicity	
White	633 (51)
African-American	262 (21)
Hispanic	289 (23)
Other	54 (4)
Postnatal age, days	
<3	1145 (90)
3–7	72 (6)
8–28	52 (4)
Male	681 (54)
Small for gestational age	72 (6)
Died within 30 days	58 (4)
Antibiotic administration pattern *	
Low long	192 (15)
Low short	89 (7)
High long	834 (66)
High short	158 (12)
Organism	
Escherichia coli	437 (34)
Enterococcus species	60 (5)
Streptococcus agalactiae	776 (61)

* Low: <75mg/kg/dose; High: >=75mg/kg/dose; Short: dosing interval of 6 or 8 hours; Long: dosing interval of 12 hour

Table 2.

Multivariate logistic and Poisson regression for different outcomes by ampicillin doses and exposures.

		Adjusted Odds Ratio (95% Confidence Interval)			
Dose or Exposure Parameter		**Death within 7 days***	**Death within 30 days***	**≥3 days of Bacteremia†**	**Duration of bacteremia‡**
Dose categories, mg/kg/dose					
	80–180	1	1	1	0
	<80	0.88 (0.35, 2.19)	0.78 (0.38, 1.59)	0.27 (0.10, 0.76)	−0.06 (−0.18, 0.06)
	>180	1.14 (0.10, 13.48)	0.57 (0.05, 5.98)	–	−0.13 (−0.47, 0.21)
Daily dose categories, mg/kg/day					
	180–220	1	1	1	0
	<180	0.90 (0.35, 2.35)	0.90 (0.42, 1.91)	0.30 (0.11, 0.82)	−0.07 (−0.20, 0.05)
	>220	0.95 (0.30, 3.02)	1.48 (0.62, 3.51)	0.28 (0.06, 1.24)	−0.11 (−0.27, 0.04)
Time above MIC, % of dosing interval					
	<50	1	1	1	0
	≥50	1.28 (0.51, 3.25)	0.97 (0.48, 1.93)	0.17 (0.07, 0.38)§	−0.19 (−0.31, −0.08) §
Area-under-the-24-hour concentration curve, per 100 µg * h/mL		0.98 (0.94, 1.03)	1.00 (0.97, 1.04)	1.00 (0.97, 1.03)	0 (0, 0)
Steady state minimum concentration, µg/mL					
	20–50	1	1	1	0
	≤20	1.38 (0.13, 14.10)	0.53 (0.06, 4.57)	0.82 (0.17, 3.94)	0 (−0.18, 0.19)
	≥50	1.29 (0.44, 3.81)	1.06 (0.48, 2.36)	0.63 (0.29, 1.38)	−0.03 (−0.15, 0.09)
Steady state maximum concentration, µg/mL					
	150–300	1	1	1	0
	<150	3.81 (1.08, 13.49)	1.86 (0.67, 5.11)	0.24 (0.05, 1.08)	−0.19 (−0.36, −0.02)
	>300	2.81 (1.00, 7.89)	1.35 (0.65, 2.81)	0.54 (0.24, 1.24)	−0.24 (−0.24, −0.01)

*Logistic regression adjusted for gestational age group, postnatal age on the day of the first positive culture, small for gestational age status, use of inotropes or mechanical ventilation on the day of the first positive culture;

†logistic regression adjusted for gestational age group, postnatal age on the day of the first positive culture, and small for gestational age status;

‡Poisson regression adjusted for gestational age group, postnatal age on the day of the first positive culture, and small for gestational age status; MIC, minimum inhibitory concentration;

§p<0.05