

# Necrotizing enterocolitis: refocusing efforts on prevention

## Abstract

Necrotizing enterocolitis (NEC) is a life-threatening disease affecting preterm, very low birth weight infants which warrants emergency medical and/or surgical intervention, often in Neonatal Intensive Care Units (NICU). NEC incidence is inversely proportional to birth weight and is more common in infants of younger gestational age. Though its etiology is not well understood, research suggests a bacterial element as the major role player in its pathogenesis. Among other causatives diet, under developed intestines, and use of enteral feedings are some being implied. To date, many preventive approaches have been suggested, introduced, and implemented though with no real success achieved.

Volume 3 Issue 4 - 2016

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**Received:** July 05, 2016 | **Published:** July 7, 2016

## Editorial

Necrotizing enterocolitis (NEC), a gastrointestinal inflammatory disorder, is one of the most serious diseases affecting preterm, very low birth weight infants and requires emergency medical and/or surgical intervention in the Neonatal Intensive Care Unit (NICU).<sup>1,2</sup> The symptoms of NEC include abdominal distension, bilious vomiting, bloody stools after 8-10 days of life and may proceed towards septic shock, disseminated intravascular coagulation, peritonitis and intestinal perforation.<sup>3,4</sup> Even though the exact etiology and pathogenesis are incompletely understood, research suggests a multifactorial basis. Suspected risk factors include genetic predisposition, intestinal immaturity, highly immunoreactive intestinal mucosa, prematurity, enteral feeding, and altered bacterial colonization of intestine resulting in immune activation followed by intestinal barrier failure.<sup>4-7</sup> NEC affects are exclusively postpartum even though the fetus has undergone stress and fetal ingestion of 150 ml/kg per day of amniotic fluid containing proteins, carbohydrates, fat, immunoglobulins, and electrolytes.<sup>5</sup>

The prevalence of NEC is estimated at around 12% of infants born weighing less than 1500g and out of those 30% will not survive. NEC is observed primarily in premature infants although 10% of those affected are infants born at full term or near term. The incidence is inversely proportional to birth weight and gestational age with more common in infants of younger gestational age.<sup>8</sup> According to Neu and Walker, NEC does not occur until at least 8-10 days postpartum. The total annual estimated cost of caring for NEC affected infants in the United States is between \$500 million to 1 billion.<sup>4</sup>

Published reports suggest that bacteria play a major role in the pathogenesis of NEC. Following this lead, probiotics have been introduced as a therapy although outcomes of such treatment are inconclusive. Populations used, sample sizes and the type of microorganisms investigated have been too wide-ranging to make reliable conclusions.<sup>9</sup> A meta-analysis conducted by Aceti et al.<sup>10</sup> shows promising results though future studies need to be designed with much emphasis on selecting the most effective probiotic products, proper dosages, and duration of supplementation. Most importantly, the studies need to be aimed at high-risk populations such as extremely low birth weight and intra uterine growth-restricted infants.<sup>10</sup>

Bacterial colonization in the gut plays a pivotal role in development of the gut immune system. Evaluating fecal samples obtained from infants before and after episodes of NEC has shown unusual intestinal bacterial species and an overall reduction in the diversity of intestinal microbiota.<sup>4</sup> According to Nanthakumar, pathogenesis of NEC is associated with an excessive inflammatory IL-8 response. Toll like receptors play a key role in the innate immune system and it is reported that TLR-4 signaling is associated with intestinal inflammation, and high TLR-4 expression is seen with human NEC.<sup>11</sup> According to Chu et al.<sup>12</sup> elevated levels of serum amyloid A (SAA), anaphylatoxin (C5a), urinary intestinal fatty acid binding protein (I-FABP), Claudin-3, stool plate activating factor (PAF), and calprotectin are associated with clinical symptoms of NEC. Also, a decreased plasma concentration of inter- $\alpha$ -inhibitory protein (Ialp) appears to be a reliable marker for the diagnosis. Numerous inflammatory markers have been suggested and tested though none is conclusive.

As stated, many different approaches have been suggested and have been used to prevent NEC though the outcomes have been inconclusive. To date, no specific strategy has proven successful in preventing NEC, except, feeding human milk as the exclusive diet of premature infants has shown a reduction.<sup>13,14</sup> Other preventative strategies usually have included enteral antibiotics, withholding enteral feedings, administering pre- and probiotic agents, administering different growth factors, anticytokines and glucocorticoids.<sup>4</sup>

Despite advances in perinatal care over the recent years, the incidence and prognosis of newborns with NEC have not improved showing a mortality rate nearing 30%.<sup>8</sup> Furthermore, survivors of NEC have poorer long-term growth and neuro developmental outcomes.

Reflecting on these facts, focus should be directed more towards preventing NEC rather than treating the symptoms. Even using culture-independent, DNA-based genomic technologies have not provided much insight into isolating any particular bacterial species involved in disease progression. However, with current molecular methodologies and techniques, combined with our knowledge base we are marching towards developing effective methods in preventing this devastating disease in the near future.

## Acknowledgments

None.

## Conflicts of Interest

None.

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