Discussing cows' milk protein and NEC

Re: **Burge DM, Drewett M, Hall NJ.** The temporal relationship between exposure to bovine milk products and surgical NEC in preterm infants. *Infant* 2018;14(2):58-61.

Thank you for raising this issue, which is often debated but poorly researched, namely the role of cows' milk protein in the pathogenesis of necrotising enterocolitis (NEC). Confusion arises when all products containing cows' protein are grouped together; this includes preterm formula, breast milk fortifier (BMF) containing whole cows' milk protein, and BMF that contains hydrolysed cows' milk protein. They are not all equal and the differences between them have not been tested in any of the papers published so far. In particular, the effects of a whole protein-based BMF vs one that is hydrolysed.

An association with use of formula and NEC is well established and the case study used by Burge et al illustrates this. However, our concern is the suggestion that the association with BMF is now also confirmed – we feel it is not. In correspondence with some of the authors of the Sullivan et al 2010 article,[1] it was confirmed that a significant number of the babies with NEC had received both formula and BMF and therefore it was not possible to distinguish which was associated with NEC (King C, personal communication). Subsequently a letter was published by Embleton et al[2] outlining other concerns around the Sullivan et al paper. In particular it was noted that the background rate of NEC in infants fed according to standard guidelines with bovine milk-based fortifiers (16% all NEC, 12% NEC surgery) is much higher than in many units.

Of the other articles referred to by Burge et al:

- The study by Cristofalo et al 2013[3] was underpowered to look at incidence of NEC.
- Hair et al 2016[4] was not a randomised controlled trial but a retrospective cohort study and therefore very weak evidence.
- Battersby et al 2017[5] noted that >50% of their cohort who developed NEC received breast milk alone and that it gave only a small protective effect. Interestingly, although there was a wide variation in feeding practices across the neonatal networks in the UK, Battersby et al noted that there was no unusual variation in the incidence of NEC.

Regarding Burge et al's article, the aim was stated as to examine the temporal relationship between the introduction of feeds containing cows' milk products and the development of surgical NEC in preterm babies in their centre. We wonder how an association with cows' milk protein products could be made when we do not know what the denominator population were fed? In some units, use of BMF or formula is high; do they have a higher incidence of surgical NEC? This would be a very interesting question to answer and would build on the work of Battersby et al.

Also, as this is observational, we do not know the incidence of other known risk factors among the population. For example, intrauterine growth restriction, gut dysbiosis, proton pump inhibitors, antenatal steroids and feeding protocols.

Lucas and Cole 1990[6] found that breast milk appeared more protective in babies born at ≥30 weeks' gestation whereas the younger gestation babies appeared to be more at risk of NEC, whatever their feed. This would suggest an increased importance of other risk factors for the less mature babies.

It would be really interesting to see the temporal relationship between days from cows' milk exposure to development of NEC subdivided by origin of the protein, ie formula, whole protein fortifier or hydrolysed protein fortifier.

In summary, we wonder if keypoint 3 is made before adequate evidence and we call for research to try and obtain that evidence. A simple start would be to carry out an *in vitro* study of peripheral blood mononuclear cell response to cows' milk-based formula, BMF containing whole protein, and BMF containing hydrolysed protein. There is a good theoretical basis to suggest that hydrolysed protein will not elicit an adverse cytokine response.

Yours sincerely

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References

1. **Sullivan S, Schanler RJ, Kim JH, et al.** An exclusively human milk-based diet is associated with a lower rate of necrotizing enterocolitis than a diet of human milk and bovine milk-based products. J Pediatr 2010;156:562-67.
2. **Embleton ND, King C, Jarvis C, et al.** Effectiveness of human milk-based fortifiers for preventing necrotising enterocolitis in preterm infants: case not proven. Breastfeed Med 2013;8:421.
3. **Cristofalo EA, Schanler RJ, Blanco CL, et al.** Randomized trial of exclusive human milk versus preterm formula diets in extremely premature infants. J Pediatr 2013;163:1592-95.
4. **Hair AB, Peluso AM, Hawthorne KM, et al.** Beyond necrotizing enterocolitis prevention: improving outcomes with an exclusive human milk-based diet. Breastfeed Med 2016;11:70-74.
5. **Battersby C, Longford N, Mandalia S, et al.** Incidence and enteral feed antecedents of severe neonatal necrotising enterocolitis across neonatal networks in England, 2012-2013; a whole- population surveillance study. Lancet Gastroenterol Hepatol 2017;2:43-51.
6. **Lucas A, Cole TJ.** Breast milk and neonatal necrotising enterocolitis. Lancet 1990;336:1519-23.

Authors' response

We thank you for your interest in our article and agree that this is a complex issue, not simplified by the wide variety of different milk products (all with different constituent proteins, peptides or amino acids) given to newborn infants. Our main aim was to highlight the potential relationship between feed type and development of NEC. We do not suggest that our data can be used to definitively prove causality. We completely support your calls for further well-designed research in this field since the incidence of NEC remains unacceptably high.

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