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Expert consensus building using e-Delphi for necrotizing enterocolitis risk assessment

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Abstract

Objective—To confirm content validity of GutCheck^{NEC}, a risk index for necrotizing enterocolitis (NEC) and to determine the level of agreement among experts about NEC risk factors in premature infants.

Design—Electronic Delphi method (e-Delphi).

Setting—Online electronic surveys and email communication supported by an interactive study website.

Participants—Nurses and physicians (N=35) from four countries and across the United States who rated themselves as at least moderately expert about NEC risk.

Methods—e-Delphi involved three rounds of surveys and qualitative thematic analysis of experts' comments. Surveys continued until criteria for consensus and/or stability were met.

Results—Of 64 initial items, 43 were retained representing 33 risk factors (final GutCheck^{NEC} CVI=.77). Two broad themes about NEC risk emerged from 242 comments: the impact of individual physiologic vulnerability and variation in neonatal intensive care unit (NICU) clinicians' practices. Controversy arose over the impact of treatments on NEC, including probiotics, packed red blood cell (PRBC) transfusions, and patent ductus arteriosus (PDA) management using indomethacin.

Conclusion—GutCheck^{NEC} achieved borderline content validity for a new scale. The e-Delphi process yielded a broad perspective on areas in which experts both share and lack consensus on NEC risk. Future testing is underway to reduce the number of risk items to the most parsimonious set for a clinically useful risk tool and test reliability.

Keywords

Necrotizing enterocolitis (NEC); neonate; e-Delphi; GutCheck^{NEC}; risk assessment; nursing; risk index; neonatal intensive care unit (NICU); NICU practice variations; outcomes

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Call-Out 1

E-Delphi was used to determine if experts agreed about necrotizing enterocolitis risk and to support the content validity of a risk index, GutCheck^{NEC}.

Call-Out 2

Experts described infants at highest risk as < 1000 grams, < 28 weeks, and formula fed. Breast milk and standardized feeding protocols reduce risk.

Call-Out 3

Practices that affect modifiable necrotizing enterocolitis risk vary widely among neonatal intensive care units, including feeding, patent ductus arteriosus, and potentially transfusion management.

Necrotizing enterocolitis (NEC) is a devastating acquired disease that strikes predominately premature infants and can lead to widespread bowel necrosis, sepsis, and death if not treated in time (Henry & Moss, 2008). Annual costs related to NEC represent nearly one-fifth of all U.S. expenditures for neonatal intensive care (Bisquera, Cooper, & Berseth, 2002). Of those infants who develop NEC, an estimated 15-30% will not survive (Henry & Moss, 2008; Luig, Lui, New South Wales [NSW], Australian Capital Territory [ACT] NICUs, 2005). Although it is still not clear, the pathogenesis of NEC is thought to be the result of an exaggerated inflammatory response in an immature gut compounded by feeding of formula and reperfusion injury from mesenteric ischemia (Henry & Moss; Neu, Mshvildadze & Mai, 2008). The timing of NEC onset is inversely related to gestational age, such that more mature infants develop it sooner and the least mature develop it later in the neonatal period (Luig et al.). The majority of cases develop in the first two to three weeks of life. Early diagnosis is critical to improving survival; and, in one study, those who died were diagnosed, on average, 3 postnatal days later than those who survived (Clark et al., 2012). Thus, if infants are diagnosed later in the disease process, the risk of death may be greater. The etiology of NEC is multi-factorial (Figure 1) and it remains unclear how multiple risk factors may relate to likelihood that a particular infant will develop NEC.

NEC is serious and life-threatening, in part because symptoms develop with little warning (Neu, Mshvildadze, & Mai, 2008). Symptoms, including abdominal distention, bloody stools, and systemic instability (e.g., apnea, bradycardia, hypotension and temperature instability) may have a slow or sudden onset making timely diagnosis difficult (Christensen et al., 2010; Gregory, Deforge, Natale, Phillips, & Van Marter, 2011). Infants require the care of a pediatric surgeon soon after they develop symptoms, and specialized care may require transporting them to a tertiary neonatal intensive care unit (NICU) many miles away (Necrotizing Enterocolitis Guideline Team, 2010).

Although recent research has increased our understanding of NEC's co-morbidities and predisposing risk factors, this knowledge has not been adequately translated for clinical use. NEC risk factors occur during the prenatal period, intra-partum period, and during the postnatal course. Risk factors for NEC have been studied predominantly in retrospective cohort studies, but the quality of the evidence varies and many studies are limited to a single center. When multiple centers have been involved, they are often affiliated with a common parent organization (e.g., Pediatrix medical group, the National Institute for Child Health and Development, or Vermont Oxford Network). In addition to prematurity and formula feeding, potential risk factors include an un-standardized approach to feeding, histamine-blocker therapy, sepsis, greater number of infections, prolonged (> 5 days) initial course of

empiric antibiotic therapy, patent ductus arteriosus (PDA), indomethacin treatment, mechanical ventilation, packed red blood cell transfusions, HIV-positive mother, maternal antenatal cocaine use, perinatal asphyxia with fetal distress, African-American or Hispanic race, cyanotic congenital heart disease, and intrauterine growth restriction (see a recent review of NEC risk by Gephart, McGrath, Effken & Halpern, 2012). Bedside clinicians, including nurses and neonatal nurse practitioners (NNPs), are likely to observe specific NEC symptoms first yet may fail to consider the symptom(s) within the context of an individual infant's overall NEC risk and thus fail to put the appropriate care planning in place. If early recognition of NEC is to improve, clinicians need sensitive and specific tools to identify infants at highest risk. For that reason, we developed GutCheck^{NEC}, a novel composite risk index for NEC.

Conceptual framework

To develop a comprehensive risk index for NEC, the risk factors identified in published research were compiled into a single tool by using theory synthesis. Theory synthesis is a strategy that brings together what is known about a phenomenon to provide a coherent view of factors leading to an outcome (Walker & Avant, 2011). It has been used to represent antecedents to disease, outcomes of an event, and to organize related scientific findings into a coherent form (Walker & Avant, 2011). In this case, the outcome of concern was NEC, and potential antecedents to NEC were compiled into a single risk index, GutCheck^{NEC} (See Figure 2).

The purpose of the present study was to confirm the content validity of GutCheck^{NEC} and concurrently determine the extent to which there is expert consensus on the NEC risk factors identified in extant literature. Achieving consensus among experts and determining content validity is the first of several phases needed to develop, refine and test prediction for GutCheck^{NEC}. Research questions included

1. Does GutCheck^{NEC} demonstrate content validity as judged by a sample of experts?
2. What modifications to GutCheck^{NEC} are recommended by an expert panel?

Methods

Design

The content validity of GutCheck^{NEC} was assessed using an e-Delphi method and nationally recognized experts. Validity has been defined as the extent to which an instrument measures what it purports to measure (Carmines & Zeller, 1979). Content validity is a measure of the degree to which the items represent the full domain of content that they are intended to characterize (Carmines & Zeller, 1979; Lynn, 1986). Therefore, validation procedures should include the intended context and purpose for which the measure is going to be used. Streiner and Norman (2008) describe two elements of validity testing: determining the nature of what is being measured, and determining its relationship to a cause. In GutCheck^{NEC}, items reflect the degree of risk for developing NEC and the composite risk when multiple risk factors are present. By using the e-Delphi we hoped to ensure that GutCheck^{NEC} reflects the current practice and knowledge basis of experts about NEC risk.

The Delphi is a consensus-building method characterized by careful description of sampling procedures, the use of experts, anonymity of experts, and the use of multiple rounds to expose uncertainty or achieve consensus (Keeney, Hasson, & McKenna, 2001; Snyder-Halpern, 2001; Snyder-Halpern, Thompson, & Schaffer, 2000). An e-Delphi has the additional benefits of economy and quick feedback of responses to panelists over multiple rounds. Neonatal nurse researchers have found the Delphi useful to evaluate best practices

for caring for vulnerable neonates (Mainous, 2008), develop a neonatal end-of-life palliative care protocol (Catlin, 2003), and adapt education for nurses using new therapies (Cornick, 2006). The extent to which experts agreed on the NEC risk elements was evaluated. Although it was anticipated that few new risk factors would be added, soliciting expert input helped ensure that the entire domain of risk factors were included in GutCheck^{NEC}.

Human Subjects Protection

The institutional review board at The University of Arizona approved the study and provided human subjects oversight throughout. A disclosure form was used to inform participants about the study and the risks and benefits of their participation. Comments of experts and survey results were de-identified and remained anonymous. Names of experts were not divulged during the survey, but they were given the option to be named once the Delphi rounds were complete and to be acknowledged in publications of the study results.

Setting and Sample

The e-Delphi was conducted online using Survey Monkey (Portland, Oregon). First, a master list of experts who had published an article within the last 10 years about necrotizing enterocolitis and/or currently worked with neonates at high risk for NEC (e.g. in a level III or higher NICU) was compiled. Inclusion criteria included the following: currently practicing physicians (neonatologists, pediatric gastroenterologists, and pediatric surgeons); NEC researchers; neonatal nurse practitioners (NNPs); and neonatal expert nurses (defined as > 5 yrs of practice in Level III NICU as well as having successfully acquired certification by a neonatal nursing certifying body). Based on the list, 100 experts were invited by email to participate and asked to forward the invitation to others they knew who met the inclusion criteria. Our goal was to recruit eight to ten representatives in each of the four categories, but no qualified experts were excluded.

Procedures

The e-Delphi was conducted via the internet. A study website was developed that included a PowerPoint presentation introducing the Delphi method and GutCheck^{NEC} (Culley, 2011). Survey Monkey was used to create a panel demographic profile, present each round of the Delphi, and track responses. Panelists were identified by a unique number assigned arbitrarily by Survey Monkey. Participants received an email giving them access to the website, a description of the study, a disclosure form, and a link to the first round of the Delphi. Email was used to alert participants to each successive round and provide feedback about the results of the previous round. Each round remained open for two weeks. Experts were alerted at least 48 hours before each round closed. Demographic data were collected from the panel, including number of years in practice, area of practice or research, self-rankings of expertise on a five-point scale (1= no expertise, 3= moderate expertise and 5= very high level of expertise), type of center in which they practiced (Level III NICU, surgical center or non-surgical center, community hospital or academic center), sex, age, and education. To be eligible, experts had to claim at least a moderate level of expertise about NEC risk. The e-Delphi questionnaire asked participants to rate the relevance of each potential risk factor using a four point scale where 4=very relevant with no revision needed, 3=relevant with minor revision needed, 2=unable to assess relevance without revision and 1=not relevant. The final question was *Are there any other risk factors that you think are relevant to include for the next round?*

The number of rounds in the modified Delphi method can be as few as two if the experts are given a preliminary list of the items they will be asked to comment on and if early group consensus is achieved. Based on other Delphi studies (Catlin, 2003; Keeney, Hasson, & McKenna, 2001; Schiebe, Skutashc, & Schofer, 2002), it was expected that two to four

rounds would be sufficient to achieve consensus and stability. Experts were invited to comment about the proposed risk factors, recommend revisions, or add new risk factors throughout the Delphi. Codes were assigned to their comments to organize and efficiently communicate the comments through structured feedback at the close of each round. Recommended revisions were incorporated into subsequent rounds unless the risk factor was deleted or retained based on consensus or stability criteria. For each risk factor that experts suggested, a literature search was conducted to identify research support. If the risk factor required additional testing (e.g., genetics, arginine, cortisol), or if only a single expert suggested it and no research support was found, it was not included in subsequent rounds (e.g., synchronized inspiratory positive airway pressure (SiPAP) and prenatal anti-depressants).

Panelist responses, statistics, and summaries of comments were distributed to the experts after each round in an anonymous format with an invitation for them to modify their responses to achieve consensus in the subsequent round. Once a round closed, responses were exported from Survey Monkey to SPSS v. 19.0 for analysis. All data were de-identified. Rounds continued until the criteria for consensus and stability were met as outlined below. To thank them for participating, a \$15 Amazon card was emailed to each expert at the close of the E-Delphi.

Data Analysis

Based on consensus, risk items were retained, modified, or eliminated. We analyzed experts' judgment of the relevance of risk items using means, percentage agreement, and change in mean response from round to round. Consensus for retaining a risk factor was satisfied by a percentage agreement of 70% (ratings of three or four) or a mean response 3.0. Items were deleted for a mean response of 2 or percentage agreement < 70% (ratings of one or two). Beginning in round two, if consensus was not met, stability was measured. Stability was determined by a change in mean response of less than 15% between rounds (Schiebe, Skutashc, & Schofer, 2002). Comments were coded, grouped into categories, and analyzed for themes. Results of each round were posted on the study website for panelists to view and consider in subsequent rounds. A content validity index (CVI) was calculated for each item and for the whole scale, consistent with Lynn's (1986) recommendations. A CVI of .80, as recommended for a new scale, was the goal.

Results

Sample Characteristics

In round one, the survey was sent to 38 experts who had agreed to participate. Of those, 35 responded (92%). Only experts who had participated in round one were sent the round two survey. Of those, 29 participated in round two (83% response rate) and 27 in round three (77% response rate). Sample characteristics are listed in Table 1. Experts practiced across the United States as well as in Switzerland, Canada, and Australia. The panel had many years of practice to their credit, most held doctorate degrees, and nearly all (94%) held advanced degrees (MDs, PhDs, and Doctors of Nursing Practice [DNP]). More women participated than men, and participants varied in age. Experts practiced in predominantly Level III NICUs in teaching hospitals, and most indicated that one of their roles was clinical. Experts could select more than one response for place of employment because many practice across settings (e.g., faculty member in a college of medicine or nursing with a local NICU practice). Experts also worked as researchers, university faculty (both in nursing and medicine), and in non-surgical NICUs (20%). All experts considered themselves knowledgeable about NEC risk. Fewer experts in round two rated their expertise as very high.

Three Delphi rounds were required to satisfy criteria for consensus and/or stability. In round one, 22 of 64 items were retained (34%), six (9%) were deleted, and 36 (56%) were carried over to round two because consensus was not reached. Items deleted in round one included Hispanic race, erythropoietin, antenatal steroids increase risk, maternal HIV positive status, surfactant, and intravenous immunoglobulin. In round two, 19 of 44 items achieved consensus (43%) and were retained, 20 (45%) were deleted because responses were stable, and five (11%) were carried over to round three after failing to meet either consensus or stability criteria. In round three, three of five potential risk factors were deleted and two were retained. Retained items are listed in Table 2 and deleted items in Table 3. Ultimately 77% of the experts who had begun the e-Delphi participated in all three rounds.

Expert panelists recommended adding a few items to GutCheck^{NEC}. Suggested risk items were included if research support could be located, they were discernible using routine procedures or documents in the NICU, and did not require any additional testing. If multiple experts recommended a risk factor, it was included regardless of available research support to confer respect for the clinical knowledge that experts possessed. For example, “Institution has an impact on NEC risk,” IUGR, and cold stress were added and retained. Abstracts for literature cited by experts were posted on the study website, and experts were referred there. Although experts recommended genetic risk factors, biomarkers, arginine, and cortisol, these were not included in the Delphi because additional testing was required. Experts recommended adding cold stress, institution of birth, genetic risk factors for severe NEC, maternal antidepressant medication during pregnancy, a clear definition of NEC diagnosis, and a process for determining disease onset to GutCheck^{NEC}. A few experts recommended stratifying risk factors by groups (e.g., by gestation or birth weight); and one suggested evaluating medical and surgical NEC separately. Cold stress during the first hour of life was added to round two, revised to include cold stress at any time with specific temperature parameters in round three where it achieved consensus. The NICU in which the infant is cared for was added and retained in round two as a risk factor.

Content Validity Index (CVI) of Retained Risk Factors

Individual item content validity was calculated as the percent of agreement among experts who rated the item a three (relevant with minor revision) or four (relevant without revision). Individual item percentage agreement for retained items ranged from 63- 94%. In round one, 22 of 64 potential risk factors were retained (CVI=.81 retained items). In round two, 19 of 44 possible items were retained (CVI=.72 retained items). In round three, two of five items were retained, (CVI= .70 retained). After three rounds, the total CVI for retained items in GutCheck^{NEC} was 0.77.

Qualitative Analysis of Experts' Comments

During the three rounds experts made 242 comments, of which 62 (22%) were recommended revisions, 35 (12%) reflected a weak evidence base and the need for more research, 19 (7%) described variation within and across NICUs, 17 (6%) reflected disagreement about PDA treatment, 17 (6%) reflected disagreement about the impact of feeding and transfusions, and 13 (5%) described variations in risk according to the birth weight and gestational age of the infant. Two broad themes with ten meta-categories were discovered. *Vulnerability*, a theme described as patient characteristics, included the meta-categories of biodemographic factors, disrupted gut colonization, exaggerated inflammatory response, mesenteric ischemia, mucosal immaturity and the “sickness factor.” *Variation* within the organizational and environmental context was a theme describing non-standardized approach to feeding, local differences, and unit-specific consistency in definitions and diagnosis. Experts noted provider practice differences within individual

NICUs related to feeding, antibiotics, PDA and transfusion management. Further variations across NICUs were noted in how NEC is diagnosed and the time of onset is determined.

Much discussion among experts centered on the institution's impact on NEC risk (Table 4). Experts described significant variation between institutions in how feedings are managed, NEC diagnosis is made, and the time of onset is determined. Therefore "The NICU in which the infant is cared for has an impact on NEC risk" was added and subsequently retained in round two. Also, based on that discussion, "The institution in which the infant is cared for may be a proxy for practices (feeding, transfusion, PDA management, fluid management, infection control, and antibiotic administration practices) that may increase or decrease NEC risk" was added and subsequently retained in round three. Several large cohort studies report broad variance in NEC rates. Among the 750 NICUs evaluated in the Vermont Oxford Network's VLBW registry (N=53,440), the best performing units (< 25th percentile) reported NEC incidence of 0-2.6% and the worst (> 75th percentile) rates of 9.1-13.2% (Horbar, Soll, & Edwards, 2010). A recent report by the Canadian Neonatal Network reports the same broad variability in NEC rates (Yee et al., 2012), as do older studies from the Neonatal Research Network (Uauy, Fanaroff, Korones, Phillips, & Wright, 1991).

Discussion

This e-Delphi was the first of its kind to describe agreement among experts about NEC risk. By engaging experts from diverse professional backgrounds, it was possible to describe the perspectives of both NEC researchers and bedside expert clinicians. Judging from the low rate of attrition over the three rounds and the quality of their comments, we surmise that experts' judged their participation in this study to be important. Many cited research, some of which was their own.

Over the three Delphi rounds, experts came to consensus about 43 items considered to be risk factors for NEC. No other researchers have sought to establish consensus among research scientists and the clinicians most likely to care for infants at risk. Experts agreed overwhelmingly that low gestational age (especially < 28 weeks), low birth weight (especially < 1000 grams), formula feeding, perinatal asphyxia, and intrauterine growth restriction (IUGR) were the highest risk factors for NEC.

Experts agreed strongly that preferential feeding of breast milk, use of standardized feeding guidelines, and a single dose of antenatal steroids reduce NEC risk. Although a few experts were uncertain about the positive role of antenatal steroids, antenatal steroids were retained as a risk reducer. In a meta-analysis of eight studies (N=1675), Roberts and Dalziel (2006) estimated that antenatal steroids reduced the risk for NEC by approximately half (RR 0.46, 95% CI 0.29-0.74, NNT= 32). Antenatal steroids are commonly given to mothers with threatened premature delivery, but it is possible that their positive effects to limit NEC are incompletely understood or overshadowed by other treatments.

The e-Delphi allowed us to identify gaps in the current state of knowledge about NEC risk as well as uptake by clinicians of research published in the last five to seven years. When unsure of the relevance of a risk item, experts described uncertainty about the strength of the evidence or expressed doubt that the evidence currently existed. Controversies that sparked the most debate included: the impact of a prolonged initial course of antibiotics when sepsis is ruled out, indomethacin therapy to close a PDA, feeding during transfusions, transfusions regardless of feeding, and the impact of antibiotic exposure. Yet, the number of research findings that might dispel these controversies is mounting.

Mounting evidence about NEC risk supports the use of ibuprofen instead of indomethacin to close a PDA. In a meta-analysis of 15 studies (N=865), Ohlsson and colleagues (2010)

found that the risk for NEC was reduced when a PDA was medically closed with ibuprofen vs. indomethacin (typical RR 0.68 [95% CI 0.47, 0.99]; typical RD -0.04 [95% CI -0.08, -0.00]; $p=.04$; NNTB 25 [95% CI 13, infinity]). Additionally, in a meta-analysis investigating the impact of standardized feeding guidelines on NEC, the most effective feeding guidelines included withholding feedings during indomethacin treatment for PDA (Patole & de Klerk, 2005). Based on this evidence, a team from Cincinnati Children's Hospital developed a clinical practice guideline that recommended using ibuprofen instead of indomethacin to medically close a PDA (Necrotizing enterocolitis Guideline Team, 2010).

Controversy among experts arose over the impact of transfusions and the extent to which withholding feedings during transfusions reduces NEC risk, suggesting an inconclusive body of evidence. Since the e-Delphi was concluded, a meta-analysis of observational studies has been released demonstrating an increased risk for NEC within 48 hours of a transfusion (unadjusted for confounders: five studies, pooled OR=3.91, 95% CI: 2.97-5.14, $I^2=58\%$ and when adjusted for confounders: four studies, OR: 2.01, 95% CI: 1.61-2.50, $I^2=91\%$). A temporal association was demonstrated between transfusions and 25-35% of NEC cases (Mohamed & Shah, 2012). Infants who developed transfusion-associated NEC (TANEC) were more likely to develop it after the first month of life, were more severely ill, less mature, and had lower birth weights than infants who developed NEC unassociated with transfusion (Mohamed & Shah, 2012). Infants in a multi-hospital system in Utah were more likely to develop NEC after a transfusion ($p<.001$), especially if they had been fed large volumes of milk in the 24 hours before and during the transfusion ($p=.04$) - particularly if fed formula instead of human milk ($p=.004$) (Christensen et al., 2010b). El-Dib and colleagues (2011) reduced their unit's NEC rates from 5.3 to 1.3% after instituting a practice change to hold feeding during transfusion. Perciaccante and Young (2008) demonstrated a reduction in incidence from 6.2% to 3.6% when holding feedings four hours before, during, and after the transfusion. More prospective studies are needed using high quality designs to explicate a possible link between feedings during transfusions and NEC (Gephart, 2012b).

Using the e-Delphi to quantify content validity was a new application of the method. The judgment of content validity of GutCheck^{NEC} (CVI= 0.77) nearly met the goal for a new scale (.80). Because the content validity scale was a four point scale unfamiliar perhaps to experts, they may have found it confusing. It is possible that others interpreted it as a Likert scale and scored it accordingly. Several factors met the criteria for a mean response 3.0 but did not meet the 70% criteria for consensus. This may have detracted from the overall content validity of the scale by including items that achieved three and four ratings with consensus ranging from 63-72%. In retrospect, more risk items might have been refined and ultimately retained or deleted if the criteria for consensus had been made more stringent (e.g., $>73\%$ and a mean >3.2). Although experts made many comments, it is unclear how the consideration of comments by others influenced experts' decision-making in subsequent rounds.

Not establishing a priori decision-making criteria for how to handle experts' suggestions for additional risk items is another study limitation. A stronger approach would have been to either include all experts' suggestions (allowing them to be reduced through the process) or specify a priori that suggested risk items must be research-based and not require additional testing. By not specifying in advance the difference between spontaneous intestinal perforation (SIP) and NEC, several experts called into question the impact of a few risk factors.

Implications for Practice

The most important implication of this study for practice is that NEC risk, while often thought to be non-modifiable, is subject to variations in practices across NICUs that are modifiable. While it may not be possible at this time to eliminate all NEC, it appears feasible to eliminate a substantial proportion to well under the current averages because high performing units now report rates well below 3% of VLBW infants. This group of experts agreed practices that reduce NEC include: preferential use of human milk, adoption of a written set of standardized feeding guidelines and administering to mothers a single course of antenatal steroids prior to birth. Importantly, meta-analyses support these practices. Two large multi-centered prospective studies identified a dose response to the proportion of human milk fed infants and reduction of NEC risk (Meinzen-Derr et al., 2009; Sullivan et al., 2010). Specifically, the closer the proportion of human milk fed to 100% of the diet, the lower the risk for NEC and other causes of neonatal mortality, especially in infants < 1000 grams.

NICU clinicians can adopt a standardized approach to infant feeding by using one of the many published feeding protocols or creating their own. Patole and De Klerk's meta-analysis of observational studies (2005) identified a significant reduction in NEC risk when a feeding guideline was used across 6 studies that each used a different guideline, suggesting that the use of any guideline is better than individually writing feeding orders day to day. Feeding guidelines usually describe how to define and handle feeding intolerance. Nurses can and should advocate for the adoption of a unit-based feeding protocol if not currently in use.

By collaborating across nursing units, several actions can be taken to understand an infant's risk for NEC prior to delivery and take action to reduce it. First, assuring that a mother has received at least one course of antenatal steroids is a nursing action. Also, NICU clinicians can visit the mother and describe her infant's critical need to receive her milk. Perinatal and lactation nurses can help the mother to begin pumping her breast milk soon after birth. Once in the NICU, clinicians can continue to praise and offer support to mothers to provide their milk. Encouraging use of human milk instead of formula and tracking the percentage of human milk an infant is fed, especially in the first 2-3 weeks of life, potentially can improve outcomes. For those mothers unwilling or unable to provide their milk, provisions to obtain donor milk for the most at risk infants can be made.

Communication about NEC risk across transitions in care is critical. Information about the prenatal and intrapartum course should be available in the patient record and communicated clearly across the postnatal course. GutCheck^{NEC}, once adequately tested, holds promise to standardize the communication of NEC risk across transitions in care such as when nurses change shifts, resident's handoff their duties or patients are transferred within and across hospitals.

A primary challenge when studying NEC risk is the ethical research dilemma limiting prospective study of the disease's risk factors. Most evidence about NEC risk has been demonstrated in observational studies and may be judged as low quality but pooling findings using meta-analysis of observational studies could be useful. In the absence of prospective, controlled trials, clinicians can evaluate the observational evidence about NEC prevention by calculating the risks and benefits practices pose to infants. Although a prolonged initial course of empiric antibiotic therapy was identified by Cotten and colleagues as a risk factor in 2009, this risk factor did not survive the e-Delphi, yet limiting the initial course of antibiotics when blood cultures are negative diminishes antibiotic exposure and does not threaten the infant. Holding feedings during transfusions has been shown in two

observational studies to relate to reduced NEC rates (El-Dib, Narang, Lee, Massaro & Aly, 2011; Perciaccante & Young, 2008); and though randomized trials have not been conducted, poses little risk. Further, when feeding is held only during a transfusion and not for several hours before or after, it is likely to impact the infant's nutrition very little or not at all. Until more research supports the practice, controversy will likely persist (Gephart, 2012b).

Implications for Research

The results of this study supported the content validity of the NEC risk items comprising GutCheck^{NEC}, but further testing of the index is underway to demonstrate prediction and reliability of the tool. To be clinically useful, reducing the number of risk items will improve its ease of use. Future studies are needed to combine the risk assessment with clinical signs of the disease to create a just-in-time clinical decision tool for bedside use. At this time, the number of risk factors retained from the e-Delphi remains unwieldy and may inhibit the clinical usefulness of GutCheck^{NEC}. Research is underway to address this challenge.

The e-Delphi is a method for research that enables consensus building among experts without barriers of time or space. By integrating online surveys, emails and web-based reporting of feedback, we were able to communicate with experts and complete three Delphi rounds over seven weeks. E-Delphi could be used in research to build consensus about a number of approaches to improve neonatal care, including the development of consensus practice guidelines to reduce ventilator acquired pneumonia, standardize feeding or develop recommendations for transfusion management.

Conclusion

In the absence of a clinically useful risk index to integrate risk items into a single, actionable bedside tool, GutCheck^{NEC} holds promise to improve risk assessment, standardize communication about NEC risk across transitions, and may enable early recognition. Over three rounds, experts reached consensus about 43 items for NEC. No other study has sought to establish consensus among both research scientists and clinicians most likely to care for infants at risk. We identified a broad perspective on NEC risk that moves beyond previous reports emphasizing the individual vulnerability of an infant to NEC to bring attention to the impact of variations in NICU practices on an infant's risk for NEC.

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Figure 1.
Multi-factorial Etiology of Necrotizing Enterocolitis

Figure 2.
Model of Necrotizing Enterocolitis Risk

Table 1**Sample Characteristics of Experts**

Characteristic	Number (%)
Role (Could indicate more than one role)	
Neonatologist	12 (34.3)
Neonatal Nurse Practitioner	11 (31.4)
Pediatric Surgeon	3 (8.6)
NICU staff Registered Nurse	3 (8.6)
Researcher	7 (20)
Professor (any rank)	5 (14.3)
Other (patient safety officer, program coordinator, developmental specialist)	3 (8.6)
Years in Current Role	
< 5 years	2 (5.7)
5-10 years	9 (25.7)
10-15 years	8 (22.9)
15-20 years	4 (11.4)
> 20 years	12 (34.3)
Self-report of expertise about NEC risk (Round 1)	
Moderate level	13 (37.1)
High level	11 (31.4)
Very high level	11 (31.4)
Self-report of expertise about NEC risk (Round 2)	
Moderate level	15 (48.4)
High level	11 (35.5)
Very high level	5 (16.1)
Geographic Location	
Northeast United States	3 (8.6)
Southeast United States	13 (37.1)
North central United States	3 (8.6)
South central United States	0 (0)
Northwest United States	1 (2.9)
Southwest United States	11 (31.4)
Canada	1 (2.9)
Australia	1 (2.9)
Europe	2 (5.7)
Highest earned degree	
PhD	6 (17.1)
PhD + MD, DNP or DO	2 (5.7)
Doctorate of Nursing Practice (DNP)	1 (2.9)
MD/DO	13 (37)
Masters	9 (25.7)
Post-masters certificate	2 (5.7)

Characteristic	Number (%)
Bachelors	1 (2.9)
Associates	1 (2.9)
NICU affiliation	
Teaching hospital	30 (85.7)
Non-teaching hospital	3 (8.6)
Not working in the hospital	2 (5.7)
Current work setting	
Level III/IV NICU with specialty surgery and ECMO	17 (48.6)
Level III with specialized surgery but not ECMO	12 (34.3)
Level III NICU without specialty surgery	5 (14.3)
Level II NICU with surgery	1 (2.9)
Level II NICU without surgery	2 (5.7)
Researcher outside of clinical setting	4 (11.4)
Faculty (NNP specialty)	1 (2.9)
Gender	
Male	12 (34.3)
Female	23 (65.7)
Age	
< 35	2 (5.7)
35-45	11 (31.4)
46-55	12 (34.3)
56-65	9 (25.7)
> 65	1 (2.9)

Note. Presented as the number of respondents (%). NNP= Neonatal Nurse Practitioner, NICU= Neonatal Intensive Care Unit

Table 2Risk Items Retained in GutCheck^{NEC} over Three Rounds of E-Delphi

Potential Risk Factor	Mean (S.D.)	% Agree
Very High Agreement (> 85%)		
BW < 1000 grams at highest risk	3.91 (.28)	100
BW 1001-1500 grams at high risk	3.74 (.51)	97.1
GA < 28 0/7 weeks at highest risk	3.89 (.40)	97
GA 28 0/7 -31 6/7 weeks at high risk	3.80 (.47)	97
Exclusively fed formula	3.74 (.66)	94
Exclusive human milk feeding reduces NEC risk	3.83 (.53)	93.3
GA 32 0/7 -33 6/7 weeks at intermediate risk	3.57 (.78)	88.5
BW 1501-2000 grams at intermediate risk	3.54 (.82)	85.7
High Agreement (75-85%)		
Fetal distress during labor with perinatal asphyxia (including persistent prolonged fetal heart rate decelerations with limited variability and an umbilical arterial cord pH < 7.1 and/or a lactate > 6.1 mmol/L)	3.50 (.94)	83.3
IUGR (birth weight < 10% of size for gestation and abdominal circumference < 2.5 percentile)	3.47 (1.00)	83.3
GA 34 0/7 -35 6/7 weeks at low risk	3.43 (1.09)	83
Lack of unit-based adoption of standardized feeding guidelines	3.46 (.92)	83
BW 2001-2500 grams at low risk	3.37 (1.17)	80
BW > 2500 grams at very low risk	3.26 (1.20)	80
Prolapsed umbilical cord with evidence of perinatal asphyxia (cord pH < 7.1 or a lactate > 6.1 mmol/L)	3.40 (1.04)	80
Hemodynamically significant PDA (demonstrated by ECHO)	3.37 (1.16)	80
GA > 36 0/7 weeks at very low risk	3.29 (1.20)	79
Fed both formula and breast milk	3.29 (1.00)	79
Congenital heart disease	3.34 (.97)	77
Late-onset sepsis (positive blood culture after fifth day of life, any cause but before NEC diagnosis)	3.40 (1.07)	76.6
Multiple infections (>2) in the first 4 weeks of life but before NEC diagnosis	3.40 (1.07)	76.6
Chest compressions needed at delivery	3.33 (1.18)	76.6
Moderate Agreement (70-74%)		
Born SGA (<10% size for gestation)	3.29 (.99)	74
Epinephrine at delivery	3.33 (1.15)	73.3
Cocaine use at any time in pregnancy	3.03 (1.20)	71.4
Breast milk fortified with cows' milk based fortifier	3.06 (1.16)	71.4
The NICU in which the infant is cared for may be a proxy for practices (feeding, transfusion, PDA management, fluid management, infection control and antibiotic administration practices) that may increase or decrease NEC risk.	3.3 (1.06)	70.4
Cold stress at delivery or any time during the clinical course (axillary temperature < 36 degrees Celsius).	3.0 (1.30)	70.4
The NICU in which the infant is cared for has an impact on NEC risk	3.20 (1.21)	70
Surgical PDA and fed while treated with indomethacin	2.94 (1.29)	70
Borderline Agreement (63-69%)		
Hemodynamic resuscitation using dopamine or dobutamine in the first week of life	3.17 (1.22)	69
Antenatal steroids with at least one dose given 12 hours before birth reduces NEC risk	3.00 (1.29)	66.7
Persistent metabolic acidosis before a diagnosis of NEC	3.13 (1.22)	66.6
Histamine 2 (H2) blocker therapy	3.03 (1.25)	66

Potential Risk Factor	Mean (S.D.)	% Agree
Early onset sepsis (Positive blood culture in first week of life)	3.03 (1.20)	65.7
Probiotics (including bifidobacterium) reduces NEC risk	3.07 (1.17)	63.4
5 minute Apgar score 6	3.00 (1.26)	63.4
Placental abruption (complete or partial, irrespective of quantity of blood loss, with abrupt fetal heart rate deceleration)	3.07 (1.29)	63.3
Chorioamnionitis (evidenced by maternal fever, treatment with antibiotics and/or histological chorioamnionitis by pathology)	3.00 (1.31)	63.3
PRBC transfusion, not NPO	3.00 (1.20)	63.3
Pregnancy induced hypertension	3.00 (1.26)	63.3
Both glucocorticoids and indomethacin	3.00 (1.21)	63

Note. Reported as mean with standard deviation (S.D.) of responses in the round in which the item was retained. Percent agreement (% Agree) was defined as the percentage of responses rated relevant with minor revision (3) or relevant without revision (4). NEC= Necrotizing Enterocolitis, NICU= Neonatal Intensive Care Unit, BW= birth weight in grams, GA= gestational age, IUGR= intrauterine growth restriction, PDA= patent ductus arteriosus, ECHO= echocardiogram, SGA= small for gestational age, PRBC= packed red blood cell and NPO= nothing per os, i.e. by mouth.

Table 3

Deleted Risk Items from GutCheck^{NEC} over Three Rounds of E-Delphi

Potential Risk Item	Round 1 Mean (SD)	Round 2 Mean (SD)	Round 2 Mean change	Round 3 Mean	Round 3 Mean Change	Agree (%)
Hispanic race	1.89 (1.23)	NA	NA	NA	NA	71.4
Antenatal steroids increase risk	1.74 (1.07)	NA	NA	NA	NA	82.8
HIV + treated with anti-retroviral therapy	1.88 (1.17)	NA	NA	NA	NA	79.4
Surfactant for RDS	1.31 (.76)	NA	NA	NA	NA	94.3
Erythropoietin	1.94 (1.26)	NA	NA	NA	NA	71.4
IVIG	2.03 (1.15)	NA	NA	NA	NA	74.3
Either mother or father's self-reported Black race	2.31(1.32)	2.23 (1.36)	-3.3	NA	NA	63.3
Male	2.31 (1.41)	2.23 (1.43)	-3.3	NA	NA	60
Multiple birth	2.66 (1.35)	2.87 (1.43)	7.7	NA	NA	40
Illicit drugs at any time in pregnancy (e.g. methadone, methamphetamine, not including cocaine)	2.34 (1.28)	2.67 (1.35)	14	NA	NA	43.3
Chronic hypertensive disease	2.53 (1.33)	2.83 (1.34)	12	NA	NA	43.3
Indomethacin prenatally to treat pre-term labor	2.51 (1.27)	2.57 (1.28)	2.3	NA	NA	50
PROM > 36 hours	2.77 (1.29)	2.63 (1.45)	-4.9	NA	NA	46.7
Duration of mechanical ventilation (the more days of ventilation, the higher the risk-settings not specified)	2.43 (1.33)	2.73 (1.28)	12.5	NA	NA	43.4
RDS	2.34 (1.24)	2.33 (1.32)	-0.3	NA	NA	60
History of bloody gastric residuals after 3 rd day of life	2.57 (1.29)	2.90 (1.30)	12.8	NA	NA	40
Antibiotic exposure: received > or = to 3 antibiotics at once to treat infection	2.57 (1.33)	2.70 (1.37)	5	NA	NA	43.3
Initial course of antibiotics > 5 days in spite of negative blood culture	2.60 (1.40)	2.57 (1.38)	-1.3	NA	NA	50
Postnatal glucocorticoids before 30 days of age	2.49 (1.29)	2.30 (1.34)	-7.5	NA	NA	60
Indomethacin (standard dose and route) NPO	2.74 (1.27)	2.73 (1.34)	-0.3	NA	NA	43.3
Indomethacin (standard dose and route) but fed during administration	2.71 (1.27)	2.90 (1.30)	6.8	NA	NA	33.3
Surgery and indomethacin (NPO)	2.63 (1.31)	2.93 (1.31)	11.6	NA	NA	33.3
Exchange transfusion (delivered in an isovolemic manner)	2.91 (1.25)	2.97 (1.30)	1.8	NA	NA	36.7
UAC > 4 days	2.29 (1.34)	2.33 (1.40)	2.1	NA	NA	56.7
PRBC transfusion, NPO during transfusion	2.69 (1.23)	2.80 (1.24)	4.3	NA	NA	40
NPO longer than 5 days for any reason, then fed	2.94 (1.24)	2.90 (1.35)	1.5	NA	NA	40
PPV at delivery longer than two minutes by BVM or ET tube.	2.14 (1.24)	2.93 (1.31)	37	1.85 (1.29)	-37	70.4

Potential Risk Item	Round 1 Mean (SD)	Round 2 Mean (SD)	Round 2 Mean change	Round 3 Mean	Round 3 Mean Change	Agree (%)
Treatment for PDA with ibuprofen only (standard dose, IV or po)	2.11 (1.23)	2.63 (1.35)	24.5	2.44 (1.39)	7.3	55.5
Prolonged (>3 days) trophic feedings at a rate of no more than 15-20 ml/kg/day	2.06 (1.21)	2.47 (1.38)	20	2.19 (1.27)	11	62.9

Note. Data were recorded as mean with standard deviation (S.D.). Agree % is the percentage of experts who rated an item as either not relevant or unable to determine relevance without major revision.
 IVIG=Intravenous immunoglobulin, HIV= Human Immunodeficiency Virus, PROM= Premature Rupture of Membranes, RDS= Respiratory Distress Syndrome, PPV= Positive pressure ventilation, BVM= Bag- valve mask apparatus, PDA= Patent Ductus Arteriosus, NPO= Nothing per os, IV= Intravenous, PO= per os, i.e. by mouth, ET= Endotracheal tube, UAC= Umbilical arterial catheter, PRBC= Packed Red Blood Cell

Table 4**Significant Statements about Organizational (NICU) Variation****Round 1**

- Reason for NPO may be important - might specify this as “unit practice” (123)
- Also standardized feeding guidelines need to be defined as a unit may have them but they may be totally screwy (128)
- Center; the Uauy paper strong suggests that the biggest risk factor is the center a baby is born in, in addition to the rest of the tested variables (131).
- In many series it appears that one of the biggest risk factors is “institution”. This probably indicates that there are multiple practices and combinations of practices that predispose to development of NEC. Not sure how this can be captured. Unfortunately, the diagnosis of NEC is, to an extent, subjective. There is often disagreement between the radiologist and the neonatologist as to whether or not to assign NEC as a diagnosis. (134)
- It may be useful to look separately as “medical NEC” and “surgical NEC” - though there may be a different threshold at one institution compared to another to proceed to laparotomy or peritoneal drain (142).

Round 2

- Feeding plus decreased perfusion of the GI tract “should” increase the risk of NEC - though indications for each may vary from institution to institution. Similarly, an institution’s practice with respect to use of Indocin (number of courses, etc) and decision to proceed directly or after a certain number of courses of Indocin or other considerations may influence whether or not these are risk factors for NEC in a given NICU (186).
- Feeding practices vary considerably among NICUs - as do rates of NEC. If there were a clear association between a specific regimen and either a low or high incidence of NEC we would have all adopted that practice! (199)
- The practice of diagnosis of NEC may vary between institutes, lack of clear differentiation in the diagnosing NEC isolated intestinal perforation can create differences in identification of risk factors (201a)
Differences in identification in the “time of onset” of NEC before the progression of disease to the advanced level may vary in different institutes (201b)
- The institution may be a proxy for the type of patients that are born in that institution as well as the types of infants transferred there after being born elsewhere. (202)
- Need to know more information about institutions. (203)
- In our center once definite diagnosis is made, the symptomatology is carefully reviewed in order to establish the “onset of NEC” in a uniform manner. In different centers the definition of NEC may vary and defining the time of onset may vary that can lead to different conclusions drawn by different experts in this field. (215)

Round 3

- I would say NICU instead of institution. This seems it’s about the NICU culture- not sure how to incorporate that other than the way it’s stated. How would you give this a “risk score”? It’s not really a “yes/no” like the others (218).
- I think there are good data in the NICHD Neonatal Research Network to support the very wide variability in NEC rates between institutions - without a clear explanation - so it must be multi-factorial! (220)
- The institution... - not sure how to answer this one. If you are saying they have standardized practices, then yes, standardized practice has been shown to have better outcomes. (222)
- Institution cannot be used as a proxy for practice due to individual variation within a center (but that doesn’t mean that center isn’t an important risk factor for NEC). (224)
- Center differences exist but there are too many items listed here together to assess risk (226)
- Just my earlier one about the NICU in which the infant being cared for having an impact and how to include that. (230)
- Need more clarification on the NICU that has impact on NEC. (232)

Note. NEC= Necrotizing Enterocolitis, NICU= Neonatal Intensive Care Unit, PDA= Patent Ductus Arteriosus, NPO= nothing per os, PRBC= Packed Red Blood Cell

Table 5**E-Delphi Experts**

State/country	Organization/City	Expert
Arizona	Tucson Medical Center and Northern Arizona University, Tucson	Shannon Angersbach, RNC, MSN
Virginia	Virginia Commonwealth University, Richmond	Brenda Baker, RN, CNS, MSN, PhD
Arizona	Phoenix Children's Hospital, Phoenix	Kay Baylor, RNC, MSN
Arizona	Arizona Children's Center at Maricopa Integrated Health System, Phoenix	Becky Bell, RN, MSN
Arizona	The University of Arizona Medical Center and the University of Arizona College of Medicine, Tucson	Alan Bedrick, MD
Switzerland	Pediatric Surgery, Children's University Hospital and University of Berne, Inselspital	Steffen Berger, MD
North Carolina	Duke University College of Nursing, Durham	Wanda Bradshaw, RN, NNP-BC, MSN
Oregon	Northwest Newborn Specialists, Portland & Salem Health, Salem	Howard Cohen, MD
North Carolina	Department of Pediatrics and Duke Clinical Research Institute, Duke University, Durham	C. Michael Cotten, MD, MHS
Arizona	Phoenix Children's Hospital, Phoenix	Shannon Dawson RN-NIC, BSN
Virginia	Children's Hospital of the King's Daughters	Donna DeLoach, MSN, PNP, NNP, RN
Massachusetts	Boston College and Brigham Women's Hospital, Boston, Boston	Katherine Gregory, RN, MSN, PhD
Arizona	The University of Arizona Medical Center, Tucson	Lisa Grisham, RN, NNP-BC, MSN
New York	Golisano Children's Hospital and University of Rochester, Rochester	Ronnie Guillet, MD, PhD
Tennessee	Vanderbilt University School of Medicine, Nashville	Scott Guthrie, MD
North Carolina	Duke University School of Nursing, Durham	Robin Knobel, RN, NNP-BC, MSN, PhD
Illinois	University of Illinois at Chicago and Children's Hospital of University of Illinois, Chicago	Akhil Maheshwari, MD
Tennessee	Vanderbilt University, Nashville	Steven McElroy, MD
Ohio	Cincinnati Children's Hospital Medical Center, Cincinnati	Jareen Meinen-Derr, MD, PhD
Virginia	Children's Hospital of the King's Daughters, Norfolk	Katherine Newnam, RN, MSN, NNP-BC, PNP, PhD-c
Florida	The University of Florida College of Nursing, Jacksonville	Leslie Parker, RN, MSN, NNP-BC, PhD
Australia	KEM Hospital for Women, University of Western Australia, Perth	Sanjay Patole, MBBS, MD, DCH, FRACP, MSc, DrPH
Virginia	Children's Hospital of Richmond, Virginia Commonwealth University, Richmond	Barbara Reyna, RN, MSN, NNP-BC, PhD
Arizona	Cardon Children's Medical Center, Phoenix	Maryann Sawyer, RN, IBCLC, RLC
Arizona	The University of Arizona Medical Center, Tucson	Andrea Saugstad, RN, NNP-BC, MSN
Florida	University of Florida at Jacksonville	Renu Sharma, MD
Arizona	Director NNP Programs, Neonatology Associates Limited, Phoenix	Ellen Tappero, RN, MSN, NNP-BC, DNP
South Carolina	Medical University of South Carolina, Charleston	Sarah N. Taylor, MD, MSCR
Florida	The University of Florida College of Medicine, Jacksonville	Joseph J. Tepas III, MD, FACS, FAAP
Ohio	Cincinnati Children's Hospital Medical Center, Cincinnati	Kurt Schibler, MD

Note. Experts who gave permission are listed here in alphabetical order by last name, six wished to be un-named.