Tennessee's Tiniest Babies: The Prevention of Necrotizing Enterocolitis (NEC)

Tennessee Initiative for Perinatal Quality Care

Inter-Institutional Quality Improvement Project

Funded under a grant from the Tennessee Department of Health (TDH)

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The Tennessee Initiative for Perinatal Quality Care (TIPQC) would like to thank Josef Neu, MD. We have learned from his efforts and initiatives and have adapted portions from this work. Together, we can make a difference!

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Specific Acknowledgments

Thanks to those who served on the Tennessee Tiniest Babies Committee to help draft and formulate the ongoing quality improvement initiatives for the Level III and IV NICUs in the state, and especially thanks to the project leaders who met weekly to develop and finalize this project. Your tireless effort and dedication to our state's smallest citizens is inspiring—and will result in improved care, outcomes, and better quality of life for these infants and their families.

A Word from our Parent, Mary Catherine Tagg Burke, Patient Family Partner

"Parents with a baby in the NICU are very overwhelmed and need guidance and support. The NICU team can stand with the family as an advocate for the babies as well. Help support them by encouraging and sometimes pushing them to use their own milk as data and research has shown that mother's milk is best. It's not always easy for the mom, but support from the team will help her achieve the goal of using her own milk."

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Introduction: *What are we trying to accomplish?*

Problem

Tennessee's preterm birth rate is amongst the highest in the nation as approximately 11% of all births in Tennessee are preterm.[1] Deaths secondary to prematurity are one of the leading contributors to Tennessee's high infant mortality rate.[2] This has historically been approximately 7 deaths per 1,000 live births.[3] A stated national priority in the "2030 Healthy People" objectives is the reduction of the US infant mortality rate to 5 deaths per 1,000 live births.[4] For Tennessee to meet this goal, there will need to be a reduction of approximately 25% of the current infant mortality rate.

Preterm birth is a multi-factorial problem that, despite national and state efforts remains relatively unchanged.[5] [6] Specifically, an increase in the number of the earliest preterm births (infants with birth weights of <750 g and gestational age of <28 weeks) has been implicated as the primary contributor to infant mortality rates.[7] Very preterm births, defined as <32 weeks and birth weight <1500g, represented 33% of all infant deaths in one report. In this study, more than two thirds of deaths attributable to preterm birth occurred during the first day of life and 27% of deaths occurred within the next 27 days. [8]

Variation in outcomes among NICUs have also been reported.[9] [10] [11] Practice variation, even amongst providers in the same group, can be a contributing factor to these varied outcomes.[12] [13] We have fortunately witnessed significant progress in the care of preterm infants over the past few decades. These advances have gradually moved from new technologies and medicines to how we care for these infants. This has led to improved survival rates and outcomes by the centers who have focused on improving the delivery of care.[14]

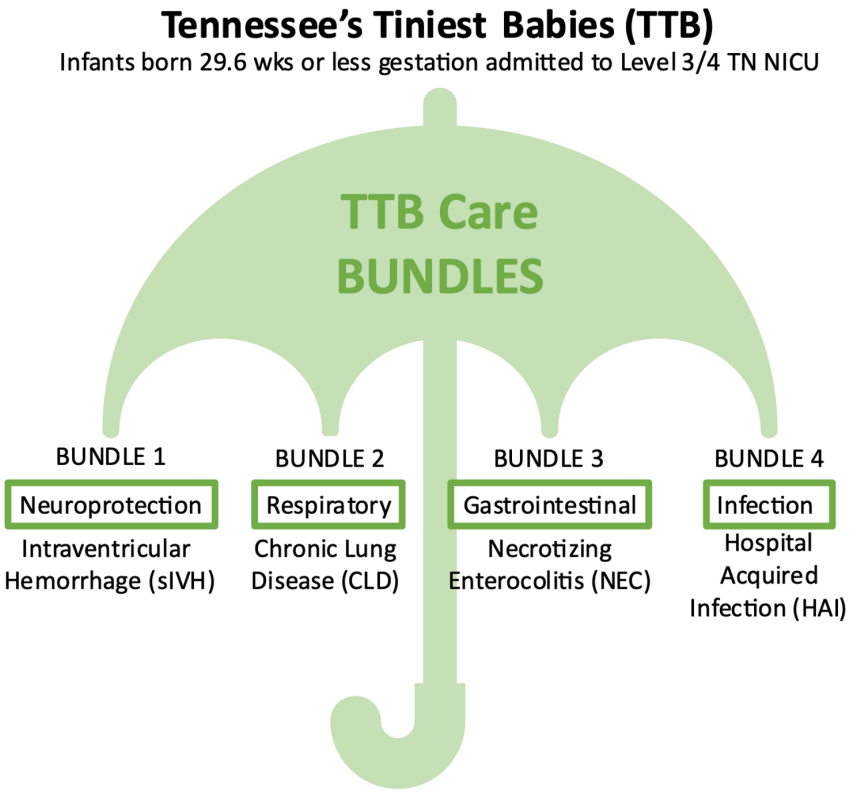
Tennessee has thirteen level 3 and 4 NICUs across the state who care for infants <32 weeks and a birth weight <1500g. In 2020, 1,352 babies, or 1.7% of live births, were born very preterm in Tennessee and cared for at these facilities. [3] Statistically, this group of infants represents approximately one-third of our state's infant deaths which include different outcomes amongst different data stratification groups. To lower Tennessee's infant mortality rate, meet the goal as put forth in the "2030 Healthy People" objectives, and improve care, a collaborative approach to the care along with the implementation of effective care strategies for Tennessee's Tiniest Babies should be undertaken.

Project Description

We are seeking to lower Tennessee's infant mortality rate to 5 deaths per 1,000 live births by focusing on the implementation of potentially better practices (PBPs) which can improve the survival rates and the outcomes of preterm infants born at less than 29.6 or less weeks gestation.

The development and implementation of the "Tennessee's Tiniest Babies'' (TTB) project will occur from Q3 2022 to Q3 2027. The project has been developed and will be launched in phases determined by specific care *bundles* – see Figure 1. The intent is to have participating hospitals implement the care bundles *cumulatively* – incorporating the potentially better practices from each bundle into their unit. *This toolkit is focused on the Necrotizing Enterocolitis (NEC) care bundle.* The project is proposed to end in Q2 2026, with data collection continuing through Q3 2026.

Figure 1: Tennessee's Tiniest Babies (TTB) Care Bundles



TIPQC agrees to the following:

- Provide a toolkit (see attachments) and other resources to participating teams.
- Offer monthly huddles, quarterly learning sessions, and annual statewide meetings.
- Facilitate the sharing between participating teams, allowing them to learn from each other.
- Facilitate capture of data metrics and provide reports to participating teams to show their progress towards improvement.
- Provide guidance and feedback to participating teams, facilitating their achievement of the project aim.

Participating teams will agree to the following:

- Hold regular, at least monthly, team meetings.
- Regularly review and revise team goals, current system, opportunities for improvement, and barriers.
- Plan and conduct tests of the recommended changes detailed in this toolkit.
- After successful testing and adaptation, implement the changes in their facility.
- Attend and actively participate in the monthly huddles, quarterly learning session, and annual statewide meetings.
- Capture and submit the defined project data as required (with minimal to no data lag).
- Submit a monthly report that includes data as well as information on changes being tested and/or implemented.
- Strive to achieve the project aim and the project's process and structure measure goals:
    - At least 90% compliance on all defined process measures.
    - Have all structures (defined by the structure measures) in place by the end of the project.

A dedicated extremely low birth weight (ELBW) team of staff (physicians, NNPs, nurses, respiratory therapist, speech/physical/occupational therapists, and lactation consultants) that have received special training in care of these babies can have a big impact on overall care delivered. Many units across the country have developed small baby units dedicated to providing care for the ELBW infants and have seen a significant reduction in mortality and morbidity in this

population. Providing detailed guidelines to develop small baby units are out of scope for this project, but each unit should assess its own capability / resources to develop specialized protocols/guidelines to care for their smallest babies.

Of note, success in the reduction of NEC has been reported by NICUs who have implemented various quality improvement initiatives such as the use of multidisciplinary teams employing standardized feeding protocols, increasing the use of human milk, and minimizing stress to the immature gut.

Rationale

Despite early improvements with concerted efforts to improve the care of expectant mothers and infants, Tennessee's preterm birth rate and infant mortality rate have shown no significant, nor maintained, drop over the past decade. Thirteen NICUs across the state care for infants which comprise approximately one-third of the state's infant mortality rate. No project has addressed the optimization of care in this population to improve the infant mortality rate despite this population's statistical importance.

There is a significant variation of care in the very preterm infant (29.6 weeks or less). Some NICUs in Tennessee have individually developed and implemented potentially better practices for the care of this population. Resources at other centers have made this difficult.

The California Perinatal Quality Care Collaborative (CPQCC) has previously demonstrated the impact a state's PQC can have on the mortality and morbidity in the very preterm infant population. CPQCC led a Delivery Room QI Collaborative which resulted in a reduction in mortality, severe intraventricular hemorrhage (sIVH), chronic lung disease (CLD), and retinopathy of prematurity (ROP) in infants 29.6 weeks or less.[15] As the state's perinatal care collaborative, TIPQC is poised to guide participating level 3 and 4 NICUs in the sharing of information and resources so that potentially better practices for this population can be developed and implemented across the network. Several of the participating hospitals already submit their data to the Vermont Oxford Network.

Expected Outcomes and Benefits

Participating in this project will help participating centers improve the care of the very preterm infant (29.6 weeks or less) at their site. If successful, this project will (in turn) result in an improved survival rate with decreased morbidities in very preterm infants born in Tennessee. This will lead to meeting the "2030 Healthy People" objective. Ultimately, improving outcomes in Tennessee's Tiniest Babies should lead to decreased long-term costs to the healthcare system.

Aim Statement

The aim of the overarching TBB quality improvement (QI) project is:

- To reduce the mortality in infants less than or equal to 29.6 weeks gestational age by 25% of the Tennessee state baseline. There should be a dose response effect seen with the implementation of bundles which address broader global aims.

<u>The aims of this NEC care bundle are:</u>

- Primary aim: 25% relative reduction (compared to 2021-2023 institutional baseline data) in necrotizing enterocolitis in infants less than or equal to 29.6 weeks gestational age in participating TN NICUs by Q2 2026, final data by Q3 2026.
- Secondary aim: 10% relative reduction in mortality of targeted infants by hospital discharge or 40 weeks corrected gestational age, whichever comes first (compared to 2021-2023 institutional baseline data) by Q2 2026, final data by Q3 2026.
- The proposed aims of the past and forthcoming care bundles are:

- 25% relative reduction (over last 3 years institutional baseline) in *severe intraventricular hemorrhage* in infants less than or equal to 29.6 weeks gestational age in participating TN NICUs by Q2 2024, with final data by Q3 2024.
- 25% relative reduction (over last 3 years institutional baseline) in *chronic lung disease* in infants less than or equal to 29.6 weeks gestational age in participating TN NICUs by Q2 2025, with final data by Q3 2025.
- 25% relative reduction (over last 3 years institutional baseline) in *hospital acquired infections* in infants less than or equal to 29.6 weeks gestational age in participating TN NICUs by Q2 2027, with final data by Q3 2027.

Summary of Evidence: *Prevention of Necrotizing Enterocolitis (NEC)*

Necrotizing enterocolitis (NEC) remains a significant and devastating condition in neonatal intensive care units (NICUs), predominantly affecting preterm infants, particularly those with very low birth weight (<1500 grams). It is characterized by intestinal inflammation, which can progress to necrosis and perforation, leading to high morbidity and mortality rates. NEC is multifactorial, with associated risk factors which include prematurity, formula feeding, intestinal ischemia, bacterial colonization, and the immaturity of the infant's immune system. The disease not only results in immediate complications like sepsis and surgical interventions but also long-term issues like neurodevelopmental impairments and growth failure. Despite advances in neonatal care, NEC incidence has not significantly decreased over the years, making it a critical area for intervention in NICUs.

Quality improvement (QI) initiatives have been implemented across various NICUs to reduce NEC, with notable success in reducing its incidence. These initiatives often involve multidisciplinary teams employing standardized feeding protocols, enhancing the use of human milk, and minimizing unnecessary interventions that could stress the immature gut. Significant reductions in NEC rates through the consistent use of human milk have been reported, with some achieving reductions from 19.5% to 6% after implementing potentially better practices (PBPs). Other reported PBPs include efforts to reduce dysbiosis by introducing probiotics, standardizing care during blood transfusions, and ensuring early and conservative feeding practices. These efforts have collectively resulted in NEC rate reductions of up to 83% in some settings, demonstrating that targeted and coordinated QI can significantly impact this disease.

The literature strongly supports several key interventions to prevent NEC. The use of human milk, particularly mother's own milk, is paramount, as it contains protective factors like immunoglobulins and growth factors that bolster gut maturation and reduce inflammation. When mother's milk is not available, donor human milk is recommended over formula. The implementation of standardized feeding protocols that advocate for uniform feeding advancement have been shown to be effective. Additionally, probiotics have emerged as a promising intervention, with evidence suggesting that certain strains can significantly lower NEC incidence. Finally, limiting the use of antibiotics to prevent disruption of the gut microbiome, careful monitoring of feeding tolerance, and promoting a healthy microbiome through other supportive measures are also endorsed by quality improvement literature as effective strategies to reduce NEC in at-risk neonates.

After a review of the literature, TIPQC recommends the following Potentially Better Practices as noted below.

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Potentially Better Practices for the Prevention of NEC

All improvement requires change. And while there are many kinds of changes that will lead to improvement, the specific changes are developed from a limited number of *change concepts*. As described in the Model for Improvement, "A change concept is a general notion or approach to change that has been found to be useful in developing specific ideas for changes that lead to improvement." These change concepts are used to design and run tests of change (i.e., Plan-Do-Study-Act (PDSA) cycles) to see if they result in improvement.

A similar idea to change concepts are *Potentially Better Practices* (PBPs), which are a set of clinical practices that have the potential to improve the outcomes of care. They are labeled 'potentially better' rather than 'better' or 'best' because until the practices are evaluated, customized, and tested in your own institution, you will not know whether the practices are truly 'better' or 'best' (or 'worse'). Depending on the circumstances in your facility, you may have to implement other practices or modify existing ones to successfully improve outcomes. The PBPs in this collection are not necessarily the only ones required to achieve the improved outcomes targeted. Thus, this list of PBPs is not exhaustive, exclusive, or all inclusive. Changes in practice, guided by these PBPs, will require testing and adaptation to your circumstances and context to achieve measured improvements in outcomes.

In designing this project and reviewing the evidence for practices that can reduce NEC, TIPQC's experts have recommended that all participating NICUs implement all these PBPs at a minimum. The relative decrease of NEC when a bundle of PBPs has been adopted has been reported to be 24.5–91%. It is vitally important that each NICU forms a multi-disciplinary team who can effectively implement these PBPs and possibly identify others which may be ideal for your facility and situation.

PBPs – Standardized Feeding Protocol

Quality improvement initiatives focusing on standardized feeding protocols (SFPs) in neonatal intensive care units (NICUs) have demonstrated significant success in reducing the incidence of necrotizing enterocolitis (NEC). These protocols typically standardize the initiation, advancement, and management of enteral feeds, aiming to provide a consistent, evidence-based approach to feeding preterm infants. Previous work has shown that SFPs can decrease NEC rates by as much as 67% to 83%, with some NICUs reporting a reduction from baseline rates of 19.5% to as low as 2-3% post-implementation. The use of SFPs reduces variability in care, minimizes feeding intolerance, and can promote the use of human milk, which is known to lower NEC risk. Importantly, these protocols can include clear guidelines for when to pause, resume, or advance feeds, based on signs of feeding tolerance or intolerance, which helps in preventing the overfeeding or underfeeding that can contribute to NEC development. The evidence underscores the necessity of SFPs for not only reducing NEC but also for improving overall neonatal outcomes by ensuring that each infant receives optimal nutritional support tailored to their physiological maturity and clinical condition.

We recommend that each NICU develop a unit specific feeding protocol that will provide clear instructions for the medical/nursing staff on advancement and fortification of feeds using available products. As an example, Jackson-Madison County General and Vanderbilt's NICUs have kindly shared their protocols. The effectiveness and safety of

JMCGH NICU protocol [Appendix 1] was recently demonstrated in the Connection study where they were shown to have the most rapid feeding rate of the 95 participating NICU's and a low rate of NEC. This protocol is adapted slightly for 22–23-week infants and other infants that staff determines may need a slower start to feeding. The Monroe Carell, Jr. Children's Hospital at Vanderbilt protocols [Appendix 2] are unique in that they use a stratified feeding based on a larger range of birth weights. The decision to move away from a "one size fits all" approach was based on a large population of ELBWs that were not able to tolerate a protocol with faster advancement.

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PBP – Mother's Own Milk

Mother's own milk (MOM) provides protection against NEC in the preterm infant, reducing risk of NEC when compared to formula feeding. Use of MOM may be dose dependent – infants have decreased risk of NEC with increasing percentage of MOM feeds. MOM contains microbes needed to develop the preterm infant microbiome and human milk oligosaccharides which support the growth of a healthy gut microbiome. Preterm milk differs from term milk and contains higher amounts of protein and fat shortly after birth and higher concentrations of beneficial bioactive compounds, such as human milk oligosaccharides and growth factors.

We recommend the following interventions to promote breast milk use and support for mothers who are providing breastmilk in the NICU. Best practices for initiation of lactation for mothers of preterm infants include initiation of pumping within one hour of birth, use of an electric pump that mimics the sucking pattern of an infant, and access to lactation consultants or providers. Establishing and maintaining a milk supply requires continued support for the mother including sharing expected volumes of milk targets (> 500 ml/day by day 14), encouragement of skin-to-skin holding of infants, and support during stressors such as returning to employment or times away from the NICU. Furthermore, we recommend that NICUs provide information to mothers on the importance of MOM and strategically place signage in the NICU so this can be encouraged.

MOM should be the priority to feed the preterm infant but when MOM is not available or is insufficient in quantity, donor breast milk is recommended. The pasteurization process to prepare donor milk destroys the bacterial pathogens in the milk but also reduces beneficial bioactive agents normally found in human milk. However, donor milk also reduces the risk of NEC and should be considered the "next best option" after MOM.

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PBP – Engaging Parents in Prevention of NEC

As noted in the beginning of this tool kit, TIPQC is indebted to our parent advisor on this project. It is critical to engage and encourage parents, and especially moms to pump and breastfeed as much as possible. It is crucial to educate parents, explaining conditions ahead of time, possibly when discussing the importance of MOM. Parents need to understand the importance and benefit of their milk to their baby, including initial drops being medicine to the baby. In addition, other ways mom can be engaged with their child might include Kangaroo Care or other PBPs as listed below. Each NICU should make parent engagement a priority and look for ways to do this with staff and signage in the NICU to encourage provision of MOM.

PBP – Donor Milk

Necrotizing enterocolitis (NEC) is a complex disease influenced by various risk factors, including immature blood flow autoregulation, intestinal dysbiosis, an impaired mucosal immune system and cellular structure, and an inflammatory response to feeding components such as bovine protein. Maternal breast milk is rich in protective elements such as secretory IgA, lactoferrin, lysozyme, prebiotics (oligosaccharides), as well as maternal macrophages and neutrophils, making it ideal for very low birth weight (VLBW) preterm neonates. However, when maternal breast milk is unavailable, donor breast milk is a preferred substitute over preterm infant formula because it retains some, though not all, protective elements found in fresh breast milk. This preference is supported by the American Academy of Pediatrics (AAP) guidelines.

Randomized controlled trials and quality improvement studies have demonstrated that the use of donor breast milk as a substitute for infant formula when maternal breast milk is not available can reduce NEC rates. These findings are summarized in a 2024 Cochrane systematic review, which states: "...donor human milk reduces the risk of NEC (risk ratio (RR) 0.53, 95% confidence interval (CI) 0.37 to 0.76; I^2 = 4%; risk difference (RD) −0.03, 95% CI −0.05 to −0.01; 11 trials, 2261 infants; high certainty evidence)." A summary of the 2022 AAP recommendations indicates: "The AAP recommends pasteurized donor human milk when a mother's milk is unavailable or contraindicated. Fortification of mother's or donor milk with either bovine or human milk-derived human milk fortifiers should be considered to optimize growth in the VLBW infant."

The Tennessee Initiative for Perinatal Quality Care (TIPQC) recommends exclusive use of maternal breast milk for infants whose birthweight is <1500 grams or gestational age at birth <32 weeks. When maternal milk is unavailable, pasteurized donor breast milk is recommended as a substitute over the use of infant formula. It remains unclear when to discontinue the use of donor breast milk and transition to formula when these preterm infants are beyond the highest risk period and maternal breast milk is still not available. Centers need to determine the appropriate corrected gestational age to transition to preterm infant formula if maternal breast milk is not available.

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PBP – Oral Immune Therapy

Oral care with breast milk or colostrum, also known as oral immune therapy, has numerous benefits to both infant and mother. Administration of small drops of breastmilk in the infant's cheeks can stimulate a positive immunological response by the infant due to direct absorption of cytokines in breast milk. Studies of oral immune therapy have shown a decrease in necrotizing enterocolitis and ventilator associated pneumonia. Parental participation when giving oral immune therapy also encourages family empowerment in infant care and promotes continued pumping. Nearly all preterm patients can benefit from oral care with breastmilk. Contraindications may include infants with recent operative repair of esophageal atresia or fistulas or with recent esophageal perforations or an inability to use maternal milk due to maternal health conditions.

We recommend that oral immune therapy be started as soon as mother's milk is available after admission in all infants unless there is a clear contraindication. Oral immune therapy should be continued until the infant is orally feeding by bottle or breast. Evidence for the use of donor milk for oral immune therapy has not been established and may not provide the same immunological benefits as mother's milk due to donor milk pasteurization. Therefore, donor milk is not recommended for oral immune therapy.

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PBP – Antibiotic Stewardship

Intestinal dysbiosis is a risk factor for NEC. A clinical practice associated with intestinal dysbiosis is unnecessary post-natal exposure to broad-spectrum antibiotics, which has been correlated with an increased risk of NEC. A meta-analysis published in 2023 demonstrated an O.R. of 0.57 for antenatal exposure to antibiotics (protective), while pooled data from 10 studies showed an O.R. 2.72 (1.65–4.47) for the development of NEC after neonatal exposure. Early antibiotic exposure with a duration <48 hours can cause transient dysbiosis, however, prolonged broad-spectrum antibiotics can cause permanent dysbiosis. Antibiotic stewardship involves reducing unnecessary exposure to broad spectrum antibiotics by limiting empiric antibiotics in infants <32 weeks at birth to those with risk factors or clear indications of sepsis, limiting the continuation of broad-spectrum antibiotics beyond 24-48 hours when blood cultures are negative, and by narrowing the spectrum of antibiotic coverage of culture-positive infections according to sensitivity patterns.

A multidisciplinary antibiotic stewardship program is a critical component of a bundle of practices aimed at reducing the incidence of NEC in VLBW/<32-week infants. Tools that can aid in antibiotic stewardship include maintaining an antibiogram of unit bacterial sensitivities to guide use of empiric antibiotics, clinician guidelines to discontinue empiric antibiotics when culture results are negative between 24-48 hours, utilizing hard stops within EMRs when antibiotics are started, having clinical pharmacists on team rounds to participate in daily team “time-outs” for all babies on antibiotics, and tracking antibiotic utilization rates (AUR) at both the unit and provider levels as a process measure.

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PBP – Non-evidence-based practices

- Avoid non-evidence-based practices which are aimed at reducing/detecting earlier NEC such as checking post-feeding residuals, holding feeds during transfusions, slow advancement of feeds after trophic feeding has been completed. Routinely monitoring gastric residuals in preterm infants is not associated with decreased NEC or mortality and it may increase time to full feeds, frequency of feeding interruptions, TPN days, and the risk of invasive infections. There is insufficient evidence that holding feeds during blood transfusions is associated with a reduced incidence of NEC. Lastly, advancement of feeds (daily increments less than 24 mL/kg) compared with faster rates do not likely reduce the risk of NEC, death, or feeding intolerance in infants less than 1500 grams. Extrapolating this information to the extremely low gestational age infant, however, should be done with caution. Faster rates of feeding advancements may also decrease the risk of invasive infection in the right population as lengthy central line days may be avoided.
- Avoid non-evidence-based practices for other conditions that may increase the risk of NEC, such as the routine use of H2-blockers and proton pump inhibitors for uncomplicated GER. Available evidence does not demonstrate a relationship between gastro-esophageal reflux and apnea, bradycardia and desaturation events, signs of infant discomfort, feeding intolerance, and infant behaviors such as arching. Evidence does, however, support an association between the use of PPIs and H2-Blockers and the development of NEC in VLBW preterm infants.

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PBP - Commercial Products

Human milk-based fortifiers

Human milk-based nutritional fortifiers are available and are advertised as being able to possibly reduce NEC in preterm infants. Studies and reviews have previously suggested that an exclusive human milk diet, including fortifiers, significantly reduces the incidence of NEC compared to diets that include cow's milk-based fortifiers or formula. This has, however, not been universal and recent studies have questioned this. Each NICU should evaluate their baseline NEC rate, the literature, and the cost of these products to determine the cost effectiveness for their setting. Some studies have argued that while there are possible health benefits, the high cost of these fortifiers might not be justifiable in every healthcare setting, especially when other options might help reduce NEC rates. Determination to use is a decision of each NICU participating in this project.

Probiotics

Probiotics have shown substantial value in preventing NEC in preterm infants, with meta-analyses and systematic reviews indicating that they can reduce the incidence of NEC by as much as 50-60%. Specific strains, particularly combinations of Bifidobacterium and Lactobacillus, have been associated with decreased NEC rates, shorter hospital stays, and improved feeding outcomes. In 2023, the US Food and Drug Administration issued warnings regarding the use of probiotics in NICUs for preterm infants due to concerns for contaminants, which essentially halted their use. They emphasized that no probiotic product has been approved by the FDA for use as a drug or biological product in infants, thereby lacking the rigorous premarket evaluation for safety, effectiveness, and quality.

The complete results of the Connection study are eagerly awaited as a pharmaceutical grade probiotic was compared to placebo in 2,153 < 1500 g infants over five years. Although the study did not achieve statistical significance for its primary endpoints of NEC prevention and sustained feeding tolerance, it did show a significant 27% reduction in all-cause mortality. Despite the lack of significance for the primary endpoints, the drug's safety profile showed no increased risk of sepsis. Publication in a peer-reviewed journal is expected in 2025 as is an FDA decision. Similar to the human milk fortifiers, the expected high cost of this product might not be justifiable in every healthcare setting, especially when other options might help reduce NEC rates. Determination to use is a decision of each NICU participating in this project.

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PBP – Nursing Focus: Education, Assessment, & Nursing Care

Standard nursing education is needed. Suggestions for this education are included in Appendix 3.

PBP - Optimal Cord Clamping (OCC)

Data suggests that delayed cord clamping (DCC) in preterm infants may reduce the incidence of necrotizing enterocolitis (NEC). Systematic reviews have shown a significant decrease in NEC with DCC, with one review indicating a 40% reduction in risk. However, individual studies vary; for instance, a 2013 study on very preterm infants did not find a statistically significant difference in NEC rates between DCC and early cord clamping (ECC) groups in primary analysis, though subgroup analysis hinted at benefits for very preterm infants. Comprehensive reviews confirm a potential benefit but stress the need for more research due to limitations like small sample sizes and undefined optimal timing for DCC. There's also specific attention to small for gestational age preterm infants, where the evidence is mixed but suggests potential benefits for severely SGA preterm infants. Overall, while promising, the evidence for DCC reducing NEC in preterm babies is not definitive, highlighting the need for larger, high-quality trials.

TIPQC has developed an Optimal Cord Clamping Project designed for all infants born in Tennessee. Further information on Optimal Cord Clamping and how to improve your rates can be obtained in the TIPQC toolkit for this project.

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Measures: *How will we know that a change is an improvement?*

Target population

Infants born *29.6 or less weeks gestation* admitted to one of the participating NICUs for care. This includes all infants including transfers admitted within 24 hours of birth.

Outcome measures

Use the following VON definition of NEC when capturing data on these Outcome Measures:

NEC is diagnosed by radiographic and clinical definition 10 days of life or later and includes at least one of the following clinical findings:

- Bilious gastric aspirate, residual or emesis
- Abdominal distension or discoloration
- Occult or gross blood in stool (no fissure)

AND at least one of the following diagnostic imaging findings:

- Pneumatosis
- Portal venous gas
- Pneumoperitoneum

Outcome measures will be calculated from the captured "TIPQC TTB- NEC PROJECT CLINICAL CARE CHECKLIST" form and entered into the SimpleQI platform. See the form for details.

#1. Percent necrotizing enterocolitis (NEC) among targeted infants born *29.6 or less weeks gestation* admitted to one of the participating NICUs for care

#2. Percent mortality of targeted infants from NEC

#3. Percent mortality by hospital discharge or 40 weeks corrected gestational age, whichever comes first (among targeted infants)

Baseline Data:

- Participating NICUs will retrospectively capture and report annual mortality and annual NEC rates (both among the target population) for the 3 years prior to the project start (2021, 2022, and 2023).
- This baseline data will serve as the "institutional baseline" from which they are trying to improve (planned 25% reduction in NEC and 10% reduction in mortality).

These Baseline Data will be calculated from the captured "TIPQC TTB- NEC PROJECT BASELINE Data Collection Form" in SimpleQI.

Process measures

- Percent of targeted infants receiving mother's own milk at any point during hospitalization
- Percent of targeted infants receiving mother's own milk from day 21-28 of their hospitalization
- Percent of targeted infants receiving oral immune therapy at any point during hospitalization
- Percent of targeted infants with cord clamped ≥ 60 seconds after birth

Reported monthly. Numerator being measure and denominator being any infant born less than 29.6 weeks gestation admitted to hospital, including transfers admitted within 24 hours of birth.

These Process measures will be calculated from the captured "TIPQC TTB- NEC PROJECT CLINICAL CARE CHECKLIST" form.

Balancing measures

- Days on TPN first month of life
- Number of blood cultures drawn until 40 weeks' CGA and number of positive blood cultures
- NPO first month of life for greater than 24 hours related to "feeding intolerance"

Reported monthly. Numerator being measure and denominator being any infant born less than 29.6 weeks gestation admitted to hospital, including transfers admitted within 24 hours of birth.

These Balancing measures will be calculated from the captured "TIPQC TTB- NEC PROJECT CLINICAL CARE CHECKLIST" form.

Structure measures

- Policy & Procedure[B]
    - Does your hospital have a standardized feeding policy and procedure (reviewed and updated in the last 2-3 years)?
        - The policy and procedure should include standardizing the initiation, advancement, the management of enteral feeds, and an agreed upon definition of feeding intolerance.
        - Should include fortification and nutritional values guidance
        - Teams should review and revise/update their policy and procedure if it already exists.
        - Examples include Connection Study Data; VUMC (3 protocols for 22-23 weekers, larger babies and late preterms)
    - Does your hospital have a standardized policy and procedure for transfusion practices (reviewed and updated in the last 2-3 years)?
        - Includes addressing myths on holding feeds
        - Teams should review and revise/update their policy and procedure if it already exists
    - Does your hospital have a standardized policy and procedure for antibiotic stewardship including choices and duration of therapy for suspected NEC or treatment of medical NEC (reviewed and updated in the last 2-3 years)?
      Teams should review and revise/update their policy and procedure if it already exists
    - Does your hospital have a standardized policy and procedure for oral immune therapy (reviewed and updated in the last 2-3 years)?
      Teams should review and revise/update their policy and procedure if it already exists
    - Does your hospital have a NICU specific lactation consultant?
    - Does your hospital have a patient/family partnership? (Likert scale: 1=not started; 3=started; 5=fully in place)

[B] *Report your progress in the implementation of guidelines percent increments (0%, 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, 100%) quarterly.*

- Provider & Nursing Education[C]
    - Addressing non-evidence-based practices and FDA approved medication and updates including:

        - Providers educated on avoiding non-evidence-based practices as indicated in the PBP section on non-evidence-based practices including checking for residuals, holding feeds during transfusions, slow advancement of feeds after trophic feeding is completed, and routine use of H2-blockers and proton pump inhibitors for uncomplicated GER.
        - Nurses educated on avoiding non-evidence-based practices as indicated in the PBP section on non-evidence-based practices including checking residuals, holding feeds during transfusions, slow advancement of feeds after trophic feeding is completed, and routine use of H2-blockers and proton pump inhibitors for uncomplicated GER.
    - Feeding Intolerance
        - Providers educated on feeding intolerance
        - Nurses educated on unit agreed upon definition of feeding intolerance
    - Care of feeding tubes, residuals
        - Nurses educated on care of feeding tubes, residuals

[C] *Using the following increments (0%, 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, 100%), report quarterly, the % of providers that have completed NEC education. Example: Q1 2024 - 10% (total %) of staff have completed training - Numerator = 10 Example: Q2 2024 - 20% (total %) of staff have completed training - Numerator = 20*

These Structure measures will be calculated from the captured in Simple QI. An example for data collection is provided in the "TIPQC TTB- NEC PROJECT QUARTERLY CAPTURE OF STRUCTURE MEASURES" form.

Data Collection

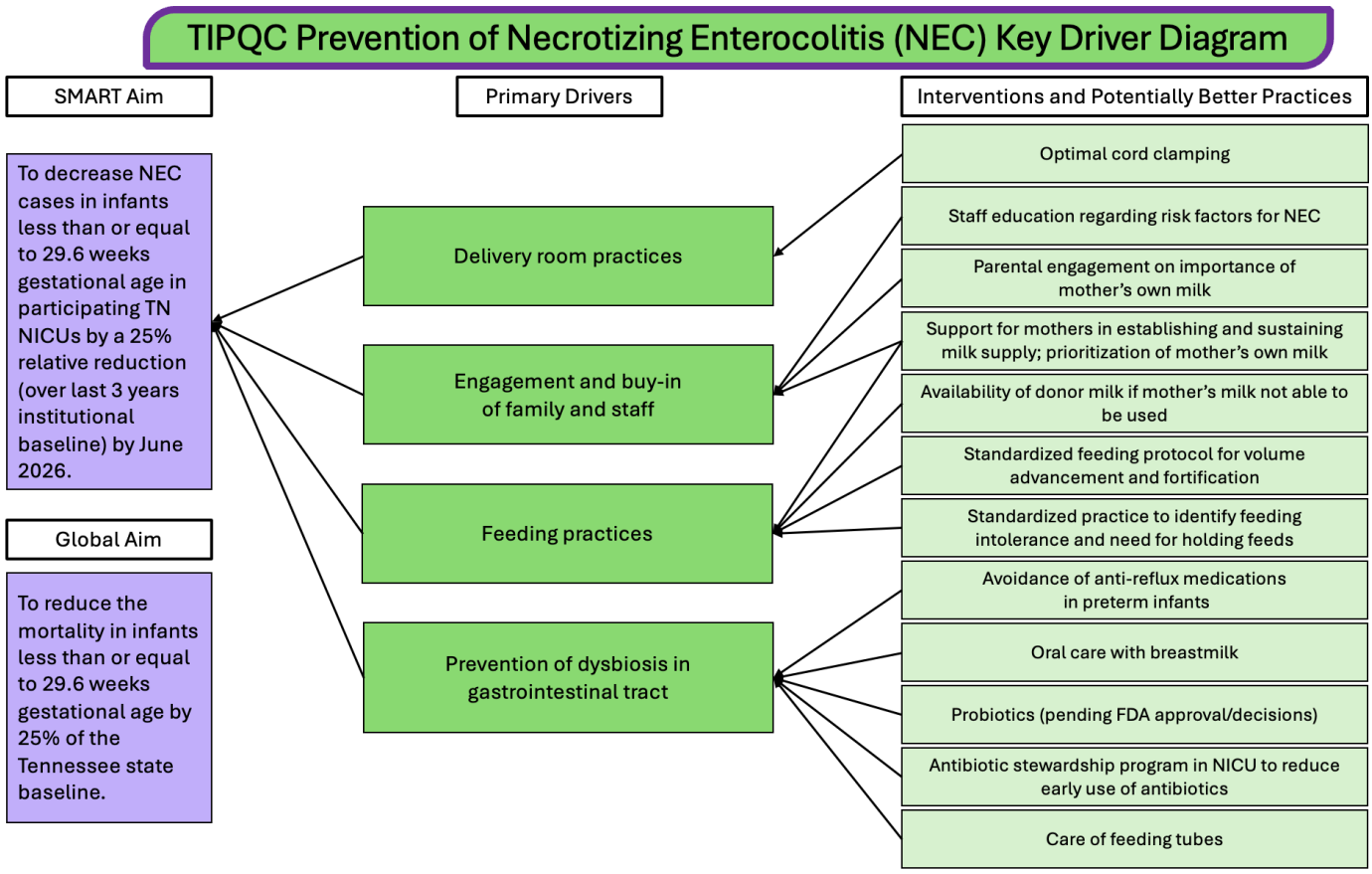
Participating NICUs will capture data on each infant using the provided "TIPQC TTB- NEC PROJECT CLINICAL CARE CHECKLIST" form. Each team will determine the process in which the data will be collected (eg, on paper at the bedside and from the targeted infant's EMR). A record for each targeted infant will be captured using SimpleQI.

As mentioned, the defined Outcome, Process, and Balancing measures will be calculated from the individual targeted infant records captured in SimpleQI. Up-to-date data reporting is available to the participating NICU teams as data is entered.

The two defined Structure measures will be collected quarterly using SimpleQI and entered in by hospital teams. An example for data collection is provided in the "TIPQC TTB- NEC PROJECT QUARTERLY CAPTURE OF STRUCTURE MEASURES" form. Each participating NICU will be sent an email each quarter as a reminder to submit their data. Generated data reports will also include summaries of these Process and Structure measures.

Key Driver Diagram

A driver diagram is a visual display of a QI collaborative's (or team's) theory of what "drives," or contributes to, the achievement of the project aim – that is, the project's "theory of change." The far-right column of the driver diagram lists the specific *change ideas to test* using PDSA cycles.



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Appendix 1 - Jackson Madison County General Hospital NICU

Neonatal ICU Feeding Protocol

Date and initial in the appropriate box to verify advancement of protocol

Day	1	2	3	4	5	6	7	8	9	10	11
Birth Weight < 600 grams	1 ml	1	2	3	4	5	6	7	8	9	10
600-699 grams	1 ml	2	3	4	5	7	9	11			
700-799 grams	2 ml	3	4	5	7	9	12	13			
800-899 grams	2 ml	3	5	7	10	13	16				
900-999 grams	2 ml	3	5	8	11	14	17				
1000-1099 grams	3 ml	6	8	12	16	20					
1100-1299 grams	4 ml	8	12	16	20						
1300-1500 grams	5 ml	10	15	20	25						

When infant reaches yellow highlighted box increase E/DBM by 6cal/oz using Prolacta +6

When infant reaches green highlighted box increase E/DBM by 2cal/oz using SHMF to 22kcal

When infant reaches blue highlighted box increase E/DBM by 4cal/oz using SHMF to 24kcal

Appendix 2 – Monroe Carell Jr. Children's Hospital at Vanderbilt NICU

Enteral Feeding Guidelines

EBM is always preferrable | DBM is recommended if no EBM for infants < 34 weeks AND < 1500g

Birth Weight < 1000 g – Volume Recommendations

Oral immune therapy with each care time

- Start trophic feeds by DOL 1 at 1 ml q 12
- Advance to 1 ml q 6 hours x 48 hours
- Advance to 1 ml q 3 hours x 24 hours
- Advance feeds by 10 ml/kg/day (nearest ml) until fortified to 24 kcal/oz **and** > 80 ml/kg/day
- Advance feeds by 20 ml/kg/day until at goal

Caution in infants with in utero abnormal blood flow (absent end diastolic flow, growth restriction) or hypotension requiring vasopressors

Birth Weight < 1000 g – Fortification Recommendations

Start with plain breastmilk until 60 ml/kg/day, then a step each day:

- Advance to **22 kcal/oz**
- Keep 22 kcal/oz for 24 hours; increase only volume that day
- Advance to **24 kcal/oz**
- Add 1 ml LP and increase volume

Increase to **26 kcal/oz** if poor growth and unable to advance feeding volume, using DBM, or mother has low milk supply.

Use Similac HMF (HP) concentrated liquid

_____

It is not recommended to advance caloric density and feeding volume the same 24 hours

Birth Weight 1001 - 1500 g - Feedings and Fortification Recommendations

Oral immune therapy with each care time

- Start initial feeds at 30 ml/kg/day and advance by 30 ml/kg/day (if hypermagnesemia present consider slower initiation and advancement)
- Fortify to 22 cal/oz with HMF when feeds advance to 60 ml/kg/day
- Fortify to 24 cal/oz with HMF the day following 22 cal/oz fortification
- Use HMF HP for babies with weight <2.5kg and ≤24kcal/oz.
- Add 1 ml liquid protein (per 50 ml breastmilk) the day following 24 cal/oz fortification

Birth Weight >1500 g - Feedings and Fortification Recommendations

Oral immune therapy with each care time

- Infants 1501-1800 g: Start initial feeds at 30 ml/kg/day and advance by 30 ml/kg/day
- Infants > 1800g: Start initial feeds at least 40 ml/kg/day and advance by 40 ml/kg/day. Healthy late preterm infants may PO ad lib/breastfeed larger volumes.
- Fortify to 22 cal/oz with HMF when feeds advance to 60 ml/kg/day
- Fortify to 24 cal/oz with HMF the day following 22 cal/oz fortification
- Use HMF HP for babies with weight <2.5kg and ≤24kcal/oz.
- Add 1 ml liquid protein (per 50 ml breastmilk) the day following 24 cal/oz fortification

Late preterm/Term infants may not need full fortification

Appendix 3 - Nursing Care

Background Information and Education for Neonatal Intensive Care Unit (NICU) Staff:

A. Definition and Etiologies of Necrotizing Enterocolitis (NEC)
   a. An acquired disease that most commonly affects preterm babies. Approximately 90% of cases are noted in preterm, occurring within the first week of life to several weeks of life. This potentially devastating disease most commonly affects the terminal ileum and proximal colon but can affect any area of the small and/or large intestine. [1, 2]
   b. The etiology for NEC is considered multifactorial. Factors may include:
      i. Intestinal ischemia and inflammation. Ischemia could be related to asphyxia, hypoxemia, hypotension, hypovolemia, patent ductus arteriosus, blood or exchange transfusions, umbilical arterial catheters, severe stress, any hypothermia. Tumor necrosis factor α and platelet activating factors may lead to inflammation, injury to the intestinal mucosa, free radical release, and ischemia-reperfusion injury. [1,3]
      ii. Bacterial colonization. Human milk facilitates the colonization of a balanced, nonpathogenic flora in the gut that helps to prevent bacterial overgrowth. Intestinal motility develops during the third trimester of gestation when the motor complexes appear and migrate. This motility is important because stasis may expose the intestinal epithelium to potentially harmful substances. [1,3]
      iii. Enteral feedings. 90-95% of NEC cases are proceeded by enteral feedings, even those who have received human milk. There is an increased risk when hyperosmolar formulas and medications are administered and when feedings are advanced rapidly. Human milk contains secretory immunoglobulin A, lactobacilli, complement components, lysozymes, lactoferrins, macrophages, and lymphocytes which are thought to provide some protection to the premature gut. [1,3]
   c. Risk factors for NEC include prematurity, prolonged duration of empiric antibiotic administration, and hypoplastic left heart syndrome (HLHS). Prematurity is the only consistent risk factor for NEC. [3] The prolonged duration of initially given empiric antibiotics is also associated with increased rates of NEC. The antibiotics are thought to disrupt the normal colonization of the neonatal intestinal microbiota. [3] There is also an association of increased NEC rates and premature babies with HLHS.

B. Diagnosis
   a. Clinical findings
      i. Abdominal distension, tenderness, visible loops, decreased peristalsis, discoloration
      ii. Lethargy
      iii. Apnea and bradycardia
      iv. Occult or frank blood in the stool
      v. Temperature instability
      vi. Decreasing urine output
      vii. Bilious vomiting
      viii. Hypotension
      ix. Hypoperfusion
         1. **Note:** In the past, the presence of gastric residuals was thought to be a clinical sign of NEC. Newer evidence reveals that residuals are not predictive of NEC, but often precipitate feedings being held and parenteral nutrition being restarted. This can

contribute to poor growth and increase the amount of time that it takes to reach full feedings. [3]

b. Radiologic findings
    i. Diffuse gaseous intestinal distension – nonspecific, but can be an early sign
    ii. Asymmetric bowel gas pattern – dilation in one area, gasless in another
    iii. Persistently dilated loop of bowel
    iv. Pneumatosis intestinalis – this is the presence of gas within the bowel wall and is considered pathognomonic of NEC.
    v. Portal venous air
    vi. Pneumoperitoneum – due to an intestinal perforation
c. Laboratory findings
    i. Abnormal complete blood count – leukopenia, thrombocytopenia, leukocytosis
    ii. Metabolic acidosis
    iii. Electrolyte imbalances
    iv. Abnormal blood gas – hypercapnia, hypoxemia
    v. Abnormal clotting studies
    vi. Blood in the stool
    vii. CHO malabsorption [1, 3]

C. Prevention Strategies
a. Mother's Own Milk (MOM). Mother's Milk should be prioritized over donor milk or formula. Human milk contains secretory immunoglobulin A, lactobacilli, complement components, lysozymes, lactoferrin (a glycoprotein that provides protection against sepsis), macrophages, and lymphocytes. These substances are thought to provide protection to the premature gut. [1,3] It also contains oligosaccharides which have probiotic characteristics that protect from bacterial colonization and overgrowth. [2] Providing a diet of MOM, donor milk, and a milk based human milk fortifier (HMF) decreases the risk of NEC. [2] Bovine based HMF products have been associated with an increased risk of NEC because they lack the bioactive components that are protective of the gut. [2] Bovine feedings should be the last choice when feeding premature babies. [2]
b. Donor Human Milk. It is recommended that donor milk be used if MOM is not available. Cohen et al. and the California Perinatal Quality Clinical Consortium (CPQCC) both report a decrease in the incidence of NEC when donor milk is available. [5] Human milk facilitates the colonization of a balanced, nonpathogenic flora in the gut that helps to prevent bacterial overgrowth. [3]
c. Minimal Enteral Nutrition (MEN). Consider providing minimal enteral nutrition. This type of nutrition has also been called "priming" or "trophic feedings". This has been used as a safe alternative to complete fasting and does not increase the risk of NEC. [6] Lack of food can lead to intestinal mucosal atrophy. Enteral feedings stimulate various hormonal secretions as well as GI tract motility. Some studies suggest that a lack of enteral feedings was associated with decreased mesenteric artery blood flow. [7]
d. Oral Care with Colostrum. Oral care for very low birthweight infants with colostrum has been shown to decrease the incidence of culture-proven sepsis and mortality. It has also been shown to decrease the hospital length of stay. Whether it decreases the incidence of NEC has been shown both ways. [8, 9]
e. Strict adherence to handwashing policies. This is a key intervention for preventing the spread of any type of infection. Many interventions have been trialed to decrease the rate of infection in vulnerable infants, but hand hygiene and the use of maternal breast milk have been shown to be the most effective. [10]
f. Care of Feeding Tubes.

i. Adhere to hospital policies regarding the method for placement and verification of feeding tubes. Parker et al. found that up to 44% of enteral feeding tubes were malpositioned which increases the risk of complications. Movement as little as 0.5 cm could move the tube out of the stomach. According to Parker et al., the nose-ear-midway to umbilicus (NEMU) method of tube insertion resulted in fewer incorrect insertion depths. Their work found that using the nose-to-ear-to-xiphoid (NEX) method or the auscultation of the "whoosh" were not as reliable when verifying tube placement.[11] Tubes should be firmly secured to help prevent dislodgement.

ii. Adhere to hospital policies regarding the dwell time for gastric tubes, and the replacement of feeding sets.

1. There is evidence that enteral feeding tubes will rapidly develop a microbial biofilm, almost serving as a reservoir of pathogens. These pathogens have been reported to grow within 8 hours of the tube being inserted. Many pathogens that have been cultured from feeding tubes are nosocomial – including coagulase negative staphylococci, enterococcus sp., and Enterobacteriaceae. When present, these pathogens are then able to inoculate new feedings as they are given. These biofilms that develop are likely influenced by both bacterial and the site of placement. [10, 11] The immaturity of the immune and GI systems, increased intestinal mucosal permeability and the presence of dysbiotic intestinal microflora also make these babies vulnerable to illness from the colonization of enteral feeding tube. [12] Longer dwell times have been associated with an increased risk of infection from central lines and urinary catheters, it is reasonable to think the same could be true of enteral feeding tubes.[12] Hurrell et al were able to quantify this in their work.[13] Variables that affected the colonization of enteral feeding tubes include gestational age, corrected age, birthweight, feeding regimen, and exposure to histamine H2 blockers, probiotics, and antibiotics [13]

iii. Enteral feeding tubes are for single use only and should be discarded if they become dislodged. [3]

iv. Handle key parts of the tube as little as possible when inserting to try to avoid contamination.

D. Nursing Care

a. Continued patient assessment. Promptly report any subtle changes in clinical exam or status to the medical staff provider. The initial signs of NEC can be vague and non-specific, and the progression can be rapid. NICU nurses play a pivotal role in the early identification and progression of the infant with NEC, often being the first to respond and notice the subtle signs and changes in the patient. [3]

b. Initiate and maintain NPO status.

c. Initiate and maintain gastric decompression with a vented sump tube (Replogle) to low continuous wall suction until gastric output is minimal. Anticipate the need to measure gastric output periodically and replace with physiologic fluid.

d. Initiate and evaluate IV access and TPN therapy.

e. Assist in obtaining labs and x-rays a septic workup.

i. Labs that may be ordered include blood culture, complete blood count, blood glucose, blood gas, electrolytes, lactate levels, c-reactive protein, PT, PTT, fibrinogen, and antibiotic levels.

f. Anticipate serial x-rays – usually every 6 to 8 hours.

g. Administer antibiotics as ordered. Anticipate that antibiotics may be given anywhere from 3 to 14 days, depending on clinical status.

h. Monitor fluid and electrolyte balance.

i. Assist with respiratory support as needed by the newborn.

j. Administer other medications as ordered
    i. Vasopressors
    ii. Pain medications
    iii. Volume expanders
k. Administer blood products as ordered – platelets, fresh frozen plasma, packed red blood cells.
    i. Obtain the newborn screen prior to the transfusion, if one has not already been obtained or a follow up screen is needed.
l. Careful monitoring of intake and output.
m. Maintain strict hand hygiene for anyone touching the infant – physicians, nurse practitioners, respiratory therapy, other professional staff, and parents.[10]
n. Be prepared for surgical intervention should it become necessary.
    i. According to Gregory et al, 20-40% of babies with NEC will need surgery. For those who survive the surgery, complications include short gut syndrome, TPN cholestasis, prolonged length of hospital stay, poor long-term outcomes and impaired growth. [3]

E. Outcomes
    a. Disease outcomes. The survival rate varies and is dependent on the amount of bowel involvement and resection. Mortality is higher if the infant is acidotic and has hypotension requiring vasopressors prior to surgery. [1]

F. Education and Support for Parents to Include the following:
    a. Definition and risk factors for NEC
    b. Importance of MOM as a prevention strategy for NEC
    c. Use of donor milk, when MOM is not available, as a prevention strategy for NEC
    d. Disease, medical management, and nursing care, as applicable
    e. Assist the mother to start pumping as soon after delivery as possible
    f. Connect mother with NICU lactation consultant for continued expert guidance
    g. Importance of handwashing
    h. Provide emotional support and initiate consults as needed or requested
    i. Facilitate the parents' involvement in the newborn's care as much as possible. This is a scary diagnosis for families, families who may still be reeling from the birth of an unexpected premature newborn. [3]

G. Other Considerations
    a. Early, consistent lactation support should be emphasized to staff and parents.
    b. Prenatal consults and discussions to include the importance of mother's own milk.
    c. Consider the use of a consent if the mother cannot or does not provide her own milk for the newborn and formula is needed.

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