Anaerobic Antimicrobial Therapy After Necrotizing Enterocolitis in VLBW Infants

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abstract

OBJECTIVE: To evaluate the effect of anaerobic antimicrobial therapy for necrotizing enterocolitis (NEC) on clinical outcomes in very low birth weight (≤1500 g) infants.

METHODS: We identified very low birth weight infants with NEC from 348 US NICUs from 1997 to 2012. Anaerobic antimicrobial therapy was defined by antibiotic exposure on the first day of NEC. We matched (1:1) infants exposed to anaerobic antimicrobial therapy with infants who were not exposed by using a propensity score stratified by NEC severity (medical and surgical). The primary composite outcome was in-hospital death or intestinal stricture. We assessed the relationship between anaerobic antimicrobial therapy and outcome by using a conditional logistic regression on the matched cohort.

RESULTS: A total of 1390 infants exposed to anaerobic antimicrobial therapy were matched with 1390 infants not exposed. Mean gestational age and birth weight were 27 weeks and 946 g, respectively, and were similar in both groups. We found no significant difference in the combined outcome of death or strictures, but strictures as a single outcome were more common in the anaerobic antimicrobial therapy group (odds ratio 1.73; 95% confidence interval, 1.11–2.72). Among infants with surgical NEC, mortality was less common with anaerobic antimicrobial therapy (odds ratio 0.71; 95% confidence interval, 0.52–0.95).

CONCLUSIONS: Anaerobic antimicrobial therapy was not associated with the composite outcome of death or strictures but was associated with an increase in intestinal strictures. This higher incidence of intestinal strictures may be explained by the fact that death is a competing outcome for intestinal strictures, and mortality was slightly lower in the anaerobic cohort. Infants with surgical NEC who received anaerobic antimicrobial therapy had lower mortality.

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WHAT'S KNOWN ON THIS SUBJECT: Necrotizing enterocolitis is associated with high mortality and morbidity in premature infants. Anaerobic antimicrobial therapy has been associated with increased risk of intestinal strictures in a small randomized trial. Optimal antimicrobial therapy for necrotizing enterocolitis is unknown.

WHAT THIS STUDY ADDS: Anaerobic antimicrobial therapy was associated with increased risk of stricture formation. Infants with surgical necrotizing enterocolitis treated with anaerobic antimicrobial therapy had lower mortality. For infants with medical necrotizing enterocolitis, there was no added benefit associated with anaerobic antimicrobial therapy.

Necrotizing enterocolitis (NEC) is a common and devastating intestinal complication of prematurity. Incidence of NEC ranges from 3% in infants with birth weight (BW) of 1251 to 1500 g to 11% for infants born weighing <750 g.[1] Despite treatment, 15% of infants who develop NEC die, and mortality approaches 50% in infants with surgical NEC.[2,3] Survivors often suffer from complications including intestinal stricture, short bowel syndrome, and poor neurodevelopmental outcomes.[4–6]

The pathogenesis of NEC involves a combination of factors, including genetic predisposition, immaturity of the intestinal tract, imbalance in microvascular tone, abnormal microbial intestinal colonization, and infectious agents.[7–10] Although no single microorganism has been identified, infection probably plays a key role in the disease process, as demonstrated by bacterial overgrowth in the intestinal mucosa and the occurrence of NEC outbreaks.[8,11,12] A wide range of pathogens are associated with NEC, including aerobic and anaerobic bacteria.[10,13–19] Therapy for NEC includes broad-spectrum antibiotics with coverage of bacteria from the intestinal tract. In a small cohort of infants with NEC, a randomized controlled trial with 42 infants observed no difference in mortality or intestinal perforation in those who received an antibiotic regimen of ampicillin, gentamicin, and clindamycin compared with those who received only ampicillin and gentamicin.[20] However, there was a higher rate of intestinal strictures in the clindamycin group. Despite this finding, clindamycin is often used for NEC in the nursery, and the safety and efficacy of other antibiotic regimens for NEC have not been established.[20–22] The objective of the current study was to assess the association of anaerobic antimicrobial therapy and subsequent clinical outcomes in very low birth weight (VLBW, ≤1500 g BW) infants.

METHODS

Study Design and Setting

We identified all VLBW infants with medical or surgical NEC discharged from 348 NICUs managed by the Pediatrix Medical Group from 1997 to 2012. The Pediatrix Medical Group maintains a data warehouse that is populated from an electronic medical record that prospectively captures information from notes generated by clinicians. Data on multiple aspects of care are entered into the system to generate admission notes, daily progress notes, procedure notes, and discharge summaries. Information is collected on maternal history and demographics, medications, respiratory support, laboratory results, culture results, procedures, and diagnoses. The study was approved by the Duke University Institutional Review Board without the need for written informed consent because the data were collected without identifiers.

Definitions

Antimicrobials were considered to provide anaerobic coverage if they were previously reported as having in vitro activity against the major obligate anaerobic bacilli from the intestinal flora. These antimicrobial agents included metronidazole, clindamycin, cefoxitin, any carbapenem, moxifloxacin, piperacillin–tazobactam, ticarcillin–clavulanate, ampicillin–sulbactam, and amoxicillin–sulbactam. An infant was defined as receiving anaerobic antimicrobial therapy based on antibiotics received on the first day of NEC. The diagnosis and severity of NEC were assigned at each site by the attending neonatologist and included either medical NEC or surgical NEC. Surgical indication included the need for a peritoneal drain. The assessment of NEC severity was not based on standardized criteria and was assigned daily by the treating physician. NEC severity was defined on the first day of the course of NEC regardless of change in severity thereafter. Infants were excluded if they received antimicrobial agents for <5 consecutive days from the start of NEC, unless they died during this 5-day period. Mortality was defined as in-hospital death from any cause. Mortality status was defined as missing for infants with nonconvalescent transfers of care. Presence of intestinal stricture was defined as any diagnosis of noncongenital intestinal obstruction after the start of the NEC episode. The diagnosis of intestinal obstruction was assigned by the treating physician in the electronic medical record, and methods used to assign this diagnosis were not available. If an infant had >1 episode of NEC, only the first episode was considered in the analysis.

Demographic data included gender, race, BW, gestational age (GA), postnatal age, and Apgar score at 5 minutes. Surrogates for severity of illness on the first day of NEC were collected and included ventilator support (yes or no), highest level of fraction of inspired oxygen (Fio_2), and inotropic support (yes or no).

Statistical Methods

The primary outcome was in-hospital death or development of an intestinal stricture. Secondary outcomes consisted of death or strictures analyzed individually. An additional secondary outcome was assessed among the subgroup of infants with medical NEC: the composite of progression from medical to surgical NEC or death within the first 7 days of the NEC episode. Outcomes were compared between infants exposed and not exposed to anaerobic antimicrobial therapy. Because infants with more severe illness are more likely to receive anaerobic antimicrobial therapy, propensity score (PS) 1:1 matching was used to

ensure comparison of similar infants.[23] We used baseline demographics and surrogates for severity of illness that might predict both anaerobic antimicrobial therapy and primary outcome to build the PS model by using a multivariable logistic regression.[24] The PS model was stratified by NEC severity and derived from the following covariates: postnatal age, ventilator support, Fio_2 requirement, inotropic support on day 1 of NEC, GA, small-for-GA status, gender, race, Apgar score at 5 minutes, discharge year, and site. Because site was analyzed as a fixed effect in the PS model, no PS could be estimated for infants belonging to a site with an insufficient number of observations or a site where every infant had the same anaerobic coverage status. We included the discharge year as a categorical variable in the PS model to adjust for changes in care over the study period. We assessed covariate balance across treatment groups by comparing covariate means. Histograms and kernel density plots of PS across groups were also examined. We performed 1:1 matching by using the nearest neighbor without replacement, and it was allowed only if the difference in PS between case and control was <0.01. On the PS-matched cohort, we assessed the effect of anaerobic antimicrobial therapy on clinical outcomes by using a logistic regression conditioned on the matched pair.[23]

Because of previous literature linking clindamycin with intestinal strictures, we investigated the effects of clindamycin specifically, as a secondary analysis. We built a separate PS model estimating the conditional probability of receiving clindamycin among infants who were exposed to clindamycin and those who were not exposed to anaerobic antimicrobial therapy, by using the same covariates as in the primary analysis. We then compared outcomes by using a conditional logistic regression after 1:1 matching based on PS.

Finally, we performed a multivariable logistic regression without matching to compare outcomes between infants exposed and not exposed to any anaerobic antimicrobial therapy, adjusting for the same covariates used in the PS of the primary analysis.

Demographic and baseline characteristics were summarized and compared between 2 groups: infants exposed and not exposed to anaerobic antimicrobial therapy on the first day of NEC. A χ^2 test for categorical variables and a Wilcoxon rank-sum test or a t test for continuous variables were used to assess differences between groups. We performed statistical analyses by using Stata 12 (Stata Corp, College Station, TX). All statistical tests were 2-sided, with significance defined as $P < .05$.

RESULTS

We identified 6737 infants meeting the inclusion criteria, of whom 3358 (50%) were exposed to anaerobic antimicrobial therapy and 3379 (50%) were not. Overall, 4958 (74%) had medical NEC, and 1779 (26%) had surgical NEC. The mean GA was 27 weeks (5th, 95th percentile: 23, 31) and 27 weeks (5th, 95th percentile: 24, 31) in the anaerobic antimicrobial therapy and control groups, respectively. The mean BW was 936 g (5th, 95th percentile: 530, 1417) and 952 g (5th, 95th percentile: 540, 1420) in infants exposed to anaerobic antimicrobial therapy and those who were not, respectively. Infants who were exposed to anaerobic antimicrobial therapy were more likely to be on ventilation (2152 [64%] vs 1467 [45%], $P < .001$) and vasopressor therapy (839 [25%] vs 283 [8%], $P < .001$) and had a higher median Fio_2 (30% vs 25%, $P < .001$) compared with infants not exposed to anaerobic antimicrobial therapy.

After nearest-neighbor PS matching, 1390 infants exposed to anaerobic antimicrobial therapy were matched to infants who were not exposed to anaerobic antimicrobial therapy to yield a final cohort of 2780 infants (41% of the initial cohort) (Fig 1). PS matching provided a well-balanced cohort based on baseline characteristics (Table 1), and PS was equally distributed in both treatment groups (Supplemental Fig 3). The mean GA and BW of the cohort were 27 weeks (23, 32) and 946 g (540, 1421), respectively. In the matched cohort, 75% (n = 2074) of infants had

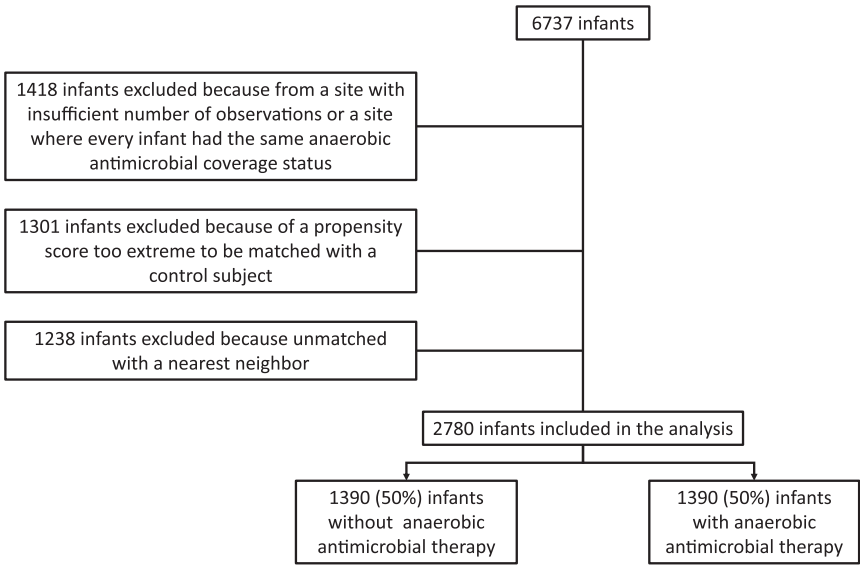

FIGURE 1
Study population flowchart.

TABLE 1 Demographics and Clinical Characteristics of the Matched Cohort

	Anaerobic Antimicrobial Therapy		*P*
	No, *n* = 1390	Yes, *n* = 1390	
GA, wk			.96
<25	228 (16)	233 (17)	
25–28	737 (53)	736 (53)	
>28	425 (31)	421 (30)	
BW, g			.39
<750	428 (31)	406 (29)	
751–1000	414 (30)	391 (28)	
1001–1250	302 (22)	330 (24)	
1251–1500	246 (18)	263 (19)	
Small for GA	275 (20)	270 (19)	.81
Male	736 (53)	742 (53)	.82
Day of life[a]			.49
≤7	124 (9)	107 (8)	
8–30	832 (60)	849 (61)	
≥31	434 (31)	434 (31)	
Race or ethnicity			.91
White	574 (41)	569 (41)	
African American	425 (31)	415 (30)	
Hispanic	329 (24)	345 (25)	
Other	62 (5)	61 (4)	
5-min Apgar score			.83
<3	70 (5)	68 (5)	
4–6	293 (21)	306 (22)	
7–10	1027 (74)	1016 (73)	
NEC stage[a]			>.99
Medical	1037 (75)	1037 (75)	
Surgical	353 (25)	353 (25)	
Mechanical ventilation[a]	747 (54)	743 (53)	.88
Inotropic support[a]	185 (13)	193 (14)	.66
Highest fraction of supplemental oxygen,[a] median (5th, 95th percentile)	27 (21, 100)	26 (21, 100)	.81

Data presented as frequency (%) unless specified otherwise.

[a] On the first day of the NEC episode.

medical NEC, and 706 (25%) had surgical NEC. Among infants with anaerobic antimicrobial therapy, clindamycin was the most frequently used anaerobic antibiotic (56%), followed by metronidazole (29%) and piperacillin–tazobactam (9%). However, clindamycin use decreased and metronidazole use increased during the study period (Fig 2).

Overall, 26% (*n* = 725) of matched cohort infants died before discharge or developed intestinal strictures; 23% of infants (*n* = 645) died, and 3% (*n* = 84) developed strictures (4 infants had strictures before death). Fewer infants experienced the composite outcome of death or strictures in the anaerobic antimicrobial therapy group, but the risk was not significantly different (odds ratio [OR] 0.96; 95% confidence interval [CI], 0.80–1.14; Table 2). We observed similar results for the individual outcome of death (OR 0.87; 95% CI, 0.72–1.05). Conversely, more infants developed strictures in the anaerobic antimicrobial therapy group compared with the control group (OR 1.73; 95% CI, 1.11–2.72).

Among infants with medical NEC (*n* = 2074), all covariates used in the PS model were well balanced after matching (Supplemental Table 4). In this subgroup, we observed a nonsignificant increase in death or strictures in infants treated with anaerobic antimicrobial therapy (OR 1.09; 95% CI, 0.87–1.37; Table 2). Death rates were similar in both treatment groups (OR 0.99; 95% CI, 0.78–1.26). Strictures were more common in infants exposed to anaerobic antimicrobial therapy (OR 1.60; 95% CI, 0.97–2.64), although this result was not statistically significant. The number of infants with medical NEC who progressed to surgical NEC or died within the first 7 days of the episode was similar in both treatment groups, with 121 (12%) and 126 (12%) infants in the nonanaerobic and anaerobic antimicrobial treatment groups, respectively (OR 1.05; 95% CI, 0.80–1.37).

Among infants with surgical NEC (*n* = 706), baseline clinical characteristics were well balanced across treatment groups after PS matching (Supplemental Table 4). In this subgroup, fewer infants either died or developed strictures in the anaerobic antimicrobial therapy group, although this result was not statistically significant (OR 0.77; 95% CI, 0.57–1.03; Table 2). Death was significantly less common in infants exposed to anaerobic antimicrobial therapy (OR 0.70; 95% CI, 0.52–0.95), whereas we observed a nonsignificant increase in strictures in exposed infants (OR 2.40; 95% CI, 0.85–6.81).

When we restrict the anaerobic cohort to the infants who received only clindamycin, the matched cohort included 1922 infants, of whom 961 (50%) were exposed to clindamycin and 961 (50%) were not exposed to any anaerobic antimicrobial therapy. Baseline characteristics used in the PS were well balanced in both treatment groups (Supplemental Table 5). The composite outcome of death or stricture was similar in the clindamycin and control groups, as were the outcomes of death alone and stricture alone (Table 3).

In addition to our primary analysis, the multivariable logistic regression model developed in the full, prematched cohort (*N* = 6737) yielded similar results to those obtained under matching but with

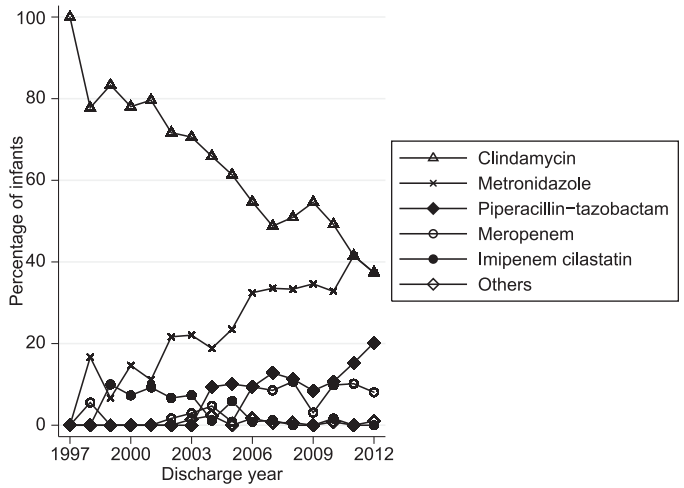

FIGURE 2
Distribution of therapy among infants receiving anaerobic antimicrobial therapy on the first day of NEC. Cohort after PS matching. Others = moxifloxacin, ticarcillin–clavulanate, cefoxitin, and ampicillin–sulbactam.

a statistically significant difference in death and strictures between treatment groups (OR of death or strictures 0.90; 95% CI, 0.76–1.07; OR of death 0.80; 95% CI, 0.67–0.97; OR of strictures 1.67; 95% CI, 1.16–2.39).

DISCUSSION

We found no significant difference in the risk of the composite outcome of death or strictures in all infants with NEC exposed or not exposed to anaerobic antimicrobial therapy. We did observe lower mortality in infants with surgical NEC treated with anaerobic antimicrobial therapy and higher risk of strictures among all infants with NEC who received anaerobic antimicrobial therapy.

The overall mortality we observed (26%) is consistent with previous data from cohorts combining infants with medical and surgical NEC (15%–25%),[20,21,25] but the incidence of intestinal strictures is in the lower range reported in the literature (3% vs 4%–30%).[4,20,21,26–30] The wide range of stricture incidence reported is probably a result of inconsistent definitions leading to ascertainment bias; some studies might report all strictures as diagnosed with radiologic tests, whereas others might report only symptomatic strictures. The diagnosis of stricture in our data is limited to those reported by the treating physician in the electronic medical record. The methods used to assign the stricture diagnosis were not standardized and may have varied between infants.

For adults and older children, evidence strongly supports the recommendation of anaerobic antimicrobial therapy as part of the empirical regimen for complicated intra-abdominal infections.[31] On the other hand, optimal antimicrobial therapy for NEC is unknown, including whether to use empirical anaerobic antimicrobial therapy. One trial randomly assigned 42 infants with NEC receiving ampicillin and gentamicin to clindamycin or no additional therapy.[20] Clindamycin did not affect mortality, intestinal perforation, or gangrene but was associated with significantly more intestinal strictures (6/15 survivors [40%] vs 1/18 [5%] in the control group; $P = .02$). Of note, infants in this previous trial were excluded if intestinal perforation occurred <12 hours after randomization and therefore are most comparable to our subgroup of infants with medical NEC. For infants with medical NEC, our findings are consistent with previous results demonstrating no added benefit of anaerobic antimicrobial therapy on mortality, but we observed only a slight nonsignificant increased risk of stricture.[20] In addition, anaerobic antimicrobial therapy did not prevent progression to surgical NEC or mortality within 7 days of the NEC episode. In contrast, anaerobic antimicrobial therapy was associated with lower mortality in infants with surgical NEC.

Post-NEC stricture is an intestinal obstruction resulting from wound healing, most prominently in the intestinal submucosa.[26] Stricture is probably a marker of severity of NEC, and it is possible that the lower rate

TABLE 2 Anaerobic Antimicrobial Therapy and Clinical Outcomes

Outcomes	Anaerobic Antimicrobial Therapy		OR (95% CI)	*P*
	No, *n* (%)	Yes, *n* (%)		
Overall, *N* = 2780[a]				
Death or strictures	368 (26)	357 (26)	0.96 (0.80–1.14)	.62
Death	338 (24)	307 (22)	0.87 (0.72–1.05)	.14
Strictures	31 (2)	53 (4)	1.73 (1.11–2.72)	.02
Medical NEC, *N* = 2074				
Death or strictures	186 (18)	199 (19)	1.09 (0.87–1.37)	.45
Death	162 (16)	161 (16)	0.99 (0.78–1.26)	.95
Strictures	25 (2)	40 (4)	1.60 (0.97–2.64)	.07
Surgical NEC, *N* = 706				
Death or strictures	182 (52)	158 (45)	0.77 (0.57–1.03)	.08
Death	176 (50)	146 (41)	0.71 (0.52–0.95)	.02
Strictures	6 (2)	13 (4)	2.40 (0.85–6.81)	.10

[a] Four infants were diagnosed with strictures before death.

TABLE 3 Outcomes and Clindamycin Therapy

Outcomes	No Anaerobic Antimicrobial Therapy, *n* (%)	Clindamycin, *n* (%)	OR (95% CI)	*P*
Overall, *N* = 1922[a]				
Death or strictures	291 (30)	279 (29)	0.94 (0.76–1.15)	.53
Death	267 (28)	242 (25)	0.87 (0.70–1.07)	.18
Strictures	27 (3)	42 (4)	1.56 (0.96–2.52)	.07

[a] Eight infants were diagnosed with strictures before death.

of strictures in the nonanaerobic treatment group was a function of the death of infants with the most severe cases of NEC, which precluded the occurrence of strictures. Strictures may also be directly related to a specific drug such as clindamycin, although the biological mechanism is unknown. Moreover, other than the study from Faix et al,[20] we found no report in the literature linking clindamycin (or any antibiotics) to intestinal strictures. The fact that we observed similar results when we limited our analysis to infants treated with clindamycin compared with infants with no anaerobic treatment suggests that clindamycin may drive this effect, but the number of infants receiving each anaerobic antimicrobial therapy was insufficient to compare outcomes for each individual therapy.

The differential effect of anaerobic antimicrobial therapy on mortality in medical and surgical NEC that we observed suggests that anaerobic bacteria play a more prominent role in the disease process of infants with surgical NEC. A wide range of pathogens are associated with NEC.[15] Several case series of infants with NEC have reported the presence of anaerobic bacteria, including *Clostridium perfringens* and *Bacteroides fragilis*, in the blood or peritoneal fluid.[17,19,32–36] A study including 25 infants with NEC showed that infants who had *Clostridium* spp. recovered from peritoneal fluid had more severe disease with more extensive pneumatosis intestinalis, higher incidence of portal venous gas, and more extensive gangrene.[33] Although the exact relationship between anaerobic bacteria and the pathophysiology of NEC has not been established, our findings suggest they are contributing to the disease process, especially in infants presenting with surgical NEC.

Anaerobic antimicrobial use changed dramatically over the study period (Fig 2); clindamycin use decreased, whereas metronidazole and piperacillin–tazobactam use increased. Factors that led to these findings might include safety concerns linking clindamycin to intestinal stricture in the literature,[20] increasing clindamycin resistance in anaerobic bacteria such as *B fragilis*,[37] and growing clinical experience with other therapeutic options. Our data do not provide sufficient information on specific agents for us to conclude which anaerobic antimicrobial should be preferred for empirical therapy. This question may be answered by an ongoing phase II/III clinical trial in infants with complicated intra-abdominal infection (NCT01994993).

This study is the largest evaluation of antibiotic treatment in VLBW infants with NEC. Strengths of this report include its large sample size, representing a large number of NICUs. However, despite our large cohort, matching resulted in the exclusion of nearly 60% of the sample population, which might have resulted in loss of power to detect differences between the 2 treatment groups. As a secondary analysis, a multivariable logistic regression without matching yielded similar results, but differences between groups (lower mortality and more strictures in the anaerobic antimicrobial therapy group) were statistically significant. Nevertheless, we believe matching based on PS provides more robust results by limiting the analysis to a cohort of infants who had similar conditional probabilities of receiving anaerobic antimicrobial therapy, given their clinical characteristics.[38] Our study is limited by its cohort design and lack of randomization; therefore, we could not completely avoid the risk of unobserved confounders. For example, documentation of clinical signs is lacking. There are also limitations surrounding diagnosis definitions. The diagnosis was not based on standardized criteria but was assigned by the treating physician. Another limitation is the potential overlap of spontaneous intestinal perforation and NEC diagnosis in the data set. Although these 2 conditions represent separate diagnoses in the data set, differentiating spontaneous intestinal perforation from NEC is difficult clinically, and the diagnosis is often not confirmed until laparotomy. Despite these limitations, this large observational study based on electronic medical records is an efficient way to compare treatment strategies in infants with NEC. A randomized controlled trial is unlikely because a sample size of >7000 VLBW infants would be necessary to detect a difference of 3% in outcomes if the incidence of such outcomes was 30% in the susceptible population (power of 80%; .05 2-sided significance level).

Our study demonstrates differential effects of empirical anaerobic antimicrobial therapy in infants with medical compared with surgical NEC. Infants with surgical NEC treated with anaerobic antimicrobial therapy had lower mortality. For infants with medical NEC, there was no survival benefit associated with anaerobic antimicrobial therapy.

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