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Antibiotic Safety and Effectiveness in Premature Infants with Complicated Intra-Abdominal Infections

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Data Sharing Statement

To help expand the knowledge base for pediatric medicine, the Pediatric Trials Network is pleased to share data from its completed and published studies with interested investigators. For requests, please contact PTN-Program-Manager@dm.duke.edu.

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Abstract

Background: In premature infants, complicated intra-abdominal infections (cIAIs) are a leading cause of morbidity and mortality. Although universally prescribed, the safety and effectiveness of commonly used antibiotic regimens has not been established in this population.

Methods: Infants ≤33 weeks gestational age and <121 days postnatal age with cIAI were randomized to ≤10 days of ampicillin, gentamicin, and metronidazole (group 1); ampicillin, gentamicin, and clindamycin (group 2); or piperacillin-tazobactam and gentamicin (group 3) at doses stratified by postmenstrual age. Due to slow enrollment, a protocol amendment allowed eligible infants already receiving study regimens to enroll without randomization. The primary outcome was mortality within 30 days of study drug completion. Secondary outcomes included adverse events, outcomes of special interest, and therapeutic success (absence of death, negative cultures, and clinical cure score >4) 30 days after study drug completion.

Results: 180 infants (128 randomized [R], 52 non-randomized [NR]) were enrolled: 63 in group 1 (45 R, 18 NR), 47 in group 2 (41 R, 6 NR), and 70 in group 3 (42 R, 28 NR). Thirty-day mortality was 8%, 7%, and 9% in groups 1, 2, and 3, respectively. There were no differences in safety outcomes between antibiotic regimens. After adjusting for treatment group and gestational age, mortality rates through end of follow-up were 4.22 (95% confidence interval [CI] 1.39–12.13), 4.53 (95% CI 1.21–15.50), and 4.07 (95% CI 1.22–12.70) for groups 1, 2, and 3, respectively.

Conclusions: Each of the antibiotic regimens are safe in premature infants with cIAI.

Clinical Trial Registration: NCT0199499

Keywords

infants; complicated intra-abdominal infection; antibiotics; safety

In premature infants, complicated intra-abdominal infections (cIAIs) are a leading cause of morbidity and mortality,[1-3] yet few studies have assessed the optimal antimicrobial management of cIAI in this population. The Infectious Diseases Society of America (IDSA) defines cIAI as an infection that extends beyond the hollow viscus of origin and is associated with either abscess formation or peritonitis.[4] Necrotizing enterocolitis (NEC) is thought to be primarily a result of prematurity and not a primary infectious pathology. Nonetheless, it is universally treated with antimicrobials; therefore, evaluating the safety of antimicrobial regimens used to treat these pathologies in this understudied population is crucial.

The IDSA guidelines for cIAI in adults and children recommend these regimens for NEC: ampicillin, gentamicin, and metronidazole; ampicillin, cefotaxime, and metronidazole; or meropenem.[4] Of these regimens, however, only meropenem is currently labeled for use in premature infants with cIAI.

We previously conducted regulatory-compliant pharmacokinetic studies of metronidazole, clindamycin, piperacillin-tazobactam, and ampicillin in premature infants to identify the appropriate dose to treat cIAI.[5-9] The Antibiotic Safety in Infants with Complicated Intra-Abdominal Infections (SCAMP) trial (NICHD-2013-ABS01; IND 108209; ClinicalTrials.gov Identifier: NCT01994993) is the last step in the path for potential United States Food and Drug Administration (FDA) labeling of metronidazole, clindamycin, and piperacillin-tazobactam in premature infants with cIAIs. Our primary objective was to evaluate the safety of drug regimens used in premature infants with cIAI. Secondary objectives included measures to assess therapeutic success, confirmatory pharmacokinetics of these antibiotics, and the impact of therapy on the developing microbiome. This manuscript reports the safety and effectiveness data from the clinical trial.

METHODS

Study Design and Population

SCAMP was a prospective, open-label, multi-site, randomized, clinical trial of infants with cIAI. We enrolled infants ≤33 weeks gestational age (GA) at birth with a postnatal age (PNA) <121 days, who demonstrated physical, radiologic, and/or bacteriologic findings consistent with a cIAI. Inclusionary diagnoses included NEC grade II or higher by Bell's criteria, intestinal pneumatosis or portal venous gas, spontaneous intestinal perforation, abdominal abscess, neonatal appendicitis, free peritoneal air, secondary peritonitis, and perforation associated with Hirschprung's disease, meconium ileus, bowel obstruction, gastroschisis, or omphalocele. Exclusion criteria included history of anaphylaxis to study drugs, serum creatinine >2 mg/dL, alanine aminotransferase >250 U/L, or aspartate aminotransferase >500 U/L within 72 hours prior to enrollment.

We randomized infants to one of three treatment regimens within 48 hours of diagnosis with cIAI: ampicillin, gentamicin, and metronidazole (group 1); ampicillin, gentamicin, and

clindamycin (group 2); or piperacillin-tazobactam and gentamicin (group 3). Antibiotic use prior to randomization was permitted. Participants were randomly assigned by the data coordinating center to the 3 drug regimen groups using a 1:1:1 allocation ratio, stratified by site. Permuted block design with randomly varying block sizes was used to ensure group balance of the randomized drug group within each block. Additional gram-positive therapy (e.g., vancomycin, nafcillin, oxacillin, linezolid) was permitted at the discretion of the treating physician.

Ampicillin was dosed as follows: PNA ≤7 days, 50 mg/kg every 12 hours; PNA >7–≤28 days, 75 mg every 8 hours; PNA >28 days, 50 mg/kg every 8 hours. Gentamicin was dosed per local guidelines at each study site. Study doses of clindamycin, metronidazole, and piperacillin-tazobactam were stratified by postmenstrual age (PMA) based on previous studies and are presented in Table 1.[5-9] Due to slow enrollment, a protocol amendment 18 months after study commencement allowed infants who were receiving all antibiotics in a given study arm per standard of care to be enrolled; dosing in infants already receiving study drug per standard of care was adjusted to meet protocol-specified dosing unless the total daily dose for each antibiotic was equal to or greater than the protocol-specified dose. Duration of therapy was not specified in the protocol, but was recorded by site personnel.

Safety Assessments

The safety population included all infants who received at least one dose of study drug. The primary safety outcome was mortality within 30 days of study drug completion. Adverse events (AEs) were collected per FDA definitions and were recorded through 3 days after study drug completion. Serious adverse events (SAEs) were recorded through 30 days after study drug completion. All AEs were assessed for relation to study drug by previously trained site investigators and classified as suspected adverse reactions if there was a reasonable possibility that the study medication caused the event. Infants were also followed for 90 days after study drug completion for pre-specified safety outcomes of special interest (OSIs), which included: occurrence of gastrointestinal surgeries (laparotomy, peritoneal drain placement, intestinal resection, ostomy placement, and intestinal anastomosis), progression to a higher Bell's stage of NEC (if NEC was the inclusionary diagnosis), development of intestinal strictures, development of intestinal perforation, positive blood culture (bacterial or fungal), development of short bowel syndrome, presence of seizures, death, and grade 3 or 4 intraventricular hemorrhage. OSIs were recorded separately and not reported as AEs or SAEs unless they were study drug regimen-related.

If infants were discharged or transferred before the pre-specified time of safety evaluation, then these data were collected at the time of discharge or transfer. A 3-member event adjudication committee reviewed all cases of intestinal stricture, intestinal perforation, and short bowel syndrome during the 90-day safety observation period. The committee also determined cause of mortality for infants who died between first dose of study drug and 30 days after the last dose of study drug. Committee members were blinded to study group and independently reviewed source documentation including radiographic reports, surgical reports, discharge summaries, and daily progress notes from the day of the event. Where available, autopsy reports and death certificates were also reviewed. Clinical laboratory

values (hematology, serum chemistries, and microbiology tests) were recorded if obtained per standard of care through 3 days after study regimen completion.

Therapeutic Success

Therapeutic success, a secondary outcome, was assessed 30 days after study drug completion. Therapeutic success was achieved if all of the following criteria were met: the infant 1) was alive; 2) had negative bacterial and fungal blood cultures from sterile sites; and 3) had clinical cure score >4.[10] The clinical cure score was based on components of the Score for Neonatal Acute Physiology II (SNAP II) and included assessments of fraction of inspired oxygen ($Fi0_2$), urine output, need for inotropes or mechanical ventilation, presence of seizure, and serum pH.[11] Specifically, one point was awarded for each of the following criteria: FiO_2 lower than at time of enrollment, absence of inotropic support, absence of mechanical ventilation, absence of seizures, and pH ≥7.25 or unmeasured. If infants were discharged or transferred before 30 days, then these data were collected at the time of discharge or transfer.

Statistical Methods and Analysis

The study was powered to estimate the incidence of death within 30 days of each drug regimen. The incidence of death in this population was expected to be 20%.[1-3] A sample size of 70 infants in each group allowed an estimate of the 20% death rate with a 95% confidence interval (CI) that has a precision (half-width) of 10% (95% CI 11.4%, 31.3%). Descriptive statistics, including number of observations, mean, median, standard deviation, standard error, minimum, and maximum, were used to summarize continuous variables. Fisher's exact test was used to compare frequency of safety OSIs between groups.

We performed sensitivity analyses to account for differences in randomized and non-randomized participants. Frequencies of AE, OSI, and effectiveness outcomes with an event rate ≥15% were estimated using logistic regression modeling adjusting for covariates, including randomization group (randomized or non-randomized). A stepwise variable selection procedure was performed to obtain the final model. Treatment group was kept in the model and the following covariates were eligible for entry in the model: randomization group, gender, race, ethnicity, PNA, PMA, GA, birth weight, actual weight, height, serum creatinine, and baseline gastrointestinal disorders derived from medical history. The significance level for a covariate to be entering and staying in the model was kept at 0.1.

Statistical analyses were performed using SAS version 9.4 (Cary, NC). This study was approved by the Duke University Institutional Review Board (IRB) and at each of the participating sites. Informed consent was obtained for all study participants according to IRB requirements at each institution.

RESULTS

A total of 180 infants were enrolled at 41 sites between May 2014 and December 2016; 178 infants received at least one dose of study drug; of these, 127 (71%) were randomized and 51 (29%) were in non-randomized arms (see Figure, Supplemental Digital Content1). Ninety-four of the 127 randomized subjects (75%) received empiric therapy

within the 48 hours prior to enrollment. The most common empiric regimens included piperacillin-tazobactam (n=24), ampicillin and an aminoglycoside (n=15), ampicillin with an aminoglycoside and metronidazole (n=14), and meropenem (n=8). Demographic and clinical characteristics are presented in Table 2. The median PNA was 14 days (range 1–113), median GA was 27.1 weeks (range 22.0–33.9), and median birthweight was 900 g (range 400–2500). NEC was the most common diagnosis at the time of enrollment, occurring in 105 (59%) participants; 81 (46%) infants had a medical history of intestinal perforation or pneumoperitoneum. Mean (standard deviation) duration of study drug was 7.2 (2.8) days in group 1, 7.9 (2.4) days in group 2, and 7.7 (2.5) days in group 3. Additional gram-positive therapy (vancomycin, linezolid, nafcillin or oxacillin) was included in the management of 134 (75%) infants: 45 (73%) in group 1, 35 (76%) in group 2, and 54 (77%) in group 3.

Twenty-nine (16%) infants were transferred or discharged before the 30-day safety and overall therapeutic success evaluations. Death within 30 days of study drug completion occurred in 14 (8%) infants: 5 (8%) in group 1, 3 (7%) in group 2, and 6 (9%) in group 3. An additional 3 (2%) infants died during the safety follow-up: 0 in group 1, 2 in group 2, and 1 in group 3.

Overall, 63 (35%) infants completed the 90-day post-treatment safety evaluation: 28 (44%) in group 1, 12 (26%) in group 2, and 23 (33%) in group 3. The most common reason for early termination was transfer or discharge. Mean (standard deviation) duration of follow-up after study drug completion was 63 (33) days in group 1, 52 (31) days in group 2, and 60 (31) days in group 3.

Ninety-five (53%) infants experienced at least one AE: 35 (57%) in group 1, 23 (50%) in group 2, and 37 (53%) in group 3 (Table 3). The most common AEs were thrombocytopenia in 11 (6%), cholestatic jaundice in 5 (3%), and anemia in 4 (2%) participants. Three AEs (one in each group) were attributable to study drug; these AEs include one episode of increased blood urea (group 1), one episode of injection site extravasation (group 2), and one episode of vascular access site complication (group 3). Forty-one (19%) infants experienced at least one SAE: 14 (23%) in group 1, 8 (17% in group 2), and 11 (16%) in group 3; none of these SAEs were attributable to study drug.

Overall, 114 (64%) infants experienced an OSI: 45 (73%) in group 1, 28 (61%) in group 2, and 41 (59%) in group 3 (Table 4). OSIs occurring in >10% of all infants include laparotomy, intestinal resection, intestinal reanastomosis, and positive blood cultures. Intestinal strictures were uncommon (5%) with no difference between groups. The adjudication committee confirmed 10/12 reported cases of intestinal perforation, 10/12 cases of short bowel syndrome, and 11/11 cases of intestinal stricture; post-adjudication results are included in this report.

Overall therapeutic success was achieved in 146 (82%) infants: 50 (81%) in group 1, 40 (87%) in group 2, and 56 (80%) in group 3. Due to the infrequency of death and positive cultures, the clinical cure score was the main determinant of success. The less commonly

achieved elements of the clinical cure score were FiO_2 <baseline (76%) and absence of mechanical ventilation (70%). All other elements were achieved by >90% of recipients.

Sensitivity Analyses

Adjusted estimates for mortality, overall therapeutic success, and all OSIs with ≥15% frequency are presented in Table 5. Randomization status was not a significant predictor for any of the models and was not included in the final model. Rates and 95% CIs of mortality through end of follow-up were 4.22% (1.39–12.13) in group 1, 4.53% (1.21–15.50) in group 2, and 4.07% (1.22–12.7) in group 3 after accounting for treatment group and gestational age.

DISCUSSION

This is the largest clinical trial to date evaluating the safety of antimicrobial regimens in infants with cIAI. There were no clinically or statistically significant differences in mortality or safety outcomes between the three study arms. AEs and SAEs were similar between arms, and OSIs did not differ between groups. Based on these data, safety of any of these regimens is not superior to others in premature infants with cIAIs.

The SCAMP trial was the culmination of several studies leading up to submission for FDA labeling of metronidazole, clindamycin, and piperacillin-tazobactam in premature infants with cIAIs. Our team conducted the Phase 1 trials in infants to determine optimal dosing of these agents in premature infants.[5-9] With these data, we developed population pharmacokinetic (PK) models to simulate drug exposure and maximize target attainment rates. These doses were then validated using a prospective phase II/III master protocol, which allowed us to collect regulatory-grade safety data and confirmatory PK data simultaneously for each drug which were submitted to the FDA for labeling change consideration. This paper is the first known study to evaluate safety of multidrug regimens commonly used in management of cIAI. There were no between-group differences in the incidence of OSIs during the 90-day safety assessment period. Specifically, the incidence of intestinal stricture during the safety follow-up was low overall and not greater in any one study arm. A previous randomized-controlled trial of 42 infants reported an increased risk of intestinal strictures, but no survival benefit, when clindamycin was added to ampicillin and gentamicin for the treatment of NEC.[12] A subsequent propensity-matched retrospective cohort study including 2780 infants found a small increase (4 vs. 2%) in development of strictures among infants with NEC who received any anaerobic therapy relative to anaerobic-free regimens, but did not identify an association between strictures and any particular agent.[13] Development of strictures was an OSI that was collected, monitored, and adjudicated based on prospectively collected radiology, clinical notes, and operative reports. Even when using this rigorous definition, we arrived at a low estimate for stricture similar to that reported in a recent large retrospective cohort,[13] and no regimen was associated with increased rates of stricture.

Our cohort included a variety of intra-abdominal pathologies; including primary infectious intraabdominal pathologies and NEC. The etiology of NEC is multifactorial and involves a combination of intestinal immaturity, hypoperfusion, and mucosal colonization with

pathologic bacteria. Although NEC may not be a primarily infectious process, affected infants are universally treated with antibiotics, and recommendations for antimicrobial management of NEC are included in the IDSA cIAI guidelines.[4] Despite these guidelines, there is no clear consensus on antibiotic regimens for NEC.[14] One recent single-center retrospective study documented use of 14 separate antibiotics for NEC in more than 20 distinct combinations over an 8-year period.[15] Ampicillin, gentamicin, and metronidazole was the most common combination, and there was no benefit to any of the broader regimens. Although not powered for efficacy, the current study similarly found no differences in these outcomes between study groups.

This study has some limitations. First, SCAMP may have been underpowered to detect small, but clinically meaningful, differences between the groups. The study was powered assuming a mortality of 20%, but the actual rate was lower. The 48-hour enrollment window likely excluded children with fulminant disease. Furthermore, infants with severe disease are less likely to be enrolled in prospective clinical trials. Second, due to difficulties enrolling critically ill infants into a randomized trial, the National Institutes of Health and the FDA agreed to a protocol amendment that allowed infants with cIAI who were receiving study drug per routine clinical care to be included in the trial. This may have introduced differences between randomized and non-randomized infants that were not accounted for in our modelling. Finally, not every antibiotic regimen was randomly assigned. Since antibiotics are universally recommended in the management of cIAI, randomization occurred up to 48 hours after the initiation of therapy, and additional gram-positive coverage was allowed; these therapies were at the discretion of the treating physician. These inclusion criteria were necessary for study feasibility and were allowed by the FDA because the primary study endpoint was safety and not efficacy. Despite these limitations, this is the largest prospective randomized clinical trial of infants with cIAI to date and is unlikely to be replicated. The data generated from this trial were submitted to the FDA for labeling change consideration.

CONCLUSIONS

In conclusion, we found no differences in the safety or tolerability of the three antibiotic regimens in critically ill premature infants with cIAI. There were no differences in mortality, AEs, or SAEs between any of the commonly utilized antimicrobial regimens. This study provides important safety data to guide recommended label changes in the premature neonate population with cIAIs.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Appendix

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Table 1.

Study Dosing Regimens

Drug	PMA (weeks)	Loading dose (mg/kg)	Maintenance dose (mg/kg)	Dosing interval (hours)
Metronidazole	<34	15	7.5	12
	≥34 – ≤40	15	7.5	8
	>40	15	7.5	6
Clindamycin	≤32	none	5	8
	>32 – ≤40	none	7	8
	>40 – ≤60	none	9	8
Piperacillin-tazobactam[a]	≤30	none	100	8
	>30	none	80	6

Abbreviations: PMA, postmenstrual age

[a]Dosing based on piperacillin-component

Table 2.

Infant Demographics and Clinical Characteristics

	Group 1 Ampicillin, Gentamicin, and Metronidazole			Group 2 Ampicillin, Gentamicin, and Clindamycin			Group 3 Piperacillin-Tazobactam and Gentamicin			Total
	R	**NR**	**Total**	**R**	**NR**	**Total**	**R**	**NR**	**Total**	
	45	17	62	40	6	46	42	28	70	178
Gestational age (weeks)										
Median	27	26.4	27	27.5	28.9	27.5	27.6	27.8	27.7	27.1
Range	(22.7, 33.9)	(24.4, 31.0)	(22.7, 33.9)	(23.0, 33.4)	(26.4, 33.0)	(23.0, 33.4)	(22.0, 33.0)	(23.0, 33.3)	(22.0, 33.3)	(22.0, 33.9)
Birthweight (g)										
Median	870	895	880	925	1273	943	830	860	830	885
Range	(440, 2260)	(680, 1410)	(440, 2260)	(560, 2470)	(720, 1750)	(560, 2470)	(400, 2330)	(500, 2040)	(400, 2330)	(400, 2470)
Postnatal age (days) at randomization/first study dose										
Median	12	8	12	16	19	16	14	20	15	14
Range	(1, 66)	(3, 59)	(1, 66)	(1, 113)	(2, 54)	(1, 113)	(1, 111)	(3, 59)	(1, 111)	(1, 113)
Postmenstrual age (weeks) at randomization/first study dose										
Median	29	28	29	30	31	30	29	30	29	29
Range	(24, 36)	(24, 34)	(24, 36)	(24, 39)	(29, 34)	(24, 39)	(23, 42)	(25, 36)	(23, 42)	(23, 42)
Gender										
Male	31 (68.9%)	13 (76.5%)	44 (71.0%)	25 (62.5%)	4 (66.7%)	29 (63.0%)	16 (38.1%)	12 (42.9%)	28 (40.0%)	101 (56.7%)
Ethnicity										
Hispanic or Latino	9 (20.0%)	3 (17.6%)	12 (19.4%)	10 (25.0%)	1 (16.7%)	11 (23.9%)	8 (19.0%)	3 (10.7%)	11 (15.7%)	34 (19.1%)
Race										
White or Caucasian	23 (51.1%)	9 (52.9%)	32 (51.6%)	22 (55.0%)	4 (66.7%)	26 (56.5%)	25 (59.5%)	11 (39.3%)	36 (51.4%)	94 (52.8%)
Black or African American	15 (33.3%)	6 (35.3%)	21 (33.9%)	10 (25.0%)	0	10 (21.7%)	11 (26.2%)	12 (42.9%)	23 (32.9%)	54 (30.3%)
Other	2 (4.4%)	1 (5.9%)	3 (4.8%)	1 (2.5%)	1 (16.7%)	2 (4.4%)	4 (9.5%)	2 (7.1%)	6 (8.6%)	11 (6.2%)
Not reported	5 (11.1%)	1 (5.9%)	6 (9.7%)	7 (17.5%)	1 (16.7%)	8 (17.4%)	2 (4.8%)	3 (10.7%)	5 (7.1%)	19 (10.7%)

Abbreviations: NR, non-randomized; PMA, postmenstrual age; PNA, postnatal age; R, randomized

Table 3.

Adverse Events by Study Group and Randomization Status

	Group 1 Ampicillin, Gentamicin, and Metronidazole			Group 2 Ampicillin, Gentamicin, and Clindamycin			Group 3 Piperacillin-Tazobactam and Gentamicin			Total
	R	**NR**	**Total**	**R**	**NR**	**Total**	**R**	**NR**	**Total**	
	45	17	62	40	6	46	42	28	70	178
Number of events/infants										
Number of AEs	72	23	95	38	3	41	47	28	75	211
Infants with at least one AE	25 (55.6%)	10 (58.8%)	35 (56.5%)	20 (50.0%)	3 (50.0%)	23 (50.0%)	22 (52.4%)	15 (53.6%)	37 (52.9%)	95 (53.4%)
Number of SAEs	16	3	19	10	0	10	10	2	12	41
Infants with at least one SAE	12 (26.7%)	2 (11.8%)	14 (22.6%)	8 (20.0%)	0	8 (17.4%)	9 (21.4%)	2 (7.1%)	11 (15.7%)	33 (18.5%)
Relationship (all AEs)										
Not-related	72	22	94	37	3	40	47	27	74	208
Related	0	1	1	1	0	1	0	1	1	3
Relationship (all SAEs)										
Not-related	16	3	19	10	0	10	10	2	12	41

Abbreviations: R, randomized; NR, non-randomized; AE, adverse event; SAE, serious adverse event

Table 4.

Outcomes of Special Interest by Treatment Group

	Group 1 Ampicillin, Gentamicin, and Metronidazole	Group 2 Ampicillin, Gentamicin, and Clindamycin	Group 3 Piperacillin-Tazobactam and Gentamicin	p-value[a]
	62	46	70	
Laparotomy	27 (44%)	15 (33%)	26 (37%)	0.53
Intestinal resection	14 (23%)	11 (24%)	11 (16%)	0.47
Intestinal anastomosis	12 (19%)	10 (22%)	13 (19%)	0.92
Positive blood culture (bacterial or fungal)	8 (13%)	4 (9%)	12 (17%)	0.43
Ostomy placement	7 (11%)	4 (9%)	6 (9%)	0.85
Mortality through end of follow-up	5 (8%)	5 (11%)	7 (10%)	0.90
Mortality through 30-days post-therapy	5 (8%)	3 (7%)	6 (9%)	0.99
Grade 3 or 4 intraventricular hemorrhage	2 (3%)	4 (9%)	4 (6%)	0.51
Short bowel syndrome	5 (8%)	3 (7%)	1 (1%)	0.21
Intestinal strictures	3 (5%)	2 (4%)	4 (6%)	0.99
Intestinal perforation	2 (3%)	4 (9%)	2 (3%)	0.34
Seizures	4 (6%)	0	2 (3%)	0.20
Peritoneal drain placement	0	2 (4%)	3 (4%)	0.22
Progression to a higher stage of NEC 3	1 (2%)	2 (4%)	0	0.19

Abbreviations: NEC, necrotizing enterocolitis

[a]Fisher's exact test

Table 5.

Adjusted Event Rates for Mortality, Selected Outcomes of Special Interest, and Overall Therapeutic Success

Event	Final Model Covariates	Group 1[a]	Group 2	Group 3
Mortality through end of follow-up	Treatment arm and gestational age	4.22 (1.39, 12.13)	4.53 (1.21, 15.50)	4.07 (1.22, 12.70)
Laparotomy	Treatment arm, ethnicity, serum creatinine, and GI disorder (surgical condition)	43.21 (30.42, 56.99)	31.17 (18.47, 47.50)	35.15 (24.10, 48.06)
Intestinal anastomosis	Treatment arm, GI disorder (surgical condition), and GI disorder (intestinal stricture/ perforation)	17.09 (9.48, 28.87)	20.01 (10.54, 34.70)	16.34 (9.23, 27.27)
Intestinal resection	Treatment arm and serum creatinine	22.08 (13.41, 34.16)	23.92 (13.59, 38.57)	15.29 (8.60, 25.73)
Positive blood culture (bacterial or fungal)	Treatment arm, ethnicity, and post menstrual age	9.22 (4.12, 19.38)	6.33 (2.15, 17.20)	11.61 (5.59, 22.56)
Overall therapeutic success	Treatment arm, gestational age, height	90.40 (79.76, 95.75)	92.51 (80.89, 97.30)	89.57 (78.49, 95.29)

Abbreviations: GI, gastrointestinal

[a]Data presented as rates and 95% confidence intervals