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Prevention and treatment of necrotising enterocolitis in preterm neonates

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Abstract

Prevention and treatment of NEC has become an area of priority for research due to the increasing number of preterm survivors at risk, and the significant mortality and morbidity related to the illness. Probiotic supplementation appears to be a promising option for primary prevention of NEC but further large trials are necessary for documenting their safety in terms of sepsis as well as long-term neurodevelopmental outcomes and immune function. As new frontiers including immunomodulating agents like pentoxifylline continue to be explored, the impact of well-established simple strategies like antenatal glucocorticoid therapy, and early and preferential use of breast milk must not be forgotten. Clinical research on manifestations of ileus of prematurity, and feeding in the presence of common risk factors such as IUGR is needed. Safety of minimal enteral feeds in terms of NEC and benefits of standardised feeding regimens need to be confirmed. Association of common clinical practices such as red cell transfusions, H2 receptor blockade, and thickening of feeds with NEC warrants attention. An approach utilising a package of potentially better practices seems to be the most appropriate strategy for the prevention and treatment of NEC.

Contents

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Necrotising enterocolitis (NEC) is the most common and potentially fatal gastrointestinal emergency in neonates. It is primarily an illness related to prematurity as term neonates account for only 5–25% of all cases [1]. Extremely preterm neonates (gestation<28 weeks) are at the highest risk [2]. Enteral feeding is probably the second important risk factor after prematurity as ~90% of cases occur in those who have been fed with milk [3]. The incidence of NEC is reported to be 1–3% of all nursery admissions or 5–10% of all very low birth weight (VLBW) neonates, and has not changed significantly despite the advances in neonatal care [1]. The improved standard of care has ironically resulted in more preterm survivors living longer to a higher risk of this potentially disastrous illness. The overall mortality related to NEC in VLBW neonates continues to be around 20–30% and is inversely proportional to the gestational age, approaching 40–50% in extremely preterm neonates. Mortality is highest in those with the most severe form of the illness and/or need for surgical intervention. The significance of NEC-related morbidity, especially in surgical cases, has been appreciated only recently and involves the significantly prolonged (as long as ≥6 months) hospitalisation and importantly, long-term neurodevelopmental impairment (NDI) [4–8]. Bisquera et al. (United States) have reported that the length of hospital stay was significantly higher for neonates with NEC (surgical or medical) compared with gestation and weight matched controls. The annual hospital charges for NEC were as high as $6.5 million or $216,666 per survivor [4].

Long-term NDI is a significant issue in survivors of NEC, especially in those who required surgery for the illness. Rees et al. have recently reported results of their systematic review and meta analysis of observational studies reporting long-term neurodevelopmental outcomes in preterm VLBW survivors of NEC [7]. The median age at follow-up was 20 months (range: 12–156). Overall, 45% of NEC survivors had NDI. Compared with infants of similar age and gestation who did not develop NEC, infants with NEC were significantly more likely to have NDI (1.6 [1.3–2.0], $p=0.0001$). The risk of cerebral palsy (1.5 [1.2–2.0], $p=0.001$), visual (2.3 [1.0–5.1], $p=0.04$), cognitive (1.7 [1.4–2.2], $p<0.0001$) and psychomotor impairment (1.7 [1.3–2.2], $p<0.0001$) was also higher. The odds ratio of NDI was 2.3 times higher in those with Bell's stage III NEC or requiring surgery ([1.5–3.6], $p=0.0001$) [7]. Soraisham et al. have also recently reported long-term NDI as a significant issue in preterm (birth weight ≤1250 g) survivors of NEC [8]. One major NDI was detected in 24% of NEC cases compared with 10% among birth weight matched controls. Survivors of NEC had significantly higher cognitive delay (i.e. cognitive index<70) and visual impairment. A logistic regression model identified NEC as a predictor of cognitive delay [8].

Overall, the significant mortality and morbidity related to the illness and the increasing number of preterm survivors at risk have resulted in the prevention and treatment of NEC becoming an important issue for those involved in neonatal intensive care.

1. Pathogenesis of NEC

Despite decades of research the pathogenesis of NEC continues to be poorly understood. Prematurity however continues to be accepted as the single most important risk factor for the illness. An interplay of various risk factors including hypoxia, formula feeding, sepsis and intestinal ischemia–reperfusion (I–R) injury against the background of a vulnerable gut is proposed to contribute to the inflammatory cascade that in some situations precipitates NEC [9]. Currently tumor necrosis factor alpha (TNF-α) and platelet activating factor (PAF) are considered to play a synergistic and central role in the inflammatory cascade that leads to NEC. The initial insult in the chain of events leading to NEC could be perinatal hypoxia or sepsis, resulting in mucosal damage. The effect of TNF-α, PAF and bacterial products then triggers a cascade of inflammatory events including neutrophil activation, increase in vascular permeability, and release of free oxygen radicals that eventually lead to vasoconstriction followed by I–R injury. The consequent breakdown of the mucosal barrier leads to a self-perpetuating vicious cycle resulting in severe NEC, shock, sepsis and, sometimes, death [9].

2. Aim and methods

The following systematic review is aimed to derive evidence-based best practice guidelines for the prevention and treatment of NEC. The focus is on simple, inexpensive, and readily available strategies that can be implemented with ease (Table 1). Directions for future research are provided. For the literature review the data bases Medline, EMBASE, CINAHL, the Cochrane Library, reference lists of review articles, and abstracts published in Pediatric Research from 1970 onwards were reviewed in October 2006. A hand search of paediatric and perinatal journals was also conducted.