HHS Public Access

Author manuscript

Pediatr Infect Dis J. Author manuscript; available in PMC 2023 March 30.

Published in final edited form as:

Pediatr Infect Dis J. 2020 September ; 39(9): e245–e248. doi:10.1097/INF.0000000000002698.

Safety of Metronidazole in Late Preterm and Term Infants with Complicated Intraabdominal Infections

Sarah Jane Commander, MD[1,2], Jamie Gao, PMP[2], Erin K. Zinkhan, MD[3], Gloria Heresi, MD[4], Sherry E. Courtney, MD[5], Adrian P. Lavery, MD[6], Paula Delmore, MSN[7], Gregory M. Sokol, MD[8], Fernando Moya, MD[9], Danny Benjamin, MD, PhD, MPH[2], Tedryl G. Bumpass, CCRA[2], Julie Debski, BS[10], Jinson Erinjeri, PhD[10], Gaurav Sharma, PhD[10], Elisabeth T. Tracy, MD[1], P. Brian Smith, MD, MPH, MHS[2], Michael Cohen-Wolkowiez, MD, PhD[2], Christoph P. Hornik, MD, PhD, MPH[2] on behalf of the Best Pharmaceuticals for Children Act – Pediatric Trials Network Steering Committee

[1]Duke University Medical Center, Department of Surgery, Durham, NC

[2]Duke University Medical Center, Department of Pediatrics, Duke Clinical Research Institute, Division of Pediatric Research. Durham, NC

[3]Division of Neonatology, Intermountain Medical Center, Salt Lake City, UT; University of Utah, Salt Lake City, UT;

[4]Division of Pediatric Infectious Diseases, University of Texas, Houston, TX

[5]Division of Neonatology, University of Arkansas for Medical Sciences, Little Rock, AR

[6]Division of Neonatology, Loma Linda University, Loma Linda, CA

[7]Wichita Medical Research and Education Foundation, Wichita, KS

[8]Division of Neonatology, Indiana University, Indianapolis, IN

[9]Coastal Carolina Neonatology, Wilmington, NC

[10]The Emmes Company LLC, Rockville, MD

Abstract

Background: Metronidazole is frequently used off-label in infants with complicated intra-abdominal infections (cIAI) to provide coverage against anaerobic organisms, but its safety and efficacy in this indication are unknown.

Methods: In the Antibiotic Safety in Infants with Complicated Intra-Abdominal Infections (SCAMP) open-label multicenter trial infants ≥34 weeks gestation at birth and <121 days postnatal age with cIAIs were administered metronidazole as part of multimodal therapy. Metronidazole safety was evaluated by reporting of adverse events and safety events of special interest. Cure from disease was determined by blood cultures and a clinical cure score >4. A blinded adjudication committee reviewed all safety events of special interest.

Correspondence: Christoph Hornik, MD. Duke University Medical Center, Department of Pediatrics, Duke Clinical Research Institute. Durham, North Carolina. christoph.hornik@duke.edu.

Conflict of Interest: The authors have no conflict of interests to disclose

Results: Fifty-five infants were included; median gestational age was 36 weeks (range: 34–41) and postnatal age was 7 days (0–63). The most common additional antibiotics received included gentamicin, piperacillin-tazobactam, ampicillin, and vancomycin. Only one adverse event, a candidal rash, was identified to be potentially caused by metronidazole administration. One infant died of cardiopulmonary failure, which was deemed unrelated to metronidazole. The most common events of special interest included feeding intolerance in 18 (33%) infants, and exploratory laparotomy in 10 (18%) requiring intestinal anastomosis in 7 (13%) infants. There was one (2%) intestinal stricture. Fifty-three infants (96%) achieved overall therapeutic success, 54 (98%) were alive through 30 days post-study therapy, and 54 (98%) had 30-day clinical cure score >4.

Conclusions: In a cohort of late pre-term and term infants with cIAIs, combination antibiotic therapy that included metronidazole was safe, and therapeutic success was high.

Keywords

complicated intra-abdominal infections; metronidazole; infants

INTRODUCTION

Complicated intra-abdominal infections (cIAIs) result from bacterial translocation across an immature or ischemic bowel wall and can progress to necrosis or perforation of the bowel.[1] The most common infantile cIAIs involve bowel necrosis and/or perforation originating from necrotizing enterocolitis (NEC), Hirschsprung's disease, gastroschisis, or omphalocele. Mortality can be as high as 30% and morbidity is common among survivors.[2]

Organisms most commonly implicated in cIAIs include: *Escherichia coli, Klebsiella pneumoniae, Enterococcus faecalis,* and *Bacteroides fragilis.*[2] The Infectious Disease Society of America guidelines recommend a multifactorial approach including aggressive fluid resuscitation, early source control, and broad-spectrum antimicrobial therapy.[3] Studies have validated the safety and efficacy of antibiotic use in adults and in select pediatric populations, but data in infants remain limited.[4]

Metronidazole is a synthetic antibacterial agent with bactericidal activity against most anaerobes through destabilization of host DNA.[5] Metronidazole has widespread use in the pediatric population, but population-specific safety data are sparse.[4] In particular, concerns have arisen that other antibiotics with anaerobic coverage, such as clindamycin, may increase the risk of intestinal strictures, but this relationship has not been proven in infants.[6]

The Antibiotic Safety in Infants with Complicated Intra-Abdominal Infections (SCAMP) trial (ABS01 trial, NCT01994993) is a multicenter multidrug safety and efficacy trial of antibiotics, including metronidazole, for the treatment of cIAIs in term and pre-term infants. The primary finding of SCAMP is that there is no significant difference in the safety or efficacy of different combination antibiotic regimens used to treat cIAIs; SCAMP trial results are published separately. Results from the main trial can be found at: https://clinicaltrials.gov/ct2/show/results/NCT01994993. This manuscript presents the results of a

secondary analysis from SCAMP of the safety and efficacy of metronidazole administered to a subset of infants ≥34 weeks gestation at birth.

METHODS

Study Population

Infants were enrolled from 05/2014 to 12/2016 at 22 centers across the United States. Full details of the methodology can be found in the published clinical trial methodology (ABS01 trial, NCT01994993). Infants eligible for inclusion in our secondary analysis were ≥34 weeks gestation (SCAMP Group 4). Infants ≤33 weeks were included in other arms of the overall trial (SCAMP Groups 1–3, 5). All infants included in SCAMP (Groups 1–5) had to be postnatal age <121 days old with sufficient venous access to permit administration of the study drug, and present with physical, radiological, and/or bacteriological findings of cIAI within 48 hours prior to study enrollment. Complicated intra-abdominal infections included secondary peritonitis, NEC grade II or higher by Bell's criteria, Hirschsprung's disease with perforation, spontaneous intestinal perforation, meconium ileus with perforation, bowel obstruction with perforation, gastroschisis with necrosis and/or perforation, omphalocele with necrosis and/or perforation, neonatal appendicitis, intestinal pneumatosis or portal venous gas, free peritoneal air on abdominal radiographic examination, or abdominal abscess. Infants were excluded if they had a serum creatinine >2mg/dL, alanine aminotransferase >250 U/L, or aspartate aminotransferase >500 U/L, history of anaphylaxis to metronidazole, or any participant safety concerns.

Dosing Schema

Metronidazole was dosed per protocol with a minimum 15mg/kg loading dose and 7.5mg/kg maintenance dose with an interval of 8 or 6 hours dependent upon gestational age ≤40 weeks or >40 weeks, respectively. Duration of antibiotic therapy was determined by the treating physician; however, a maximum of 10 days was considered the treatment phase. All other therapy, including additional antibiotics, were per site standard of care.

Study Outcomes

The primary outcome for this analysis was the prevalence of adverse and safety events of special interest including death, gastrointestinal surgeries, and intestinal strictures or perforation. Events of special interest were reviewed by a blinded adjudication committee of 3 physician members, who met to reach agreements settled by simple majority vote. Secondary outcomes included time to first full enteral feeds (>100 mL/kg/day), incidence of feeding intolerance, and overall therapeutic success; defined based upon survivorship, negative bacterial blood cultures, and clinical cure score >4 (defined per Score for Neonatal Acute Physiology II).[7] There was no central laboratory for culture data. Aerobic and anerobic cultures were obtained as standard of care using site practices of collection, handling, and analysis at the individual site laboratories.

Statistical Analysis

Descriptive statistics were reported for continuous data, while counts and percentages were used for categorical data. All statistical analyses were conducted by the study coordinating center, the Emmes Company (Rockville, MD).

RESULTS

Demographics

Fifty-five infants were included in this analysis. Fifty-six infants were enrolled; however, one patient did not receive any doses of metronidazole, so this patient was excluded from the final analysis. Median gestational age was 36 weeks (range: 34–41) and postnatal age was 7 days (0–63). Median birth weight was 2450 g (1379–4050) and weight at enrollment was 2650 g (1535–5190). Twenty-eight infants (51%) were male, 35 (64%) were Caucasian, and 12 (22%) reported Hispanic ethnicity. NEC was diagnosed in 25 infants (46%) and was the most common cause of cIAI. Metronidazole therapy was administered for a mean of 8 days (standard deviation: 2.5), mean daily dose was 23 mg/kg (3.3) and maximum daily dose was 45 mg/kg. Additional antimicrobial therapies received by this group were per site standard of care for cIAI treatment. The most common additional antibiotics received included gentamicin (24%), piperacillin-tazobactam (11%), and ampicillin (7%).

Safety

While receiving metronidazole, eighteen infants (33%) had feeding intolerance, ten (18%) required an exploratory laparotomy, seven (13%) required intestinal anastomosis at time of surgery, and one (2%) had intestinal perforation (Table 1). One (2%) infant died of cardiopulmonary failure; however, upon review by a blinded panel of physicians, this was not attributed to metronidazole. One intestinal stricture was observed in the study group. There were a total of 35 adverse events (AEs) reported in 18 infants (33%). The severity of these AEs were 21 mild, 12 moderate, and 3 severe (Supplemental Tables 1 and 2). Only 1 AE, a candidal rash, was determined to be possibly related to metronidazole.

Infection Resolution

At 30 days after completion of therapy, 53 (96%) infants achieved overall therapeutic success; 54 infants (98%) were alive; 54 (98%) had a clinical cure score >4; 54 (98%) had absence of seizures; 53 (96%) had reduced or equal oxygen requirements than prior; 51 (93%) did not require ventilatory support; and 55 (100%) were making adequate urine, were free of ionotropic support, and had a blood pH ≥7.25. Two (4%) infants had positive blood cultures and one had a positive urine culture, organisms isolated included *Enterobacter* sp., coagulase negative *Staphylococcus*, and *Streptococcus viridans*. Eleven (20%) infants had missing bacterial blood culture at 30 days, but were alive and had a clinical cure score >4, so were considered overall to have achieved therapeutic success.

DISCUSSION

We present safety and efficacy data from a trial that prospectively enrolled infants ≥34 weeks gestation. Infants received metronidazole in addition to local standard of care

antibiotic regimens for the treatment of cIAIs. While morbidity was high in this population, only 1 AE was determined to be related to metronidazole therapy, and overall therapeutic success was 96%. These findings support the use of metronidazole in combination with other antibiotics for the treatment of cIAIs in infants.

Only 2 trials performed in the 1980s compared antibiotic regimens for treatment of cIAIs in infants. In the first study, 20 infants with a mean gestational age of 35 weeks diagnosed with NEC were randomized to receive intravenous ampicillin and gentamicin with or without enteral gentamicin for 4 days. There were no differences in observed mortality, bowel perforation, or intestinal stricture (1 stricture was identified).[8] Another study of 42 infants diagnosed with NEC, with a mean gestational age of 29 weeks, randomized patients to receive ampicillin and gentamicin with or without clindamycin for 10–14 days. There was no statistically significant difference in mortality (risk ratio [RR] 1.10; 95% confidence interval [CI] 0.32 to 3.83) or bowel perforation (RR 2.20; 95% CI 0.45 to 10.74).[6] There was a higher incidence of stricture with the addition of clindamycin (6% vs. 40%, RR 7.20; 95% CI 0.97 to 53.36), though the estimate of relative risk did not reach statistical significance. Nonetheless, this finding raised the question whether anaerobic coverage could result in increased stricture risk. The study authors postulated that alteration of gastrointestinal microbiota by antimicrobials with anti-anaerobic properties, and increased risk of subsequent *C. difficile* superinfection, may be responsible for the observed association. Though intestinal inflammation secondary to infection or ischemia has been linked with strictures in adult patients, and may be viewed as a likely mechanism for stricture formation in infants, the extent to which microbiota alteration by antimicrobials may modulate this risk in infants remains unknown. Our study revealed only one stricture among late-preterm and term infants with cIAI treated with metronidazole, suggesting the possibility that the association of anaerobic coverage with intestinal strictures is unlikely in this population.

To our knowledge, the efficacy of metronidazole as an adjunctive antibiotic therapy for the treatment of cIAI in infants has not been previously studied. While not powered to discern efficacy, preliminary data for efficacy was assessed; in our cohort, we observed 98% survival and 96% clinical cure. Additionally, fewer infants required surgery (18%) compared to other reports (20–30%).[9] This study demonstrated improved mortality, and decreased bowel perforation and stricture rates than other similar antimicrobial studies in the literature, with only one attributable adverse event. The single death was also not due to metronidazole administration.

Despite its strengths, our study has several limitations. The overall trial has a partially randomized design, whereby a fixed portion of infants were randomized to treatment arms, while others were enrolled and allocated into the appropriate arm based upon the antibiotics already being administered as standard of care for cIAI. In the subgroup described in this manuscript, there was no randomization. The lack of randomization in this arm and blinding leaves open the possibility of unexplained residual bias. Eleven infants did not have blood cultures taken at the end of the 30-day time period, so surrogate markers for clinical cure had to be utilized to infer successful treatment, including survivorship and clinical cure score >4. While our overall sample size was larger than prior studies, it is still most likely too low

to capture drug-specific adverse events, and to characterize possible relationships between dose, duration of treatment, or exposure, as well as the occurrence of strictures. Given the prevalence of metronidazole use in infants with cIAI, future phase 4 pharmacovigilance studies, including the use of real-world data, may provide a more efficient mechanism to identify rare adverse events attributable to metronidazole.

In conclusion, in a cohort of late pre-term and term infants with cIAIs, metronidazole therapy at protocol-specified dosage was safe. Therapeutic success, when administered as part of various combined antibiotic regimens, was achieved in 96% of patients. Our data did not suggest a significant relationship to serious AEs, including intestinal stricture, feeding intolerance, sepsis, or death. These findings support a role for metronidazole in the multimodal treatment of cIAIs in infants ≥34 weeks, but do not provide evidence of superiority to other antibiotics. Larger pharmacovigilance studies will be required to establish the true safety and efficacy of metronidazole in neonates and young infants with cIAIs.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements:

PTN Steering Committee Members: Daniel K. Benjamin Jr., Christoph P Hornik, Kanecia O. Zimmerman, Phyllis Kennel, and Rose Beci, Duke Clinical Research Institute, Durham, NC; Chi Dang Hornik, Duke University Medical Center, Durham, NC; Gregory L. Kearns, Scottsdale, AZ; Matthew Laughon, University of North Carolina at Chapel Hill, Chapel Hill, NC; Ian M. Paul, Penn State College of Medicine, Hershey, PA; Janice Sullivan, University of Louisville, Louisville, KY; Kelly Wade, Children's Hospital of Philadelphia, Philadelphia, PA; Paula Delmore, Wichita Medical Research and Education Foundation, Wichita, KS

The Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD): Perdita Taylor-Zapata, June Lee

The Emmes Company LLC (Data Coordinating Center), Rockville, MD: Ravinder Anand, Gaurav Sharma, Gina Simone, Kim Kaneshige, and Lawrence Taylor

PTN Publications Committee: Chaired by Thomas Green, Ann & Robert H. Lurie Children's Hospital of Chicago, Chicago, IL

Study Site Investigators, Coordinators or other Designees: Erin Zinkhan, Jill Burnett, Kim Weaver-Lewis, Intermountain Medical Center, Murray, UT; Gloria Heresi, Elizabeth Aguilera, University of Texas Health Science Center, Houston, TX; Sherry Courtney, D'Ann Pierce, Lee Howard, Arkansas Childrens Hospital, Little Rock, AR; Fernando Moya, Danielle Kurtz, Julie Oliver, Coastal Carolina Pediatrics, Wilmington, NC; Adrian Lavery, Melissa Rundquist, Loma Linda University School of Medicine, Loma Linda, CA; Gregory Sokol, Susan Gunn, Riley Hospital for Children at Indiana University, Indianapolis, IN; Erin Zinkhan, Carrie Rau, Susan Schaefer, Laura Cole, University of Utah, Salt Lake City, UT; Barry Bloom, Paula Delmore, Wesley Medical Center, Wichita, KS; Roger Kim, Chika Iwuchukwu, Brookdale University Hospital and Medical Center, Brooklyn, NY; Stuart Goldstein, Cassie Kirby, Cincinnati Childrens Hospital, Cincinnati, OH; C. Michael Cotton/Chi Hornik, Lacey Andrews, Duke University Medical Center, Durham, NC; Andrea Trembath, Eileen Goldblatt, Rainbow Babies and Childrens Hospital, Cleveland, OH; Christiane Dammann, Amanda Dimeo, Karen Murray, Haregwoin, Tufts Medical Center, Boston, MA; Matthew Laughon, Janice Bernhardt, Cynthia Clark, UNC Chapel Hill, Chapel Hill, NC; Mark Hudak, Kristy Rica, Michele Burke, Shelly Crawford, University of Florida Jacksonville Shands Medical Center, Jacksonville, FL; Catherine Bendel, Jensina Ericksen, Jenna Wassenaar, University of Minnesota Amplatz Childrens Hospital, Minneapolis, MN; Hala Chaaban, Kimberly Benjamin, University of Oklahoma Health Science Center, Oklahoma City, OK; Naveed Hussain, Jennifer Querim, Connecticut Childrens Medical Center, Farmington, CT; Scott MacGilvray, Sherry Moseley, East Carolina University, Greenville, NC; Rakesh Chhabra, Mary Ellen Riordan, Hackensack University Medical Center, Hackensack, NJ; Jprn-Hendrik Weitkamp,

Steven Steele, Vanderbilt Childrens Hospital, Nashville, TN; Mark Hudak, Ashley Maddox, Shelly Crawford, Wolfson Childrens Hospital, Jacksonville, FL

Study Operational Teams: Duke Clinical Research Institute, Durham, NC: Jamie Gao (Project Leader), Tedryl Bumpass (Lead Clinical Research Associate), Deborah Howard and Kimberly Cicio (Clinical Research Associate)

The Emmes Company LLC (BPCA-Data Coordinating Center), Rockville, MD: Julie Debski (Project Manager), Jinson Erinjeri (Statistician)

Funding:

This work was funded under National Institute of Child Health and Human Development (NICHD) contract HHSN275201000003I for the Pediatric Trials Network (PI Danny Benjamin). The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health

REFERENCES

1. Blot S, De Waele JJ. Critical issues in the clinical management of complicated intra-abdominal infections. Drugs. 2005;65:1611–1620. [PubMed: 16060697]
2. Blackwood BP, Hunter CJ, Grabowski J. Variability in antibiotic regimens for surgical necrotizing enterocolitis highlights the Need for New Guidelines. Surg Infect (Larchmt). 2017;18:215–220. [PubMed: 28048964]
3. Solomkin JS, Mazuski JE, Bradley JS, et al. Diagnosis and management of complicated intra-abdominal infection in adults and children: guidelines by the Surgical Infection Society and the Infectious Diseases Society of America. Clin Infect Dis. 2010;50:133–164. [PubMed: 20034345]
4. Cohen-Wolkowiez M, Ouellet D, Smith PB, et al. Population pharmacokinetics of metronidazole evaluated using scavenged samples from preterm infants. Antimicrob Agents Chemother. 2012;56:1828–1837. [PubMed: 22252819]
5. Aldridge KE, Ashcraft D, Cambre K, et al. Multicenter survey of the changing in vitro antimicrobial susceptibilities of clinical isolates of Bacteroides fragilis group, Prevotella, Fusobacterium, Porphyromonas, and Peptostreptococcus species. Antimicrob Agents Chemother. 2001;45:1238–1243. [PubMed: 11257040]
6. Faix RG, Polley TZ, Grasela TH. A randomized, controlled trial of parenteral clindamycin in neonatal necrotizing enterocolitis. J Pediatr. 1988;112:271–277. [PubMed: 3276864]
7. Harsha SS, Archana BR. SNAPPE-II (Score for Neonatal Acute Physiology with Perinatal Extension-II) in Predicting Mortality and Morbidity in NICU. J Clin Diagn Res. 2015;9:SC10–12. [PubMed: 26557585]
8. Hansen TN, Ritter DA, Speer ME, et al. A randomized, controlled study of oral gentamicin in the treatment of neonatal necrotizing enterocolitis. J Pediatr. 1980;97:836–839. [PubMed: 7000998]
9. Arul GS, Singh M, Ali AM, et al. Damage control surgery in neonates: Lessons learned from the battlefield. J Pediatr Surg. 2019;54:2069–2074. [PubMed: 31103271]

Table 1.

Safety Events

Event	N=55 (%)
Intestinal perforation	1 (2%)
Feeding intolerance	18 (33%)
Exploratory laparotomy	10(18%)
Intestinal anastomosis	7 (13%)
Intestinal stricture	1 (2%)
Short bowel syndrome	1 (2%)
Seizure	1 (2%)
Intraventricular hemorrhage grade 3 or 4	0 (0%)
Positive bacterial culture	3 (6%)
Mortality	1 (2%)

Table 2.

Serious Adverse Events*

SAE Description	System Organ Class	Preferred Term	Outcome	Severity	Related to Drug	Action Taken	Event Associated With
Cardiorespiratory failure	Cardiac disorders	Cardiopulmonary failure	Death	Severe	No	No action taken	Death
Apnea of infant, unknown etiology	Respiratory, thoracic and mediastinal disorders	Infantile apnoea	Resolved	Moderate	No	No action taken	Prolongation of hospitalization
Bilateral retinal detachment	Eye disorders	Retinal detachment	Resolved by convention	Severe	No	No action taken	Important medical event

*Adverse events: metronidazole and antibiotic regimen per standard of care (N=55)

Pediatr Infect Dis J. Author manuscript; available in PMC 2023 March 30.

Table 3.

All Adverse Events* by System Organ Class

All Adverse Events	Metronidazole and Antibiotic Regimen per Standard of Care (N=55)	
System Organ Class (Preferred Term)	**Patients with Event N (%)**	**Total Events N**
Blood and lymphatic system disorders	**4 (7.3%)**	**4**
Anemia	3 (5.5%)	3
Anemia neonatal	1 (1.8%)	1
Cardiac disorders	**2 (3.6%)**	**2**
Cardiopulmonary failure	1 (1.8%)	1
Tachycardia	1 (1.8%)	1
Congenital, familial and genetic disorders	**1 (1.8%)**	**2**
Atrial septal defect	1 (1.8%)	1
Pulmonary artery stenosis congenital	1 (1.8%)	1
Eye disorders	**1 (1.8%)**	**1**
Retinal detachment	1 (1.8%)	1
Gastrointestinal disorders	**3 (5.5%)**	**3**
Abdominal distension	1 (1.8%)	1
Gastroesophageal reflux disease	1 (1.8%)	1
Hematemesis	1 (1.8%)	1
Hepatobiliary disorders	**1 (1.8%)**	**1**
Hyperbilirubinemia	1 (1.8%)	1
Infections and infestations	**2 (3.6%)**	**3**
Enterobacter pneumonia	1 (1.8%)	1
Peritonitis bacterial	1 (1.8%)	1
Skin candida	1 (1.8%)	1
Injury, poisoning, and procedural complications	**1 (1.8%)**	**1**
Wound	1 (1.8%)	1
Investigations	**3 (5.5%)**	**4**
Bilirubin conjugated increased	1 (1.8%)	1
Blood alkaline phosphatase increased	1 (1.8%)	1
Blood triglycerides increased	1 (1.8%)	1
Hematocrit decreased	1 (1.8%)	1
Metabolism and nutrition disorders	**5 (9.1%)**	**8**
Hyperchloremia	1 (1.8%)	1
Hyperkalemia	1 (1.8%)	1
Hypoalbuminemia	1 (1.8%)	1
Hypokalemia	2 (3.6%)	2
Hypomagnesaemia	1 (1.8%)	1
Hyponatremia	1 (1.8%)	1

All Adverse Events	Metronidazole and Antibiotic Regimen per Standard of Care (N=55)	
System Organ Class (Preferred Term)	**Patients with Event N (%)**	**Total Events N**
Metabolic acidosis	1 (1.8%)	1
Renal and urinary disorders	**1 (1.8%)**	**1**
Hydronephrosis	1 (1.8%)	1
Respiratory, thoracic, and mediastinal disorders	**3 (5.5%)**	**3**
Infantile apnea	1 (1.8%)	1
Pneumothorax	1 (1.8%)	1
Respiratory failure	1 (1.8%)	1
Vascular disorders	**2 (3.6%)**	**2**
Hemorrhage	1 (1.8%)	1
Hypoperfusion	1 (1.8%)	1

*Adverse events: metronidazole and antibiotic regimen per standard of care (N=55)