Laparotomy Versus Peritoneal Drainage for Necrotizing Enterocolitis or Isolated Intestinal Perforation in Extremely Low Birth Weight Infants: Outcomes Through 18 Months Adjusted Age

Martin L. Blakely, Jon E. Tyson, Kevin P. Lally, Scott McDonald, Barbara J. Stoll, David K. Stevenson, W. Kenneth Poole, Alan H. Jobe, Linda L. Wright, Rosemary D. Higgins and for the NICHD Neonatal Research Network

*Pediatrics* 2006;117:e680-e687; originally published online Mar 20, 2006;
DOI: 10.1542/peds.2005-1273

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://www.pediatrics.org/cgi/content/full/117/4/e680
Laparotomy Versus Peritoneal Drainage for Necrotizing Enterocolitis or Isolated Intestinal Perforation in Extremely Low Birth Weight Infants: Outcomes Through 18 Months Adjusted Age

Martin L. Blakely, MDa, Jon E. Tyson, MD, MPHb, Kevin P. Lally, MDa, Scott McDonald, BS, Barbara J. Stoll, MDc, David K. Stevenson, MDd, W. Kenneth Poole, PhD,Alan H. Jobe, MDg, Linda L. Wright, MDh, Rosemary D. Higgins, MDi, for the NICHD Neonatal Research Network

aSection of Pediatric Surgery, University of Tennessee Health Science Center, Memphis, Tennessee; bDepartment of Neonatology, University of Texas Health Science Center, Houston, Texas; cRTI International, Research Triangle Park, North Carolina; dDepartment of Neonatology, Emory University, Atlanta, Georgia; eDepartment of Neonatology, Stanford University School of Medicine, Palo Alto, CA; fDepartment of Neonatology, Research Triangle Institute, Research Triangle Park, North Carolina; gDepartment of Pediatrics, University of Cincinnati, Cincinnati, Ohio; hDepartment of Neonatology, National Institute of Child Health and Human Development, Center for Research for Mothers and Children, Bethesda, MD; iDepartment of Neonatology, National Institute of Child Health and Human Development, Center for Development Biology and Perinatal Medicine, Bethesda, MD

The authors have indicated they have no financial relationships relevant to this article to disclose.

ABSTRACT

OBJECTIVE. Extremely low birth weight (ELBW; ≤1000 g) infants with necrotizing enterocolitis (NEC) or isolated intestinal perforation (IP) are treated surgically with either initial laparotomy or peritoneal drain placement. The only published data comparing these therapies are from small, retrospective, single-center studies that do not address outcomes beyond nursery discharge. The objective of this study was to conduct a prospective, multicenter, observational study to (1) develop a hypothesis about the relative effect of these 2 therapies on risk-adjusted outcomes through 18 to 22 months in ELBW infants and (2) to obtain data that would be useful in designing and conducting a successful trial of this hypothesis.

METHODS. A prospective, cohort study was conducted at 16 clinical centers within the National Institute of Child Health and Human Development Neonatal Research Network. To assist in risk adjustment, the attending pediatric surgeon recorded the preoperative diagnosis and intraoperative diagnosis and identified infants who were considered to be too ill for laparotomy. Predefined measures of short- and longer-term outcome included (1) either predischarge death or prolonged parenteral nutrition (>85 days) after enrollment and (2) either death or neurodevelopmental impairment on a standardized examination at 18 to 22 months’ adjusted age.

RESULTS. Severe NEC or IP occurred in 156 (5.2%) of 2987 ELBW infants; 80 were treated with initial drainage, and 76 were treated with initial laparotomy. By 18 to 22 months, 78 (50%) had died; 112 (72%) had died or were shown to be impaired. Outcome was worse in the subgroup with NEC. Laparotomy was never performed in 76% (28 of 36) of drain-treated survivors.

doi:10.1542/peds.2005-1273

Key Words
necrotizing enterocolitis, neonatal surgery, neurodevelopmental outcomes

Abbreviations
NEC—necrotizing enterocolitis
ELBW—extremely low birth weight
NICHD—National Institute of Child Health and Human Development
NDI—neurodevelopmental impairment
IP—intestinal perforation
PN—parenteral nutrition
CP—cerebral palsy
HFOV—high-frequency oscillator ventilation
PIP—peak inspiratory pressure
OR—odds ratio
CI—confidence interval

Accepted for publication Sep 19, 2005
Address correspondence to Martin L. Blakely, MD, Division of Pediatric Surgery, University of Tennessee, Memphis, 777 Washington Ave, Suite P220, Memphis, TN 38105. E-mail: mblakely@utmem.edu

PEDIATRICS (ISSN Numbers: Print, 0031-4005; Online, 1098-4275). Copyright © 2006 by the American Academy of Pediatrics
CONCLUSIONS. Drainage was commonly used, and outcome was poor. Our findings, particularly the risk-adjusted odds ratio favoring laparotomy for death or impairment, indicate the need for a large, multicenter clinical trial to assess the effect of the initial surgical therapy on outcome at ≥18 months.

NECROTIZING ENTEROCOLITIS (NEC) is diagnosed in 6% of very low birth weight (<1500 g) and 8% of extremely low birth weight (ELBW; <1000 g) infants.1,2 Surgically treated NEC occurs in 5% of ELBW infants within the Neonatal Research Network of the National Institute of Child Health and Human Development (NICHD).2 Isolated intestinal perforation (IP), a less common disorder that affects ~2% of ELBW infants, is thought to be a distinct clinical entity with presenting signs similar to those of NEC.3,4 These 2 disease processes are currently treated similarly, both medically and surgically, in part because of the uncertain accuracy of preoperative diagnoses of these disorders. ELBW infants who are surgically treated for NEC or IP have a mortality rate of ~50%.5–9 Moreover, survivors often experience severe morbidity, including prolonged inability to tolerate feedings and a high rate of neurodevelopmental impairment (NDI).10,11

It is unknown whether simple peritoneal drainage or laparotomy (and likely intestinal resection) should be the initial surgical therapy for ELBW infants and whether the same procedure should be used for both disorders.12,13 Laparotomy has been the traditional treatment. During the 1970s, peritoneal drainage first was used as a temporizing measure for critically ill neonates who were considered to be too ill for a laparotomy.14 The original rationale was to stabilize the infant and later perform a laparotomy with resection of diseased bowel. In recent years, however, peritoneal drainage increasingly has been used with a plan to perform a later laparotomy only if clinical deterioration or specific complications (eg, intestinal strictures, enterocutaneous fistulas) occur.12,15–17 Unfortunately, the only published data comparing laparotomy and drainage for the initial therapy for NEC or IP were obtained in small, retrospective, single-center studies,13 and these studies do not address outcomes beyond nursery discharge. Recent18 and previous19 experience in caring for high-risk infants indicates the continuing importance of assessing the effects of neonatal interventions on neurodevelopmental outcomes.

The relative value of these 2 therapies would be most clearly determined in a large, multicenter, randomized trial that assesses outcomes before neonatal discharge and at follow-up. However, it has been difficult to complete even short-term, single-center trials of any surgical treatment,20 particularly in patients with life-threatening illnesses.21,22

The primary goal of our study was to conduct a prospective, multicenter, cohort study with a sufficient number of patients to (1) develop a hypothesis on the basis of prospective clinical research about the relative effect of these 2 therapies on risk-adjusted outcomes among ELBW infants through 18 to 22 months’ adjusted age (postterm), an age when NDI first may be reliably assessed, and (2) obtain data that could be used in designing and conducting a multicenter, randomized trial of this hypothesis.

METHODS

Patients and Setting

All ELBW infants who were born from February 2001 to August 2002 and treated in the NICHD Neonatal Network were screened for NEC and IP, and data regarding their treatment were collected prospectively. Included were all infants whose birth weight was between 401 and 1000 g and who developed severe NEC or IP that required surgical intervention as judged by the attending pediatric surgeon on the basis of either pneumoperitoneum identified by an abdominal radiograph or clinical deterioration with increasing ventilatory requirement, labile blood pressure, vasopressors, or other clinical indicators. On the basis of the physical examination, demographic data, clinical course, and radiologic imaging studies, the attending pediatric surgeon recorded the preoperative diagnosis (NEC or IP) at the time of the decision for surgery. Before enrollment, questionnaires were completed by participating surgeons regarding the distinction between NEC and IP preoperatively. The majority of surgeons indicated that there was indeed a distinction and that using the available information mentioned above this distinction could be determined in many cases. Postoperative diagnosis was determined by gross inspection of the intestines at operation (for those who underwent laparotomy). Twenty-nine patients who were enrolled in a separate ongoing randomized trial (NEC Steps Trial; L. Moss, Principle Investigator) had the initial surgical treatment determined by randomization. The surgical intervention was chosen by the attending pediatric surgeon for 127 patients. Data regarding preoperative patient characteristics and intraoperative findings were collected by participating surgeons. Other baseline data and the outcome measures were collected by trained Neonatal Network research nurses. Duration of parenteral nutrition and other clinical data were recorded to 120 days or discharge, whichever occurred first. Data regarding extent of disease at laparotomy, extent of resection, and postoperative surgical complications were also collected and are reported separately.21

Outcome Measures

To capture both mortality and severe morbidity before discharge, our outcome variables included the composite
outcome of either death or prolonged parenteral nutrition (PN) after the initial surgery. Prolonged PN reflects the combined effects of multiple problems (eg, short gut syndrome, intestinal malabsorption, strictures, complications from indwelling vascular catheters) and is associated with high costs and toxic effects from PN. Prolonged PN was predefined as >85 days of PN after surgery, a value that is likely to be associated with >100 total days of PN. To provide information that is useful for assessing potential confounders and for planning a future trial, the surgeon for each infant was asked to specify at enrollment whether the infant was considered to be too ill for laparotomy or for drainage.

Longer term evaluations were conducted as part of the ongoing standardized assessments performed in network centers to evaluate prospectively all ELBW survivors at 18 to 22 months’ corrected age (postterm). The initial surgical treatment of some infants would have been discernible from their abdominal scars. However, the evaluators were not told the infants’ initial surgical treatment, were not included in planning the study, and were unlikely to be aware of it or the issues that were under investigation at the time when the patients were assessed. Neurologic examiners were trained and certified in the examination procedure during an annual 2-day workshop. Cerebral palsy (CP) was defined as a nonprogressive central nervous system disorder characterized by abnormal muscle tone in at least 1 extremity and abnormal control of movement and posture. Developmental delay was identified by scores of <70 on the Bayley Scales of Infant Development II. Scores of 49 were assigned to infants whose extremely severe neurologic impairment or NDI prevented their examination. Blindness was defined as use of hearing aids in both ears. Deafness was defined as no useful vision in either eye. NDI was defined as 1 or more of the following: Mental Developmental Index <70, Psychomotor Developmental Index <70, CP, deafness, or blindness. Weight, length, and head circumference measurements were also made at the time of the 18- to 22-month follow-up visit. Determination of weight, length, and head circumference percentiles for age were based on age corrected for prematurity. Statistical Analyses

Statistical analyses were performed by statisticians (S.A.M. and W.K.P.) at RTI International. Univariate analyses were performed to assess baseline differences between treatment groups, the relationship of patient characteristics to outcome, and the agreement between preoperative and intraoperative diagnosis among patients who underwent laparotomy. Mean values were analyzed with t tests, and proportions were analyzed with Fisher’s exact or χ² analyses. Agreement beyond chance (of pre- and intraoperative diagnoses) was assessed with the κ statistic. For avoiding bias in selecting the final multivariable models relating surgical treatment to outcome, the baseline variables were selected a priori on the basis of clinical judgment and the results of univariate analyses. These variables were treatment planned at enrollment (initial laparotomy or initial drainage), preoperative diagnosis (NEC or isolated IP), birth weight, and 4 measures of severity of illness at enrollment (fraction of inspired oxygen, pH, treatment with vasopressors, and use of high-frequency oscillator ventilation (HFOV) or use of conventional mechanical ventilation with a peak inspiratory pressure (PIP) >30 mm Hg). Similar multivariable logistic regression analyses were performed for the neurodevelopmental outcome measures, adjusted for the same variables listed above. Separate analyses were performed for the original cohort and for a restricted cohort after exclusion of patients who were considered to be too ill for laparotomy at study enrollment. The latter analyses were performed to reduce selection biases in comparing the 2 surgical therapies, to facilitate a valid assessment of their relative effectiveness, and to identify a group of patients who were representative of those who could be enrolled in a later clinical trial. Infants who were considered by the surgeon to be “too ill” for a laparotomy would be unlikely to be enrolled in a future trial.

Sample Size

We planned to enroll 150 total infants and determine their outcome at 18 to 22 months’ adjusted age. This sample size was judged to provide a reasonable balance between obtaining data needed to develop an evidence-based hypothesis and properly plan a randomized trial without unduly delaying the trial’s initiation.

RESULTS

Description of Cohort and Overall Outcome

Between February 2001 and August 2002, 2987 ELBW infants were treated at network sites. A total of 156 (5.2%) patients were judged to require surgical treatment for NEC or IP; 96 (62%) patients had a preoperative diagnosis of NEC, and 60 (38%) had presumed IP. All were enrolled in the study and received a surgical intervention; 76 had initial laparotomy, and 80 had initial drainage. The flow of all patients from enrollment to outcome is shown in Fig 1.

Overall outcome was poor. A total of 76 (49%) died before discharge, and 93 (60%) either died or received prolonged PN as previously defined. Seventeen (11% of enrolled infants) survivors received prolonged PN. Of the 80 survivors to nursery discharge, 4 were lost to follow-up, 5 had incomplete evaluations, and 2 died after discharge. Outcome at 18 to 22 months was determined for 71 (89% of survivors at discharge) infants. Death or NDI at 18 to 22 months was identified for 112 (72% of the cohort) infants. Among all survivors, NDI
was documented in 49% (34 of 69). A Mental Developmental Index <70 was ascertained in 45% of infants assessed; a Psychomotor Developmental Index <70 in 32%; CP in 24%; moderate or severe CP in 12%; vision impairment in 30%; blindness in 3%; and deafness in 5%.

Relation of Treatment to Patient Characteristics

Characteristics of patients who were treated by each surgical method are shown in the first 2 data columns of Table 1. For facilitating a valid evaluation of the relative effectiveness of the 2 surgical treatments, the second 2 data columns indicate patient characteristics for the restricted cohort excluding the 40 patients who were considered to be too ill by the attending surgeon to perform a laparotomy. The restricted cohort includes 115 patients, 41 who underwent initial drainage and 74 who underwent initial laparotomy. (One patient was not included in the restricted cohort because the “too ill” information was not recorded; therefore, 41 total patients were excluded from the overall cohort to yield the restricted cohort.) In both the overall and the restricted cohorts, patients who were treated with initial drainage placement had a lower average gestational age, postnatal age, and systolic blood pressure at enrollment compared with infants who underwent initial laparotomy. They also were more likely to be treated with HFOV or with a PIP >30 mm Hg when conventional ventilation was used. They were less likely to have a preoperative diagnosis of NEC than were laparotomy-treated patients. Other preoperative measures of disease severity (eg, pH, platelet count) did not significantly differ between the 2 treatment groups.

Relation of Patient Characteristics to Outcome

Data relating patient characteristics to outcome for both the overall and the restricted cohorts are summarized in Figure 1. Flow of patients through study. aInitial surgical treatment; bNDI at 18 to 22 months; cpercentage of survivors who had full follow-up assessment.

### Table 1

**Relation of Treatment to Patient Characteristics**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Overall Cohort (N = 156)</th>
<th>Restricted Cohort (N = 115)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Drain (n = 80)</td>
<td>Laparotomy (n = 76)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gestational age, mean (range), wk</td>
<td>24.7 (22–30)</td>
<td>25.7 (23–31)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Birth weight, mean (range), g</td>
<td>703.4 (424–1000)</td>
<td>756.4 (485–997)</td>
<td>.01</td>
</tr>
<tr>
<td>Age at operation, mean (range), d</td>
<td>14.7 (1–89)</td>
<td>23.5 (1–68)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Male gender, n (%)</td>
<td>48 (60)</td>
<td>44 (58)</td>
<td>.87</td>
</tr>
<tr>
<td>Any ventilation, n (%)</td>
<td>77 (97)</td>
<td>74 (97)</td>
<td>1.0</td>
</tr>
<tr>
<td>Blood pressure, mean (range), mmHg</td>
<td>34.7 (8–60)</td>
<td>40.6 (20–68)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>HFOV or PIP &gt;30, n (%)</td>
<td>24 (32)</td>
<td>8 (11)</td>
<td>.002</td>
</tr>
<tr>
<td>Fio2 level, mean (range)</td>
<td>0.72 (0.21–1)</td>
<td>0.59 (0.21–1)</td>
<td>.01</td>
</tr>
<tr>
<td>pH, preoperative blood gas, mean (range)</td>
<td>7.3 (6.8–7.5)</td>
<td>7.3 (6.9–7.6)</td>
<td>.41</td>
</tr>
<tr>
<td>Platelet count, mean (range), n/mm³</td>
<td>140 (11–558)</td>
<td>165 (18–581)</td>
<td>.18</td>
</tr>
<tr>
<td>Preoperative diagnosis of NEC, n (%)</td>
<td>38 (48)</td>
<td>58 (76)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Preoperative diagnosis of IP, n (%)</td>
<td>42 (53)</td>
<td>18 (24)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Drain (n = 11)</td>
<td>Laparotomy (n = 74)</td>
<td>P</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gestational age, mean (range), wk</td>
<td>24.7 (22–27)</td>
<td>25.7 (23–31)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Birth weight, mean (range), g</td>
<td>711.5 (424–999)</td>
<td>757.6 (485–997)</td>
<td>.08</td>
</tr>
<tr>
<td>Age at operation, mean (range), d</td>
<td>13.7 (2–43)</td>
<td>23.7 (1–68)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Male gender, n (%)</td>
<td>22 (52)</td>
<td>43 (59)</td>
<td>.56</td>
</tr>
<tr>
<td>Any ventilation, n (%)</td>
<td>17 (40)</td>
<td>19 (26)</td>
<td>.15</td>
</tr>
<tr>
<td>Blood pressure, mean (range), mmHg</td>
<td>40.95 (19–52)</td>
<td>41.0 (22–68)</td>
<td>&lt;.007</td>
</tr>
<tr>
<td>HFOV or PIP &gt;30, n (%)</td>
<td>12 (30)</td>
<td>7 (10)</td>
<td>.009</td>
</tr>
<tr>
<td>Fio2 level, mean (range)</td>
<td>0.71 (0.21–1)</td>
<td>0.59 (0.21–1)</td>
<td>.04</td>
</tr>
<tr>
<td>pH, preoperative blood gas, mean (range)</td>
<td>7.3 (6.8–7.5)</td>
<td>7.3 (6.9–7.6)</td>
<td>.92</td>
</tr>
<tr>
<td>Platelet count, mean (range), n/mm³</td>
<td>162 (23–558)</td>
<td>165 (18–581)</td>
<td>.87</td>
</tr>
<tr>
<td>Preoperative diagnosis of NEC, n (%)</td>
<td>17 (40)</td>
<td>55 (75)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Preoperative diagnosis of IP, n (%)</td>
<td>25 (60)</td>
<td>18 (25)</td>
<td></td>
</tr>
</tbody>
</table>

P values are from t test or Fisher’s exact test, as appropriate. Fio2 indicates fraction of inspired oxygen.

a Blood gas (arterial, venous, or capillary) at time of enrollment.
Table 2. Characteristics that were associated consistently in univariate analyses with adverse outcomes included vasopressor requirement at enrollment and treatment with HFOV or with conventional ventilation with PIP >30 mm Hg. A preoperative diagnosis of NEC (versus IP) was associated with adverse neonatal outcomes (death and death or prolonged PN) but not with NDI. Specifically, among infants with a preoperative diagnosis of NEC, 80% (70 of 87) either died or developed NDI at 18 to 22 months compared with 69% (40 of 58) of infants with a preoperative diagnosis of IP. The relative risk for NDI or death for a preoperative diagnosis of NEC was 1.17 (95% confidence interval [CI]: 0.96–1.43; \( P = .13 \)). Among surviving infants with a preoperative diagnosis of NEC, 50% (17 of 34) had NDI versus 49% (17 of 35) of those with a preoperative diagnosis of IP (relative risk: 1.03; 95% CI: 0.64–1.66; \( P = .9 \)).

Relation of Preoperative and Intraoperative Findings
There was a high degree of agreement (95%) between the recorded preoperative diagnosis and the intraoperative diagnosis for patients who underwent initial laparotomy (n = 76; \( \kappa = .85; P < .0001 \)).

Relationship of Surgical Treatment to Outcome
Among patients who underwent initial laparotomy, 40 (53%) of 76 infants either died before discharge or received prolonged PN compared with 53 (66%) of 80 infants in the initial drainage group. Mortality before discharge in the initial laparotomy group was 43% (33 of 76), and 7 (9%) survivors had prolonged PN. Among initial drainage patients, 43 (54%) infants died before hospital discharge and 10 (12.5%) survivors had prolonged PN. At 18 to 22 months, 34 (45%) of the infants in the initial laparotomy group had died and 48 (68%) had either died or developed NDI. In the initial drain group, 44 (55%) infants had died and 64 (84%) had either died or developed NDI.

With these findings, the crude (unadjusted) odds ratios (ORs) for adverse outcomes in the laparotomy group relative to the drain group are substantially less than 1.0, favoring the laparotomy group (Table 3). Because of the greater severity of illness among the drainage group than the laparotomy group, adjustment for multiple potential confounders and restriction of the cohort by exclusion of those who were considered to be too sick for a laparotomy raised the OR. In the restricted cohort, the adjusted ORs for death at 18 to 22 months was 1.1 (95% CI: 0.41–3.21). However, the OR for death or NDI was 0.56 (95% CI: 0.19–1.69).

Subsequent Laparotomy After Initial Drainage or Laparotomy
Among the initial drainage cohort (n = 80), 62 infants received no subsequent laparotomy. Of these, 28 infants (35% of drainage cohort; 45% of those who had no laparotomy) survived. Among the 18 infants who were treated with a subsequent laparotomy, 9 survived (11% of drainage cohort; 50% of those who were treated with laparotomy). Therefore, an initial laparotomy was avoided in 37 drainage-treated survivors (46% of drainage cohort).

The survival rate with drainage only (no subsequent laparotomy) did not vary significantly according to preoperative diagnosis. For patients with presumed NEC, survival after drainage without subsequent laparotomy was 32% (12 of 38) versus 38% (16 of 42) in patients with preoperative diagnosis of IP. Overall, of the 37 survivors after initial drainage, the use of drainage avoided a laparotomy in 28 (76%); of these 28, 16 had a preoperative diagnosis of isolated IP and 12 had NEC.

DISCUSSION
In this multi-institutional cohort study, initial drain placement was commonly used as initial surgical therapy. Infants with a preoperative diagnosis of NEC were more often treated initially with laparotomy, whereas patients who were presumed to have IP were more often treated with initial drainage. Only 23% of patients had a

### Table 2: Relation of Patient Characteristics to Outcome

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Overall Cohort</th>
<th>Restricted Cohort</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>RR for Death(^a) or Prolonged PN</td>
<td>RR for Death(^b)</td>
</tr>
<tr>
<td>Birth weight (100 g)</td>
<td>0.91 (0.82–1.00)</td>
<td>0.88(^c) (0.77–0.99)</td>
</tr>
<tr>
<td>Gestational age</td>
<td>0.92 (0.84–1.00)</td>
<td>0.89(^b) (0.80–0.99)</td>
</tr>
<tr>
<td>Vasopressor required</td>
<td>1.44(^d) (1.12–1.84)</td>
<td>1.61(^d) (1.17–2.21)</td>
</tr>
<tr>
<td>HFOV or PIP &gt;30</td>
<td>1.65(^d) (1.31–2.07)</td>
<td>1.79(^d) (1.31–2.44)</td>
</tr>
<tr>
<td>Median pH ≤7.26</td>
<td>1.32(^d) (1.02–1.71)</td>
<td>1.20 (0.87–1.65)</td>
</tr>
<tr>
<td>Fi(_O2)</td>
<td>3.02(^d) (1.86–5.06)</td>
<td>3.82(^d) (2.01–7.26)</td>
</tr>
<tr>
<td>Preoperative diagnosis of NEC</td>
<td>1.38(^d) (1.02–1.86)</td>
<td>1.44 (0.99–2.08)</td>
</tr>
</tbody>
</table>

\(^a\) Excludes 40 infants who were considered to be too ill for laparotomy and 1 infant for whom “too ill for lap” was not recorded.

\(^b\) Death before discharge.

\(^c\) \( P < .05 \).

\(^d\) \( P < .01 \).
subsequent laparotomy after initial drainage. Hence, this study indicates that drains are being used commonly and often as the only therapy rather than as a temporizing procedure before laparotomy.

As in studies that have included no attempt to adjust for baseline differences, the unadjusted ORs for adverse outcomes were substantially less than 1.0, favoring the laparotomy group. However, there are major differences between the treatment groups, and these ORs increased after adjustment for multiple potential confounders and after exclusion of infants who were considered to be too ill for laparotomy. Currently, 2 clinical trials are being conducted to test the hypothesis that mortality is substantially lower with drainage than with laparotomy.25,26 This hypothesis is not supported by our data. Moreover, our findings are compatible with an important advantage of laparotomy over drainage with respect to the likelihood of death or NDI (risk-adjusted OR in the restricted cohort of 0.56; 95% CI: 0.19–1.69). However, the CI is relatively wide.

Given the great uncertainty about the relative effectiveness of these 2 surgical interventions, these results support the need for a randomized trial to evaluate the effect of them on outcome at ≥18 months’ corrected age. How would the results of our study be used in the planning of such a trial? Our findings suggest that nearly 75% of those enrolled would die or have impairment at 18 to 22 months. On the basis of this rate of adverse outcome and the OR identified, we would hypothesize that death or impairment would occur in 78% of the drainage group and in 66% of the laparotomy group.27 If so, then the number needed to treat with laparotomy rather than drainage to gain 1 additional unimpaired survivor would be only 8 infants.27 Across the range of medical and surgical interventions, this would be a very low number needed to treat, particularly for such an important benefit.28–30

If our hypothesis is correct, then laparotomy would be preferred over drainage as the initial treatment of ELBW infants with NEC or IP. If the hypothesis is incorrect and initial laparotomy does not improve outcome, then drainage would likely be preferred as a simpler and less traumatic procedure in these high-risk infants. For these reasons, it is important to launch a large, multicenter, clinical trial to provide the clearest possible determination of the effect of the initial surgical therapy on the short- and long-term outcomes of these infants. Although such a trial would not be performed easily, we found a high degree of cooperation among neonatologists and pediatric surgeons in this observational study. The feasibility of a clinical trial to address the same issues may be augmented by design or analysis features that are recommended to facilitate trials that involve a rare disease31–33 or diseases for which there is a strong treatment preference among clinicians.34

**APPENDIX: NICHD NEONATAL RESEARCH NETWORK, PARTICIPATING SITES AND STUDY PRINCIPAL INVESTIGATORS**

**Other Authors**

R. Lawrence Moss, MD, Douglas C. Barnhart, MD, Rebecca Brown, MD, Arlet G. Kurkchubasche, MD, Walter J. Chwals, MD, and Richard R. Ricketts, MD.

**NEC Observational Study Group**

- **Case Western Reserve University**
  - PI: Ronald N. Goldberg, MD; Surgery PI: Michael A. Skinner, MD; Study Coordinator: Kathy Auten, BS; Follow Up PI: Betty Vohr, MD; Follow Up Coordinator: Melody Lohmeyer, RN.

- **Brown University**
  - Women & Infant’s Hospital PI: William Oh, MD; Surgery PI: Arlet G. Kurkchubasche, MD; Study Coordinator: Angelita Hensman, BSN, RNC; Follow Up PI: Betty Vohr, MD; Follow Up Coordinator: Lucy Noel, RN.

- **Duke University**
  - PI: Ronald N. Goldberg, MD; Surgery PI: Michael A. Skinner, MD; Study Coordinator: Kathy Auten, BS; Follow Up PI: Ricki Goldstein, MD; Follow Up Coordinator: Melody Lohmeyer, RN.

- **Emory University**
  - Grady Memorial Hospital and Crawford Long Hospital PI: Barbara J. Stoll, MD; Surgery PI: Richard R. Ricketts, MD; Study Coordinator: Ellen Hale, RN, BS.
Indiana University
Riley Hospital for Children and Methodist Hospital PI: James A. Lemons, MD; Surgery PI: L.R. Scherer, MD; Study Coordinators: Diana Dawn Appel, RN, BSN, Lucy Miller, RN, BSN; Follow Up PI: Anna Dusick, MD; Follow Up Coordinator: Leslie Richard, RN.

Stanford University
PI: David K. Stevenson, MD; Surgery PI: R. Lawrence Moss, MD; Study Coordinator: M. Bethany Ball, BS, CCRC; Follow Up PI: Susan R. Hintz, MD.

University of Alabama at Birmingham
University Hospital-UAB PI: Waldemar A. Carlo, MD; Surgery PI: Douglas C. Barnhart, MD; Study Coordinators: Monica Collins, RN, BSN, Shirley Cosby, RN, BSN; Follow Up PI: Myriam Peralta-Carcelen, MD; Follow Up Coordinator: Vivien Phillips, RN, BSN.

University of Cincinnati
The University Hospital, Cincinnati Children’s Hospital Medical Center PI: Edward F. Donovan, MD; Surgery PI: Rebecca Brown, MD; Study Coordinators: Cathy Grisby, BSN, Barb Alexander, RN, Jody Shively, RN, Holly Mincey, RN; Follow Up PI: Jean Steichen, MD; Follow Up Coordinator: Teresa Gratton, PA.

University of California–San Diego
UCSD Medical Center and Sharp Mary Birch Hospital for Women PI: Neil N. Finer, MD; Surgery PI: Mary L. Hilfiker, MD; Study Coordinators: Chris Henderson, CRTT, Wade Rich, RRT-NPS, Kathy Arnell, RN; Follow Up PI: Yvonne E. Vaucher, MD, MPH; Follow Up Coordinator: Martha Fuller, RN, MSN.

University of Miami
PI: Shahnaz Duara, MD; Surgery PI: W. Raleigh Thompson, MD; Study Coordinator: Ruth Everett, BSN; Follow Up PI: Charles R. Bauer, MD.

University of Rochester
Golisano Children’s Hospital at Strong PI: Dale L. Phelps, MD; Surgery PI: Walter Pegoli, MD; Study Coordinator: Linda Reubens, RN; Follow Up PI: Gary Myers, MD; Follow Up Coordinator: Diane Hust, RN.

The University of Texas
Southwestern Medical Center at Dallas: Parkland Hospital PI: Abbot R. Laptook, MD; Surgery PI: Philip C. Guzetta, MD; Study Coordinators: Susie Madison, RN, Gay Hensley, RN, Nancy Miller, RN; Follow Up PI: Roy Heyne, MD, Sue Broyles, MD; Follow Up Coordinator: Jackie Hickman, RN.

University of Texas–Houston
Memorial Hermann Children’s Hospital PI: Jon E. Tyson, MD, MPH; Surgery PI: Martin L. Blakely, MD; Study Coordinators: Georgia McDavid, RN, Esther G. Akpa, RN, BSN, Claudia Y. Franco, RN, BNS, MSN, NNP, Patty A. Cluff, RN, Anna E. Lis, RN, BSN; Follow-Up PI: Brenda H. Morris, MD, Pamela J. Bradt, MD, MPH.

Wake Forest University
PI: T. Michael O’Shea, MD; Surgery PI: Robert W. Letton, Jr., MD; Study Coordinator: Nancy J. Peters, RN; Follow Up PI: Robert G. Dillard, MD; Follow Up Coordinator: Barbara G. Jackson, RN, BSN.

Wayne State University
Hutzel Women’s Hospital & Children’s Hospital of Michigan PI: Seetha Shankaran, MD; Surgery PI: Michael D. Klein, MD; Study Coordinators: Rebecca Bara, RN, BSN, Geraldine Muran, RN, BSN; Follow Up PI: Yvette Johnson, MD; Follow Up Coordinator: Debbie Kennedy, RN.

Yale University
New Haven Children’s Hospital PI: Richard A. Ehrenkranz, MD; Surgery PI: Robert J. Touloukian, MD; Study Coordinator: Patricia Gettner, RN; Follow Up Coordinator: Elaine Romano, RN

NICHD Neonatal Research Steering Committee
Brown University: William Oh, MD; Case Western University: Avroy A. Fanaroff, MD; Duke University: Ronald N. Goldberg, MD; Emory University: Barbara J. Stoll, MD; Indiana University: James A. Lemons, MD; Stanford University: David K. Stevenson, MD; University of Alabama at Birmingham: Waldemar A. Carlo, MD; University of Cincinnati: Edward F. Donovan, MD; University of California–San Diego: Neil N. Finer, MD; University of Miami: Shahnaz Duara, MD; University of Rochester: Dale L. Phelps, MD; University of Texas–Dallas: Abbot R. Laptook, MD; University of Texas–Houston: Jon E. Tyson, MD, MPH; Wake Forest University: T. Michael O’Shea, MD, MPH; Wayne State University: Seetha Shankaran, MD; Yale University: Richard A. Ehrenkranz, MD, Chair, Alan Jobe, University of Cincinnati.

Data Coordinating Center: RTI International
PI: W. Kenneth Poole, PhD; NEC Study Statistician: Scott McDonald, BS; Coordinators: Betty Hastings and Carolyn M. Petrie, MS.

NICHD
Program Scientists: Rosemary D. Higgins, MD, Linda L. Wright, MD; Coordinator: Elizabeth McClure, MEd.
REFERENCES


2. NICHD Neonatal Research Network, Summary Tables of Generic Database, 2003


34. Lilford RJ, Thornton JG, Braunholtz D. Clinical trials and rare disease: a way out of the conundrum. BMJ. 1999;311:1621–1625


Laparotomy Versus Peritoneal Drainage for Necrotizing Enterocolitis or Isolated Intestinal Perforation in Extremely Low Birth Weight Infants: Outcomes Through 18 Months Adjusted Age

Martin L. Blakely, Jon E. Tyson, Kevin P. Lally, Scott McDonald, Barbara J. Stoll, David K. Stevenson, W. Kenneth Poole, Alan H. Jobe, Linda L. Wright, Rosemary D. Higgins and for the NICHD Neonatal Research Network

Pediatrics 2006;117;e680-e687; originally published online Mar 20, 2006; DOI: 10.1542/peds.2005-1273