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Surgical necrotizing enterocolitis

Jamie R. Robinson, MD[a,b], **Eric J. Rellinger, MD**[a], **L. Dupree Hatch, MD, MPH**[c], **Joern-Hendrik Weitkamp, MD**[c], **K. Elizabeth Speck, MD**[a], **Melissa Danko, MD**[a], and **Martin L. Blakely, MD, MS**[a,*]

[a]Department of Pediatric Surgery, Vanderbilt University Medical Center, Nashville, TN

[b]Department of Biomedical Informatics, Vanderbilt University Medical Center, Nashville, TN

[c]Division of Neonatology, Department of Pediatrics, Vanderbilt University Medical Center, Nashville, TN

Abstract

Although currently available data are variable, it appears that the incidence of surgical necrotizing enterocolitis (NEC) has not decreased significantly over the past decade. Pneumoperitoneum and clinical deterioration despite maximal medical therapy remain the most common indications for operative treatment. Robust studies linking outcomes with specific indications for operation are lacking. Promising biomarkers for severe NEC include fecal calprotectin and S100A12; serum fatty acid-binding protein; and urine biomarkers. Recent advances in ultrasonography make this imaging modality more useful in identifying surgical NEC and near-infrared spectroscopy (NIRS) is being actively studied. Another fairly recent finding is that regionalization of care for infants with NEC likely improves outcomes. The neurodevelopmental outcomes after surgical treatment are known to be poor. A randomized trial near completion will provide robust data regarding neurodevelopmental outcomes after laparotomy versus drainage as the initial operative treatment for severe NEC.

Keywords

Surgical necrotizing enterocolitis; Surgical NEC

Introduction

Necrotizing enterocolitis (NEC), especially when requiring surgical treatment, remains a potentially devastating condition. The mortality rate of extremely low birth-weight (ELBW) infants with surgical NEC approaches 50%,[1] neurodevelopmental impairment occurs in the majority of survivors,[2] and new therapies are limited. Specific surgical treatments have not changed since the 1970s and generally include either bedside peritoneal drain placement or standard laparotomy. If laparotomy is performed, the most common management is resection of grossly diseased intestine and creation of ostomies. There have been three fairly recent studies comparing important patient outcomes with laparotomy versus drainage.[1,3,4]

*Correspondence to: Department of Pediatric Surgery, Vanderbilt University Medical Center, 2200 Children's Way, Suite 7100, Nashville, TN 37232-2730. Martin.blakely@vanderbilt.edu (M.L. Blakely).

These studies indicate that within high quality randomized trials and in a prospective observational study, there is no significant difference in mortality between infants treated with laparotomy or peritoneal drain placement. In a meta-analysis of the two existing randomized trials, the odds ratio for death comparing peritoneal drainage versus laparotomy was 0.99 (95% confidence interval: 0.64–1.52).[5] Neither of the randomized trials measured neurodevelopmental outcomes beyond hospital discharge.

Our purpose is to provide an updated review of the literature regarding several important topics related to surgical NEC. We aim to draw attention to methods of earlier identification of infants that require surgical treatment, center and treatment factors influencing patient outcomes, and the need for greater focus on neurodevelopmental outcomes of survivors.

Incidence of NEC—Jamie R. Robinson, MD, K. Elizabeth Speck, MD

The true incidence of NEC is challenging to discern due to reported inconsistencies in the current literature; however, it appears the incidence has been stable since it was first reported in the 1960s. The diagnosis of spontaneous intestinal perforation (SIP) likely has contributed to the variability in NEC incidence within the literature, as it is misclassified as NEC in many sources.[6] Zani and Pierro[7] also describe the lack of robust epidemiologic data due to inconsistencies in diagnosis and data collection. In particular, diagnosis of NEC may be problematic due to the difficult to identify “mild” or “initial” cases, corresponding to stage I Bell’s classification.[7]

Few multicenter or population-based studies have reported the epidemiology of NEC. A large review of the Kids’ Inpatient Database for the year 2000 reported over 4400 hospitalizations associated with NEC, resulting in a rate of approximately one neonate with NEC per 1000 live births.[8] They also found 27% of infants with NEC required surgical intervention with an overall case-fatality rate of 15%. A review from the National Institute of Child Health and Human Development (NICHD) Neonatal Research Network data from 1998 to 2001 reported a 7% incidence of NEC among very low birth-weight (VLBW) infants (787 NEC cases out of 11,936 VLBW infants studied).[9]

The most consistent finding in the literature is that the incidence of NEC has stayed relatively stable over time in VLBW infants. Although there is variability in incidence of NEC between studies with rates 3–15% among VLBW infants with data collected over varying time points from 1997 to 2008, each study suggests a relative stability in the reported incidence over time.[10–14] In 1994, Stoll[15] stated the incidence of NEC to be 10%, which is commonly quoted in the literature.[5,16] Yee et al[6] noted the incidence of NEC in the Canadian Neonatal Network (CNN) has stayed relatively stable over time in VLBW infants with an incidence of 5.1% in their cohort of almost 17,000 preterm infants from 2003 to 2008 similar to their prior report in 1996–1997.[17] In 2008, Henry and Moss[18] reviewed the most recent studies available at the time and noted an incidence ranging from 3% to 7%. A more recent report from the NICHD Neonatal Research Network in 2010 reported an incidence of 11–15% in neonates <1500g or <32 weeks, which accounted for 485% of their cases.[11] A subsequent article in the New England Journal of Medicine in 2011[19] reported the incidence of NEC to be relatively unchanged at approximately 7% in infants weighing

500–1500 g since it is recognition in the 1960s based upon multiple large, neonatal network database studies between 2002 and 2006.[8,9,12,20]

Select studies suggest the incidence of NEC has *increased* in recent decades in both the United States and Canada due to improved survival of preterm and low birth-weight infants.[7,18,21] In contrast, a regional study in Australia[22] has reported a *decreased* incidence of NEC during the surfactant era (exogenous surfactant use began in 1991) and with widespread use of corticosteroids prior to delivery of preterm infants (approximately 1994). They performed a retrospective cohort study and noted a decrease in incidence of NEC from 12% in both 1986–1987 and 1992–1993 to 6% in 1998–1999.[22] Similarly, a more recent (2016) study[23] of approximately 60,000 VLBW neonates during a 7-year time period noted a decrease in the incidence of NEC after instituting the "100,00 Babies Campaign," a quality improvement program that incorporated education and restructuring of Neonatal Intensive Care Unit (NICU) care on a large scale within the Pediatrix Neonatal Network. In this review, the overall incidence of NEC decreased from 6.6% in 2007 to 3.9% in 2013 ($p < 0.0001$), with a decrease in both medical (4.4–2.8%, $p < 0.0001$) and surgical (2.2–1.2%, $p < 0.0001$) NEC.[23] This suggests that although the incidence of NEC decreased, the proportion of neonates with NEC requiring surgical intervention remained stable over time (approximately 30%).

In summary, the available data is variable with regards to the true incidence of NEC; however, most findings show stability of incidence over time, with only one recent report showing a decline over the past decade.[23] Among VLBW infants, 10% emerges as the best approximation of overall incidence with the proportion of those requiring surgical intervention ranging from 27% to 52%.[8,23,24] With improvements in therapies to allow preterm infants to survive at even earlier gestational ages, it is crucial to ensure accurate reporting of the diagnosis and gain improved insight into the true incidence of this very challenging disease.

Indications for operation—Eric J. Rellinger, MD

The primary goals of surgical intervention in NEC are to control enteric spillage and/or resect necrotic intestine while maximizing the length of viable intestine.[18] Evidence of pneumoperitoneum on plain radiography is the only absolute criteria for operative intervention.[18,25] Pneumoperitoneum is present in less than half of all infants with intestinal perforation or necrosis at the time of operative exploration, demonstrating that it is a relatively insensitive marker of infants with surgical NEC.[26,27] Clinical deterioration despite maximal medical therapy is considered a relative indication for peritoneal drainage or exploratory laparotomy.[25] Ideally, surgical intervention would occur in infants with demarcated, irreversible intestinal necrosis prior to intestinal perforation and/or progressive physiologic derangement. Despite considerable efforts over the past four decades to identify predictors of intestinal necrosis, imaging, clinical, and laboratory parameters have limited reliability in identifying children who would benefit from a laparotomy or peritoneal drain placement.

Infants with NEC routinely undergo serial radiographic surveillance and physical examination as part of evaluating the need for operative intervention. Physical exam findings of a fixed abdominal mass or abdominal wall erythema are the most specific signs of intestinal necrosis but are infrequent findings suggestive of late stage disease.[26] Kosloske retrospectively evaluated a cohort of 147 infants with NEC to identify preoperative indicators of intestinal gangrene or perforation at operative exploration and autopsy.[26,28] Within this cohort, pneumoperitoneum, portal venous gas, and positive paracentesis (defined as the presence of brown fluid or positive bacteria on gram stain) were identified as the "best indicators" for operative intervention featuring a positive predictive value approaching 100% and a prevalence 410%.[26] Indications for performing a paracentesis are controversial, but Kosloske recommended paracentesis for patients with extensive pneumatosis intestinal is or who fail medical management.[26] The poor prognostic significance of portal venous air has been validated in several retrospective reviews with mortality rates approaching 71%. However, Sharma et al., who report that nearly half of infants with portal venous gas survive without an operation, have questioned the significance of portal venous gas as an indication for operative intervention.[29–31]

Considerable controversy exists in the optimal management of infants with severe physiologic derangements in the absence of pneumoperitoneum. Progressive clinical deterioration despite maximum medical management remains a relative indication for operation, but early predictors of medical failure are lacking.[32] Initial cohort studies have identified individual parameters, such as severe thrombocytopenia, as indicators of underlying intestinal necrosis, but broad applications to the surgical decision-making process are limited at best.[32,33] Tepas et al.[34] have proposed seven criteria of metabolic derangement (MD7 parameters; positive blood culture, acidosis, bandemia, thrombocytopenia, hyponatremia, hypotension, or neutropenia) that may be predictive of the need for operative intervention. Variables are scored in a binary manner to facilitate ease of clinical application; the presence of three or more variables was associated with advanced disease and recommendation for surgical intervention. A single, uncontrolled trial has been completed comparing the outcomes of an institution utilizing MD7 parameters in their operative decision-making with a comparable institution that elected to operate based primarily on radiologic evidence of free air.[34] Overall, the institution utilizing MD7 parameters demonstrated significantly improved outcomes with 76% (versus 34%) of infants with Bell's stage II or III NEC tolerating full enteric feeds at discharge, suggesting that the presence of three or more metabolic derangements may predict timely operative intervention.[35] While promising, predictive models have not been shown to improve survivorship in a prospective or randomized fashion, limiting the generalizability of these scoring systems in surgical decision-making.

Overall, radiographic evidence of pneumoperitoneum remains the only absolute criteria for peritoneal drain or laparotomy in NEC. Physiologic deterioration despite maximal medical therapy remains a relative indication for operation. Clinical scoring systems featuring imaging, clinical, and laboratory markers offer promising predictive models that may identify infants and neonates with irreversible intestinal necrosis who may benefit from early operative intervention. Prospective evaluation of such scoring systems in infants with NEC without radiologic evidence of pneumoperitoneum is a logical and meaningful next step in

determining the utility of these predictive models in the surgical management of NEC. Future trials should focus on survival, neurodevelopmental, and intestinal function outcomes to determine the risks and benefits of new, proposed treatment algorithms.

Biomarkers predicting surgical NEC—Joern-Hendrik Weitkamp, MD

Early identification of infants at highest risk for progression of disease toward surgical NEC has been a long-standing research priority.[36] Accurate prediction of surgical NEC may improve outcomes by leading to earlier transfer to surgical centers and potentially salvage of viable bowel. Furthermore, earlier transfer may help avoid unnecessary invasive procedures associated with increased risk of death or neurodevelopmental impairment (NDI).[1,37] Although extensively studied and previously discussed, clinical parameters alone have been inadequate in predicting progression to surgical NEC.[38,39] Therefore, intensive research efforts have been invested in biomarker discovery.

An international survey among pediatric surgeons reported the most commonly used biochemical markers to be platelet count (99%), C-reactive protein (CRP) concentration (90%), white blood cell count (83%), and lactate levels (43%).[40] According to this survey, 10% of surgeons rely on fecal calprotectin and approximately 10% on interleukins (IL) 6 or 8. Fatty acid-binding protein and serum amyloid A (SAA) did not appear to be part of routine clinical practice at the time of survey. Biomarkers used to differentiate surgical from medical NEC along with relevant studies are listed in the below (Table).

Platelet counts are readily available and severe thrombocytopenia ($<100 \times 10^9$/L) correlates well with disease extension, mortality, and indication for laparotomy.[33,41,42] Reisinger et al.[43] reported accurate detection of surgical NEC by combining urinary serum SAA with platelet count (sensitivity 94%, specificity 83%, and AUC 0.95).

Fecal calprotectin (S100A8/S100A9 heterodimer), a marker of intestinal inflammation, has been used for diagnosis and differentiation of limited NEC (Bell's stage II) from NEC with systemic illness (Bell's stage III) disease with 76% sensitivity and 92% specificity.[44] Fecal levels of a related protein, S100A12, were significantly higher in infants with suspected NEC who subsequently developed bowel perforation than in those who did not [median = 2400 μg/kg (range: 5–93,000 μg/ kg; $n = 13$) versus 122 μg/kg (range: 5–24,500 μg/kg; $n = 17$); $p < 0.05$].[45] Interestingly, in the same study, S100A12 levels were increased 1–2 weeks prior to the clinical onset of NEC in 18 infants compared to controls, suggesting prolonged intestinal inflammation is a risk factor for NEC rather than an acute event. Utility of fecal calprotectin and S100A12 as predictive markers for severe NEC is limited because of high inter-individual and intra-individual variability as well as dependence on gestational and postnatal age.[45–47] In addition, using fecal samples has significant weaknesses, as bowel movements are infrequent and unpredictable in ELBW and VLBW infants.

Acute phase proteins such as SAA and CRP as well as cytokines/chemokines have been studied for their value in diagnosis, management, and prognosis of NEC.[48] While normal serial CRP levels may indicate resolution of inflammation and suggest safe discontinuation of antibiotics and resumption of enteral feedings, persistently elevated CRP levels may be a

sign for disease progression.[49] Some studies suggest elevated CRP levels may indicate advanced stage NEC[50] while others found no relation to disease severity.[45] Gaudin et al.[51] reported that both mean maximum concentration of CRP and mean duration of CRP elevation were significantly increased in infants who developed intestinal strictures following NEC. Most notably however was that the negative predictive value of negative CRP levels (<10 mg/dL) for stricture development was 100%. IL-8 levels have also been shown to be significantly elevated in patients developing surgical NEC (median = 2625 pg/mL; range: 27–7500) compared to medically managed NEC (median = 156 pg/mL; range: 5–7500; $p < 0.001$).[52] IL-8 levels have also been able to discriminate *NEC totalis* from focal and multifocal disease and predict 60-day mortality.[53]

One promising biomarker of intestinal injury and progression to more severe NEC is intestinal fatty acid-binding protein (I-FABP). I-FABP is a 15 kD cytosolic protein located mainly in mature enterocytes of small intestinal villi.[54] It is released into the blood stream after cell disruption and subsequently excreted into the urine. Elevated I-FABP levels have been found in plasma, serum, and urine in adults with sepsis, intestinal trauma, and mesenteric/intestinal ischemia.[55–57] At onset of symptoms, I-FABP concentrations have been shown to be significantly higher in infants who later developed surgical NEC compared to those with limited disease.[58]

Since NEC occurs mainly in ELBW and VLBW infants, urine collection may be less invasive and more feasible than blood sampling, especially if done serially to monitor disease progression. In addition, urine may represent a more reliable sample since it is stored in the bladder over a period of time. A pilot study in 2010 found significantly higher urinary I-FABP to creatinine ratios in infants with extensive disease requiring surgery [7.4pg/mmoL (2.1–35.0 pg/mmoL)] compared to those with focal disease [1.1 pg/mmoL (0.3–1.7 pg/mmoL), $p = 0.002$].[59] Later, Ng et al.[60] used a combination of bio-markers (liver-FABP, I-FABP, and trefoil factor 3) to compile a score (LIT score) capable of identifying surgical NEC with 83% sensitivity and 100% specificity with LIT score > 4.5. Furthermore, a LIT score of 6 identified non-survivors of NEC with 78% sensitivity and 91% specificity. In a recent study by Schurink et al.,[61] serial plasma and urinary I-FABP measurements accurately predicted development of complicated disease, defined as surgical intervention and/or death. Cut-off values were 19 ng/mL for plasma and 232 ng/mL for urinary I-FABP levels with positive likelihood ratios of 10 (1.6–70) and 11 (1.6–81), respectively. Complicating the ability to serially measure I-FABP is its time course, with I-FABP levels peaking early in disease course but then gradually declining.[61] Rather than actual clinical improvement, this may represent affected epithelial cell loss as part of necrosis or lack of mesenteric perfusion, with I-FABP no longer being released into the blood stream.

With recent advances in biomedical technologies and medical engineering, machine learning algorithms can be applied to complex datasets from “omics” approaches of biomarker discovery and generate prediction models for diagnosis, disease progression, and outcome.[62,63] One such study combined multiple clinical parameters with a group of urine peptide biomarkers in a combined algorithm resulting in the correct prediction of NEC outcomes in all cases tested.[64] The same group identified a panel of seven proteins (α_2-macroglobin-like protein 1, cluster differentiation protein 14, cystatin 3, fibrinogen α chain, pigment

epithelium-derived factor, and retinol binding protein 4 and vasolin) in urine capable of identifying NEC patients progressing toward surgical disease.[65]

In a retrospective analysis of 97 infants with NEC, commercial monitors with algorithms based on abnormal heart rate characteristics (HRC) were analyzed as predictive tools for NEC. The HRC index increased significantly 16 h before the clinical diagnosis of surgical NEC versus 6 h before medical NEC. At the time of clinical diagnosis, the HRC index was higher in patients with surgical versus medical NEC (3.3 ± 2.2 versus 1.9 ± 1.7, $p < 0.001$).[66]

One important limitation of most biomarker studies is their practical clinical application. Many studies lack explanation of how clinical management could be modified based on predicted severity of NEC. Treatment of severe NEC (withholding enteral feedings, enteric decompression, and broad-spectrum antibiotics) is not much different from standard of care for suspected or “mild” NEC. Other supportive measures such as volume resuscitation, catecholamines, or transfusion of blood products would be based on real-time clinical parameters rather than prediction scores. In addition, most surgeons are unlikely to operate sooner based on scores predicting severe disease given that optimal timing and type of surgery (drain versus laparotomy) remain controversial.[7,40,67] On the other hand, if the prediction models declare low risk for surgical NEC, the clinical question remains if therapy should be modified, such as withholding serial abdominal x-rays obtained to rule-out pneumoperitoneum, resumption of enteral feedings, cessation of antibiotics, or narrowing down the antimicrobial spectrum. Any proposed change in management away from the current standard of care based on predicted low risk would have to be tested for safety in clinical trials prior to universal recommendation. In this context, proven management guidelines and a more uniform practice style among neonatologists and surgeons could greatly improve the utility of new biomarkers for prediction of surgical NEC.[68]

Update on novel imaging methods—Melissa Danko, MD, Eric Rellinger, MD

As numerous studies have revealed, the pathogenesis of NEC is likely multifactorial making it challenging to develop predictive and preventive approaches to the disease. Radio-graphic imaging has always been the hallmark for detecting NEC with abdominal films and more recently ultrasound (US) guiding management and interventions. Currently the early progression of NEC usually remains undetected, and the disease is not diagnosed until obvious clinical and radio-graphic signs are manifested.

Sonographic evaluation of infants with NEC may represent an emerging adjunct in evaluating the need for an operation in children with Bell’s stage II (limited disease) and stage III (associated with systemic illness) NEC.[69] Silva et al.[70] in 2008 reported 100% correlation between abdominal US findings of intra-abdominal free air or focal fluid collection with the need for surgical intervention or death. US is more sensitive than plain radiography in identifying fluid collections, while also offering insight into the character of the intra-abdominal fluid.[71] Dynamic features of US also permit real-time visualization of bowel wall thickness, peristalsis, and perfusion when performed with Doppler. In particular, bowel wall thinning and avascularity may be signs of impending necrosis, but the

significance of such findings remains in question.[70] Inherent limitations of US include operator-dependent variability, potential lack of 24 h availability, and questions regarding whether or not concerning sonographic findings successfully identify patients who would benefit from an operation.

One promising modality that has been around for a few decades is near-infrared spectroscopy (NIRS). This technique is a noninvasive method of measuring local tissue hemoglobin oxygen saturation by measuring the difference between oxyhemoglobin and deoxyhemoglobin. Oxygen uptake in a specific tissue bed can be measured in real time. It was first applied to pediatrics to monitor the change in cerebral oxygenation of preterm infants over time.[72] Fortune et al.[73] applied NIRS to the abdomen of neonates to examine splanchnic perfusion. Ten neonates with acute surgical abdomens were compared to 29 infants admitted for medical reasons. A significantly lower cerebro-splanchnic oxygenation ratio (CSOR) was demonstrated in neonates with an acute abdomen. They also discovered that when the CSOR < 0.75, intestinal ischemia was identified with a positive predictive value of 0.75. When the ratio was above 0.75, intestinal ischemia was excluded with a negative predictive value of 0.96. This suggested that abdominal NIRS could detect splanchnic ischemia in neonates, reflecting alterations in bowel oxygenation and perfusion. This concept was applied to a large animal model of premature piglets.[74] Abdominal NIRS was able to detect changes in the tissue oxygenation of the small intestine, with lower values measured in the piglets that developed NEC compared to a healthy control group. This difference was evident soon after delivery, suggesting that abdominal NIRS could possibly identify piglets at risk for the development of NEC.[74]

Since intestinal ischemia is hypothesized to be the critical inciting event in the pathogenesis of NEC,[75] this principle was applied to neonates. In 2011, Cortez et al.[76] reported the feasibility and safety of NIRS monitoring in preterm neonates. They measured daily mean regional splanchnic oxygen saturation (rsSO2) values in 19 premature infants during the first 14 days of life. In two infants that developed NEC, low rsSO2 values were observed with loss of variability and high signal dropout. These observations occurred prior to the clinical diagnosis of NEC, suggesting a possible role of NIRS in the early detection of NEC.[76] Patel et al.[77] performed a prospective cohort study that was able to establish normal values for local tissue oxygenation (StO_2) for preterm infants using abdominal NIRS. They also demonstrated that during the first week of life, the mean StO_2 of normal infants was significantly higher than the mean StO_2 of infants who developed NEC. In addition to having a decreased mean StO_2 value, the infants who developed NEC had more variation in NIRS readings during feeds and postprandially.[77]

There are limitations of the NIRS technology. The different algorithms and software for each manufacturer’s NIRS device makes comparisons across devices almost impossible. Intestinal peristalsis and the large surface area of the intestine can make data collection and interpretation difficult. Despite these challenges, NIRS still holds promise as a noninvasive modality to possibly assist in the early detection and treatment for NEC. Combining NIRS with other modalities is a currently area of interest. Zamora et al.[78] recently hypothesized that continuous abdominal NIRS monitoring combined with plasma I-FABP levels could identify NEC prior to the onset of clinical symptoms in premature piglets. In their study, I-

FABP was confirmed to be a sensitive and specific indicator of NEC onset and severity. By combining these modalities in future studies, they would ideally like to utilize abdominal NIRS as a screening tool and a plasma biomarker, such as I-FABP, as a confirmatory test for NEC.[78]

Regionalization and Center Effect on Outcomes—L. Dupree Hatch, MD, MPH

Since the 1970s, the March of Dimes and the American Academy of Pediatrics have advocated for the regionalization of neonatal care, in which high-risk pregnancies and neonates are triaged to tertiary, regional centers.[79–82] As part of the regionalization movement, NICUs have been classified based on the complexity of care they provide. A key component of these levels of care is the breadth of the surgical care that is provided.[79,82] Given the often complex needs of the infant with surgical NEC, it has been hypothesized that regionalization of care leads to improved morbidity and mortality in infants with both medical and surgical NEC.

It has been known for some time that the level and volume of neonatal intensive care at the hospital of birth is strongly associated with all-cause neonatal mortality, with increasing level and volume associated with lower mortality.[83–85] Recent studies have shown this association holds true for infants with medical and surgical NEC.[86,87] Kastenberg et al.[87] performed a retrospective cohort study using data collected from the California Perinatal Quality Care Collaborative (CPQCC), which captures data from > 90% of the perinatal centers in California, to assess the impact of level and volume of neonatal intensive care at the hospital of birth on risk-adjusted mortality in infants with NEC. The study cohort included 30,566 VLBW infants, of whom 1879 (6.1%) were diagnosed with NEC and approximately 700 (~2.3%) with surgical NEC. NICUs were stratified by patient volume and level of care: Level II (no surgical services), Level IIIA (minor surgical capability, not including laparotomy or peritoneal drainage), Level IIIB-low volume [full pediatric surgery services excluding extracorporeal membrane oxygenation (ECMO) and cardiopulmonary bypass (CPB)], Level IIIB-high volume/ IIIC (full surgical services including ECMO and CPB). The authors found that risk-adjusted mortality was significantly higher in lower level (IIIA) NICUs [odds ratio (OR) = 1.51, 95% confidence interval [CI]: 1.05–2.15] and lower volume (IIIB-low volume) NICUs (OR = 1.42, 95% CI: 1.08–1.87) compared to higher volume, higher level units. Although not statistically significant due to small sample size, infants with surgical NEC also had a 20% increase in the odds of mortality if they were born into lower level or lower volume units. Jensen and Lorch[86] also tested the association of NICU level and volume with the composite outcome of NEC or all-cause mortality in a large population-based cohort study. They linked birth and death certificate data with hospital records for a cohort of 72,431 VLBW infants born in three states (California, Missouri, and Pennsylvania) over a 10-year period. In multivariable models, both patient volume and level of care were associated with the composite outcome of death or NEC. When both patient volume and level of care were added to the model together, lower volume of deliveries at the hospital of birth emerged as the stronger risk factor for death or NEC with the highest risk

adjusted odds at hospitals with 10 or less VLBW infants per year (OR = 1.33, 95% CI: 1.12–1.57).[86]

While an association between NICU level/volume and NEC/ mortality clearly exists, the mechanism for this increased mortality is unclear. One proposed mechanism is the impact of transport to a surgical center and potential delay in operative intervention in an infant with necrotic bowel. Kelly-Quon et al.[88] evaluated this in a cohort of 1272 VLBW infants with surgical NEC who underwent operative intervention in one of 70 California NICUs. Of these infants, 406 (32%) were transferred to another center for surgical care with the remainder receiving surgical care at their primary NICU. Unadjusted mortality (37% in the transport group versus 40% in the no-transport group) and adjusted odds of mortality were similar between the groups, taking into account multiple confounders including NICU level of care. An Australian study evaluating transfer and NEC mortality also suggested transfer itself does not increase mortality risk.[89]

For policy makers and practicing clinicians, many questions arise. Should all infants at highest risk of surgical NEC (i.e., those with birth weights <1500 g) be cared for in centers with high-volume pediatric surgery programs? If not, when should infants with suspected or proven NEC be transferred to surgical centers? Should the use of biomarkers for surgical NEC (discussed elsewhere in this review) be used to inform decisions about early transfer? For infants at surgical centers, should surgical teams be involved in the care of all infants with suspected NEC or only those with indications for operative intervention? Multicenter collaborative research is needed to answer these questions about how to structure our healthcare delivery systems for infants with NEC.

In summary, like many infants in the NICU, those with surgical NEC require a well-coordinated multidisciplinary approach to ensure optimal outcomes. Though the exact mechanism is unknown, it is likely that regionalized centers with higher surgical volumes have a more effective and rehearsed multidisciplinary team. While no “magic bullet” exists to prevent NEC and our current treatments leave much to be desired, our focus must be on optimizing the delivery of evidence-based interventions and furthering our understanding of the components of regionalized care leading to improved outcomes. These components can thus be the substrates for quality improvement initiatives. Given the number of VLBW infants born in the US annually[90] and the high mortality of surgical NEC,[24] small changes in the delivery of regionalized neonatal care could significantly affect overall outcomes.

Neurodevelopmental Outcomes -Jamie R. Robinson, MD, Martin L. Blakely, MD, MS

With mortality rates approaching 50% in extremely low birth-weight (ELBW) infants who require surgical treatment of NEC,[37,91–93] it is understandable that longer-term neurodevelopmental outcomes have not been the primary area of focus for research thus far. However, survival without impairment is the primary goal of both physicians and parents, leading to more prevalent investigation of long-term outcomes.[94]

Among ELBW infants, the diagnosis of NEC, treated medically or surgically, has been shown to be an independent risk factor for adverse neurodevelopmental outcomes.[95,96] In 2005, Hintz et al.[2] reported one of the most robust descriptions of neurodevelopmental and growth outcomes of ELBW infants after NEC, comparing 124 infants with surgical NEC, including drain placement and/or laparotomy, to those with NEC treated medically or infants without NEC. They found that among ELBW infants, those with surgical NEC had a significantly higher incidence of neurodevelopmental impairment (NDI) as a whole, including cerebral palsy, deafness, and blindness in addition to significant growth reduction. NEC treated medically was not associated with NDI or growth reduction. A systematic review by Schulzke et al.[97] including 4239 VLBW infants born between 1977 and 2002 also found that survivors of NEC are at risk for long-term NDI, particularly if they require surgical treatment for NEC (OR = 1.99; 95% CI: 1.26–3.14). Rees et al.[98] found similar results in a meta-analysis of 821 VLBW infants with NEC. Overall, the surgical NEC group was 2.34 (95% CI: 1.51–3.60) times more likely to have NDI than the medical NEC group.

Although the studies separate NEC treated surgically from medically, a major limitation is the lack of correlation of outcomes with the type of surgical management, either peritoneal drainage or laparotomy. In one of the few studies linking specific surgical treatment details with neurodevelopmental assessment, Blakely et al.[1] performed a multicenter prospective cohort study of 156 ELBW infants with NEC or intestinal perforation. At 18–22 months corrected age, 68% (48/70) of infants in the initial laparotomy group either died or developed NDI compared to 84% (64/76) of infants in the peritoneal drainage group. This nonrandomized observational study was confounded by large differences in the baseline risk characteristics among infants in the two treatment groups. Nevertheless, with exclusion of patients considered too ill for laparotomy and controlling for patient differences by multivariate analysis, the adjusted OR for death or NDI with initial laparotomy compared to initial drainage was 0.56 (95% CI: 0.19–1.69). While not statistically significant, it raised the question of differential neurodevelopmental outcomes based on type of initial surgical management, potentially with peritoneal drain placement being associated with worse neurodevelopmental outcomes. These findings in part led to the development and implementation of the Necrotizing Enterocolitis Surgery Trial (NEST)[99] for ELBW infants. The primary outcome of this multicenter, randomized trial is death or NDI at 18–22 months corrected age, and currently the trial has enrolled over 90% of its expected sample size.

Each of the studies referenced above regarding NDI in infants with NEC have used the Bayley Scales of Infant Development, seconds edition[100] or third edition[101] (BSID-II or BSID-III). Most have defined NDI as 1 or more of the following: Mental Developmental Index (MDI) < 70 or Psychomotor Developmental Index (PDI) < 70 within the BSID-II, cerebral palsy (CP), deafness, or blindness. Some suggest the BSID-II and BSID-III may not correlate in preterm children.[102–104] Novel methods of follow up that neonatal surgery trials could use include neuroimaging with cranial US or magnetic resonance imaging (MRI). Focal white matter damage seen on cranial US are associated with delayed mental and psychomotor development.[105] MRI at term has been shown to be more sensitive in detection of cranial abnormalities and correlate with neurodevelopmental outcomes[106,107]; however, this remains a costly study that fails to identify every patient at risk for NDI.[106,108] Parent-completed assessment tools, rather than time intensive, expensive provider-assessment with

BSID-III, have been shown to be potential alternatives for NDI screening.[109,110] However, further studies are needed to determine the best way to incorporate these screening tools into practice.

Several mechanisms have been postulated to lead to a decrease in NDI in ELBW infants with NEC; however, there is lack of significant data to determine the exact cause of increased risk for poorer outcomes in patients with NEC requiring surgery.[2] Surgery itself is associated with increased risk of death and NDI in VLBW[91]; however, it is unknown whether the adverse effect associated with surgery results from the anesthetic drug, noxious effects of other perioperative drugs, stress, and/or unidentified physiological alterations. It is speculated to be multifactorial in infants with NEC[2] and the question remains whether initial management with peritoneal drain placement versus laparotomy can influence these factors.

NEC results in a profound inflammatory response that may be associated with the release of chemical mediators such as tumor necrosis factor-α, interleukin-6, platelet activating factor, and nitric oxide, claimed to contribute to a mechanism that leads to hemodynamic instability, tissue necrosis, and white matter injury.[111–113] Due to these inflammatory cytokines, sepsis, and nutritional deprivation, preterm and ELBW neonates with NEC may be at high risk for long-term NDI. Survivors of surgically managed NEC may especially be at a higher risk after exposure to higher levels of pro-inflammatory cytokines for a longer duration due to more advanced disease. Pierro et al.[114] demonstrated that in neonates with <1000 g body weight and perforated NEC, peritoneal drainage was not a definitively effective procedure, as 74% of the infants required a rescue laparotomy. This would suggest infants treated with peritoneal drainage versus laparotomy could sustain an even longer period of exposure to high levels of pro-inflammatory cytokines.

Further research is needed to determine if earlier intervention using clinical parameters or biomarkers along with different treatment approaches such as peritoneal drainage, laparoscopy, or laparotomy have an affect on these longer-term neurodevelopmental outcomes. There is a profound need for multicenter and *multidisciplinary* research focusing on early identification of infants that will likely require surgical treatment, more robust measurements of the impact of center type on patient outcomes, and increasing the focus on neurodevelopmental outcomes of survivors.

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Table

Biomarkers used to differentiate surgical from medical NEC.

Biomarker	Ref.
Platelet count	33,41–43
C-reactive protein	49–50
Serum amyloid A (SAA)	43,50
Fecal calprotectin	55,46–47
S100A12	45
IL-8	52
Intestinal fatty acid-binding protein (I-FABP)	58–59,61
Liver-fatty acid-binding protein (L-FABP), I-FABP, and trefoil factor 3 = LIT score	60
Urine peptides	64–65
Heart rate characteristics (HRC) index	66