Ampicillin Safety in Hospitalized Infants

The Pediatric Pharmacology Research unit (PPRU) Antimicrobial Pharmacokinetics (PK) Study in High Risk Infants

Investigational Product: Ampicillin

IND Number: 113,645

Design: Multi-center, Open-label, Opportunistic PK study of Ampicillin in premature infants.

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1 GLOSSARY OF ABBREVIATIONS AND TERMS

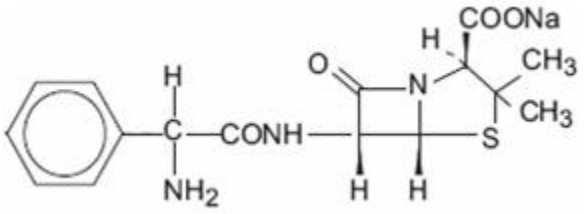
AE	Adverse Event
ALT	Alanine Transaminase
AST	Aspartate Transaminase
BUN	Blood Urea Nitrogen
BW	Birth Weight
CSF	Cerebrospinal Fluid
FDA	Food and Drug Administration
GA	Gestational Age
GCP	Good Clinical Practice
GGT	Gamma-glutamyl transferase
GNR	Gram-negative rods
GPC	Gram-positive cocci
HIPAA	Health Insurance Portability and Accountability Act
IB	Investigator Brochure
ICF	Informed Consent Form
IEC	Independent Ethics Committee
IRB	Institutional Review Board
IVH	Intraventricular Hemorrhage
NEC	Necrotizing Enterocolitis
NICHD	National Institute of Health and Human Development
NICU	Neonatal Intensive Care Unit
PK	Pharmacokinetics
PDA	Patent Ductus Arteriosus
PNA	Postnatal Age
PPRU	Pediatric Pharmacology Research Unit
ROP	Retinopathy of Prematurity
SAE	Serious Adverse Event
VLBW	Very Low Birth Weight

2 INTRODUCTION

2.1 *Ampicillin*

Ampicillin is an antibacterial agent with a broad spectrum of bactericidal activity against both penicillin-susceptible Gram-positive organisms and many common Gram-negative pathogens.[1]

Figure 2-1: Ampicillin chemical structure



2.1.1 *Ampicillin therapy for bacterial sepsis in infants*

Bacterial sepsis remains a leading cause of death in infants admitted to neonatal intensive care units (NICUs). The incidence of early onset sepsis (<4 postnatal days) in infants admitted to the NICU is 1.2% to 2% and for late onset sepsis (4-120 postnatal days) 14% to 36%. The incidence of late onset sepsis is higher in very low birth weight infants (VLBW, birth weight <1500 g).[2,3] The most commonly administered medication in the NICU, with an exposure rate of 693 per 1000 NICU-discharged infants, is ampicillin.[4] Ampicillin is a beta-lactam antibiotic approved by the FDA to treat local and disseminated infections caused by susceptible organisms in patients of all age groups.[1]

2.1.2 *Ampicillin Safety in infants*

Although ampicillin is the most commonly administered medication in the NICU, its safety in the neonatal population is poorly described. Adverse events (AE) listed on the FDA label for ampicillin are not specific to the neonatal population. Ampicillin AEs are mostly due to sensitivity phenomena that are more common in people with a history of penicillin exposure. This is very uncommon in the neonatal population. In a recent study comparing clinical efficacy of ampicillin or penicillin in combination with gentamicin therapy for early onset sepsis in infants (including GA <26 weeks), both were well tolerated with no difference in AEs or laboratory abnormalities. However, the focus of this study was clinical effectiveness comparison, and not safety profiling.[5] Among the potential serious AEs in infants is the risk of ampicillin induced seizures.[1] As with other penicillin's, β-Lactam-induced neurotoxicity is of concern if cerebrospinal fluid concentrations of ampicillin are high. This has been reported in adult case reports, but the incidence of seizures in infants, treated with ampicillin, has not been evaluated.[6,7] Another known side-effect of ampicillin most commonly seen after repeated dosing is inhibition of the coagulation cascade. The prevalence of this AE in the neonatal population, which is at risk of coagulopathy, is unknown.[8] Overall, given the importance of safety and improved long term outcomes in the neonatal population, a more detailed description of the safety of this commonly used antibiotic is warranted.

3 STUDY OBJECTIVES

The objective of the study is to evaluate the safety profile of ampicillin administered to infants per standard of care by their treating caregiver.

4 INVESTIGATIONAL PLAN

4.1 *Overall Design and Plan Description*

The Pediatric Pharmacology Research unit (PPRU) Antimicrobial Pharmacokinetics (PK) in High Risk Infants study was a multi-center, open-label, opportunistic PK study of antimicrobial products, including ampicillin, in premature infants. Safety data was collected from infants enrolled in the study at Redacted who received ampicillin per standard of care. Results of this safety data analysis are presented here.

4.2 *Study Population*

4.2.1 *Inclusion Criteria*

All infants who received ampicillin while enrolled in the PPRU Antimicrobial PK in High Risk Infants study at Redacted.

4.2.2 *Exclusion Criteria*

None

4.2.3 *Classification of Participants*

Participants were classified by PNA as follows:

- Cohort 1: PNA ≤7 days
- Cohort 2: PNA ≥8 days

4.3 *Study Medication*

Administration of drug(s) was not part of the PPRU protocol or this PTN protocol. Safety information was captured for infants exposed to ampicillin as part of the PPRU Antimicrobial PK in High Risk Infants study at Redacted.

4.4 *Definitions*

The primary objective of this study was to evaluate the safety of ampicillin. The safety of ampicillin for the purpose of this study was evaluated by reporting the frequency of laboratory abnormalities, culture results obtained, and diagnoses made while on ampicillin. In addition, growth parameters including weight, height and head circumference were collected at the beginning and at the end of the study, and a complete physical examination was performed one day prior to ampicillin therapy and daily while on ampicillin (Table 4-1).

Table 4-1 Data Collection

	Date of birth	-3 days	-2 days	-1 day	On ampicillin	+1 day	+2 days	+3 days
Demographics								
Weight	X			X		X		
Length	X			X		X		
Head circumference	X			X		X		
Adverse Events (new onset)								
Cardiorespiratory arrest					X			
Hypotension					X			
Tachypnea					X			
Tachycardia					X			
Medical NEC					X			
Surgical NEC					X			
Focal intestinal perforation					X			
Grade II IVH					X			
Grade III or IV IVH					X			
Periventricular leukomalacia					X			
Cystic periventricular leukomalacia					X			
PDA requiring medical treatment					X			
PDA requiring surgical treatment					X			
Rash					X			
Seizure					X			
ROP requiring laser surgery					X			
Hyperbilirubinemia requiring exchange transfusion					X			
Laboratory Values*								
AST		X	X	X	X	X	X	X
ALT		X	X	X	X	X	X	X
WBC count		X	X	X	X	X	X	X
Hematocrit		X	X	X	X	X	X	X
Platelets		X	X	X	X	X	X	X
BUN		X	X	X	X	X	X	X

	Date of birth	-3 days	-2 days	-1 day	On ampicillin	+1 day	+2 days	+3 days
Creatinine		X	X	X	X	X	X	X
Physical Exam								
Abnormality				X	X			
Positive Blood/Urine/CSF Cultures								
Organism		X	X	X	X	X	X	X
Antimicrobial sensitivities		X	X	X	X	X	X	X
Ampicillin dosing**								
Date/time					X			
Dose (mg)					X			

*If laboratory value obtained on start day of ampicillin course, time of day should be recorded

**Only start of/changes in/last dose of ampicillin dosing/frequency associated with the ampicillin course in which PK samples were obtained were recorded

4.4.1 *Unit of observation*

Data was analyzed at the infant level. A unit of observation for this report is defined as any infant who received ampicillin while enrolled in the PPRU Antimicrobial PK in High Risk Infants study at Redacted.

4.4.2 *Laboratory values*

Daily laboratory values were collected while infants were exposed to ampicillin as well as three days prior to and three days after exposure to ampicillin. A laboratory abnormality was attributed to ampicillin if it occurred on a day that the infant was exposed to ampicillin or one day after exposure to ampicillin. Laboratory abnormalities attributed to ampicillin were categorized as abnormalities (AEs) or serious abnormalities (SAEs) based on pre-specified laboratory cut-off values (Table 4-2).

Table 4-2 Laboratory values

Laboratory values	Abnormality (AE)	Serious abnormality (SAE)
Renal dysfunction		
Elevated BUN	> 70 mg/dL	> 100 mg/dL
Elevated creatinine	> 1.7 mg/dL	> 3.0 mg/dL

Laboratory values	Abnormality (AE)	Serious abnormality (SAE)
Liver dysfunction		
Elevated AST	> 600 U/L	> 1200 U/L
Elevated ALT	> 225 U/L	> 450 U/L
Complete blood count		
Leukocytosis	> 25,000/mm^3	> 40,000/mm^3
Leukopenia	< 5000/mm^3	< 2000/mm^3
Thrombocytopenia	< 100,000/mm^3	< 30,000/mm^3
Thrombocytosis	> 600,000/mm^3	> 1,000,000/mm^3

4.4.3 *Clinical Adverse Events*

A clinical AE was defined by the occurrence of one of the pre-specified diagnoses. A clinical AE was attributed to ampicillin if it occurred while on ampicillin. Pre-specified diagnoses are listed in Table 4-3.

Table 4-3 Pre-specified clinical adverse events (AE)

Adverse Event
Gastrointestinal
Focal Intestinal Perforation
Medical NEC
Surgical NEC
Cardiovascular
Cardiorespiratory arrest
Hypotension
PDA requiring medical treatment
PDA requiring surgical treatment
Tachycardia
Respiratory
Tachypnea
Neurologic
Cystic periventricular leukomalacia
Grade II IVH
Grade III or IV IVH
Periventricular leukomalacia
Seizure
Ophthalmologic
ROP requiring laser surgery

Hematologic
Hyperbilirubinemia requiring exchange transfusion
Dermatologic
Rash
Death

4.4.4 *Physical examination*

A complete physical examination was performed on all infants while on ampicillin and within one day prior to initiation of ampicillin. Only newly emergent findings were recorded after ampicillin initiation. Abnormalities recorded were listed by body systems.

4.4.5 *Microbiology results*

All positive cultures from blood, urine or cerebrospinal fluid (CSF) obtained while on ampicillin or up to three days before or three days after therapy with ampicillin were recorded. Information about culture source, type of organism grown and susceptibility to ampicillin were recorded.

4.4.6 *Growth Parameters*

Length, weight, and head circumference were recorded for all patients at birth, one day prior to ampicillin exposure and one day after ampicillin exposure. Changes in weight, length and head circumference were defined as the difference between each measurement before and after ampicillin therapy.

4.5 *Statistical and Analytical Plans*

The number of observations, mean, median, standard deviation, minimum, and maximum are presented for continuous variables (such as age, weight, etc.). Counts, proportions, and percentages are presented for categorical variables.

4.5.1 *Demographics Characteristics*

The number of participants and demographic variables including gestational age, birth weight, one and five minute Apgar scores, postnatal age at first antibiotic exposure, race/ethnicity and gender are summarized. Demographics characteristics are also presented by postnatal age group.

4.5.2 *Physical Examinations*

Physical examination data collected before and after the start of ampicillin dosing are summarized separately. Laboratory findings or diagnoses reported in the electronic data capture as physical examination findings are excluded from this summary.

4.5.3 *Laboratory AE and SAE*

Laboratory data, such as hematology and serum chemistry data were analyzed by postnatal age group. Mean, median, standard deviation, minimum and maximum values are reported for each

laboratory test. Data are also presented as percentage of obtained laboratory values that met criteria for an AE or SAE.

4.5.4 *Clinical AE*

Pre-specified diagnoses defined as clinical AEs were analyzed by postnatal age group. Data are presented as counts and percentages of infants with a diagnosis by postnatal age group.

5 STUDY PARTICIPANTS

5.1 *Disposition of Participants*

A total of 68 infants were included. Infant disposition by cohort is shown in Table 5-1.

Table 5-1 Participants

	Cohort 1 (PNA ≤7 days)	**Cohort 2 (**PNA ≥8 days)	**Total**
N	42	26	68

5.2 *Demographics and Baseline Data*

All infants were <32 weeks GA and ≤1800 g birth weight. The lowest GA and birth weight was 23 weeks and 440 g. PNA at first exposure to ampicillin ranged from 0 and 106 days. The majority of infants were Caucasian (53%) and non-Hispanic ethnicity (97%) (Table 5-2).

Table 5-2 : Demographics

	Cohort 1 (PNA ≤7 days)	**Cohort 2 (**PNA ≥8 days)	**Total**
Post-Natal Age on Day of First Dose (days)			
N	42	26	68
Mean (SD)	0.2 (0.7)	27.8 (22.6)	10.8 (19.4)
Median (Min-Max)	0.0 (0.0 - 4.0)	20.5 (8.0 - 106.0)	0.0 (0.0 - 106.0)
Gestational Age (weeks)			
N	42	26	68
Mean (SD)	26.8 (2.3)	26.2 (2.0)	26.6 (2.2)
Median (Min-Max)	27.0 (23.0 - 31.0)	26.5 (23.0 - 31.0)	27.0 (23.0 - 31.0)

Weight at Birth (g)			
N	42	26	68
Mean (SD)	981.2 (333.6)	877.0 (214.5)	941.4 (296.4)
Median (Min-Max)	975.0 (440.0 - 1800)	825.0 (570.0 - 1390)	920.0 (440.0 - 1800)
Length at Birth (cm)			
N	42	26	68
Mean (SD)	35.0 (4.0)	33.4 (3.4)	34.4 (3.8)
Median (Min-Max)	34.0 (28.0 - 41.0)	33.3 (28.0 - 41.0)	34.0 (28.0 - 41.0)
Head Circumference at Birth (cm)			
N	42	26	68
Mean (SD)	24.6 (2.8)	23.4 (1.9)	24.1 (2.6)
Median (Min-Max)	25.0 (19.2 - 31.8)	23.1 (20.3 - 27.0)	24.0 (19.2 - 31.8)
One Minute Apgar Score			
N	41	26	67
Mean (SD)	4.0 (2.3)	3.5 (2.3)	3.9 (2.3)
Median (Min-Max)	4.0 (0.0 - 9.0)	3.0 (0.0 - 7.0)	3.0 (0.0 - 9.0)
Five Minute Apgar Score			
N	41	26	67
Mean (SD)	6.9 (1.9)	6.0 (1.5)	6.5 (1.8)
Median (Min-Max)	8.0 (2.0 - 9.0)	6.0 (3.0 - 8.0)	7.0 (2.0 - 9.0)
Gender, N (%)			
Male	25 (60)	17 (65)	42 (62)
Female	17 (41)	9 (35)	26 (38)
Race, N (%)			
Asian	0	1 (4)	1 (1)
Black or African American	22 (52)	8 (31)	30 (44)
White or Caucasian	19 (45)	17 (65)	36 (53)
Not reported	1 (2)	0	1 (1)
Ethnicity, N (%)			

Hispanic or Latino	1 (2)	0	1 (1)
Not Hispanic or Latino	40 (95)	26 (100)	66 (97)
Not reported	1 (2)	0	1 (1)

5.2.1 *Physical examination findings prior to ampicillin initiation*

The most common physical examination finding prior to ampicillin initiation was an abnormal skin finding, which was found in 24/68 (35%) of infants (Table 5-3).

Table 5-3: Physical examination, N (%)

Body System	**Cohort 1 (PNA ≤7 days) (N=42)**	**Cohort 2 (PNA ≥8 days) (N=26)**	**Total (N=68)**
Skin	19 (45)	5 (19)	24 (35)
Respiratory	15 (36)	4 (15)	19 (28)
Abdomen	8 (19)	9 (35)	17 (25)
Cardiovascular	0	10 (38)	10 (15)
Eyes and Vision	6 (14)	2 (8)	8 (12)
General Behavior	7 (17)	1 (4)	8 (12)
Extremities	3 (7)	1 (4)	4 (6)
Nervous System	4 (10)	0	4 (6)
Head	0	2 (8)	2 (3)
Blood/Lymphatic	1 (2)	0	1 (1)
Ears, Nose and Throat	0	1 (4)	1 (1)
General Appearance	1 (2)	0	1 (1)
Other	2 (5)	2 (8)	4 (6)

5.3 *Dosing*

Dosing is summarized in Table 5-4. Weight-adjusted dose was calculated using baseline weight. All infants were on study drug for at least 2 calendar days. The fewest administered doses

received by an infant was 3. Also, all infants received doses >180 mg/kg/day in the form of 100 mg/kg BID or approximately 67 mg/kg TID dosing.

Table 5-4: Dosing summary

	Cohort 1 (PNA ≤7 days) (N=42)	**Cohort 2 (PNA ≥8 days) (N=26)**	**Total (N=68)**
Calendar Days on Ampicillin			
Mean (SD)	6.7 (3.6)	5.0 (3.3)	6.1 (3.6)
Median (Min-Max)	7 (2 - 21)	4 (2 - 17)	5 (2 - 21)
Maximum Daily Dose Per Infant (mg/kg)			
Mean (SD)	215.6 (36.7)	208.7 (22.0)	213.0 (31.9)
Median (Min-Max)	200.0 (194.0 - 326.4)	201.7 (181.2 - 294.6)	200.0 (181.2 - 326.4)

5.4 *Laboratory adverse events*

5.4.1 *Summary of laboratory values obtained*

All infants in the study had at least one WBC, hematocrit, platelet, creatinine and BUN value obtained. ALT and AST values were obtained for 32/68 (47%) of infants (Table 5-5).

Table 5-5: Laboratory values

	Cohort 1 (PNA ≤7 days) (N=42)	Cohort 2 (PNA ≥8 days) (N=26)	Total (N=68)
Number of ALT Values per Infant			
Number of Infants	15	17	32
Mean (SD)	1.7 (1.2)	2.3 (1.3)	2.0 (1.3)
Median (Min-Max)	1.0 (1.0 - 5.0)	2.0 (1.0 - 5.0)	2.0 (1.0 - 5.0)
ALT Values (U/L)			
Number of Samples	26	39	65
Mean (SD)	43.5 (56.0)	28.6 (13.0)	34.6 (37.2)
Median (Min-Max)	21.5 (8.0 - 212.0)	24.0 (13.0 - 62.0)	23.0 (8.0 - 212.0)
Number of AST Values per Infant			
Number of Infants	15	17	32
Mean (SD)	1.7 (1.2)	2.3 (1.3)	2.0 (1.3)
Median (Min-Max)	1.0 (1.0 - 5.0)	2.0 (1.0 - 5.0)	2.0 (1.0 - 5.0)
AST Values (U/L)			
Number of Samples	26	39	65
Mean (SD)	168.0 (402.7)	42.1 (21.9)	92.4 (259.8)
Median (Min-Max)	39.5 (15.0 - 1731)	34.0 (15.0 - 122.0)	35.0 (15.0 - 1731)
Number of Blood Urea Nitrogen (BUN) Values per Infant			
Number of Infants	42	26	68
Mean (SD)	8.7 (5.0)	8.9 (4.8)	8.8 (4.9)
Median (Min-Max)	8.0 (2.0 - 25.0)	8.5 (2.0 - 19.0)	8.0 (2.0 - 25.0)

	Cohort 1 (PNA ≤7 days) (N=42)	Cohort 2 (PNA ≥8 days) (N=26)	Total (N=68)
BUN Values (mg/dL)			
Number of Samples	365	231	596
Mean (SD)	35.0 (24.7)	30.5 (24.2)	33.2 (24.6)
Median (Min-Max)	27.0 (2.0 - 110.0)	25.0 (2.0 - 126.0)	26.0 (2.0 - 126.0)
Number of Creatinine Values per Infant			
Number of Infants	42	26	68
Mean (SD)	8.7 (4.9)	8.9 (4.8)	8.8 (4.9)
Median (Min-Max)	8.0 (2.0 - 25.0)	8.5 (2.0 - 19.0)	8.0 (2.0 - 25.0)
Creatinine Values (mg/dL)			
Number of Samples	366	231	597
Mean (SD)	1.2 (0.5)	1.2 (0.6)	1.2 (0.5)
Median (Min-Max)	1.1 (0.3 - 3.2)	1.0 (0.2 - 3.1)	1.1 (0.2 - 3.2)
Number of White Blood Cell (WBC) Values per Infant			
Number of Infants	42	26	68
Mean (SD)	6.4 (4.1)	4.4 (3.1)	5.6 (3.8)
Median (Min-Max)	5.0 (2.0 - 22.0)	3.5 (1.0 - 16.0)	5.0 (1.0 - 22.0)
WBC Values (10^3/uL)			
Number of Samples	269	115	384
Mean (SD)	14.9 (11.6)	14.2 (6.8)	14.7 (10.4)
Median (Min-Max)	12.3 (1.4 - 67.8)	12.2 (5.6 - 42.0)	12.3 (1.4 - 67.8)
Number of Hematocrit Values per Infant			
Number of Infants	42	26	68

	Cohort 1 (PNA ≤7 days) (N=42)	Cohort 2 (PNA ≥8 days) (N=26)	Total (N=68)
Mean (SD)	7.1 (4.8)	5.1 (3.1)	6.4 (4.3)
Median (Min-Max)	6.0 (2.0 - 26.0)	4.5 (1.0 - 16.0)	5.0 (1.0 - 26.0)
Hematocrit Values (%)			
Number of Samples	299	133	432
Mean (SD)	37.8 (6.7)	32.4 (4.5)	36.1 (6.6)
Median (Min-Max)	37.0 (22.0 - 60.0)	32.0 (20.0 - 46.0)	36.0 (20.0 - 60.0)
Number of Platelet Values per Infant			
Number of Infants	42	26	68
Mean (SD)	7.0 (4.8)	4.6 (3.4)	6.1 (4.5)
Median (Min-Max)	5.0 (2.0 - 25.0)	3.5 (1.0 - 17.0)	5.0 (1.0 - 25.0)
Platelet Values (10^3/uL)			
Number of Samples	296	120	416
Mean (SD)	208.7 (126.9)	299.7 (167.4)	235.0 (145.6)
Median (Min-Max)	179.5 (10.0 - 716.0)	268.5 (29.0 - 739.0)	207.0 (10.0 - 739.0)

5.4.2 *Infants with laboratory AE and SAE*

The most common laboratory AE was leukocytosis, which was found in 19/68 (28%) of infants. Elevated creatinine (>1.7 mg/dL), which occurred in 17/68 (25%), and leucopenia, which occurred in 16/68 (23%), were also reported in at least 20% of infants. None of 32 infants who had ALT values checked were found to have an abnormally elevated ALT value while only 1/32 (3%) infants who had AST values checked was found to have an AST value >1200 U/L (Table 5-6).

Table 5-6: Laboratory AEs and SAEs, N (% of infants with associated lab records)

	Cohort 1 (PNA ≤7 days) (N=42)	**Cohort 2 (PNA ≥8 days) (N=26)**	**Total (N=68)**
Elevated ALT*			
Normal	15 (100)	17 (100)	32 (100)
Elevated AST*			
AE	1 (7)	0	1 (3)
SAE	1 (7)	0	1 (3)
Normal	14 (93)	17 (100)	31 (97)
Elevated BUN*			
AE	8 (19)	4 (15)	12 (18)
SAE	1 (2)	1 (4)	2 (3)
Normal*	34 (81)	22 (85)	56 (82)
Elevated Creatinine*			
AE	10 (24)	7 (27)	17 (25)
SAE	1 (2)	2 (8)	3 (4)
Normal	32 (76)	19 (73)	51 (75)
Leukocytosis*			
AE	14 (33)	5 (19)	19 (28)
SAE	5 (12)	1 (4)	6 (9)
Normal	28 (67)	21 (81)	49 (72)
Leukopenia*			
AE	16 (38)	0	16 (23)
SAE	1 (2)	0	1 (1)
Normal	26 (62)	26 (100)	52 (76)

	Cohort 1 (PNA ≤7 days) (N=42)	Cohort 2 (PNA ≥8 days) (N=26)	Total (N=68)
Thrombocytopenia*			
AE	10 (24)	2 (8)	12 (18)
SAE	2 (5)	1 (4)	3 (4)
Normal	32 (76)	24 (92)	56 (82)
Thrombocytosis*			
AE	2 (5)	4 (15)	6 (9)
Normal	40 (95)	22 (85)	62 (91)

*Based on pre-specified cut off values from Table 4-2

5.5 *Clinical AE*

A total of 67 clinical AE were recorded in 46 infants. The most commonly reported clinical AE was hypotension which occurred 25/68 (37%) of infants. Many predefined clinical AEs were not observed in this cohort, including seizures (Table 5-7).

Table 5-7: Clinical AE, N (%)

	Cohort 1 (PNA ≤7 days) (N=42)	Cohort 2 (PNA ≥8 days) (N=26)	Total (N=68)
Number of Adverse Events	46	21	67
Number of Infants with Adverse Events	30 (71)	16 (62)	46 (68)
Number of Infants with Adverse Events by Description			
Gastrointestinal			
Focal Intestinal Perforation	0	0	0
Medical NEC	0	1 (4)	1 (1)
Surgical NEC	0	0	0
Cardiovascular			
Cardiorespiratory arrest	0	0	0
Hypotension	17 (41)	8 (31)	25 (37)
PDA requiring medical treatment	10 (24)	1 (4)	11 (16)
PDA requiring surgical treatment	1 (2)	1 (4)	2 (3)

	Cohort 1 (PNA ≤7 days) (N=42)	Cohort 2 (PNA ≥8 days) (N=26)	Total (N=68)
Tachycardia	2 (5)	2 (8)	4 (6)
Respiratory			
Tachypnea	10 (24)	6 (23)	16 (24)
Neurologic			
Cystic periventricular leukomalacia	0	0	0
Grade II IVH	2 (5)	1 (4)	3 (4)
Grade III or IV IVH	2 (5)	0	2 (3)
Periventricular leukomalacia	0	0	0
Seizure	0	0	0
Ophthalmology			
ROP requiring laser surgery	0	0	0
Hematology			
Hyperbilirubinemia requiring exchange transfusion	0	0	0
Dermatology			
Rash	1 (2)	1 (4)	2 (3)
Death	1 (2)	0	1 (1)

5.6 *Microbiology results*

There were 46 positive cultures in 35 infants. Of the 35 infants with positive cultures, 14 were <7 days postnatal age (40%) and 21 were >8 days postnatal age (60%). The most commonly cultured organism was Staphylococcus species. Sensitivity to ampicillin was available in 7 infants with positive cultures. Of those, 5 (71%) were sensitive to ampicillin, 1 (14%) had intermediate sensitivity and 1 (14%) was resistant. Sensitivity to vancomycin was available for only 2 infants with positive cultures and both were sensitive (Table 5-8).

Table 5-8: Microbiology results, n (%)

	Cohort 1 (PNA ≤7 days)			Cohort 2 (PNA ≥8 days)			Total		
	Pre	**During**	**Post**	**Pre**	**During**	**Post**	**Pre**	**During**	**Post**
Number of Positive Cultures	0	9	10	11	13	3	11	22	13
Number of Infants with Positive Cultures	0	7 (17)	7 (17)	9 (35)	9 (35)	3 (12)	9 (13)	16 (24)	10 (15)
Number of Infants with Positive Findings by Organism									
Citrobacter sp.	0	0	0	1 (4)	0	0	1 (1)	0	0
CMV	0	1 (3)	0	0	1 (4)	0	0	2 (3)	0
Enterococcus sp.	0	0	0	3 (12)	1 (4)	0	3 (4)	1 (1)	0
Escherichia coli	0	1 (3)	0	1 (4)	0	0	1 (1)	1 (1)	0
Methicillin resistant staphylococcus aureus	0	1 (3)	0	0	0	0	0	1 (1)	0
Staphylococcus sp.	0	0	0	0	1 (4)	0	0	1 (1)	0
Staphylococcus sp. (coagulase negative)	0	0	4 (10)	2 (8)	3 (12%)	2 (8)	2 (3)	3 (4)	6 (9)
Other	0	5 (12)	4 (10)	4 (15)	6 (23)	1 (4)	4 (6)	11 (16)	5 (7)

5.7 *Growth parameters*

Weights were available prior to ampicillin therapy in 68 and following therapy in 67 infants (Table 5-9). Length and head circumferences were available in 42 infants prior to ampicillin therapy and 1 and 2 infants post therapy, respectively. Of the 67 infants with available weights before and after ampicillin therapy, 47 (70%) lost weight during ampicillin therapy.

Table 5-9: Growth parameters

	Cohort 1 (PNA ≤7 days)			Cohort 2 (PNA ≥8 days)			Total		
	Pre	**Post**	**Change**	**Pre**	**Post**	**Change**	**Pre**	**Post**	**Change**
Weight (g)									
N	42	41	41	26	26	26	68	67	67
Mean (SD)	975.4 (330.6)	853.8 (301.1)	-109 (85.0)	1021 (423.2)	1052 (450.3)	31.4 (72.6)	992.7 (366.3)	930.7 (375.8)	-54.6 (105.5)
Median (Min-Max)	965.0 (440.0 - 1800)	805.0 (384.0 - 1664)	-99.0 (-349 - 82.0)	919.0 (455.0 - 2225)	929.5 (427.0 - 2360)	23.5 (-130 - 185.0)	960.0 (440.0 - 2225)	899.0 (384.0 - 2360)	-54.0 (-349 - 185.0)
Length (cm)									
N	41	1	1	1	0	0	42	1	1
Mean (SD)	34.8 (4.0)	39.0	2.5	43.0			35.0 (4.2)	39.0	2.5
Median (Min-Max)	34.0 (28.0 - 41.0)	39.0	2.5	43.0			34.0 (28.0 - 43.0)	39.0	2.5
Head Circumference (cm)									
N	41	2	2	1	0	0	42	2	2

	Cohort 1 (PNA ≤7 days)			Cohort 2 (PNA ≥8 days)			Total		
Mean (SD)	24.5 (2.9)	26.8 (3.2)	0.3 (0.4)	38.0			24.9 (3.5)	26.8 (3.2)	0.3 (0.4)
Median (Min-Max)	25.0 (19.2 - 31.8)	26.8 (24.5 - 29.0)	0.3 (0.0 - 0.5)	38.0			25.0 (19.2 - 38.0)	26.8 (24.5 - 29.0)	0.3 (0.0 - 0.5)

5.8 *Physical examination findings after ampicillin initiation*

Table 5-10 shows newly emergent abnormal physical examination findings that were reported after the start of ampicillin administration. Respiratory findings were the most commonly reported finding. These were report in 25/68 (37%) of infants. Abdomen, skin, and cardiovascular findings were also reported in at least 20% of infants.

Table 5-10: Physical examination, N (%)

Body System	Cohort 1 (PNA ≤7 days) (N=42)	Cohort 2 (PNA ≥8 days) (N=26)	Total (N=68)
Respiratory	17 (41)	8 (31)	25 (37)
Abdomen	12 (29)	8 (31)	20 (29)
Skin	18 (43)	1 (4)	19 (28)
Cardiovascular	10 (24)	4 (15)	14 (21)
General Behavior	5 (12)	3 (12)	8 (12)
Extremities	2 (5)	1 (4)	3 (4)
Eyes and Vision	3 (7)	0	3 (4)
General Appearance	3 (7)	0	3 (4)
Head	2 (5)	0	2 (3)
Ears, Nose and Throat	1 (2)	0	1 (1)
Other	1 (2)	0	1 (1)

6 DISCUSSION

We described the safety profile of ampicillin in 68 infants enrolled in the PPRU Antimicrobial PK in High Risk Infants study at Redacted.

We found that 46/68 (68%) of infants experienced one of the pre-specified diagnoses. We found a low rate of diagnoses listed on the ampicillin label including rashes in only 2/68 (3%) of infants and necrotizing enterocolitis in only 1/68 (2%) of infants. Other previously described diagnoses associated with ampicillin exposure in infants include seizures and intraventricular hemorrhage[6,7] . In this cohort, 3/68 (4%) of infants had a grade II IVH and 2/68 (3%) of infants had a grade III or IV IVH. None of the infants experienced a seizure while on ampicillin. It is possible that more infants were diagnosed with IVH or developed seizures after ampicillin therapy was discontinued, but information about diagnoses made after ampicillin exposure was not captured in this study. The most common diagnosis made while on ampicillin therapy was

hypotension in 25/68 (37%) of infants. In this descriptive safety analysis, we did not control for infant severity of illness at the time of ampicillin exposure.

Laboratory abnormalities were overall less common. Moderate elevation in AST has been noted after ampicillin administration, particularly in infants. In our study, only 1/32 (3%) infants with available AST values were found to have an abnormality. Given that AST elevation in infants is most likely related to release from myocytes at the site of intramuscular injection, it is not surprising that the incidence of this laboratory abnormality would be lower in a cohort of infants receiving intravenous ampicillin as part of a PK study. The most common laboratory abnormality seen in our cohort was leukocytosis in 19/68 (28%) of infants. In this cohort, thrombocytopenia and leukopenia occurred in 12/68 (18%) and 16/68 (24%) of infants, respectively. Again, these abnormalities are not listed on the ampicillin label, but severity of illness and concomitant administration of nephrotoxic medications may explain the high rate of these laboratory abnormalities. This is especially true for infants of younger postnatal age, who may be sicker at the time of ampicillin administration. In our study there was a trend towards infants ≤7 days of postnatal age suffering more laboratory abnormalities than infants in the older PNA cohort.

7 CONCLUSION

In this study of 68 infants exposed to ampicillin, 46 (68%) experienced one of the pre-specified clinical diagnoses. Laboratory abnormalities were less common, with 19 infants (28%) having leukocytosis, the most common laboratory abnormality.

8 REFERENCES

1. Ampicillin package literature. http://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?id=31468. Accessed Feb, 2013.
2. van den Hoogen A, Gerards LJ, Verboon-Maciolek MA, Fleer A, Krediet TG. Long-term trends in the epidemiology of neonatal sepsis and antibiotic susceptibility of causative agents. *Neonatology.* 2010;97(1):22-28.
3. Stoll BJ, Hansen NI, Bell EF, et al. Neonatal outcomes of extremely preterm infants from the NICHD Neonatal Research Network. *Pediatrics.* Sep 2010;126(3):443-456.
4. Clark RH, Bloom BT, Spitzer AR, Gerstmann DR. Reported medication use in the neonatal intensive care unit: data from a large national data set. *Pediatrics.* Jun 2006;117(6):1979-1987.
5. Metsvaht T, Ilmoja ML, Parm U, Maipuu L, Merila M, Lutsar I. Comparison of ampicillin plus gentamicin vs. penicillin plus gentamicin in empiric treatment of neonates at risk of early onset sepsis. *Acta Paediatr.* May 2010;99(5):665-672.
6. Shaffer CL, Davey AM, Ransom JL, Brown YL, Gal P. Ampicillin-induced neurotoxicity in very-low-birth-weight neonates. *Ann Pharmacother.* Apr 1998;32(4):482-484.
7. Barrons RW, Murray KM, Richey RM. Populations at risk for penicillin-induced seizures. *Ann Pharmacother.* Jan 1992;26(1):26-29.

8. Sheffield MJ, Lambert DK, Henry E, Christensen RD. Effect of ampicillin on the bleeding time of neonatal intensive care unit patients. *J Perinatol.* Aug 2010;30(8):527-530.