

Ampicillin Safety in Hospitalized Infants



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Background

Ampicillin is the most commonly prescribed medication in the neonatal intensive care unit (NICU).

Studies of ampicillin in infants provide limited safety data due to small study size and the Food and Drug Administration (FDA) label does not include adverse events (AE) for infants.

We evaluated the safety of ampicillin in a large cohort of infants admitted to the NICU.

Methods

We included all infants discharged from 322 Pediatric NICUs from 1997–2010 exposed to ampicillin; gentamicin; vancomycin; or cefotaxime.

We attributed an AE to an antibiotic if it occurred between the start through 1 day following the end of therapy and was not present the day prior to therapy.

We classified AEs as AEs or severe AEs (SAEs) based on the severity of the diagnosis and prespecified laboratory cut-offs.

We compared AEs between infant days of exposure against infant days of no exposure to ampicillin.

We used multivariable logistic regression with generalizing estimating equations to calculate the odds of AEs while on ampicillin.

We included the following covariates in all models: gentamicin and vancomycin exposure, gestational age, postnatal age, bacteremia, inotropic support, and mechanical ventilation.

Results

224,332/490,736 (46%) of infants exposed to ampicillin suffered at least one AE.

The incidence of any AE was 154/1000 infant days on ampicillin vs. 190/1000 infant days on control antibiotics (p<0.001).

The odds of all AEs combined were lower on ampicillin: odds ratio (OR)=0.93 (95% confidence interval 0.91, 0.95).

The odds of any AE were lower, OR=0.93 (0.91, 0.95), while the odds of any SAE were not different, OR=0.97 (0.94, 1.01).

Table 1: Demographics

	Total N=503,719
Gestational age, weeks	
<26	20,112 (4%)
26-28	34,558 (7%)
29-32	84,770 (17%)
33-36	168,968 (34%)
≥37	194,893 (39%)
Birth weight, g	
<1000	42,896 (9%)
1000-1499	53,342 (11%)
1500-2499	161,912 (32%)
2500-3499	169,641 (34%)
≥3500	74,894 (15%)
Postnatal age at first antibiotic, days	
<3	479,105 (95%)
3-6	11,594 (2%)
7-29	11,229 (2%)
30-59	1,344 (<1%)
60-120	447 (<1%)
Race/ ethnicity	
Caucasian	249,542 (52%)
African-American	82,480 (17%)
Hispanic	124,903 (26%)
Other	24,480 (5%)
Male	286,630 (57%)
Inborn	414,081 (83%)
Caesarean section	266,493 (54%)
Died	14,576 (3%)

Table 2: Odds ratios of laboratory AEs for days on ampicillin vs. not on ampicillin.

		Adjusted OR(95% CI) ^			
		AE		SAE	
Serum Electrolytes		1.01 (0.99, 1.05)		1.03 (0.97, 1.08)	
Hyperglycemia	> 250 mg/dL	1.11 (1.00, 1.24)	> 400 mg/dL	0.97 (0.74, 1.26)	
Hypoglycemia	< 40 mg/dL	0.96 (0.89, 1.04)	< 20 mg/dL	0.95(0.80, 1.12)	
Hypnatremia	> 155 mmol/L	1.30(1.20, 1.40)	> 160 mmol/L	1.09 (0.85, 1.40)	
Hyponatremia	< 125 mmol/L	0.76 (0.69, 0.83)	< 115 mmol/L	0.64 (0.43, 0.96)	
Hyperkalemia	> 6 mmol/L	1.00 (0.97, 1.03)	> 7.5 mmol/L	0.93 (0.85, 1.02)	
Hypokalemia	< 3 mmol/L	1.03 (0.96, 1.10)	< 2.5 mmol/L	0.97 (0.83, 1.12)	
Hypercalcemia	> 12.5 mg/dL	1.25 (1.04, 1.50)	> 13.5 mg/dL	1.14 (0.83, 1.57)	
Hypocalcemia	< 6.0 mg/dL	1.05 (1.01, 1.10)	< 5.0 mg/dL	1.13 (1.06, 1.19)	
Renal Dysfunction		0.91 (0.82, 1.00)		1.02 (0.82, 1.28)	
Elevated BUN	> 70 mg/dL	1.15 (1.06, 1.25)	> 100 mg/dL	1.18 (0.98, 1.42)	
Elevated Creatinine	> 1.7 mg/dL	0.78 (0.73, 0.83)	> 3.0 mg/dL	0.94 (0.80, 1.10)	
Liver Dysfunction		1.08 (0.99, 1.18)		1.14 (0.98, 1.32)	
Elevated AST	> 600 U/L	0.82 (0.57, 1.17)	> 1200 U/L	0.88 (0.52, 1.18)	
Elevated ALT	> 225 U/L	0.86 (0.66, 1.12)	> 450 U/L	0.71 (0.45, 1.11)	
Elevated GGT	> 90 U/L	1.11 (1.03, 1.21)	> 180 U/L	1.22 (1.09, 1.38)	
Blood Count		0.84 (0.81, 0.87)		0.88 (0.80, 0.95)	
Leukocytosis	> 25,000/mm ³	0.72 (0.71, 0.75)	> 40,000/mm ³	0.92 (0.86, 0.98)	
Leukopenia	< 5000/mm ³	1.24 (1.18, 1.31)	< 2000/mm ³	1.01(0.84, 1.21)	
Neutropenia	< 500/mm ³	1.15 (1.02, 1.30)	< 100/mm ³	1.17 (0.81, 1.69)	
Thrombocytopenia	< 100/mm ³	0.77 (0.75, 0.79)	< 30/mm ³	0.61(0.55, 0.67)	
Thrombocytosis	> 600,000/mm ³	0.98 (0.91, 1.06)	> 1,000,000/mm ³	0.81 (0.43, 1.50)	
Any laboratory		0.92 (0.90, 0.95)		0.80 (0.77, 0.83)	

AE: adverse event, SAE: severe adverse event, BUN: blood urea nitrogen, AST: aspartate aminotransferase, ALT: alanine transaminase, GGT: gamma-glutamyltransferase.. * p < 0.05

Table 3: Antibiotic exposure, mean (5th and 95th %tile)

	Ampicillin	Gentamicin	Cefotaxime	Vancomycin
Total number of infants	490,736	458,356	65,434	66,001
Total days of exposure	2,720,417	434,858	204,455	668,998
Age at first exposure	1 (0, 2)	1 (0, 2)	2 (0, 10)	13 (0, 43)
Days of exposure	6 (2, 11)	5 (1, 13)	7 (1, 17)	11 (1, 31)

Table 4: Incidence of clinical AEs, and odds ratios of clinical AEs for days on ampicillin vs. not on ampicillin

	Adjusted OR (95% CI) *
Dermatologic abnormality	0.79 (0.62, 1.02)
Hyperbilirubinemia requiring exchange transfusion	1.71 (1.01, 2.90)
Focal intestinal perforation	0.98 (0.75, 1.28)
Surgical necrotizing enterocolitis	1.21 (1.12, 1.31)
Seizure	0.94 (0.82, 1.08)
Grade III - IV intraventricular hemorrhages	1.17 (1.01, 1.33)
Grade II intraventricular hemorrhages	1.35 (1.13, 1.60)
Death prior to discharge	0.75 (0.66, 0.86)
Any clinical AE	1.08 (1.02, 1.14)

Conclusions

AEs were overall less frequent on ampicillin compared to other antibiotics.

Serum electrolyte abnormalities were the only laboratory AEs and SAEs more common while exposed to ampicillin.

A number of clinical AEs were more common while exposed to ampicillin.

Our study supports the overall safety of ampicillin, but highlights a number of adverse events of relevance to the clinician prescribing ampicillin to hospitalized infants.

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