Necrotizing Enterocolitis: An Enduring Enigma

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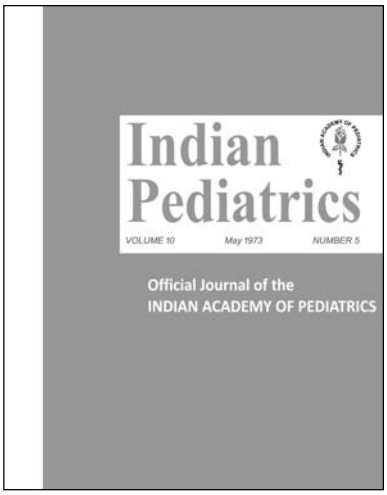
Necrotizing enterocolitis (NEC) is one of the most destructive gastrointestinal emergencies in premature neonates. First described over a century ago, this disease still poses a conundrum. The evidence on pathogenesis is exiguous, diagnostic criteria are nebulous, management is arduous and frequently fruitless, and prevention strategies are often inefficacious. This is especially exasperating to neonatologists because it mainly affects preterms who have often survived the initial stormy days, and when everyone believes the battle to be won, they are surprised by a vexatious disease with high fatality and crippling sequelae. Published fifty years back, the article on necrotizing enterocolitis in the newborn by Karan and Pathak [1] was the first reported case series from India, and deserves a thorough review in view of the persisting perplexities posed by this disease.



THE PAST

The case series by Karan and Pathak was done over a nine-month period in the neonatal nurseries in the Institute of Child Health, Niloufer Hospital Hydera-bad, between January and September 1972. During this period, 24 cases were diagnosed as NEC, with an incidence of 1.9% and a nearly equal male to female ratio. All but three babies had low birth weights and were preterm. The seven hospital born babies and a few extramural cases were admitted by 16 hours, while the rest of referred cases were admitted between 2 to 18 days. Nine of the babies had suffered from severe birth asphyxia or respiratory distress in the early neonatal period.

The authors found that while diarrhea of varying severity was almost always the initial event in combination with abdominal distention (75%), other presentations included blood stained stools (67%), and bilious, blood stained, or fecal vomiting (54%). The full blown picture of NEC emerged within seven days of onset of diarrhea in a majority of cases. Refusal to feed and lethargy, along with jaundice, were the most common nonspecific signs and symptoms, followed by temperature instability, respiratory difficulties, and shock and pallor in terminal cases. Stool culture was done in nearly half the cases and revealed multidrug-resistant coli-form organisms. In radiological features, intestinal distention with or without fluid levels, pneumatosis intestinalis, hepatic portal venous gas, and pneumoperitoneum were classical findings. Aspiration pneumonia or staphylococcal pneumonia were the most common associated features. Serial *X*-rays were important in delineating clinical stage, as features were determined largely by the timing of the *X*-rays. Histological features were characterized by necrosis and ulceration of mucous membranes, inflammatory exudates, gas spaces in submucosa and subserosa, and pseudomembrane formation. The babies were kept nil per orally, gastric decompression done, intravenous fluids infused, and blood transfusion planned as required. Local and systemic antibiotics were given in all cases. One case underwent ileal perforation repair and anastomosis but succumbed postoperatively. Despite the aforesaid therapy, mortality was ubiquitous, with only one survivor.

The first reported case resembling NEC was described by Billard in 1928, while working at the Hspital des Enfants-Trouvés (Hospital for Foundling Children) in Paris [2]. Terming the disease as 'gangrenous enterocolitis,' he described a nine-day-old, sick neonate with swollen abdomen, copious green diarrhea, subsequently having tense abdomen with passage of bloody stool, slowing of heart rate, and finally death. Autopsy revealed red and swollen and blood covered terminal ileum. The

mucosa was friable and "*so soft that it turns to mash when scraped with fingernail*" [2]. Similar reports came from Berlin (Siebold, 1825) and Vienna (Bednar, 1850), and due to clustering of cases was often regarded as a nosocomial infection. Around 1950, Schimdt and Quaiser described 85 preterm deaths in Graz in two reports from a disease causing ileocecal enterocolitis and coined the term 'enterocolitis ulcerosa necrotisans' [3]. In 1951, radiologist Steinnon observed peumatosis intestinalis, while Wolfe and Evans described pneumatosis portalis, which have now become the radiological hall-marks of NEC [4,5]. During the next decades, increased survival of premature infants and rapid development of intervention therapies led to increased incidence of NEC. An 'outbreak' in New York Babies Hospital prompted extensive analysis and animal experimentation, which concluded that mesenteric hypoperfusion was an important initiator of intestinal injury, but that multifactorial models with immaturity, enteral feedings, intestinal microbiome, immune dysfunction, and inflammation all contributed to the final common pathway of disease [6]. Those days, surgical intervention was considered inevitable, and despite vigorous therapy, fatality was almost invariable.

THE PRESENT

NEC is often described as an inadvertent side-effect of advancement of obstetric and neonatal care. It never occurs in utero, and the risk is inversely proportional to birthweight and gestational age. A systematic review has shown global incidence of 7% in very low birth weight (VLBW) infants in NICU [7]. Incidence is difficult to ascertain in India as many cases of NEC get coded as 'sepsis.' A vexing aspect of NEC is the continued poor understanding of etiopathogenesis despite extensive research. The pathogenesis of NEC is proposed to be complex multifactorial cascade in response to developmental immaturity of gut motility, digestive enzyme secretion, barrier protections, and circulatory regulation exacerbated by formula feeding, intestinal ischemia, and bacterial effects. Recent studies have highlighted the role of platelet aggregation factor (PAF), an endogenous phospholipid initiator of inflammatory response. Premature infants have low PAF degrading enzymes, and human milk contains PAF antagonists. In another exciting discovery, it was shown that mice deficient in the pathogen recognition molecule, toll-like receptor 4 (TLR-4), were protected from NEC, proving the role of TLR-4 in inducing enterocyte apoptosis in response to altered bacterial enterocyte signalling. Timing, content, modality, and advancement of feeding were always suspected as major triggers for NEC. As the cases were mounting in 1970s, Brown and Sweet at Mount Sinai Hospital in New York popularised a strict enteral feeding regimen based on delayed initiation and very slow prolongation of feeding. However, as lower gestational age born babies continued to survive and develop NEC, the confidence in this regimen fell, and early feeding protocols with prog-ressive and infact total enteral feeding were reinstituted. Despite wide divergence in practices, evidence mostly shows that human milk in standardized feeding regimens reduces NEC, especially in VLBW babies, and incidence is unaffected by early initiation, rapid advancement or by off-label fortification of expressed human milk with infant milk formula widely practiced in developing countries [8].

The diagnosis of NEC is hampered by lack of a single pathognomonic sign or test. Just five years after the case series under review was published, Bell, et al. [9] combined clinical and radiological data to classify NEC into three stages, which were modified and subdivided by Walsh and Kliegman [9]. Despite the understanding that NEC is a potpourri of phenotypes and Bell criteria are both outdated and insensitive to distinguish the multiple diseases masquerading as NEC, there is a dearth of pragmatic replacements that can easily fit into clinical care algorithms. Bowel ultrasound, with its advantages of non-ionizing radiation, repeated assessments, improved spatial specificity for pneumatosis intestinalis, increased sensitivity for intermittent gas bubbles in portal venous system, and doppler-guided detection of bowel wall ischemia has the potential for improving staging of NEC. Other modalities being tried are bowel magnetic resonance imaging (MRI) and near-infrared spectroscopy (NIRS). The classic triad of NEC i.e., thrombocytopenia, hyponatremia, and acidemia is present in minority of cases. Biomarkers like plasma and urinary levels of intestinal fatty acid binding protein (I-FABP) and urinary I-FABP: Cr (creatinine) ratios have been studied for diagnosis and assessment of severity but wider acceptance is somewhat limited by small size of the studies [10]. There has been little change in the approaches for conservative management of NEC, characterized by bowel rest, bowel decompression, and intravenous antibiotics with adjunctive therapy for cardiopulmonary and hematological support. The dependence on blood sampling, denial of feed, and use of antibiotics in a disease caused by anemia, hypoperfusion, intestinal dysfunction, and dysbiome is ironical and needs further research. Other therapies like lactoferrin supplementation and intravenous pentoxifylline still lack concrete evidence. In surgical cases, primary peritoneal drainage has emerged as an alternative to laparotomy. Preventive strategies revolve around standard feeding protocols using human milk feeding with dose-dependent relation between breast milk consumption and decline in risk of NEC. Antenatal steroids, avoidance of anti-reflux medications, and antibiotic stewardship are the other strategies. One of

the most controversial topics in NEC prevention is the role of enteral probiotics. Despite evidence of some benefits, concerns about timing, dose, formulation, lack of pharmaceutical grade quality, and concerns regarding cross-contamination prohibit recommendations for routine use. Other potential preventative strategies involve prebiotics (nondigestible dietary supplements like human milk oligosaccharides), postbiotics (bacterial metabolites like butyrates), isolated MAMPs, or bioavailable TLR ligands. Mortality ranges from 10-50%, and common sequelae like neurodevelopmental delay, failure to thrive, strictures, and short bowel synd-rome with or without intestinal failure can debilitate the survivors.

THE FUTURE

NEC is an enduring challenge, especially poignant due to its crippling affliction of seemingly stable, very small babies weeks after birth. Changed understanding of NEC pathogenesis has ignited much optimism. While genomic identifiers may aid in identification of at-risk infants, stool microbiome analyses and metabolomics, and vola-tile organic compounds (VOC) analyses can ease diag-nosis of NEC precursors [11]. Increased attention to NEC prevention must include better comprehension of feeding practices for premature infants and probiotic-mediated manipulation of the microbial environment. For management of devastating sequelae of short bowel syndrome, newer therapies like autologous artificial intestine with bioscaffold of collagen or synthetic polymers coated with biologic matrix seeded with growth factors like VEGF that can recruit endogenous blood supply or implantation of stem cells hold out hope [12]. With thorough and focused research, in time, a specific cure might be available for premature infants who develop this devastating disease.

Funding: None; *Competing interests*: None stated.

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