Title: Relationship of necrotizing enterocolitis (NEC) rates to adoption of prevention practices in U.S. neonatal intensive care units

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Acronyms and abbreviations: Very low birth weight (VLBW), necrotizing enterocolitis (NEC), mother's own milk (MOM), adherence score (AdSc), quality improvement (QI), neonatal intensive care unit (NICU), Vermont-Oxford Network (VON), Food and Drug Administration (FDA), donor human milk (DHM), United States (US), standardized feeding protocol (SFP)

ABSTRACT

Background: Applying quality improvement methods has reduced necrotizing enterocolitis (NEC) in some neonatal intensive care units (NICUs) by 40-90%.

Purpose: This study was conducted to: 1) Examine relationships between adoption of prevention practices using the NEC-Zero adherence score and NEC rates, and 2) Describe implementation strategies NICUs use to prevent NEC.

Methods: A descriptive cross-sectional correlational study was completed among US quality improvement-focused NICUs. Relationships of the NEC-Zero adherence score to NEC rates were examined. Subgroup analyses explored relationships of a human milk adherence sub-score and differences between high NEC rate ($\geq 8\%$) and low rate ($\leq 2\%$) NICUs.

Results: NICUs (N=76) ranged in size from 18 to 114 beds. The mean adherence score was 7.3 (SD 1.7; range 3-10). The 10 point adherence score was not related to the NEC rate. The human milk sub-score related to lower NEC rates ($\rho = -0.26$, $p = .049$), as was colostrum for oral care ($\rho = -0.27$, $p = 0.032$). Units who used a feeding protocol showed higher NEC rates ($\rho = 0.27$, $p = 0.03$), although very few addressed use of effective implementation strategies to track adherence or to assure consistency among clinicians. Those units who used colostrum for oral care were more likely to adopt strategies to limit inappropriate antibiotic exposure ($\rho = 0.34$, $p = 0.003$).

Implications for Practice: Broader use of evidence-based implementation strategies could bolster delivery of NEC prevention practices. Maternal lactation support is paramount.

Implications for Research: Future studies are needed to identify how individual clinicians deliver prevention practices, the extent to which this relates to overall delivery of prevention and to study effects of bundles on NEC outcomes.

Necrotizing enterocolitis (NEC) is a gastrointestinal disease that affects predominantly premature infants and is a major cause of emergent surgery in the neonatal intensive care unit (NICU).^{1,2} A diagnosis of NEC necessitates many invasive interventions, longer stays in the neonatal intensive care unit (NICU), and heightens the risk for potentially chronic serious complications and death.³⁻⁵ While uncommon and occurring in 2-12% of very low birth weight infants (VLBW), NEC is serious with up to 30% needing surgery to treat it.^{6,7} Of those requiring surgical treatment, mortality is as high as 50%.⁸ For NEC surgery survivors, many will need to stay in the NICU for months and may become dependent long-term on parenteral nutrition. Lifelong impacts can include delayed neurodevelopment; high infection risk; or liver, intestinal or kidney failure.

Risk factors for NEC is often attributed to being born early, but multiple factors contribute to the likelihood that an infant will develop NEC.⁹ In a comprehensive review of NEC risk, Samuels and team identified 43 non-modifiable NEC risk items across neonatal studies.³ At highest risk were infants born small for gestation, those who required assisted ventilation, experienced hypotension or sepsis, born after premature rupture of membranes or outside of the care hospital (i.e. "outborn").³ Black or Hispanic infants have higher rates of NEC than Non-Hispanic White infants.^{10,11} Modifying NEC risk can be driven by promoting mother's own milk- especially in the first 28 days of life,¹²⁻¹⁴ adopting standardized feeding guidelines,^{15,16} and minimizing exposures to unnecessary antibiotics and histamine-2 antagonist blockers. Many add probiotic treatment to the list of protective treatments to avoid NEC, although there remains controversy that stalls implementation in US clinical practice.

In a study by our team in 2014, we tested and determined the relative contribution of different factors to predict NEC (i.e. in a score called "GutCheck^{NEC}"). One of the major risk factors was the variation in practices and NEC rates between NICUs. Revealing strong variations in NEC rates across 284 NICUs, ultimately this pointed to how much the practices within a NICU heavily contribute to the likelihood that a baby would develop the disease, in that

NICU.¹¹ Other cohorts confirm broad variation in NEC occurrence, although the exact mechanisms for differences are unclear.¹⁷⁻¹⁹

Important Components of NEC Prevention Quality Improvement

Feeding high proportions of mother's own human milk, especially in the first 14 days of life, is protective against NEC although it is not a panacea.¹² Adoption and consistent use of standardized feeding protocols can reduce risk,^{15,16} and that prolonged antibiotic exposure or administration of histamine-2 antagonists increase risk.¹⁶ Indeed, prioritizing the delivery of prevention evidence through quality improvement methods has decreased NEC rates in some units. Tracking improvement across NICUs from 2005-2014, the Vermont-Oxford Network (VON) showed that 75% of the lowest performing neonatal intensive care units (NICUs) engaged in improvement work could reduce NEC but the pace of improvement took 5-8 years.²⁰ Quality improvement for NEC prevention has been shown to decrease NEC rates by 41-92% (See Table 1).^{13,18,21-24}

--- Insert Table 1 about here---

NEC-Zero Description

In 2015, a multi-disciplinary group of clinical and research experts addressed the current scientific and practice-based evidence about NEC prevention and strategies to promote timely recognition. Different from a systematic review, their "scoping review" focused on using existing literature to answer key clinical questions about evidence that was ready for implementation and potential strategies used to do so.¹⁶ The initiative is called "NEC-Zero" to reflect a common goal to move NEC to "zero incidence." Informed by a theoretical framework from implementation science, Titrer's *Translating Research into Practice framework*,²⁵⁻²⁷ NEC-Zero aimed to influence adoption of prevention practices by leveraging communication strategies to users who work within a social system and through a simple, non-controversial, bundled intervention.¹⁶ NEC-Zero applies ready to implement, evidence-supported and minimally controversial practices that do not require extra equipment or additional prescriptions. Four essential components comprise

the bundle, and are informed by the state of the science: 1) human milk feeding that prioritizes mother's milk beginning with colostrum for oral care; 2) use of a unit-approved feeding protocol (sufficiently described and formalized so that one can "take a picture" of it); 3) minimizing exposure to prolonged empiric antibiotics (i.e. < 4 days when initial blood cultures are negative directly after birth) and avoidance of histamine-2 antagonist blockers; and 4) specifying an approach to risk awareness and timely recognition (e.g. using a NEC risk tool like GutCheck^{NEC} combined with a focused communication tool for when symptoms arise). The NEC-Zero team elected to exclude two potentially beneficial practices: use of probiotics (i.e. requires a prescription, is not regulated by the FDA, and to some may be controversial) and the choice of donor human milk derived fortifiers (due to cost). While all NEC-Zero practices are evidence-based, it was not entirely clear if certain practices confer greater benefit than others.

NEC-Zero Adherence Score

In 2016, a consensus building approach using an electronic Delphi process was conducted to identify, among experts not affiliated with NEC-Zero, how well the recommendations fit current knowledge and beliefs and to "weight" in a 10 point score.²⁸ Still focused on implementation, the NEC-Zero team aimed to use the 10 point score as one strategy in an audit and feedback intervention. Via audit and feedback, the score could be a quick way to indicate how adherent to the prevention bundle the care had been. The Delphi ended after two rounds once consensus was achieved to weight the score. Components in the final NEC-Zero adherence score included: prioritized human milk feeding (5 points- 3 points for dose of human milk, 1 point for oral colostrum care and 1 point for donor human milk availability), standardized feeding protocol (3 points), medication stewardship (1 point) and a unit-specified approach to foster timely recognition (1 point).²⁸ During the Delphi, holding feeding during packed red blood cell transfusion was determined to be controversial, so it was dropped from the score. We asked participants about it to identify the prevalence of the practice in this study. It was not known if the 10 point NEC-Zero score relates to actual NEC rates or nuances for implementation could

be made consistent. In a review of evidence in 2018 in PubMed and the Cochrane Database of Systematic Reviews using “necrotizing enterocolitis” and “implementation strategies” and “prevention,” only the NEC-Zero scoping review was identified. No studies were found to describe the broad state of adoption of NEC prevention practices in US NICUs.

Purpose

This study was conducted to: 1) Examine relationships between adoption of prevention practices using the NEC-Zero adherence score and NEC rates and; 2) Describe implementation strategies NICUs use to prevent NEC. Research questions explored were:

1) To what extent does the adoption of NEC prevention practices (via the NEC-Zero adherence score) relate to NEC rates?

2) How are NICUs implementing NEC prevention?

3) To what extent are there differences between the adoption of NEC prevention practices in NICUs with low rates ($\leq 2\%$) compared to those with high ($\geq 8\%$) NEC rates?

We hypothesized that units with higher adoption of NEC prevention practices would report lower rates of NEC.

Methods

Design

A descriptive cross-sectional correlational study was completed using an investigator-developed questionnaire to explore adoption of NEC prevention practices and their relationship to NEC rates in US NICUs. The questionnaire was composed of closed-ended and open-ended questions. Relationships of the NEC-Zero adherence score to NEC rates were explored.

Survey Item Development

Items for the survey were developed with insight from the previous two steps of the process (i.e. recommendations from the NEC-Zero group and the Delphi study). Questions were phrased as yes/no or open-response options to query if their NICU had implemented: 1) prioritized human milk feeding; 2) colostrum for oral care; 3) standardized feeding protocols; 4)

a unit-based approach to timely recognition of NEC; 5) restriction of feeding during PRBC transfusion; and 6) restricting the initial course of antibiotics to < 5 days if blood cultures were negative. Self-reported NEC rates were collected such that the NICU representative used their Vermont-Oxford Network data (with definition for NEC) to report their 2014 rate and their 5 year rate (2009-2014). Open-ended questions explored approaches used in their NICU to implement: 1) strategies for the promotion of an exclusive human milk diet; 2) monitoring compliance to standardized feeding protocols; 3) strategies for communication to foster NEC timely recognition; 4) teamwork across the disciplines; 5) practices to alter enteral feeding around PRBC transfusion; and 6) strategies used to reduce prolonged empiric antibiotic therapy.

Procedures

All study procedures occurred online using convenience sampling with direct email and snowball recruitment. One unit participant (the nursing leader, quality director, or medical director) was recruited to complete the survey. Only participants from the US were eligible. Recruitment targeted NICU nursing leadership quality list serves, attendees at quality improvement meetings, Children's Hospital Research Network list serves and directly to NICUs identified from email lists. Once invited, participants viewed a disclosure document about the study and proceeded to the survey delivered via the Qualtrics platform (Provo, Utah). The questionnaire was open for 10 days and reminders were sent 48 hours before it closed. The institutional review board at the University of Arizona approved this study as exempt and provided oversight for the protection of human subjects.

Assignment of Adherence Score

The Adherence Score (AdSc) for each NICU was calculated by giving a numbered score for each category of NEC prevention practice asked about in the survey (see Table 2 scoring criteria). The scores for having a unit-derived standardized feeding protocol and for encouraging intake of mother's own milk (MOM) were weighted more heavily based on results of the previous Delphi study. NICUs received points for indicating adoption of each adherence score

item. For MOM availability, NICUs received 3 points for indicating > 75% infants' enteral intake was from MOM administration, 2 points for 50 - 74%, 1 point for 25 – 49%, and 0 points for < 25%. For human donor milk (HDM) availability and oral colostrum administration they received 1 point for the adoption of each practice and 0 points for not adopting the practice. If a NICU indicated they had adopted a feeding protocol they were given 3 points, and 0 points if they did not use one. For the practice of antibiotic stewardship, NICUs were given 1 point if they described some type of measure to monitor or limit the length of the initial empiric antibiotic course. Examples that enabled the 1 point to be issued included if they specified that they used pharmacist oversight, automatic stop dates on medication orders, auditing, or for active participation in an antibiotic stewardship initiative. If no approach was specified or if they said they relied solely on clinical memory, 0 points were given. Lastly, NICUs were given 1 point for standardized timely recognition practices if they described a tangible process (i.e. you could take a picture of it or it involved a structured group process) to enhance timely recognition of NEC and 0 points if they did not. Examples of tangible approaches to timely recognition addressed advanced monitoring systems (e.g. heart rate vulnerability monitors), specialized tools for communication or applying intentional risk awareness via use of risk tools (e.g. GutCheckNEC, NeoNEEDs, or eNEC). Total adherence scores represented the sum of these items (10 points maximum). The human milk sub-score (5 points maximum) represented the sum of the values for MOM, DHM, and oral colostrum administration. Because of findings from the earlier Delphi study, no points were given for enteral feeding around the time of PRBC transfusion because of inconsistent evidence for the practice although we did ask to determine the prevalence of altering feeding around transfusion.

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Data Analysis

Quantitative data (i.e. AdSc and the NICU NEC rate) were described using descriptive statistics. Relationships between the AdSc and the NICU NEC rate were analyzed using the

Spearman correlation coefficients. Non-parametric analyses using the Mann-Whitney U test were used to identify if there were differences in AdSc between units with low ($\leq 2\%$) and high ($\geq 8\%$) NEC rates. Content analysis was applied to the open-ended responses after counts of practices were collected about the different implementation strategies that NICUs used to prevent NEC in their own words. Coding categories were identified by question, using both conventional and directed methods focused on identifying actionable implementation strategies.²⁹⁻³¹

Results

NICU Characteristics

Unique responses from 76 NICUs located in the U.S. were obtained (See Table 3, Sample characteristics). NICUs ranged in size from 18 to 114 beds but most were moderate (47%) to high volume (29%) and cared for the sickest neonates (46% AAP designated Level III, and 51% Level IV). All were active in some quality improvement collaborative. Participants reported annual NEC rates from 0-12.6% (Mean 4.6, SD 3). Four NICUs reported rates of 0%.

-- Insert Table 3 about here--

Relationship of Adherence Score to NEC Rates

Adoption of components of prevention evidence ranged from 11% who identified a strategy for timely recognition to 87% who had adopted a standardized feeding guideline (Figure 1). Adherence scores ranged from 3 to 10. The mean adherence score was 7.3 (SD 1.7). The 10 point adherence score was not related to the NEC rate across the sample. When a human milk sub-score was computed, it was related to lower NEC rates ($\rho = -0.26$, $p = .049$). Using colostrum for oral care was related to lower NEC rates ($\rho = -0.27$, $p = 0.032$). Units who used a feeding protocol showed higher NEC rates ($\rho = 0.27$, $p = 0.03$). Those units who used colostrum for oral care were also more likely to adopt strategies to limit inappropriate antibiotic exposure ($\rho = 0.34$, $p = 0.003$).

Human Milk Feeding Practices

The most consistently adopted prevention practice was to promote human milk, specifically mother's own milk (MOM) for feeding, with most units reporting use of multiple strategies in place. The most frequently reported strategies promoting human milk were the use of donor human milk (DHM) (n = 66; 86.8%) and the use of mother's colostrum for oral care (n = 57, 75%). When asked about strategies to promote human milk feeding, however, only 55% of clinicians who reported using DHM and 8.8% of clinicians who reported using oral colostrum identified these two practices as *strategies to promote the use of human milk* in their institutions. Two other common practices involved educating parents (n = 33, 43%) about the importance of human milk, especially MOM, and having lactation specialists to support mothers in providing milk for their infants (n = 28, 36.8%). Some clinicians also reported promoting early initiation of milk pumping (n = 12, 15.7%) and skin-to-skin holding (n = 11, 14.5%) as practices to increase a mother's milk production. Institution-based initiatives such as Baby Friendly Hospital designation were mentioned by some participants as facilitators to promoting breastfeeding and the use of human milk. Implementing peer lactation support was rarely used.

Standardized Feeding Protocol (SFP) Practices

Most respondents reported using SFPs (n = 67, 88%). The details of these SFPs regarding advancement, weight variations, time to fortification, and time to full feeding volume were not explored in this study. Importantly, participants revealed that how well they monitored compliance to the protocol was highly variable and largely infrequent. The most common compliance practice was to audit use (n = 31, 45.5%), but only 9 of those 31 (13.2% of total responding NICUs) reported auditing at regular intervals. A fraction (12 units, 18% of all NICUs) incorporated accountability to ancillary staff members such as nutritionists, dieticians, and developmental specialists into their SFP implementation plans. Other strategies to assure consistent SFP use included using a standard order set for the protocol and using visual cues like reminder cards where clinicians placed orders (Table 4). Ten NICUs identified that SFP

compliance was supported by “habit,” “peer pressure,” or group “buy-in.” Overall, there was very high “implementation” of SFPs but given the complexity of SFPs, the need for consistent delivery, and the opportunity for fragmented care we are concerned that actual use of SFPs may be much lower than participants reported.

--- Insert Table 4 about here---

Feeding Practices during PRBC Transfusion

There was wide variance in practice to withhold or administer enteral feeding during and around the time of PRBC transfusions (Shown in Figure 2). Specifically, 48 clinicians (63%) reported that they held feedings before, during, and/or after transfusion, and 17 (22%) reported that they did not. Of those who continued feedings, some made other adjustment such as reverting to trophic feedings (10 mL/kg/day; $n = 4$) or reducing feeding volume in half. Responses relating to length of time feedings were held varied among clinicians who reported holding feedings. Intervals ranged from 12 hours *before* transfusion to 24 hours *after* transfusion and most commonly included holding feedings *before, during, and after* transfusion. Only 2 reported holding feedings only during the transfusion. 28 respondents only reported a single time (i.e. 4 hours, 4-6 hours) rather than indicating the time in relation to the transfusion (i.e. 4 hours before, during, and after transfusion). Some of these respondents also indicated variation in their or their colleagues' practice (i.e. 6-12 hours) but did not include rationale for this variance. The most common interval reported was 3 hours before, during, and 3 hours after transfusion ($n = 8$, 10.5%), although a relative few used such an interval.

--- Insert Figure 2 about here---

Timely Recognition Practices

The question regarding communication during timely recognition of NEC revealed interesting and varied results. Very few actually addressed communication and the majority did not have a standardized process to quantify NEC risk, recognize and communicate NEC warning signs and ensure prompt treatment when NEC was suspected. For the purpose of

quantitative analysis, if a participant described a timely recognition strategy that you could take a picture of, it was counted as a systematic unit-centered strategy. If it relied on individual memory or use alone (and was not codified as a printed policy) it was coded as “no timely recognition practice.” Most responses addressed assessment and diagnostic strategies, such as abdominal assessments, abdominal x-rays, and laboratory testing (n = 23). Some participants noted the use of special tools and monitors to help recognize potentially critical illness in early stages, such as the HeRO monitor, pediatric early warning score (PEWS), and feeding tolerance algorithms. No clinicians mentioned using specific tools to improve communication (e.g. SBAR), risk scores (e.g. GutCheck^{NEC}, NeoNEEDS or eNEC) or strategies to engage parents in early warning or risk awareness.

Antibiotic Stewardship Practices

Respondents gave the fewest responses (n = 48, 63%) for strategies related to antibiotic stewardship (Table 5). Of these, 27% reported that they did not have a process to practice antibiotic stewardship. Of those who did have a process, the most common response was that a 48 hour rule-out period at birth was simply a “routine practice” that relied on the provider to remember to discontinue the antibiotics. Some used the EHR to automatically cancel the antibiotic after a rule-out period (17%) or relied on laboratory data to cancel antibiotics (16.7%). Rarely, respondents participated in a dedicated antibiotic stewardship program through their institution or health system (12.5%). Avoiding routine antibiotic administration on admission and working with pharmacists to monitor appropriate use was also described infrequently.

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Comparison of High Rate NICUs and Low Rate NICUs

We next evaluated practices in NICUs with very low rates of NEC (i.e. < 2%) to see if they differed from NICUs with very high rates of NEC (i.e. > 8%, Table 6). On average, low NEC rate NICUs were more likely to be a lower acuity or level and have lower bed capacity than high NEC rate NICUs. NICUs from the Western and Midwestern US were more represented in the

low NEC rate group, and NICUs from the Southern and Northeastern US were more represented in the high NEC rate group. The mean adherence score was similar between both groups, but the mean adherence score for combined human milk elements of the score was a full point higher in the low NEC rate group. Neither the total adherence score nor the human milk sub-score significantly differed between high rate and low rate NICUs.

The data demonstrated 5 areas in which NICUs with low rates of NEC differed from NICUs with high rates of NEC (Table 7). NICUs with low rates of NEC adopted all practices promoting a human milk diet more often (43.7%), especially the use of colostrum for oral care (75%). These NICUs also described more practices of antibiotic stewardship (68.7%) than the NICUs with high rates of NEC (55.6%). Alternatively, NICUs with high rates of NEC demonstrated better adoption of standard feeding protocols (100%), though whether providers were monitored regarding adherence to these protocols was unclear. High rate NICUs also demonstrated more adoption of standard practices for timely recognition of NEC, but the rates of adherence for timely recognition was low overall.

--- Insert Tables 6 and 7 about here---

Discussion

This study surveyed a diverse group of NICU clinicians representing many different geographic regions in the U.S., types of institutions, and levels of awareness about NEC prevention. Clinicians of varying roles (RN quality managers, Nursing managers, Medical directors, Physicians) responded to the survey, contributing to the breadth of perspectives elicited. Although the comprehensive 10 point NEC-Zero adherence score did not relate to lower NEC rates, the human milk adherence sub-score comprised of total use of human milk, donor milk use, and colostrum for oral care did. The only single component of the adherence score that was individually correlated with a lower NEC rate was the use of colostrum for oral care. Across the units, adoption of feeding protocols was common although monitoring adherence and assuring consistent strategies to assure it was used were rare.

This study highlights the wide variety of practices used in NICUs to prevent NEC. Strategies to promote a human milk diet were the most prevalent, with many units having multiple strategies to support mothers in lactation to provide human milk to babies. The practice of administering colostrum during oral care may help encourage mothers to provide milk in early postpartum days, but it may be beneficial independent of this support. This practice has been increasingly adopted since 2011 based on theoretical evidence that colostrum applied to the buccal mucosa and absorbed by the lymph tissue boosts immune system growth and decreases inflammatory response.^{32,33} Respondents did not describe their specific approach to administer colostrum for oral care (e.g. using non-absorbent swabs vs. small volume syringes; administration by parents or by staff). Quality improvement practices to bolster use of human milk have shown decreases in NEC, including the human milk bundle used in California,¹⁸ and the comprehensive program used in Canada.²³ Both programs prioritized lactation support, early pumping, and monitoring of human milk volumes.

Variation in NEC prevention practices was demonstrated despite each NICU's active involvement in quality improvement. Arguably, this detail limits the generalizability of our findings and may over-estimate the prevalence of NEC prevention in the U.S although respondents were not necessarily focusing their QI efforts on NEC prevention or reduction. Horbar and colleagues estimated the general pace of improvement for NEC as around 8 years that it would take for the lowest performing to achieve rates typical of the best performing, highlighting the wide variation from NICU to NICU.²⁰ Respondents indicated that actual practice may be sporadic and is often provider-dependent. Our findings reveal that implementation strategies for antibiotic stewardship and timely recognition were plagued by clinical uncertainty. Low awareness was made clear by some respondents who questioned the appropriateness of antibiotic stewardship or timely recognition in a NEC-related survey.

The comparison of low and high rate NICUs did not demonstrate clear differences in the adoption of most NEC prevention practices, although their application of implementation

strategies could be arguably different. The percentage of low NEC rate NICUs with the highest adoption of HM practices, however, was double the percentage of those from high rate NICUs and approached statistical significance. Practices more common in units with very low rates of NEC (i.e. $\leq 2\%$) compared to very high rates (i.e. $\geq 8\%$) included high human milk use, colostrum for oral care, and a practice in place to avoid prolonged antibiotics. Support to help parents provide skin-to-skin care, receive help from NICU-focused lactation specialists, or providing information about the value of human milk varied.

Likely the most surprising and contradictory finding of this study was the association we showed between high use of feeding protocols and higher NEC rates. This study was limited in that we did not ask details of their protocol or require them to have certain features to assure they used it consistently. We did ask about implementation strategies which left many immediate opportunities for improvement. The association of feeding protocols with higher NEC rates contradicts meta-analyses that show feeding protocols decrease NEC risk by approximately 67% in very low birth weight infants (9 studies, N=4755 infants),¹⁶ and by nearly 80% among infants born < 2500 grams (15 studies, N=18,160 infants).¹⁵ With that in mind, the recommendation to use a feeding protocol is unchanged in spite of the unexpected association in this self-report, survey based study. Ultimately, the most important thing to remember is that when using a feeding protocol, implementation strategies to make its adoption consistently should be considered (e.g. integration into standard order sets, use of audit and feedback, making other team members part of the implementation and adherence tracking). It is also essential to adopt an algorithm and a definition for feeding intolerance to determine when infants in the unit using the protocol should have their feeding interrupted. Readers may find Patel and colleagues experience with NEC QI and their feeding protocol modifications made along the way informative.¹³

This study revealed that the practice of holding feedings during and around PRBC transfusions was widely adopted, but there was a wide variation in the amount of time feedings

were held. The evidence to support this practice is somewhat contradictory and controversial.³⁴⁻

³⁶ Some cases of NEC cluster in the period within 24-48 hours after a PRBC transfusion, especially in the anemic infant.³⁷ Yet, the overall quality of the evidence linking transfusion to NEC is “very low” when systematically assessed using the GRADE criteria.³⁸ Our findings showed that it was common to hold, alter, or significantly reduce feedings before, during, and after transfusions. Respondents cited this uncertainty as their reasons for either not holding feedings or the variation in their practice for feeding during transfusions.

Limitations

While this study contributes better description of the state of NEC prevention practice adoption in US NICUs, it has important limitations. All data was self-reported by participants and may over- or under- estimate actual care. The NEC rate reporting was based on the standard definition for NEC used by the Vermont-Oxford Network, which some argue may over-estimate actual NEC.³⁹ We did not identify if radiologic or medical reviews were conducted to affirm the diagnosis of NEC within the units reporting. While open-ended response options followed direct and specific questions, participants may not have answered the questions in a way that would thoroughly describe their practices. One indication of this was the noted mismatch between responses to these questions and responses to direct questions (e.g. Do you use donor human milk?). While these response options allowed providers to elucidate specific practices or variations on practices within their unit, these responses were occasionally contradictory with other responses or were completely unrelated to the question. However, we managed this limitation by using the closed-ended responses only for calculating the adherence score. Finally, because we included quality-focused NICUs, our results have limited generalizability to others. Our respondents may have been more aware of current evidence-based practices, regularly share clinical practices within their community of practice or be more readily engaged in measuring their processes and NEC outcomes. We revealed high adoption of feeding protocols but did not systematically ask about its details that enabled better characterization of them. This

may have influenced our finding that feeding protocols were related to higher NEC, which contrasts sharply with meta-analyses that consistently show NEC reductions.^{15,16} There were also very few responses from Level II NICUs. While these units may not care for babies at highest risk for NEC, they do care for late-preterm babies who may develop NEC.

Implications for Practice

An encouraging finding from this study is that most NICUs prioritized human milk, especially MOM. Participants indicated most often that promoting MOM was their first-line intervention to prevent NEC. Empowering mothers to provide milk requires consistent messaging from clinicians about its benefits and lactation support. While respondents indicated a commitment to promote human milk feeding, studies have shown wide disparities in how consistently support is offered.^{40,41} Supporting availability of donor milk if MOM is not available will require changes to organizational policies and making stronger connections with milk banks. Reimbursement for donor milk varies widely although some states have made it reimbursable (Texas, California, Missouri, Kansas, and New York).⁴² At least one study showed that when donor milk was available, the use of MOM improved.⁴³ The high adoption of feeding protocols but low adherence monitoring and rare integration into electronic order sets is an opportunity that all NICUs can act on today. Strategies to engage families could strengthen the efforts of the clinical team (See <https://www.neczero.nursing.arizona.edu/>).

Implications for Research

Future studies are needed to explore the role of an adherence score to change clinicians' behavior and raise awareness about NEC. Testing the multi-faceted NEC-Zero bundle on clinical outcomes is needed. Transfusion-associated NEC continues to be a controversial topic for many clinicians, and our study demonstrated that this controversy plays out in wide variation in practices of feeding during blood transfusions. Recent studies suggest that it is perhaps severe anemia followed by a blood transfusion, not the transfusion itself that creates a high risk for NEC after a transfusion.⁴⁴ This controversy and confusion can only be

alleviated with more high-quality research examining transfusion-associated NEC and the potential detriment of holding feedings for long periods.

Conclusion

This study showed that adopting colostrum for oral care was associated with lower NEC rates and that units with the lowest rates had practices in place to adopt feeding protocols, minimize antibiotic exposures, promote human milk feeding and foster team collaboration for timely recognition. While the adherence score NEC-Zero was not related to NEC rate, the results demonstrate wide variation in NEC prevention practices across US NICUs. Adoption of using colostrum for oral care was the only individual prevention practice associated with a lower rate of NEC, though a combination score including the 3 prevention practices relating to use of human milk was also associated with lower NEC rates. Standardized feeding protocols and antibiotic stewardship were common but monitoring compliance to those protocols or practices was uncommon. Standardized practices for early recognition were not widely reported, and withholding feedings related to blood transfusion has become controversial due to current evidence. More consistent use of evidence-based implementations strategies including clinical decision support systems, standard order sets, and application of audit and feedback could improve delivery of NEC prevention practices in US NICUs. Maternal lactation support is paramount to accomplish this goal.

Legend of Tables & Figures

Table 1. *NEC Reductions after Quality Improvement Interventions*

Table 2. *Scoring Criteria for NEC-Zero Adherence Score*

Table 3. *Characteristics of NICUs Responding*

Table 4. *Standardized Feeding Protocol Compliance Practices*

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What this study adds:

- Among quality focused NICUs, the 10 point NEC-Zero adherence score did not relate to reported NEC rates but the human milk sub-score did.
- Across participating US NICUs general adoption of NEC prevention practices are widespread but use of evidence-based implementation strategies are less common.
- Variance in timing for holding feeding during transfusion was widespread. There was not consistency in the interval for feeding cessation and unclear criteria for restarting.

Summary of Recommendations for Practice and Research	
What we know:	<p>Necrotizing enterocolitis devastates fragile infants and though rare, leads to long-term complications for survivors.</p> <p>Variations in NEC rates are shown across neonatal intensive care units.</p> <p>Prevention practices to avoid NEC, when adopted using quality improvement methods, reduce NEC by 40-80%</p>
What needs to be studied:	<p>Impact of adherence to NEC prevention practices at the individual level.</p> <p>Motivators and barriers to adopting NEC prevention evidence.</p> <p>Impact of using a NEC prevention adherence score at NICU, system, and population level.</p>
What we can do today:	<p>Promote human milk feeding consistently and in a way that honors the mother's experience but prioritizes the message that her milk is medicine.</p> <p>Consider implementation strategies to improve use of evidence-based prevention. Go to https://www.neczero.nursing.arizona.edu/ for tools.</p> <p>Engage as a team to honor collective knowledge and integrate best practice into daily care for every infant.</p>

Table 1. NEC Reductions after Quality Improvement Interventions

Authors (years of QI)	N	Pre-QI Rate (%)	Post-QI Rate (%)	%NEC Decrease
Ellsbury (2007-2013) ¹⁸	58,555	6.6	3.9	- 41%
Patel (2009-2011) ¹⁰	389	16	3	- 81%
Talavera (2010-2012) ²¹	941	8	3.1	- 61%
Benjamin (2003-2012) ¹⁹	397	12	1	- 92%
Lee 2012 (2008-2011) ¹⁵	1,833	7	2.4	- 66%
AlShaikh (2009-2012) ²⁰	443	8.9	4.7	- 47%

Table 2. *Components of Adherence Score*

Score Component	Points Assigned
Usual dose of MOM*	
>75%	3
50-74%	2
25-49%	1
0-24%	0
Availability of HDM*	
Yes	1
No	0
Oral colostrum care*	
Yes	1
No	0
Standardized feeding protocol	
Yes	3
No	0
Medication stewardship	
Yes	1
No	0
Standard for timely recognition	
Yes	1
No	0
Total possible	10
* Items used to calculate human milk sub-score	

Table 3. *Characteristics of NICUs Responding*

N = 76	
NICU Level* N (%)	
2	2 (2.6)
3	36 (47.4)
4	38 (50)
Geographic Region** N (%)	
US West	15 (19.7)
US South	23 (30.3)
US Midwest	18 (23.7)
US Northeast	20 (26.3)
Capacity N (%)	
< 30 beds	15 (19.7)
30 – 59 beds	31 (40.8)
≥ 60 beds	30 (39.5)
Quality Improvement Level of Involvement N (%)	
Local	31 (40.8)
Regional	48 (63.2)
National	18 (23.7)
International	66 (86.8)
NEC Rates***	
≤ 2%	16 (21)
2.1 – 4.9%	11 (14)
5 – 7.9%	24 (32)
≥ 8%	10 (13)
Not reported	15 (20)
Mean NEC rate (SD)	4.61% (0.03)

Mean adherence score (SD)	7.34 (1.69)
Mean human milk adherence score (SD)†	3.96 (0.98)
<p><i>*AAP designation</i></p> <p><i>**Based on US Census regions</i></p> <p><i>***Based on rate for 2014; % of who responded</i></p> <p><i>†Combined score for oral colostrum use, donor milk, and availability of MOM</i></p>	

Table 4. *Implementation Strategies for Standardized Feeding Protocol Compliance Monitoring*

Strategy used among respondents (N= 68, 89% of NICUs)	N (%)
Auditing	31 (45.6)
Auditing at regular intervals	9 (13.2)
Accountability to multi-disciplinary team member (e.g. dietitian, nurse)	12 (17.6)
Standard order set within electronic health record	5 (7.4)
Visual reminder of protocol/ Quick reference guide	5 (7.4)
"Habit"/ "Peer pressure"/ "Buy in"	10 (14.7)
No practice to assure compliance	7 (10.3)
Note: Respondents could identify more than one implementation strategy or method to assess compliance	

Table 5. *Implementation Strategies for Antibiotic Stewardship*

Strategy used among responders (N=48, 63% of all NICUs)	N (%)
48 hour rule out period (order manually discontinued by provider)	22 (45.8)
Auto-stop on antibiotic orders	8 (16.7)
Antibiotic stewardship program at hospital or system level	6 (12.5)
Holding antibiotics on admit for non-septic causes of preterm labor	4 (8.3)
Pharmacist monitoring	2 (4.2)
Use of other lab values to justify stopping antibiotics	8 (16.7)
No implementation strategy reported	13 (27.1)

Table 6. *Characteristics of Low NEC Rate ($\leq 2\%$) and High NEC Rate ($\geq 8\%$) NICUs*

	NEC Rate $\leq 2\%$ N = 16	NEC Rate $\geq 8\%$ N = 10
NICU Level* N (%)		
2	1 (6.3)	0
3	8 (50)	4 (40)
4	7 (43.7)	6 (60)
Geographic Region** N (%)		
US West	5 (31.3)	1 (10)
US South	2 (12.4)	3 (30)
US Midwest	5 (31.3)	2 (20)
US Northeast	4 (25)	4 (40)
Capacity N (%)		
< 30 beds	7 (43.7)	2 (20)
≥ 30 beds	9 (56.3)	8 (80)
Mean NEC rate (SD)	1.03% (0.77)	9.6% (1.34)
Mean adherence score (SD)	8.38 (1.07)	8.11 (1.54)
Mean human milk adherence score (SD)†	4.25 (0.78)	3.56 (1.01)
*AAP designation **Based on US Census regions; non-US regions = 0 †Combined score for oral colostrum use, availability of DHM, and availability of MOM		

Table 7. *Difference in Adoption of NEC prevention practices by Low NEC compared to High NEC NICUs*

	Low NEC Rate $\leq$ 2% N = 16	High NEC Rate $\geq$ 8 % N = 9
Infants received > 50% maternal milk	16 (100)	8 (88.9)
Donor human milk available	13 (81.3)	7 (77.8)
Colostrum for oral care	12 (75)*	3 (33)
Promoting all HM strategies	7 (43.7)*	2 (22.2)
Standardized feeding protocol adopted	14 (87.5)	9 (100)*
Feedings held related to blood transfusion	12 (75)	7 (77.8)
Standardized approach to antibiotic stewardship	11 (68.7)*	5 (55.6)
Standardized approach to early recognition	1 (6.3)	2 (22.2)*
Adherence score $\geq$ 10	5 (31.3)	2 (22.2)
Note: 1 unit excluded from the high rate group because of missing data for the adherence score. Only significant differences are marked. * $P < 0.05$		

Figure 2. Duration of withholding enteral feeding in relationship to blood transfusion

- = Temporal-specific interval given (e.g. 4 hours before, during, and 4 hours after transfusion)
- = Non-specific interval (e.g. 6 hours)
- = Variation in time given (e.g. 4-6 hours)

Figure 1. Percentage of NICUs who had adopted a practice (N=76)