Anatomy of a disaster – overview of necrotising enterocolitis

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When an infant is born prematurely, many of the body's systems are not quite developed enough to resist the onslaught of the world outside the womb. The gastrointestinal tract is just one of them. Despite many decades of research and clinical experience, necrotising enterocolitis (NEC) in the premature infant remains an enormous, often unexpected challenge from a diagnosis and treatment perspective, as well as the associated morbidity and mortality, as well as poor outcomes of survivors. Being aware of the risk factors can assist in earlier detection and possible avoidance of severe, surgical NEC as these infants have the worst outcomes. Implementing exclusive breast milk feeding protocols, avoidance of lower saturation targets, and supplementing the infant to enhance the robustness of the microbiome with probiotics are among the most valuable treatment algorithms currently evidenced in research.

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Introduction

Necrotising enterocolitis (NEC) is one of the most puzzling, dreaded conditions in the Neonatal Intensive Care Unit (NICU). It remains the most common gastrointestinal tract (GIT) emergency with significant neonatal morbidity resulting from premature birth.[1] More than 90% of cases are found in premature infants, 90% of the time after feeds have been initiated.[1] It is a disease of multifactorial pathogenesis that often leads to mortality.[2] Despite NEC being the topic of numerous research projects over the last forty to fifty years since its first description in the 1950s and 1960s, the incidence and outcomes have not changed dramatically.[2] Delving into the pathophysiology of NEC introduces a plethora of possibilities as to exactly what causes, worsens and might improve, or even prevent, this perfect storm.[3]

In this article, the author will attempt to review the history, diagnosis and staging, treatment, outcomes and evidence-based techniques for prevention.

Background

In 1978, Dr Martin Bell and colleagues from the Departments of Surgery and Pediatrics at the Washington University School of Medicine and St Louis Children's Hospital in St Louis, Missouri, published an article entitled "Neonatal Necrotizing Enterocolitis Therapeutic Decisions Based upon Clinical Staging". They reviewed a group of newborn infants that were evaluated, admitted and treated at two hospitals in the late 1960s and the early 1970s. All forty-eight infants were prospectively classified and treated according to a basic staging system – hence, the Bell's staging system of NEC was first used.[4]

Infants (n = 48) were categorised into three stages, based on the severity of the infant's condition – varying from suspected to confirmed, and finally severe. It is worth mentioning that the majority of the infants were being fed infant formula, one had only sterile water as a feed and the remaining one had not received any feed whatsoever.[4]

Stage 1, or "Suspected NEC", included a combination of more general signs and symptoms of neonatal disorders, some GIT manifestations with radiographic evidence of mild ileus and including any history of maternal stress. Stage 2, the "Definite" stage included more specific signs and symptoms of occult or GIT bleeding together with abdominal x-rays confirming "significant intestinal distention"; other disorders such as malrotation must have been excluded at this stage. Stage 3 was considered "Advanced", including deterioration of the vital signs with bowel necrosis or at least evidence of pneumoperitoneum on x-ray.[4]

Treatment of suspected NEC commenced by stopping feeds and undertaking numerous blood tests, stool and urine sample analysis as well as "nasogastric decompression" along with daily x-rays. Once the diagnosis became that of "definite NEC", topical antibiotics were introduced (nasogastric gavage) along with the mentioned treatment and often continued intravenously for 10–14 days. Feeds were only re-introduced after the patient was asymptomatic

for 72-hours. Stage 3 invariably included surgical intervention due to intestinal perforation or failure to respond to treatment, and thus deterioration. The thirty-eight infants that were diagnosed as Stage 2 and 3 ranged in gestational age from 26 to 40 weeks, with a weight range of 780 grams to 3 620 grams. A total of twelve infants demised, and six of these deaths (15%) were attributable to NEC, according to the researchers.[4]

Today, forty-two years later, current publications in the form of research articles and textbooks of neonatal care still refer to Bell's staging – although the current literature is littered with many nuances such as "classical NEC", and there is a strong belief that what is still being diagnosed in clinical neonatology as NEC, is a range of diseases with similar signs and symptoms rather than a single disease entity.[5]

A recent review of the incidence of NEC in developed countries, confirms the incidence of NEC mortality being up to 23.5% (Bell stage 2+), increasing to over 50% for extremely low birthweight (ELBW) infants who underwent surgery. Morbidity is significant among survivors – neurodevelopmental delay varies between 25–61% and intestinal complications 15–35%. These numbers confirm the devastation of a disease among a cohort of patients where current survival of premature infants (28 to 32 weeks gestation) is approaching 90% intact survival and 95% overall.[6]

Models from the USA estimate the cost of NEC between 500 million and 1 billion dollars annually, with hospital stay increasing by as much as 20 to 60 days for affected infants (compared to other premature infants).[5]

In South Africa, one publication (2012) reports the incidence of NEC in a subset of low birth weight infants (< 2 500 grams) screened for sepsis, up to 30% with no indication of mortality due to NEC.[7]

Prematurity is not a condition that resolves upon discharge of the infant from the NICU, adding the long-term sequelae of NEC, such as continued gastrointestinal side-effects, often requiring follow-up surgery and repeated hospitalisation, delayed growth as well as poorer neurodevelopmental outcomes than their peers, all adding to the already substantial burden of cost.[6]

NEC is not to be confused with spontaneous intestinal perforation, which adds to the challenge of prevention of these devastating diseases. NEC in the very low birth weight infant (VLBW) mostly occurs during week three to four of life and is of multifactorial origin as will be discussed below. Spontaneous intestinal perforation (SIP) is more common within the first two weeks after birth and has strong associations with extreme prematurity in combination with the use of nonsteroidal anti-inflammatory drugs as well as delayed passing of meconium.[8]

Currently, there seems to be little agreement on a clear diagnostic framework, which further complicates an already complicated disease.

See Figure 1 for the Vermont Oxford Network Manual of Operations for 2020 definition of NEC for the purpose of recording on the network.[9]

…Necrotising enterocolitis (NEC) diagnosed at surgery, at post-mortem examination, or **clinically and radiographically using the following criteria:**

At least one of the following clinical signs present:

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

And

At least one of the following radiographic findings present:

- Pneumatosis intestinalis
- Hepato-biliary gas
- Pneumoperitoneum

Figure 1: The Vermont Oxford Network Manual of Operations for 2020 definition of NEC for the purpose of recording on the network.

Increasing awareness of the most notable risk factors might assist in accurately identify NEC at the earliest possible opportunity (see Table I).

The publication of evidence-based guidelines for the prevention of NEC is not necessarily succinctly summarised in publications, but careful analysis of what not to do, offers guidance towards what can be done.

It is well accepted that an exclusive breast milk diet is the preferred option for VLBW infants due to the immunological benefits conferred by breast milk and the subsequently reduced incidence of NEC.[14]

Implementation of structured feeding protocols with regards to stopping, starting, fortification and advancement of feeds is known to offer numerous advantages to the NICU patient – among which is the reduced incidence of NEC.[15]

Anaemia in the ELBW infant is never ideal, but the latest evidence suggests that transfusion-associated necrotising enterocolitis (TANEC) might not be related to the transfusion of red blood cells, but rather inflammation as a result of the anaemia. Recently, the association between increased proteobacteria in infants with a haematocrit less than 30% has been confirmed.[16]

Further evidence was found in an animal model, establishing the link between NEC and anaemia,[16] whilst retrospective data analysis showed a correlation between restrictive blood transfusion protocols and reduction in the incidence of various morbidities – among which periventricular

Table I: Summary of the most notable risk factors for NEC

Risk factors from evidence-based research	Risk
Perinatal conditions	
Chronic conditions such as intrauterine growth restriction, small for gestational age or acute instances such as placental abruption	Increased risk[10]
Delivery – normal vaginal delivery (NVD) vs. Caesarean section	Inconclusive – many complex variables such as microbiome[10]
Delayed cord clamping at premature delivery	Inconclusive in various randomised controlled trials (RCT)[10]
Early neonatal	
Reduced gestational age (GA) and birth weight (BW)	Increased risk[10]
Ante-natal steroid (ANS) use	Reduced risk internationally,[10] not so in SA[11]
Poor transitioning after birth (as indicated by low APGAR or early mechanical ventilation)	Only observational, not contributary[10]
Indwelling umbilical catheters	Inconclusive[10]
Patent ductus arteriosus (treated or untreated)	No association[10]
Sepsis	Increased risk[10]
Anaemia	Associated risk[10]
Red cell transfusion	No increased risk, may be protective[10]
Feeding during transfusion	Review of moderate-quality evidence suggests "withholding feeds during the peritransfusion period may reduce the risk of TANEC in preterm infants"[12] Adequately powered RCTs are needed to confirm these findings*
Early erythropoietin (< 8 days)	Decreased risk[10]
Restricted fluid intake	Decreased risk[10]
Caffeine (intravenous) and postnatal steroids	Not a risk factor[10]
Supplements such as lactoferrin, arginine	Protective effect[10]
Feeding	
Breastmilk only	Decreased risk[10]
Supplemental fortified donor human milk versus preterm formula	Decreased risk vs. formula[10]
Delayed feeding in infants < 1500 g or < 32 weeks	No difference in NEC risk[10]
Feeding advancement at slow rate (10–20 mL/kg/day) versus a faster rate (30–40 mL/kg/day)	No difference[10]
Standardised feeding protocols	80% reduction in NEC vs. non-standardised [10]
Probiotics	Decreased risk[10] "Administration of multispecies lactobacillus and bifidobacterium probiotics has been associated with a significantly decreased risk of NEC and late-onset sepsis in our neonatal unit, and no safety issues"[13]
Medications that promote acid suppression	Significant increased risk[10]

*Transfusion-associated necrotising enterocolitis (TANEC) as stage ≥ 2 NEC occurring within 72 h of packed red blood cell (PRBC) transfusion.[12]

leukomalacia (PVL), retinopathy of prematurity (ROP), sepsis and the diagnosis of NEC.[17]

Additionally, Stenson delved further into the data that was collected during the Neonatal Oxygenation Prospective Meta-analysis (NeOProM) trials, further investigating the most concerning result. In an effort to reduce the incidence of ROP by using a lower target range (85–89%) of oxygen saturation (SpO_2), rates of mortality and certain morbidities were, in fact, increased. Deduction from this result is therefore suggestive of increasing saturation target limits to 93–97% might protect against NEC more – but more research is needed in this area for the development of clearer guidelines.[18]

Current treatment paradigms to reduce the incidence of sepsis and NEC should be considered. Introducing routine use of multi-strain probiotics have been shown to decrease the incidence of NEC, surgical NEC and late-onset sepsis.[13,19,20]

A Cochrane review in 2014 suggested preparations containing *lactobacillus* in combination with *bifidobacterium* would be the most effective. In 2019 a NICU in the UK reported routine use of multispecies lactobacillus and bifidobacterium probiotics significantly decreased the risk of NEC and late-onset sepsis without safety issues. They found it to be a relatively cost-effective and easy treatment paradigm with significant results.[13]

Keeping in mind the summary of risk factors above, preventing NEC completely could be a very challenging task. Because NEC is such a devastating disease with such far-

reaching long-term outcomes, there are some tools available for early detection and prevention of more severe stages of NEC.

SIGNEC or the Special Interest Group for Necrotising Enterocolitis (SIGNEC – https://signec.org/) was founded in 2012 in the UK by a clinician with an interest in NEC. Since then, special interest groups have been founded across the globe – NEC Society in the USA (https://necsociety.org/), the Pequenos Grandes Guerreiros (PGG) Institute in Brazil (http://pequenosgrandesguerreiros.org/en/) and The NEC Alliance in Australia (https://web.facebook.com/thenecalliance/?_rdc=1&_rdr).

Most of them offer guidance to both families of infants with NEC as well as healthcare professionals with regards to NEC specialists, definitions, treatment options, and research projects. The Department of Nursing at the University of Arizona (https://neczero.nursing.arizona.edu/gutchecknec) went one step further and formalised a Neonatal NEC Risk Index measurement tool, GutCheck^{NEC}.[21] They offer free downloadable documents for the purpose of doing research, using it as a quality improvement project, or similar clinical projects. The documents offer guidance regarding NEC risk assessment for infants in two weight categories, less than 2 500 grams and less than 1 500 grams. Also included is a SBAR section – a "structured communication form for clinical concern" when NEC is suspected – SBAR being an acronym for situation, background, assessment, and recommendation.

Conclusion

The global incidence of premature birth is a constant reminder that certain conditions will probably never be completely preventable. While we care for the many premature infants in NICUs around the world, our activities are focused on nurturing them to ensure optimal, intact development and growth whilst trying our best to successfully manage the numerous challenges along the way.

NEC is a common, multifactorial, most likely inflammation-mediated disruption of the premature infant's microbiome that can lead to devastating morbidities, long-term gastro-intestinal and neurodevelopmental sequelae in survivors and sometimes even mortality. Through regular updates of the latest evidence, we can increase awareness of early signs and symptoms, keep risk factors in mind and implement changes to daily practice – enhancing the ability to avoid and better manage such a perfect storm.

Conflict of interest

The author is employed by Safeline Pharmaceuticals who distribute LaBiNIC Infant Probiotics Drops in South Africa.

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Links to GutCheck^{NEC} documents

GutCheckNEC (superscripted) can be accessed at https://neczero.nursing.arizona.edu/gutchecknec