HHS Public Access

Author manuscript

Am J Perinatol. Author manuscript; available in PMC 2016 May 01.

Published in final edited form as:

Am J Perinatol. 2015 May ; 32(6): 565–570. doi:10.1055/s-0034-1543955.

Rifampin Use and Safety in Hospitalized Infants

Christopher J. Arnold, MD[1,2], **Jessica Ericson, MD**[1,3], **Jordan Kohman**[1], **Kaitlyn L. Corey**[1], **Morgan Oh**[1], **Janet Onabanjo**[1], **Christoph P. Hornik, MD, MPH**[1,3], **Reese H. Clark, MD**[4], **Daniel K. Benjamin Jr., MD, PhD, MPH**[1,3], **P. Brian Smith, MD, MPH, MHS**[1,3], and **Vivian H. Chu, MD, MHS**[1,2] **on behalf of the Best Pharmaceuticals for Children Act – Pediatric Trials Network Administrative Core Committee***

[1]Duke Clinical Research Institute, Durham, NC

[2]Division of Infectious Diseases, Department of Medicine, Duke University, Durham, NC

[3]Department of Pediatrics, Duke University, Durham, NC

[4]Pediatrix Medical Group, Sunrise, FL

Abstract

Objective—To examine the use and safety of rifampin in hospitalized infants.

Study Design—Observational study of clinical and laboratory adverse events among infants exposed to rifampin from 348 neonatal intensive care units managed by the Pediatrix Medical Group between 1997 and 2012.

Result—2500 infants received 4279 courses of rifampin; mean gestational age was 27 weeks (5^{th}, 95^{th} %tile; 23, 36) and mean birth weight was 1125 g (515, 2830). Thrombocytopenia (121/1000 infant days) and conjugated hyperbilirubinemia (25/1000 infant days) were the most common laboratory adverse events. The most common clinical adverse events were medical necrotizing enterocolitis (64/2500 infants, 3%) and seizure (60/2500 infants, 2%).

Conclusion—The overall incidence of adverse events among infants receiving rifampin appears low; however, additional studies to further evaluate safety and dosing of rifampin in this population are needed.

Correspondence: Vivian H. Chu, MD, MHS, Division of Infectious Diseases, Department of Medicine, Duke University Medical Center, Box 102359, Durham, NC 27710; telephone: 919-668-7174; fax: 919-681-7494; vivian.chu@duke.edu.

*See Acknowledgments for listing of committee members.

The content is solely the responsibility of the authors and does not necessarily represent the official views of the NIH.

Conflicts of Interest

Dr. Hornik receives salary support for research from the National Center for Advancing Translational Sciences of the National Institutes of Health (NIH) (UL1TR001117). Dr. Benjamin receives support from the United States government for his work in pediatric and neonatal clinical pharmacology (1R01HD057956-05, 1K24HD058735-05, UL1TR001117, and NICHD contract HHSN275201000003I) and the nonprofit organization Thrasher Research Fund for his work in neonatal candidiasis (www.thrasherresearch.org); he also receives research support from industry for neonatal and pediatric drug development (www.dcri.duke.edu/research/coi.jsp). Dr. Smith receives salary support for research from the NIH and the National Center for Advancing Translational Sciences of the NIH (HHSN267200700051C, HHSN275201000003I, and UL1TR001117); he also receives research support from industry for neonatal and pediatric drug development (www.dcri.duke.edu/research/coi.jsp). Dr. Ericson receives support from the National Institute of Child Health and Human Development of the NIH (5T32HD060558). The remaining authors have no potential conflicts of interest to disclose.

Keywords

rifampin; broad-spectrum antibiotic; infectious disease; neonatal intensive care unit

Introduction

Rifampin is a broad-spectrum antibiotic used for a variety of infections in children.[1] Possessing excellent anti-staphylococcal activity, rifampin, when added to an anti-staphylococcal penicillin or vancomycin, is effective in the treatment of refractory cases of bacteremia due to coagulase-negative staphylococci (CoNS) in infants.[2–5] Rifampin is also used as adjunctive therapy for infections of ventriculoperitoneal (VP) shunts with staphylococcal organisms in infants.[6–9] CoNS and *Staphylococcus aureus* are the most common causes of sepsis in the neonatal intensive care unit (NICU).[10] The use of rifampin as adjunctive therapy is a logical consideration for these infections[10]; therefore, understanding its safety profile in this population is important.

Adverse events (AEs) reported with rifampin use include hepatotoxicity, renal failure, rash, and hematological abnormalities including thrombocytopenia.[1,11] However, few data exist on its safety in infants. Rifampin is not labeled by the Food and Drug Administration (FDA) for infants <3 months of age.[12] The largest previous report of rifampin use in the neonatal population was a retrospective analysis of 137 premature infants that examined clearance of bacteremia and C-reactive protein levels, but this study did not report safety outcomes.[4] Here, we describe the use of rifampin among a large cohort of hospitalized infants and the incidence of clinical and laboratory AEs associated with its use.

Methods

Data source and definitions

We identified all infants discharged from 348 NICUs managed by the Pediatrix Medical Group between 1997 and 2012 exposed to rifampin in the first 120 days of life. We excluded infants with major congenital anomalies. Data were obtained from a database that captures electronic medical record information from clinicians on all infants cared for by the Pediatrix Medical Group. Data collected include: maternal history, demographics, medications, laboratory results, microbiology results, and diagnoses. Dosing and dosing intervals were not available in the data.

We defined a rifampin course as uninterrupted days of exposure to rifampin. We classified rifampin courses as associated with a positive culture if a culture (blood, urine collected by in-and-out catheterization or suprapubic tap, or cerebrospinal fluid [CSF]) was positive on days of exposure to rifampin or up to 5 days prior to the first day of rifampin exposure. Multiple positive cultures for the same organism within a 21-day period were considered a single infectious episode. We defined CoNS sepsis as 2 positive cultures for CoNS within a 4-day period, 3 positive cultures for CoNS within a 7-day period, or 4 positive cultures for CoNS within a 10-day period. We excluded positive cultures from organisms considered contaminants, including non-speciated streptococci, *Bacillus* spp., gram-positive rods (not

including *Listeria* spp.), *Lactobacillus* spp., *Micrococcus* spp., *Stomatococcus* spp., and *Bacteroides* spp.

An AE was attributed to rifampin if it occurred on a day of exposure to rifampin. AEs included laboratory and clinical AEs (surgical necrotizing enterocolitis [NEC], medical NEC, focal intestinal perforation, grade III–IV intraventricular hemorrhage [IVH], seizures, rash, and pulmonary hemorrhage). Each new clinical diagnosis occurring while an infant was exposed to rifampin was counted as a separate AE. Laboratory AEs were categorized as an AE or a severe adverse event (SAE) based on pre-specified cut-off values. Each laboratory abnormality was counted as a separate AE or SAE, and was counted each day that it occurred while an infant was exposed to rifampin. We defined concomitant antibiotic use as any antibiotic administered on a day of exposure to rifampin.

Statistical analysis

We used standard summary statistics including counts and percentages and means, medians, and percentiles to describe categorical and continuous study variables, respectively. We reported laboratory AEs occurring while on rifampin as both number of days with an AE per 1000 infant days of exposure to rifampin and the proportion of courses of rifampin during which an AE was reported on at least 1 day. We reported clinical AEs as proportions occurring at both the course and infant level. All analyses were performed using Stata 12 (College Station, TX). The study was approved by the Duke University Institutional Review Board without the need for written informed consent as the data were collected without identifiers.

Results

Infant characteristics and outcomes

We identified 2500 infants who received 4279 courses of rifampin for a total of 23,701 infant days. The mean gestational age (GA) was 27 weeks (5^{th}, 95^{th}%tile; 23, 36), and the mean birth weight was 1125 g (515, 2830) (Table 1). Mean weight at the time of first rifampin exposure was 1518 g (650, 3380).

Microbiology

There were 1455 courses (34%) administered to 1249 infants for a total of 8874 infant days in the setting of positive cultures and 2824 courses (66%) of rifampin administered to 1251 infants for a total of 14,827 infant days in the setting of negative cultures. The majority of positive cultures were obtained from blood—1332/1380 (97%). The most commonly cultured organisms were gram-positive (1273/1380 [92%]), and CoNS was the most common pathogen (670/1380 [49%]) (Table 2). Among the infants with negative cultures, 715/1251 (57%) had either a single culture positive for CoNS or a surface culture positive for methicillin-resistant *Staphylococcus aureus* (MRSA).

Nineteen infants (0.8%) with VP shunts received 40 courses (0.9%) of rifampin for a total of 4270 infant days. There were 15 positive cultures obtained in these infants; 6/15 (40%) of these were from blood, and 9/15 (60%) from the CSF. All 9 positive CSF cultures grew

gram-positive organisms, while the 6 positive blood cultures included 2 gram-positive, 2 gram-negative, and 2 fungal organisms.

The mean duration of a rifampin treatment course was 7 days (1, 17) in those infants with positive blood cultures and 9 days (1, 28) in those with positive CSF cultures. Vancomycin was the most common concomitantly administered antibiotic, followed by penicillins and cephalosporins (Table 3).

Safety

Laboratory AEs and SAEs were observed on 249 per 1000 infant days and 53 per 1000 infant days, respectively (Table 4). The majority of rifampin courses had at least 1 laboratory AE (3493/4279 [82%]). Laboratory SAEs occurred in a lower proportion of courses (1782/4279 [42%]). The most common electrolyte abnormality was hyperkalemia (19/1000 infant days). Conjugated hyperbilirubinemia was the most common laboratory AE associated with liver dysfunction (25/1000 infant days). Renal laboratory AEs, including elevated blood urea nitrogen (BUN) or creatinine, occurred on 13/1000 infant days, with SAEs occurring at 5 per 1000 infant days. On the 22,548/27,979 (81%) days that vancomycin and rifampin were given concomitantly, the incidence of elevated creatinine as an AE was similar to the days where rifampin was given without concomitant vancomycin at 8.4/1000 infant days and 7.2/1000 infant days, respectively. Leukocytosis (61/1000 infant days) and thrombocytopenia (121/1000 infant days) were the most common complete blood count abnormalities (Table 4). Clinical AEs occurred in 197/4279 (8%) of infants (Table 5). The most commonly observed clinical AEs were seizure, medical NEC, and IVH (Table 5).

Use of rifampin over time

There was an increase in rifampin use from 1997 (1/1000 infants) through 2007 (4/1000 infants) (Figure 1). The use of rifampin decreased to 1/1000 infants in 2012.

Discussion

We present the largest study of rifampin use in infants to date, with 2500 infants receiving the drug over a 15-year period. Thirty-four percent of rifampin courses were given in the setting of positive cultures. Laboratory AEs were commonly observed during rifampin exposure, with conjugated hyperbilirubinemia and thrombocytopenia having the highest incidence. In this cohort of infants receiving rifampin, clinical AEs occurred infrequently.

Rifampin is often used as adjunctive treatment for refractory gram-positive bacteremia, particularly bacteremia caused by staphylococci.[2–5,13] The majority of patients in our cohort with culture-proven infection had staphylococcal bacteremia (predominantly CoNS). While our study suggests that the use of rifampin in the setting of persistently positive cultures is consistent with the limited existing evidence, there was a significant amount of rifampin use in situations where the cause of infection was less well-defined.

The use of rifampin increased from 1997 to a peak in 2007 before declining. Although the reasons for this trend are unclear, the increasing use of rifampin coincides with the emergence of community-acquired MRSA in infants, children, and adults.[14,15] Similarly, the

subsequent decline in rifampin use may have been influenced by an increasing emphasis on improving central line care practices, which several studies indicate has resulted in an overall decline in central line-associated blood stream infections, which are most commonly caused by gram-positive organisms.[16–18] Alternatively, the decrease in rifampin use could be due to increasing attention on antibiotic stewardship programs. In our data, there was no significant change in the proportion of rifampin use in the setting of negative cultures from 2007–2012.

Laboratory AEs were common in our cohort, occurring in 249 per 1000 infant days of administration. The FDA label for rifampin recommends that liver function tests be monitored due to the potential for a transient rise in transaminases and bilirubin.[12] In our cohort, the incidence of conjugated hyperbilirubinemia was high—743/4279 (17%) of courses.[19] Hematologic laboratory AEs were also common in this cohort of infants. Thrombocytopenia is a known potential effect of rifampin therapy.[20,21] The FDA label states that thrombocytopenia occurs primarily with high-dose, intermittent therapy and "rarely occurs with well supervised daily therapy."[12] In our cohort, thrombocytopenia occurred frequently (48% of infants). Although leukocytosis was also common, leukocytosis and thrombocytopenia are often seen in the setting of infection and may be an indicator of coexisting disease pathology rather than direct drug effect. The FDA label includes elevated BUN as a potential adverse reaction. The incidence of renal dysfunction in our cohort was relatively low, with elevated BUN and creatinine occurring in 5% of infants. As a comparison, other cohorts of infants with sepsis have reported incidences of acute kidney injury as high as 26%.[22–24] The overall incidence of clinical AEs was only 10% at the course level and 8% at the patient level. Rash, included on the FDA label and commonly associated with rifampin use, was uncommon (<1%) in this cohort of hospitalized infants.

This study has important limitations. Because this is an observational study, we are limited to identifying associations rather than assessing causal relationships. Identification of clinical AEs was limited to what was documented by the clinicians, and laboratory AEs may be affected by the frequency of laboratory draws, which occurred at the discretion of the treating clinician. In addition, attribution of AEs to rifampin is difficult because it is almost universally administered in combination with other drugs in the setting of an acutely ill infant. Finally, information about drug dose and interval was not available, thus limiting our ability to evaluate any dose-dependent effects.

Using prospectively collected data from a large, diverse, multicenter cohort of infants, we examined AEs associated with rifampin use. Our study suggests that rifampin is generally safe for use in infants, although bilirubin levels and platelets should be monitored while on therapy. Further studies are needed to determine the optimal dosing, timing, and duration of rifampin use in infants.

Acknowledgments

Sources of support: This work was funded under contract HHSN2752010000031 from the National Institute of Child Health and Human Development (NICHD) for the Pediatric Trials Network; award number 5T32-HD060558 from the NICHD; and award number 1R25-HD076475-01 from the NICHD. Research reported in this publication was also supported by the National Center for Advancing Translational Sciences of the National Institutes of Health (NIH) under award number UL1TR001117.

References

1. Alsayyed B. Rifampin. Pediatr Rev. 2004; 25:216–217. [PubMed: 15173456]
2. Shama A, Patole SK, Whitehall JS. Intravenous rifampicin in neonates with persistent staphylococcal bacteraemia. Acta Paediatr. 2002; 91:670–673. [PubMed: 12162600]
3. Soraisham AS, Al-Hindi MY. Intravenous rifampicin for persistent staphylococcal bacteremia in premature infants. Pediatr Int. 2008; 50:124–126. [PubMed: 18279222]
4. van der Lugt NM, Steggerda SJ, Walther FJ. Use of rifampin in persistent coagulase-negative staphylococcal bacteremia in neonates. BMC Pediatr. 2010; 10:84. [PubMed: 21092087]
5. Tan TQ, Mason EO Jr, Ou CN, Kaplan SL. Use of intravenous rifampin in neonates with persistent staphylococcal bacteremia. Antimicrob Agents Chemother. 1993; 37:2401–2406. [PubMed: 8285624]
6. Bayston R. Hydrocephalus shunt infections. J Antimicrob Chemother. 1994; 34 (Suppl A):75–84. [PubMed: 7844076]
7. Forward KR, Fewer HD, Stiver HG. Cerebrospinal fluid shunt infections. A review of 35 infections in 32 patients. J Neurosurg. 1983; 59:389–394. [PubMed: 6886752]
8. Gombert ME, Landesman SH, Corrado ML, Stein SC, Melvin ET, Cummings M. Vancomycin and rifampin therapy for *Staphylococcus epidermidis* meningitis associated with CSF shunts: report of three cases. J Neurosurg. 1981; 55:633–636. [PubMed: 7277012]
9. McGirt MJ, Zaas A, Fuchs HE, George TM, Kaye K, Sexton DJ. Risk factors for pediatric ventriculoperitoneal shunt infection and predictors of infectious pathogens. Clin Infect Dis. 2003; 36:858–862. [PubMed: 12652386]
10. Chapman RL, Faix RG. Persistent bacteremia and outcome in late onset infection among infants in a neonatal intensive care unit. Pediatr Infect Dis J. 2003; 22:17–21. [PubMed: 12544403]
11. O'Brien RJ, Long MW, Cross FS, Lyle MA, Snider DE Jr. Hepatotoxicity from isoniazid and rifampin among children treated for tuberculosis. Pediatrics. 1983; 72:491–499. [PubMed: 6604257]
12. Rifadin IV (rifampin for injection) package insert. Bridgewater, NJ: Sanofi-Aventis US LLC; 2013.
13. Bliziotis IA, Ntziora F, Lawrence KR, Falagas ME. Rifampin as adjuvant treatment of gram-positive bacterial infections: a systematic review of comparative clinical trials. Eur J Clin Microbiol Infect Dis. 2007; 26:849–856. [PubMed: 17712583]
14. Fortunov RM, Hulten KG, Hammerman WA, Mason EO Jr, Kaplan SL. Community-acquired *Staphylococcus aureus* infections in term and near-term previously healthy neonates. Pediatrics. 2006; 118:874–881. [PubMed: 16950976]
15. Gerber JS, Coffin SE, Smathers SA, Zaoutis TE. Trends in the incidence of methicillin-resistant *Staphylococcus aureus* infection in children's hospitals in the United States. Clin Infect Dis. 2009; 49:65–71. [PubMed: 19463065]
16. Borghesi A, Stronati M. Strategies for the prevention of hospital-acquired infections in the neonatal intensive care unit. J Hosp Infect. 2008; 68:293–300. [PubMed: 18329134]
17. Li S, Bizzarro MJ. Prevention of central line associated bloodstream infections in critical care units. Curr Opin Pediatr. 2011; 23:85–90. [PubMed: 21124224]
18. Schulman J, Stricof R, Stevens TP, Horgan M, Gase K, Holzman IR, et al. Statewide NICU central-line-associated bloodstream infection rates decline after bundles and checklists. Pediatrics. 2011; 127:436–444. [PubMed: 21339265]
19. Moyer V, Freese DK, Whitington PF, Olson AD, Brewer F, Colletti RB, et al. Guideline for the evaluation of cholestatic jaundice in infants: recommendations of the North American Society for Pediatric Gastroenterology, Hepatology and Nutrition. J Pediatr Gastroenterol Nutr. 2004; 39:115–128. [PubMed: 15269615]
20. Grosset J, Leventis S. Adverse effects of rifampin. Rev Infect Dis. 1983; 5 (Suppl 3):S440–S450. [PubMed: 6356277]
21. Lee CH, Lee CJ. Thrombocytopenia—a rare but potentially serious side effect of initial daily and interrupted use of rifampicin. Chest. 1989; 96:202–203. [PubMed: 2736979]

22. Mathur NB, Agarwal HS, Maria A. Acute renal failure in neonatal sepsis. Indian J Pediatr. 2006; 73:499–502. [PubMed: 16816511]

23. Agras PI, Tarcan A, Baskin E, Cengiz N, Gurakan B, Saatci U. Acute renal failure in the neonatal period. Ren Fail. 2004; 26:305–309. [PubMed: 15354981]

24. Stapleton FB, Jones DP, Green RS. Acute renal failure in neonates: incidence, etiology and outcome. Pediatr Nephrol. 1987; 1:314–320. [PubMed: 3153295]

The Pediatric Trials Network Administrative Core Committee

Katherine Y. Berezny, Duke Clinical Research Institute, Durham, NC; Edmund Capparelli, University of California–San Diego, San Diego, CA; Michael Cohen-Wolkowiez, Duke Clinical Research Institute, Durham, NC; Gregory L. Kearns, Children's Mercy Hospital, Kansas City, MO; Matthew Laughon, University of North Carolina at Chapel Hill, Chapel Hill, NC; Andre Muelenaer, Virginia Tech Carilion School of Medicine, Roanoke, VA; T. Michael O'Shea, Wake Forest Baptist Medical Center, Winston Salem, NC; Ian M. Paul, Penn State College of Medicine, Hershey, PA; John van den Anker, George Washington University School of Medicine and Health, Washington, DC; Kelly Wade, Children's Hospital of Philadelphia, Philadelphia, PA; Thomas J. Walsh, Weill Cornell Medical College of Cornell University, New York, NY.

The Eunice Kennedy Shriver National Institute of Child Health and Human Development: David Siegel, Perdita Taylor-Zapata, Anne Zajicek, Alice Pagan

The EMMES Corporation (Data Coordinating Center): Ravinder Anand, Gina Simone

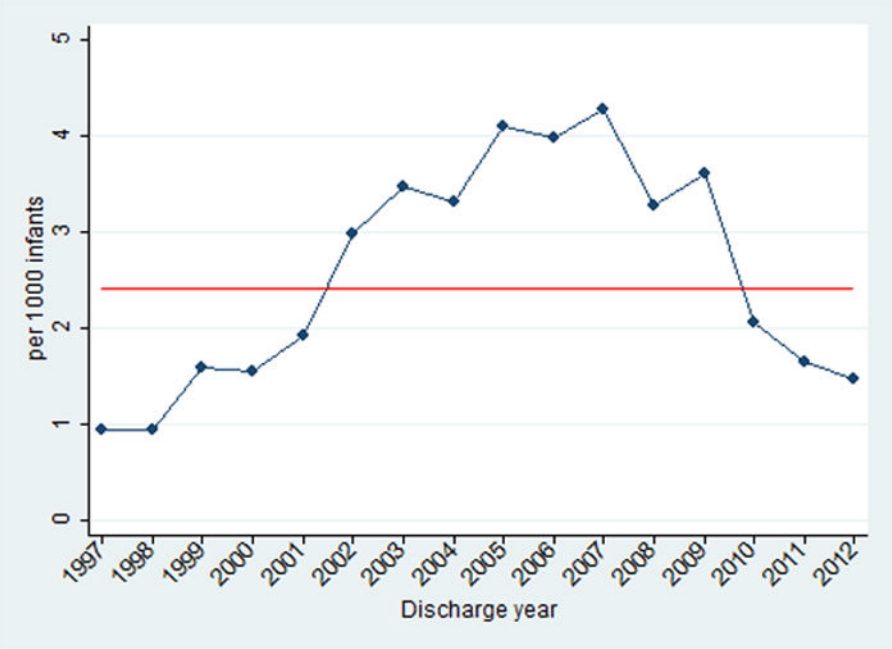

Figure 1.
Rifampin use over time. The red line indicates the mean number of infants exposed to rifampin during the study period.

Table 1

Demographics

	Infants exposed to rifampin (N=2500)
Gestational age, weeks	
<26	888 (36%)
26–28	822 (33%)
29–32	450 (18%)
33–36	203 (8%)
≥37	137 (5%)
Birth weight, g	
<1000	1531 (61%)
1000–1499	524 (21%)
1500–2499	252 (10%)
2500–3499	140 (6%)
≥3500	49 (2%)
Age at first rifampin exposure, days	
<3	5 (0.2%)
3–6	8 (0.3%)
7–29	1634 (65%)
30–59	628 (25%)
60–120	225 (9%)
Race/ethnicity	
White	1019 (42%)
African American	624 (26%)
Hispanic	683 (28%)
Other	95 (4%)
Male	1334 (53%)
Caesarean delivery	1771 (72%)
Mean (5^{th}, 95^{th} percentile) length of NICU stay, days	85 (20, 160)
Died	242 (11%)

Abbreviation: NICU, neonatal intensive care unit.

Table 2

Culture results for rifampin courses associated with a positive culture

	Blood N=1332	Urine N=8	CSF N=40	Total N=1380
Gram-positive				
CoNS	649 (49%)	0	21 (53%)	670 (49%)
S. aureus	477 (36%)	0	13 (33%)	490 (36%)
Other*	105 (8%)	3 (38%)	5 (13%)	113 (8%)
Gram-negative				
E. coli	3 (0.2%)	1 (13%)	0	4 (0.3%)
Other†	40 (3%)	0	0	40 (3%)
Fungus	41 (3%)	4 (50%)	0	45 (3%)
Other‡	17 (1%)	0	1 (3%)	18 (1%)

Abbreviations: CSF, cerebrospinal fluid; CoNS, coagulase-negative staphylococci; *S. aureus, Staphylococcus aureus; E. coli, Escherichia coli.*

*Reported organisms included *Enterococcus* and group B *Streptococcus*; also includes those reported as gram-positive cocci for which speciation was not available.

†Reported organisms include *Acinetobacter*, *Citrobacter*, *Enterobacter*, *Klebsiella*, *Serratia*, and *Pseudomonas*; also includes those reported as gram-negative rods for which speciation was not available.

‡Organism not clearly specified or not clearly categorized (e.g., *Mycoplasma*).

Table 3

Concomitant antibiotics administered

	Days of concomitant rifampin exposure (N=23,701)
Vancomycin	18,270 (77%)
Penicillins	4175 (18%)
Cephalosporins	2425 (10%)
Linezolid	734 (3%)
Clindamycin	702 (3%)
Carbapenems	628 (3%)
Trimethoprim/sulfamethoxazole	134 (1%)
Daptomycin	29 (0.1%)

Table 4

Laboratory adverse events and serious adverse events

		Adverse events			Serious adverse events	
		Courses, n (%) N=4279	**Days (/1000 infant days)**		**Courses, n (%) N=4279**	**Days (/1000 infant days)**
Serum electrolytes						
Hyperglycemia	*> 250 mg/dL*	145 (3%)	1	*> 400 mg/dL*	7 (0.2%)	0
Hypoglycemia	*< 40 mg/dL*	345 (8%)	5	*< 20 mg/dL*	74 (2%)	0.8
Hypernatremia	*> 150 mmol/L*	215 (5%)	3	*> 160 mmol/L*	10 (0.2%)	0.1
Hyponatremia	*< 125 mmol/L*	321 (8%)	4	*< 115 mmol/L*	10 (0.2%)	0.1
Hyperkalemia	*> 6 mmol/L*	1069 (25%)	19	*> 7.5 mmol/L*	135 (3%)	2
Hypokalemia	*< 3 mmol/L*	504 (12%)	10	*< 2.5 mmol/L*	123 (3%)	2
Hypercalcemia	*> 12.5 mg/dL*	64 (2%)	1	*> 13.5 mg/dL*	25 (0.6%)	0.3
Renal dysfunction						
Elevated BUN	*> 70 mg/dL*	204 (5%)	8	*> 100 mg/dL*	58 (1%)	2
Elevated creatinine	*> 1.7 mg/dL*	232 (5%)	8	*> 3.0 mg/dL*	60 (1%)	3
Liver dysfunction						
Elevated AST	*>500 U/L*	7 (0.1%)	0	*> 1 000 U/L*	2 (0.05%)	0
Elevated ALT	*> 500 U/L*	15 (0.4%)	0.4	*> 1 000 U/L*	2 (0.05%)	0
Elevated GGT	*> 100 U/L*	178 (4%)	4	*> 200 U/L*	81 (2%)	2
Conjugated bilirubin	*> 5 mg/dL*	743 (17%)	25	*> 10 mg/dL*	199 (5%)	6
Complete blood count						
Leukocytosis	*> 25,000/mm^3*	1567 (37%)	61	*> 40,000/mm^3*	546 (13%)	14
Leukopenia	*< 5000/mm^3*	493 (12%)	8	*< 2 000/mm^3*	65 (2%)	1
Thrombocytopenia	*< 100 000/mm^3*	2045 (48%)	121	*< 30,000/mm^3*	606 (14%)	11
Thrombocytosis	*> 600 000/mm^3*	145 (3%)	4	*> 1,000,000/mm^3*	4 (0.09%)	0.1

Abbreviations: BUN, blood urea nitrogen; AST, aspartate aminotransferase; ALT, alanine transaminase; GGT, gamma-glutamyl transpeptidase.

Table 5

Clinical adverse events associated with rifampin use

	Courses, n (%) N=4279	Patient level, n (%) N=2500
Gastrointestinal		
Necrotizing enterocolitis – medical	133 (3%)	64 (3%)
Necrotizing enterocolitis – surgical	41 (1%)	19 (1%)
Focal intestinal perforation	3 (0.07%)	1 (0.04%)
Neurologic		
Intraventricular hemorrhage – grade III or IV	91 (2%)	36 (1%)
Seizure	132 (3%)	60 (2%)
Dermatologic		
Rash	33 (1%)	15 (0.6%)
Pulmonary		
Pulmonary hemorrhage	50 (1%)	22 (1%)
Any clinical adverse event	426 (10%)	197 (8%)