Introduction to the Necrotizing Enterocolitis Surgery Trial (NEST)

A Multi-center Randomized Trial of Laparotomy vs. Drainage as the Initial Surgical Therapy for ELBW Infants with Necrotizing Enterocolitis (NEC) or Isolated Intestinal Perforation (IP): Outcomes at 18-22 months Adjusted Age

Gail E. Besner, M.D.
SIGNEC UK, 4th International Conference
September 26, 2016
Surgical Options

NEC WITH PERFORATION

LAPAROTOMY
MID-ABDOMINAL INCISION
FULL EXPLORATION
RESECT NECROTIC BOWEL
CREATE INTESTINAL STOMAS

PPD
1/4” INCISION RLQ
DRAIN PUS AND STOOL
IRRIGATE
DRAIN
Surgery for NEC in Human Infants: a Randomized US Trial

The NEW ENGLAND JOURNAL of MEDICINE
354:2225-2234, 2006

ORIGINAL ARTICLE

Laparotomy versus Peritoneal Drainage for Necrotizing Enterocolitis and Perforation

R. Lawrence Moss, M.D., Reed A. Dimmitt, M.D., M.S.P.H.,
Douglas C. Barnhart, M.D., Karl G. Sylvester, M.D., Rebecca L. Brown, M.D.,
David M. Powell, M.D., Saleem Islam, M.D., Jacob C. Langer, M.D.,
Thomas T. Sato, M.D., Mary L. Brandt, M.D., Hanmin Lee, M.D.,
Martin L. Blakely, M.D., Eric L. Lazar, M.D., Ronald B. Hirschl, M.D.,
Brian D. Kenney, M.D., M.P.H., David J. Hackam, M.D., Ph.D.,
Daniel Zelterman, Ph.D., and Bonnie L. Silverman, Ph.D.*

- A 15 site multi-center clinical trial
- First multi-center clinical trial in pediatric surgery in US
- Funded by NICHD
- Analyzed mortality, TPN at 90 d, LOS
Surgery for NEC in Human Infants: a Randomized European Trial

**Randomized Controlled Trials**


Peritoneal Drainage or Laparotomy for Neonatal Bowel Perforation?

* A Randomized Controlled Trial

Clare M. Rees, MB, ChB, MRCS,* Simon Eaton, PhD,* Edward M. Kiely, FRCSI, FRCS, FRCPCH(Hon),* Angie M. Wade, PhD, CStat,† Kieran McHugh, FRCR,‡ and Agostino Pierro, MD, FRCS(Engl), FRCS(Edin), FAAP(Hon)*

- Infants randomized from 18 NICUs in 8 countries (Italy, Greece, Canada, UK, Hong Kong, New Zealand, Switzerland, Austria)
- Funded by charitable grants from Switzerland
- Analyzed mortality, LOS, TPN, time to feeds, vent depend
US and European Trials

- Neither trial reached the recruitment target
  US: (130 patient goal) 62 lap vs. 55 PD (funding ended)
  Europe: (200 patient goal) 33 lap vs. 35 drain
  Data Monitoring and Ethics Committee reccomendation

- Neither trial showed a significant benefit from drain or laparotomy

- Meta-analysis of the 2 trials indicates no clear benefit from either treatment
Rationale for New RCT

- Previous studies showed similar mortality between laparotomy and PD
- No trial with NDI as outcome measure
- Observational study: trend towards ↑NDI after PD
- Drainage has increased in popularity in US and used more as definitive treatment
Brandon – DOB 1/22/10

- Second attempt at *in vitro* fertilization
- Delivered by stat C-section due to decreased fetal heart tones
- Apgars 1, 1, 4 at 1, 5 and 10 min
- Amniotic fluid embolus / arrest at delivery
- Extremely rare
- Amniotic fluid and fetal cells enter the maternal circulation
- Maternal mortality 80%, most with neurologic deficits
- Brandon’s mother resuscitated and recovered
- Brandon was born at 26 weeks gestation weighing 910 g
Brandon – DOB 1/22/10

- Intubated in DR
- TPN
- Indomethacin x 3 for PDA
- HFOV, inhaled NO, R chest tube x 2
- Multiple blood transfusions
- Grade I IVH
- Transferred to NCH for persistant PDA
- PDA ligated - 1/25/10
- Feeds (donor BM) started 1/29/10 and slowly advanced
Brandon – 5 weeks old

- Feeding intolerance with residuals, emesis, abdominal distention
- Dopamine drip started
- AXR: free air, no pneumatosis
- Surgery consult
- Peritoneal drain placed
Brandon – 5 weeks old

- Advanced NEC, clearly would not survive without surgery
- Surgery performed at bedside
- 50% of entire small bowel removed

- 50 cm of SB, ileocecal valve and colon viable
- Jejunostomy and mucous fistula created
- Initially quite ill but eventually slowly improved and survived
Brandon – 4 months old

- Returned to OR for jejunostomy closure
- Small bowel length 100 cm
- Stoma closed, G tube placed
- Brandon survived NEC
- Normal pressure hydrocephalus, cerebral atrophy, profound neurodevelopmental delays and disabilities

- **DRAIN = 80**
  - 44 (55%) died
  - 4 lost
  - 20 (63%) with NDI
  - 12 (37%) = no NDI

- **LAP = 76**
  - 34 (45%) died
  - 5 lost
  - 23 (62%) = no NDI
  - 14 (38%) with NDI

**Drain: 84% died or NDI**

**Lap: 68% died or NDI**

Unadjusted OR for DEATH or NDI at 18-22 months =

OR 0.39, 95% CI (0.18-0.86), favoring laparotomy
**Hypothesis** Among surgically treated ELBW infants with NEC or IP, laparotomy results in a higher rate of survival without neurodevelopmental impairment compared to initial PD.
19 Participating Clinical Sites

- UT Houston (58)
- Alabama (37)
- Duke (33)
- Emory (20)
- Indiana (20)
- Brown (20)
- Nationwide Children’s (17)
- CHOP (12)
- UT Southwestern (11)
- Stanford (11)
- UCLA (11)
- Cincinnati (9)
- U Rochester (9)
- Wayne State (8)
- Children’s Mercy (6)
- U Iowa (5)
- U Utah (3)
- Tufts (2)
- U New Mexico (2)
Inclusion / Exclusion Criteria

**Inclusion**
- BW ≤1,000 gm
- Decision to perform surgery for NEC or IP
- < 8 weeks of age
- At center able to do either procedure

**Exclusion**
- Major anomaly
- Congenital infection
- Prior NEC (Stage II or greater) or IP
- Follow up not possible
- Prior abdominal operation
# NEST (Necrotizing Enterocolitis Surgery Trial)
Initial Laparotomy versus Initial Drain  
A Neonatal Research Network (NRN) Study

## Inclusion Criteria:
- BW ≤ 1,000g
- < 8 weeks of age (at time of eligibility assessment)
- Decision to perform surgery for suspected NEC or IP

## Exclusion Criteria:
- Major anomaly
- Congenital infection
- Prior NEC (≥ Stage II) or IP
- Prior abdominal operation
- Follow-up not possible
- Full support not being provided
- Note: presumed NEC totalis is NOT an exclusion criteria

## Enrollment Process:
1. Screening of patients for potential enrollment will be done by Neonatal fellows/attendings and NRN staff. Potential patients will be reported to Surgical fellows/attendings and NRN Study Coordinator.
2. Surgical fellows/attendings will be notified of potential patients. Neonatal fellows/attendings and NRN staff will approach parents, explain study, and obtain “provisional consent.” Surgical fellows/attendings will obtain final consent for study participation. Note that phone consent is allowed.
3. Once final consent is obtained, infant will be randomized by the NRN Study Coordinator.

## Surgeon Responsibilities:
1. Consider approach of all families for randomization
2. Cooperate with Network coordinators
3. Record pre-operative diagnosis (NEC or SIP)
4. Record extent of disease data:
   - cm of resected intestine
   - cm of remaining small intestine
   - Location of resected intestine

## Note that:
1. Initial procedure (Lap vs. drain) determined by randomization
2. Subsequent care according to standard practice and discretion of surgeon
3. Subsequent Lap allowed if clinically needed
4. Recommend reevaluation in 24h to determine need for laparotomy
5. If patient not approached for randomization due to presumed NEC totalis, record this reason so that correlation of pre-op diagnosis with intra-op findings can occur

## Contact Numbers:

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<tbody>
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**IMPORTANT NOTE:**
If not already done, please contact the RN Study Coordinator immediately in order to enroll a patient in the NEST trial

**Julie Gutentag – primary coordinator**

If Julie is unavailable contact **Patty Luzander – backup coordinator**
Surgical Treatment

- Initial procedure determined by randomization
- Subsequent care according to standard practice
- Subsequent laparotomy allowed if thought to be needed (indications recorded)
- Recommend reevaluation 12-24 hours after PD to consider need for laparotomy
  - If improved – no laparotomy
  - Treatment after initial randomization left to discretion of surgeon
Data Collection

- Primary outcome = death / NDI at 18-22m
- Secondary outcomes
  - Growth, complications (e.g. intestinal stricture or fistula, wound dehiscence, procedure-related liver injury, PNAC, others)
- Follow up evaluation
  - Standardized evaluations at 18-22 months adjusted age (growth, hearing, vision, neurologic status, Bayley III scales), and rehospitalizations
Neurodevelopmental Assessment (18-22 months)

- Neurologic exam
- Bayley Scales of Infant Develop. III
- Social/Behavioral eval – BITSEA
- Neurodevelopmental impairment (NDI)
  - Moderate – severe cerebral palsy
  - Bayley III cognitive score <85
  - <20/200 bilateral vision
  - Permanent hearing loss
Sample Size Requirement

- 300 infants randomized and assessed at 18-22 months
- Predict 50% consent for randomization and 90% follow up
- First patient randomized January 2010
- Originally proposed 4 year enrollment
- Need 6.25 randomized infants / month
Enrollment After 4 Years

NEST Enrollment

- Projected
- Randomized
- Eligible

Based on all forms completed between 1/1/2010 and 04/16/2014
Graph produced on 04/16/2014
Barriers to Recruitment

- Physician refusal
- Parent refusal
- Timing of presentation and staff availability
- Acute presentation and overwhelming situation for parents
- Transfer with the expectation of “one procedure”
- Infant in extremis (coding, rapid escalation of therapy, etc)
965 eligible  293 randomized (30%)  263 in preference cohort (Stopped several years ago)
NEST Enrollment

Number of Infants

Study Month

Based on all forms completed between 1/1/2010 and 9/7/2016
Graph produced on 9/12/2016
Neurodevelopmental Follow-up

- **Preference cohort (stopped several years ago):**
  133 / expected 144 infants have completed extensive 2-yr neurodevelopmental follow up assessment (92%)

- **Randomized cohort:**
  139 / expected 145 have completed assessment (96%)
Neurodevelopmental Follow-up

- When completed, > 300 ELBW infants with operative NEC/IP will have had an extensive neurodevelopmental assessment at 2 years of age.

- Unlike neurologic follow up for patients with NEC, this study will provide detailed surgical treatment information for these patients.

- The results of this study are likely to significantly influence the surgical treatment of NEC patients in the future.
THANK YOU