

# Initial Laparotomy Versus Peritoneal Drainage in Extremely Low Birthweight Infants With Surgical Necrotizing Enterocolitis or Isolated Intestinal Perforation

## A Multicenter Randomized Clinical Trial

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Enterocolitis Surgery Trial was designed to be the largest feasible trial evaluating the impact of initial laparotomy versus drainage on the rates of death or NDI and whether the preoperative diagnosis of NEC versus IP affects the outcomes. The primary hypothesis was that laparotomy would result in a lower rate of death or NDI at 18 to 22 months corrected age. We also hypothesized there would be no significant interaction between treatment and preoperative diagnosis, given our limited sample size.

## METHODS

### Trial Design and Participants

This was a prospective randomized trial conducted at 20 U.S. centers within the Eunice Kennedy Shriver National Institute of Child Health and Human Development Neonatal Research Network from January 2010 to March 2017 with follow up completed in August 2019. Infants were randomized in a 1:1 ratio to initial laparotomy versus peritoneal drainage using variable block sizes. The trial was approved by the institutional review board at each center and infants were enrolled and randomized after written informed parental consent was obtained. Eligible infants that were not randomized were offered enrollment into a prospective observational cohort with surgical treatment decided by surgeon and the same outcomes were measured. Enrollment into this parallel cohort required consent and was discontinued February 14, 2013. The treatment and outcome of eligible nonrandomized infants will be addressed in a separate manuscript. The trial was registered with ClinicalTrials.gov as NCT01029353.

Inclusion criteria were birth weight  $\leq 1000$  g, age  $\leq 8$  weeks and 0 days, a decision to perform surgery for suspected NEC or IP, and hospital capability to perform both laparotomy and drain placement. Exclusion criteria included a major congenital anomaly affecting surgical considerations or the likelihood of the primary outcome; congenital nonbacterial infection; prior NEC or IP; prior laparotomy or drain placement; or parental or attending physician refusal. We excluded infants for whom full support was not provided or for whom follow-up was deemed unlikely, which was assessed by study coordinators at each site.

### Randomization and Masking

Infants were stratified by center and estimated baseline risk of death or NDI ( $\leq 0.74$ ;  $>0.74$ ) using a formula derived from our prior observational study that included gestational age, birth weight, vasopressor administration at enrollment, high-frequency ventilation at enrollment,  $\text{FiO}_2$  at enrollment, pH before and closest to randomization, and the surgeon's preoperative diagnosis (NEC or IP).<sup>2</sup> The randomization sequence was computer-generated by the data coordinating center and was concealed to all trial personnel. Eligibility criteria were entered into the Neonatal Research Network (NRN) telephone randomization system by study coordinators. If all inclusion criteria were met the infant was randomized and the coordinator received the randomization number and treatment group assignment. Masking of the care providers, study coordinators entering data until discharge, and families of the study subjects were not thought to be feasible. Examiners for the standardized neurologic examination and the Bayley Scales of Infant & Toddler Development, Third Edition (Bayley-III) at 18 to 22 months corrected age were not told of the treatment group assignment.

### Procedures

Peritoneal drainage involved placement of a 1/4 inch Penrose drain in the lower abdomen in the neonatal intensive care unit (NICU) with local anesthesia and sedation. Laparotomy was performed under general anesthesia in the operating room or NICU. Surgeons recorded details of either initial surgical procedure,

including location of peritoneal drain, intraoperative findings at laparotomy, and occurrence of intraoperative complications in both treatment groups. Operative details and the decision to perform a subsequent laparotomy were at the discretion of the attending pediatric surgeon. Subsequent laparotomy was discouraged during the first 12 hours after initial drainage and the indications for all subsequent laparotomies were recorded. Operative reports and pathology reports for resected specimens were uploaded to the trial database. Trained study coordinators collected data at randomization, for all operations, and at 120 days in hospital, transfer to another healthcare facility, death, or discharge (whichever came first). Criteria for the surgeon's preoperative diagnosis of NEC or IP were based on surgeon judgment and pre-trial discussions. Infants were assessed at 18 to 22 months corrected age according to standard practices within the NRN.<sup>14</sup>

### Outcomes

The primary outcome was a composite of death or NDI at 18 to 22 months corrected age. NDI was defined as any of the following: moderate to severe cerebral palsy (CP) with Gross Motor Function Classification System level  $\geq 2$ , Bayley-III cognitive composite score  $< 85$ , severe bilateral visual impairment consistent with vision  $< 20/200$ , or permanent hearing loss despite amplification that prevents communication or understanding the examiner. Prespecified secondary outcomes included intraoperative complications (hemorrhage, hypothermia, coagulopathy, cardiopulmonary resuscitation, death), postoperative surgical complications (wound dehiscence, intestinal stricture or fistula, other), number of surgical procedures for each infant, sepsis episodes, duration of parenteral nutrition, development of parenteral nutrition-associated cholestasis, length of hospital stay, rehospitalizations, and each component of the composite primary outcome. Ostomy closure was excluded in reporting subsequent laparotomy after either initial surgical treatment.

### Statistical Analyses

Partly based on our observational study,<sup>2</sup> we hypothesized that 80% of infants randomized to initial drain and 65% randomized to laparotomy would die or develop NDI. To achieve 80% power with a 2-sided alpha of 0.05, 150 randomized infants per treatment group with primary outcome data were required.

The primary analysis assessed the effect of treatment (laparotomy or drainage) on death or NDI at 18 to 22 months. Intent-to-treat analyses were performed. Robust Poisson regression models were used to determine the adjusted relative risk (aRR) and adjusted absolute risk difference (aRD) for the primary outcome, including baseline risk of death or NDI as a covariate and center as a clustering effect in a generalized estimating equation framework. Primary analyses also included a prespecified assessment of interaction between treatment and preoperative diagnosis (NEC or IP). Although there was some prior evidence that laparotomy may be preferable for NEC<sup>2</sup> and drainage better for IP,<sup>6,7</sup> we hypothesized that no significant interaction between treatment and preoperative diagnosis would be identified in our trial due to the fairly limited sample size. In accordance with best practices for conducting and reporting subgroup effects,<sup>15–18</sup> this single subgroup analysis was prespecified in the trial protocol, was hypothesis-testing not hypothesis-generating, and is consistent with prior publications.<sup>6,7</sup>

Preplanned secondary analyses aimed at enhancing the interpretation of study findings included Bayesian analyses assessing the aRR, aRD, and posterior probability of benefit for the primary and secondary outcomes.<sup>19–24</sup> Neutral prior probabilities (centered at an aRR of 1.0 and aRD of 0) were used with a 95% credible interval (CrI) that included the treatment effects on important clinical outcomes identified in almost all neonatal trials (aRR of 0.33–3.00).<sup>25</sup>

The agreement between the preoperative and intraoperative diagnosis in infants who had an initial laparotomy was assessed with kappa values. Analyses were performed with SAS, version 9.4 (SAS Institute) and R, version 3.6.1 (R Project for Statistical Computing). Additional information about the analyses is provided in the Supplement, <http://links.lww.com/SLA/D295>.

## RESULTS

Between January 2010 and March 2017, 310 infants were randomized to initial laparotomy (n=148) or initial drainage (n = 162) (Fig. 1). Seven infants did not receive the assigned treatment and two were withdrawn. Complete primary outcome data at 18 to 22 months were available for 96% (295/308). Treatment groups were comparable at baseline except that more drain infants (29%) than laparotomy infants (19%) received postnatal steroids (Tables 1 and 2). The numbers of subjects assessed for different outcomes varied slightly depending on missing data and exact numbers are shown in Tables 3–5.

### Primary Outcome

Death or NDI at 18 to 22 months corrected age (primary outcome) occurred in 69% of infants (97/141) after initial laparotomy and 70% (108/154) after drainage (aRR = 1.0, 95% CI: 0.87–1.14). Mortality at 18 to 22 months was 29% (89/308) overall; 41 of 146 (28%) with initial laparotomy and 48 of 162 (30%) with initial drainage (aRR = 1.0; 95% CI: 0.69–1.45). The effect of initial treatment on the primary outcome differed according to the preoperative diagnosis of NEC versus IP ( $P = 0.03$  for an interaction for aRR and  $P = 0.04$  for aRD).

Due to the significant interaction between initial treatment and the preoperative diagnosis, the relationship of initial treatment to primary and major secondary outcomes is reported separately by preoperative diagnosis according to accepted statistical recommendations (Table 3).<sup>15,16</sup> Among 94 infants assessed at 18 to 22 months with a preoperative diagnosis of NEC, 29 of 42 (69%) died or had NDI after initial laparotomy versus 44 of 52 (85%) after drainage. The frequentist aRR for initial laparotomy versus drainage was 0.81

(95% CI: 0.64–1.04); the Bayesian aRR = 0.81 (95% CrI: 0.63–1.00); and the Bayesian aRD = –14% (95% CrI: –31 to 1) favoring laparotomy. The Bayesian posterior probability that laparotomy resulted in a lower rate of death or NDI than did drainage (aRD <0) was 97% (Fig. 2). The posterior probabilities that laparotomy reduced death or NDI by at least 1%, 2%, and 3% were 95%, 94%, and 92%, respectively. Among 201 infants with a preoperative diagnosis of IP, death or NDI occurred in 68 of 99 (69%) with initial laparotomy and in 64 of 102 (63%) with initial drainage; frequentist aRR = 1.11 (95% CI: 0.95–1.31); the Bayesian aRR = 1.09 (95% CrI: 0.90–1.33); Bayesian aRD = 6% (95% CrI: –7 to 18). The Bayesian posterior probability of a lower rate of death or NDI with initial laparotomy than drainage (aRD <0) was 18%. Mortality at 18 to 22 months occurred in 44 of 95 (46%) with preoperative diagnosis of NEC versus 45 of 213 (21%) with a preoperative diagnosis of IP. Among infants with a preoperative diagnosis of NEC, mortality was 40% (17/42) with initial laparotomy versus 51% (27/53) with initial drainage. The aRR was 0.77 (95% CI: 0.52–1.13) and the Bayesian aRD for mortality was –11% (95% CrI: –30,8) favoring laparotomy; the probability of a lower death rate (aRD <0) with laparotomy was 87% (Table 3). Among infants with a preoperative diagnosis of IP, 23% (24/104) died after initial laparotomy versus 19% (21/109) with initial drainage. The aRR was 1.28 (95% CI: 0.79–2.06); the Bayesian aRD for mortality was 5% (95% CrI: –7 to 20); and the probability of a lower death rate (aRD <0) with laparotomy was 20%. Infants with the same preoperative diagnosis in the two treatment groups were comparable at baseline (Supplemental Table 2, <http://links.lww.com/SLA/D295>).

### Secondary Outcomes

Findings similar to those for death or NDI and death were observed for other major follow-up outcomes (Table 5). The probability of benefit (aRD <0) with laparotomy relative to drainage with a preoperative diagnosis of NEC ranged from 92% to 99% for all major follow-up outcomes, including death or moderate to severe cerebral palsy, death or blindness, and death or hearing loss. In contrast, the probability of benefit with laparotomy relative to drainage for infants

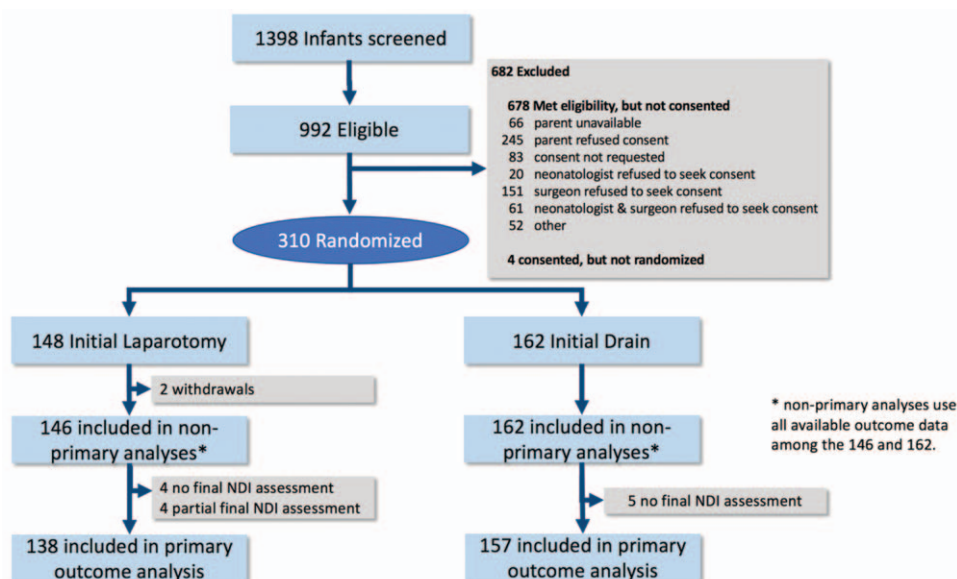


FIGURE 1. Participant flow.

**TABLE 1.** Baseline Infant Characteristics (Information Before or on Day of Enrollment)

Characteristic	Initial Laparotomy Group (n = 146)	Initial Drainage Group (n = 162)
Infant		
Gestational age, mean (SD), wk	25.1 (1.7)	24.9 (1.7)
Birth weight, mean (SD), g	721.2 (138.4)	711.4 (135.9)
Small for gestational age, no. (%)	15 (10.3)	16 (9.9)
Male, no. (%)	80 (54.8)	98 (60.9)
Inborn status, no. (%)	82 (56.2)	90 (55.6)
Apgar score at 1 min, median (min, max)	3 (0, 9)	3 (0, 9)
Apgar score at 5 min, median (min, max)	6 (0, 9)	6 (1, 10)
PDA present, no. (%)	59 (43.4)	62 (42.2)
Received postnatal steroids, no. (%)	27 (18.5)	47 (29.0)
Received indomethacin, no. (%)	74 (51.8)	82 (52.6)
Received enteral feedings, no. (%)	90 (79.7)	95 (76.6)
Early-onset sepsis, no. (%)	1 (0.69)	6 (3.8)
Late-onset sepsis, no. (%)	37 (25.3)	47 (29.4)
Severe intraventricular hemorrhage (Grade III or IV), no. (%)	17 (12.1)	23 (14.7)

with a preoperative diagnosis of IP ranged from 8% to 26%, except for 1 outcome (62% for death or moderate to severe cerebral palsy). Supplemental Table 3, <http://links.lww.com/SLA/D295> provides follow-up outcomes for survivors.

Initial laparotomy did not increase the time to full feedings or duration of mechanical ventilation, parenteral nutrition, or hospitalization (Table 1). The total number of operations was similar for treatment groups [mean of 2.0 (SD 1.3) with initial laparotomy versus 2.1 (SD 1.5) with initial drainage]. Subsequent laparotomy was performed more often after initial drain (81/162, 50%) than after initial laparotomy (35/145, 24%) (Table 2). Among initial drainage infants that had a subsequent laparotomy, 61 of 79 (77%) died or had NDI at 18 to 22 months and 25 of 81 (31%) died. Of the 53 infants with a preoperative diagnosis of NEC and initial drainage, 23 received drain only and 11 survived (48% survival). Of the 109 infants with a preoperative diagnosis of IP and initial drainage, 58 were treated with drain only and 47 survived (81%).

Compared to infants with a preoperative diagnosis of IP, those with a preoperative diagnosis of NEC were older at initial operation (mean 21 vs 8 days for IP); more often had pneumatosis on imaging (36% vs 5%), as well as portal vein air (19% vs 2%), and more

commonly received postnatal steroids (36% vs 19%) or enteral feedings before enrollment (93% vs 72%); all  $P \leq 0.001$  (Supplemental Table 4, <http://links.lww.com/SLA/D295>). Infants with a preoperative diagnosis of IP more commonly had pneumoperitoneum (93% vs 51%) and were smaller at initial operation (mean 707 vs 900 g);  $P < 0.001$ , (Supplemental Table 4, <http://links.lww.com/SLA/D295>).

Among infants who underwent an initial laparotomy and had intraoperative diagnostic data (n = 138), the intraoperative diagnosis was concordant with the preoperative diagnosis in 64% (89/138) of cases; kappa = 0.33. With a preoperative diagnosis of NEC, the concordance rate was 78% and with IP it was 59%. In 7% of infants (10/138) an intraoperative diagnosis other than NEC or IP was made at initial laparotomy, including 2 cases of intestinal volvulus, 2 gastric perforations, and 6 other diagnoses.

Intraoperative complications occurred in 20% of infants (29/145) with initial laparotomy and 13% (21/162) with drainage (Table 2). The most common intraoperative complication with initial laparotomy was liver hemorrhage (7/145, 5%); mortality was 43% (3/7) in these patients. Four infants had other hemorrhage, 3 had intraoperative CPR, and there were no intraoperative deaths.

**TABLE 2.** Baseline Characteristics at Time of Randomization

Characteristic	Initial Laparotomy Group (n = 146)	Initial Drainage Group (n = 162)
Age, mean (SD), days	11.6 (10.0)	12.1 (9.9)
On vasopressors, no. (%)	41 (28.1)	59 (36.4)
Receiving HFOV or HFJV, no. (%)	32 (21.9)	48 (29.6)
pH, mean (SD)	7.25 (0.1)	7.23 (0.1)
FiO <sub>2</sub> , mean (SD)	44.8 (26.3)	45.9 (24.1)
Mean blood pressure, mean (SD), mm Hg	37.1 (10.3)	37.0 (11.5)
Lowest platelet count, mean (SD)	155.7 (96.0)	150.4 (80.9)
Surgeon's preoperative diagnosis, N. (%)		
Necrotizing enterocolitis	42 (28.8)	53 (32.7)
Isolated intestinal perforation	104 (71.2)	109 (67.3)
Baseline predicted risk of death or NDI		
Baseline Risk, mean (SD)	0.62 (0.27)	0.68 (0.24)
Baseline Risk, median (p25–p75)	0.63 (0.42–0.88)	0.71 (0.51–0.89)

**TABLE 3.** Primary and Major Secondary Outcomes by Preoperative Diagnosis

Outcome	Initial Laparotomy (N = 146) n/N (%)	Initial Drainage (N = 162) n/N (%)	Frequentist Adjusted Relative Risk (95% CI)	Bayesian Adjusted Relative Risk (95% CrI)	Bayesian Adjusted Risk Difference (95% CrI)	Bayesian Posterior Probability (%) of RD <0 with Laparotomy
Death or NDI						
NEC	29/42 (69%)	44/52 (85%)	0.81 (0.64 to 1.04)	0.81 (0.63 to 1.00)	-14% (-31 to 1)	97
IP	68/99 (69%)	64/102 (63%)	1.11 (0.95 to 1.31)	1.09 (0.90 to 1.33)	6% (-7 to 18)	18
Death						
NEC	17/42 (40%)	27/53 (51%)	0.77 (0.52 to 1.13)	0.82 (0.53 to 1.20)	-11% (-30 to 8)	87
IP	24/104 (23%)	21/109 (19%)	1.28 (0.79 to 2.06)	1.18 (0.74 to 1.87)	5% (-7 to 20)	20
Survival with NDI						
NEC	12/42 (29%)	17/52 (33%)	0.73 (0.42 to 1.27)	0.76 (0.48 to 1.18)	-19% (-45 to 7)	92
IP	44/99 (44%)	43/102 (42%)	1.11 (0.85 to 1.45)	1.08 (0.83 to 1.42)	5% (-10 to 20)	26
Death or moderate to severe cerebral palsy						
NEC	22/42 (52%)	38/52 (73%)	0.70 (0.47 to 1.05)	0.73 (0.52 to 0.96)	-18% (-38 to -2)	99
IP	36/100 (36%)	41/105 (39%)	0.95 (0.76 to 1.19)	0.95 (0.68 to 1.32)	-2% (-16 to 12)	62
Death or Bayley cognitive composite score <85						
NEC	28/42 (67%)	41/50 (82%)	0.81 (0.61 to 1.06)	0.80 (0.61 to 1.01)	-13% (-32 to 2)	96
IP	67/99 (68%)	59/101 (58%)	1.17 (1.01 to 1.37)	1.15 (0.94 to 1.42)	9% (-4 to 22)	8

\*Denominators in each cell reflect the number of infants with complete data for each outcome reported.

**TABLE 4.** Other Secondary Outcomes by Preoperative Diagnosis

Outcome	Initial Laparotomy (N = 146) mean (SD)	Initial Drainage (N = 162) mean (SD)	Frequentist Mean Difference (95% CI)
Duration of mechanical ventilation, days			
NEC	31.0 (22.6)	31.7 (22.5)	-1.27 (-14.10 to 11.6)
IP	34.1 (26.6)	42.2 (28.0)	-7.85 (-15.84 to 0.13)
Duration of parenteral nutrition, days			
NEC	53.5 (31.3)	65.3 (42.0)	-11.57 (-27.15 to 4.01)
IP	56.3 (35.2)	63.6 (33.7)	-7.63 (-17.46 to 2.20)
Final bowel length, cm			
NEC	62.7 (25.0)	64.0 (44.2)	4.00 (-18.84 to 26.83)
IP	83.1 (20.9)	74.7 (22.4)	9.05 (-13.29 to 31.38)
Time to full feeds, days			
NEC	29.6 (18.9)	32.3 (21.3)	-3.13 (-24.62 to 18.36)
IP	52.4 (50.4)	56.3 (27.1)	-2.39 (-14.42 to 9.63)
Length of hospital stay, days			
NEC	80.2 (77.8)	99.3 (87.7)	-18.43 (-48.41 to 11.55)
IP	109.6 (67.0)	121.3 (64.7)	-11.95 (-31.96 to 8.06)

\*Denominators in each cell reflect the number of infants with complete data for each outcome reported.

## DISCUSSION

Our trial was powered to test the hypothesis that initial laparotomy would result in a 15% absolute lower incidence of death or NDI at 18 to 22 months corrected age compared to initial drainage. We found no overall difference in death or NDI rates in the initial laparotomy versus drainage groups (aRR = 1.0, 95% CI: 0.87–1.14). Our analysis plan included a prespecified assessment of an interaction between treatment and preoperative diagnosis (NEC or IP) that identified preoperative diagnosis as an effect modifier for death or NDI ( $P = 0.03$ ). Two prior randomized trials found no overall difference in mortality between laparotomy and drain groups but did not assess whether the overall treatment effect was modified by the preoperative diagnosis and did not assess neurodevelopmental outcomes.<sup>10,11</sup>

Asking whether the overall treatment effect in a RCT applies to subjects with different baseline characteristics and estimating the treatment effect in subgroups is relevant to most RCTs, although it is

not without controversy, and caution is warranted.<sup>18</sup> As a result, there are explicit guidelines informing the conduct of such analyses.<sup>15–18</sup> Although the interaction we identified might be due to chance, such interactions are most credible when, as in our study, they address the primary outcome and are prespecified in the protocol, hypothesis-testing, limited in number, assessed in proper statistical analyses of interaction, and biologically plausible.<sup>15–18</sup> It is plausible that initial laparotomy would more likely benefit infants with NEC, especially those with multiple perforations and extensive intestinal necrosis and peritonitis whereas infants with IP and a single and often small perforation may require only a peritoneal drain. Multiple pediatric surgery groups presently use clinical practice guidelines that advise treating infants with NEC with laparotomy and those with IP with initial peritoneal drainage.<sup>6,7,26</sup>

Despite the fact that we prespecified the interaction testing and planned to estimate the treatment effect in each diagnostic subgroup, due to sample size constraints our treatment effect estimates in these subgroups should be considered as secondary findings. In accordance

**TABLE 5.** Other Secondary Outcomes by Preoperative Diagnosis

	Initial Laparotomy (N = 146), n/N (%)	Initial Drainage (N = 162), n/N (%)	Frequentist Adjusted Relative Risk (95% CI)	Frequentist Adjusted Risk Difference (95% CI)
Subsequent laparotomy*				
NEC	12/41 (29.3%)	30/53 (56.6%)	0.53 (0.31–0.89)	–26% (–40 to –11)
IP	23/104 (22.1%)	51/109 (46.8%)	0.44 (0.29–0.66)	–26% (–36 to –15)
Any intraoperative complication				
NEC	8/41 (19.5%)	7/53 (13.2%)	1.44 (0.58–3.57)	6% (–8 to 19)
IP	21/104 (20.2%)	14/109 (12.8%)	1.63 (1.06–2.50)	8% (1 to 14)
Wound dehiscence				
NEC	6/42 (14.3%)	3/53 (5.7%)	2.52 (0.84–7.55)	8% (0 to 17)
IP	5/104 (4.8%)	5/109 (4.6%)	1.05 (0.38–2.88)	0% (–4 to 5)
Intra-abdominal abscess				
NEC	2/42 (4.8%)	1/53 (1.9%)	1.78 (0.82–3.86)	Not estimable
IP	3/104 (2.9%)	3/109 (2.8%)	1.16 (0.42–3.20)	Not estimable
Intestinal stricture				
NEC	4/42 (9.5%)	3/53 (5.7%)	1.68 (0.35–8.05)	Not estimable
IP	3/103 (2.9%)	6/109 (5.5%)	0.50 (0.10–2.44)	Not estimable
Sepsis				
NEC	7/42 (16.7%)	7/53 (13.2%)	1.29 (0.62–2.69)	4% (–6 to 14)
IP	16/104 (15.4%)	27/107 (25.2%)	0.60 (0.27–1.32)	–10% (–23 to 4)
PN-associated cholestasis				
NEC	11/42 (26.2%)	19/53 (35.9%)	0.75 (0.41–1.36)	–9% (–28 to 10)
IP	25/104 (24.0%)	27/109 (24.8%)	0.99 (0.69–1.42)	0% (–9 to 8)
Severe IVH				
NEC	1/39 (2.6%)	3/51 (5.9%)	0.43 (0.04–4.45)	Not estimable
IP	17/101 (16.8%)	22/106 (20.8%)	0.81 (0.44–1.49)	Not estimable

\*Denominators in each cell reflect the number of infants with complete data for each outcome reported.

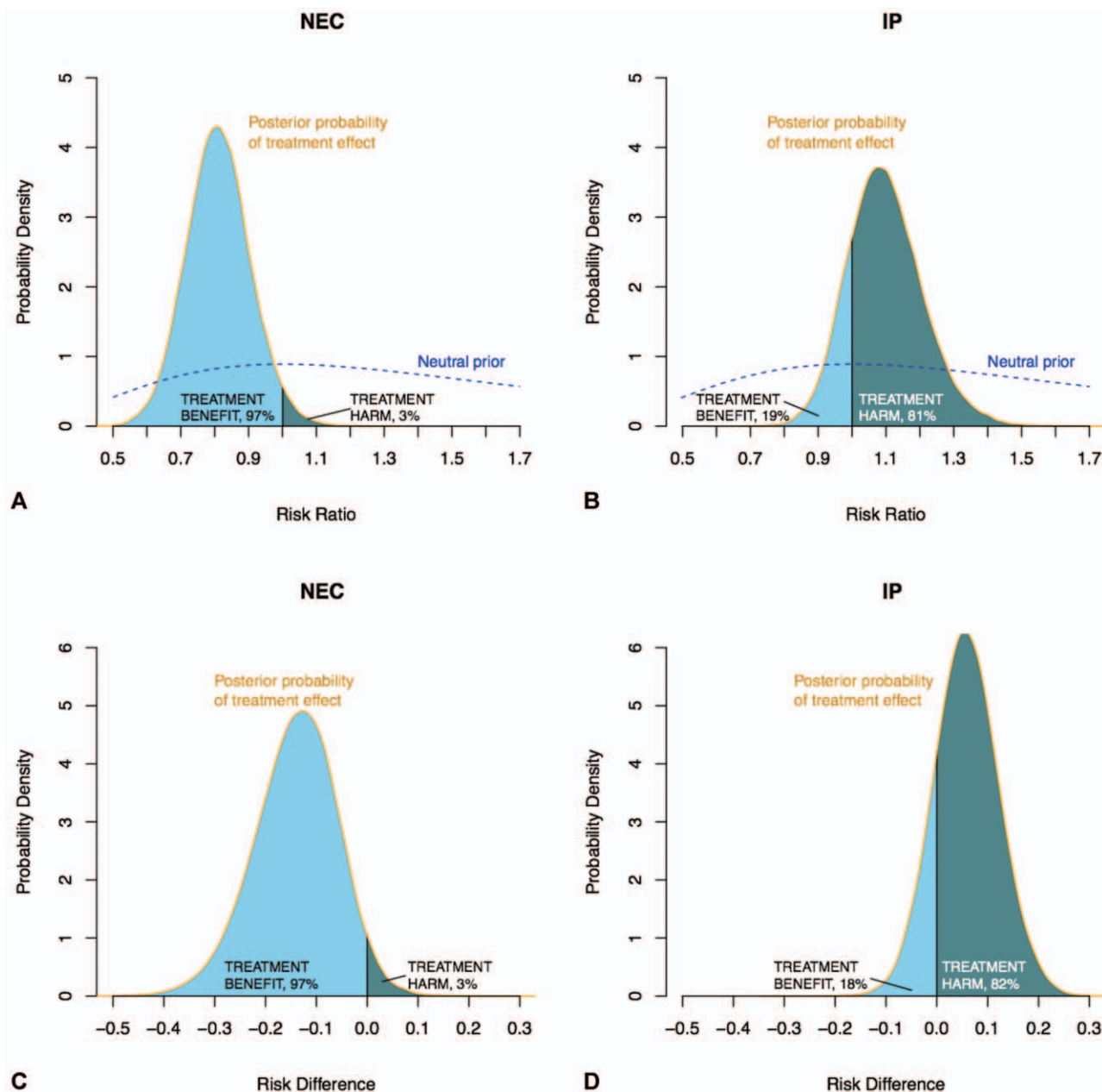
with the American Statistical Association and others, we utilized multiple statistical approaches to augment the interpretation of our trial.<sup>20,24,27,28</sup> We used Bayesian analyses to estimate the probability of treatment benefit, a quantity that cannot be assessed with traditional frequentist analyses.<sup>19–24</sup> Bayesian analyses have been strongly recommended for analyzing trials with limited statistical power, those involving rare diseases,<sup>19,24</sup> and for subgroup analyses like ours.<sup>20–23</sup> Bayesian analyses of our trial provides needed information for providers and other stakeholders that must act with limited information that frequentist analyses do not clearly provide, which has also been shown in other trials.<sup>29</sup>

The *P* value ordinarily designated for statistical significance (<0.05) was not met in assessing the benefit of initial laparotomy for ELBW infants with NEC, and the 95% confidence interval does not exclude the possibility initial laparotomy is harmful. However, as emphasized by the American Statistical Association, a *P* value >0.05 does not necessarily imply evidence in favor of the null hypothesis; many other hypotheses may be equally or more consistent with the data, and scientific conclusions should not be based on whether a *P* value passes a specific threshold.<sup>27,28</sup> For these reasons, a recent commentary in *Nature* with more than 800 signatories called for avoiding dichotomous thinking, eliminating the use of statistical significance from the medical literature, and promoting more nuanced conclusions.<sup>28</sup> Although our findings favoring initial laparotomy are not definitive, it is reassuring that our Bayesian analyses identified a 97% posterior probability of benefit with laparotomy. With a preoperative diagnosis of IP, the differences between treatment groups are smaller and more uncertainty remains.

Limitations of our trial include a limited sample size and randomization of 31% of eligible infants. Treatment effects may differ in eligible, nonrandomized infants and will be addressed in

future analyses. Excluding infants because follow-up was considered very unlikely (*n* = 28) could introduce selection bias, although including them may increase the proportion of infants that do not have primary outcome data. By chance, treatment groups differed by 10% in baseline postnatal corticosteroid treatment. It is unclear whether such treatment increases or decreases the risk death or NDI among high-risk infants like those enrolled.<sup>29,30</sup> The correlation between preoperative and intraoperative diagnosis, assessable of only in the laparotomy group, was not high. This was especially true when the preoperative diagnosis was IP, which surgeons should carefully consider when applying the results of our trial. The lack of a true reference standard for these diagnoses is likely partly responsible and should be addressed in future studies. We infer that the preoperative diagnosis, based on physician judgement, is more predictive of outcome than intraoperative findings. Future investigations might include the impact of the rapidity of disease progression, the overall severity of disease, and individual prognostic factors on outcomes.

Important considerations for our findings are the rarity of the conditions studied; the difficulty of conducting trials of emergency surgical therapies, and the slim possibility that new RCTs will compare laparotomy and peritoneal drainage in the foreseeable future. Although peritoneal drainage was introduced in 1977, there have only been two prior RCTs comparing drainage to laparotomy.<sup>8,10–12</sup> Our trial was powered for the overall treatment groups and was conducted within a large, well-established research network experienced in conducting difficult neonatal RCTs with robust follow-up to identify effects on NDI. Yet, the trial still required almost 10 years to achieve its sample size and complete the neurodevelopmental assessments for 96% of participants. Our trial highlights questions about the level of evidence that can realistically be



**FIGURE 2.** Posterior distribution of the effect of initial surgical treatment (Initial Laparotomy vs. Initial Drainage) on Death or Neurodevelopmental Impairment (NDI) at 18 to 22 months corrected age. Posterior probability distributions of the adjusted risk ratio and risk difference (Initial Laparotomy minus Initial Drainage) derived by combining a prior distribution with trial results. The dashed blue line plots a neutral prior distribution centered at a risk ratio of 1.0, indicating that a priori an equal number of infants would be expected to benefit by either laparotomy or drainage. Light blue shaded areas indicate the posterior probability of reduced death or disability with initial laparotomy (benefit). Dark blue shaded areas indicate the posterior probability of increased death or disability with initial laparotomy (harm). The total area under each probability density curve equals 1. Among infants with a preoperative diagnosis of NEC (a and c), light blue areas indicate a 97% probability that death or NDI in infants treated with Laparotomy is less likely than in infants treated with initial drainage (benefit). Among infants with a pre-operative diagnosis of IP (b and d), the dark blue areas indicate the probability of death or disability among infants treated with Laparotomy is higher than for infants treated with Initial Drainage (harm).



expected or required for treatment recommendations for rare and difficult to study diseases.<sup>19,22,23</sup>

## CONCLUSIONS

In ELBW infants with NEC or IP, there is no difference in the rates of death or NDI at 18–22 months corrected age when compared in overall treatment groups of initial laparotomy versus initial peritoneal drainage. Preoperative diagnosis (NEC vs IP) is an effect modifier, and our data suggest that initial laparotomy is more likely than initial drainage to reduce death or NDI among infants with a preoperative diagnosis of NEC.

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