Lactoferrin impact on gut microbiota in preterm infants with late-onset sepsis or necrotising enterocolitis: the MAGPIE mechanisms of action study

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Declared competing interests of authors: Janet Berrington reports grants from Prolacta Biosciences US (Duarte, CA, USA) and Danone Early Life Nutrition (Paris, France), and personal fees from the Nestlé Nutrition Institute (La Tour-de-Peilz, Switzerland). Jon Dorling reports grants from the National Institute for Health Research (NIHR) during the conduct of the study and has been a member of the following committees: Health Technology Assessment (HTA) Efficient Study Designs (2015–16); HTA Maternity, Newborn and Child Health (MNCH) Panel (2014–18); and HTA General Board (2016–19); and HTA Post-Funding Committee teleconference (2015–18). Jon Dorling also reports grants from NIHR and Nutrinia (Ramat Gan, Israel) outside the submitted work. Jon Dorling was also funded by Nutrinia in 2017 and 2018 for part of his salary to work as an expert advisor on a trial of enteral insulin.

Nicholas Embleton reports grants from Prolacta Biosciences US and grants from Danone Early Life Nutrition. Nicholas Embleton also reports personal fees (honoraria) from the Nestlé Nutrition Institute, Astarte Medical (Morrisville, PA, USA) and Baxter (Deerfield, IL, USA). Christopher Lamb reports grants from Nestlé (Vevey, Switzerland) and grants from NIHR during the conduct of the study. Edmund Juszczak reports grants from NIHR during the conduct of this study. Edmund Juszczak was a member of the HTA Commissioning Board (2013–16) and the NIHR HTA General Board (2016–17), and is presently a member of the NHS England and NIHR partnership programme (2019 to present). During the project, William McGuire is or has been a member of the following: the HTA Commissioning Sub-Board (2016–17), NIHR HTA and Efficacy and Mechanism Evaluation Editorial Board (2012–present), and HTA Commissioning Board (2013–18). Christopher Stewart reports honorarium from Danone Nutricia (Paris, France) and has performed consultancy work for Astarte Medical.

Published September 2021
DOI: 10.3310/eme08140

Scientific summary

The MAGPIE mechanisms of action study

Efficacy and Mechanism Evaluation 2021; Vol. 8: No. 14
DOI: 10.3310/eme08140

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Scientific summary

Background

Preterm birth before 37 weeks' gestation is associated with increased risks of mortality and serious morbidity. This is especially true for the 8000 infants born very preterm (< 32 weeks' gestation) in the UK every year. Around 1 in 10 very preterm infants will not survive, and many who do survive do so with longer-term physical and cognitive problems. In very preterm infants, the most common reason for death in the first few days of life is respiratory complications, but this risk has decreased substantially in the last two to three decades. After the first few days of life, the most common reasons for death and serious illness are late-onset sepsis and gut complications, especially necrotising enterocolitis. Necrotising enterocolitis is a serious gut inflammatory condition that is closely associated with changes in gut bacteria and metabolic function. The risk of death in childhood because of the preterm complications of necrotising enterocolitis and late-onset sepsis is higher than the combined risk of death of all childhood (aged 0–18 years) cancers.

Necrotising enterocolitis and late-onset sepsis both have a rapid onset that can be non-specific and difficult to predict and diagnose, and both are challenging disorders to study in a high-risk, vulnerable population. This means that there is a lack of mechanistic research in both the mechanisms of action of clinical interventions and the mechanisms leading to disease. Both necrotising enterocolitis and late-onset sepsis show close associations with feeding and nutritional practices. Mothers' own expressed breast milk decreases the risk of both complications, yet milk feeding takes time to establish. Many infants develop these diseases despite receiving breast milk only.

Lactoferrin is a milk protein with a wide range of anti-infective activity that includes actions on gut bacteria, metabolites and gut epithelial cell function. Basic scientific studies suggest that supplemental enteral lactoferrin may reduce the risk of necrotising enterocolitis and late-onset sepsis, and several randomised controlled trials and a meta-analysis have shown beneficial effects for both diseases. The Enteral LactoFerrin In Neonates (ELFIN) trial was a pragmatic trial of lactoferrin supplementation conducted in over 35 neonatal intensive care units in the UK to determine whether or not routine supplementation decreased the risk of late-onset sepsis; however, the ELFIN trial did not include a mechanistic study. The Mechanisms Affecting the Gut of Preterm Infants in Enteral feeding (MAGPIE) study aimed to determine the gastrointestinal actions of lactoferrin on gut function in a subset of infants recruited to the ELFIN trial.

Aim and objectives

We aimed to determine the impact of lactoferrin on gut microbiota and bacterial metabolic correlates owing to lactoferrin, and dynamic changes in the period immediately preceding disease onset (necrotising enterocolitis or late-onset sepsis). We aimed to recruit 480 preterm infants from neonatal intensive care units participating in the ELFIN trial and collect daily stool and urine samples to determine effects in both the stool and the urinary metabolome, because these may reflect changes in the bacterial or host metabolism, or both. We aimed to determine if the abundance of key pathogens, such as *Staphylococcus* and *Enterobacter* spp., was reduced by lactoferrin and whether or not there was any increase in the proportion of 'healthy bacteria', such as *Bifidobacterium* spp. However, increases or decreases in the relative proportions of key bacterial species may not be reflected in metabolic activity of bacteria.

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Therefore, we also aimed to determine metabolomic profiles using both liquid chromatography–mass spectrometry and gas chromatography–mass spectrometry, and test the following hypotheses:

1. Lactoferrin will result in detectable increases or decreases in the proportion of key bacterial species that will be paralleled by changes in gut bacterial metabolic function.
2. Infants who develop necrotising enterocolitis or late-onset sepsis will have increases in the proportion of likely pathogenetic bacterial species, and these increases will also be paralleled by changes in bacterial and host metabolic profile in the stool and/or urine in the period preceding disease onset, compared with control infants.
3. There will be detectable differences in gut tissue inflammatory response between surgically resected gut tissue affected by necrotising enterocolitis and control tissue.

We planned to achieve these objectives by determining the following outcomes:

1. the gut microbial diversity and proportions of key bacterial taxa measured using 16S rRNA in stool samples
2. the association between the gut bacterial proportions and the stool metabolome measured using gas chromatography–mass spectrometry and/or liquid chromatography–mass spectrometry
3. the pattern of gut microbiota, presence or absence of key bacterial species and/or metabolites prior to the onset of necrotising enterocolitis or late-onset sepsis, compared with samples from control infants who do not develop disease
4. the gut tissue inflammatory response in surgically resected gut tissue affected by necrotising enterocolitis and in non-necrotising enterocolitis control tissue.

Methods

Preterm infants at 1 of 12 NHS hospital trusts (13 separate neonatal intensive care unit locations) were eligible if they were enrolled in the ELFIN trial. Parents gave written informed consent after receiving an information sheet. The bedside nurse or research team collected daily stool and urine samples that were stored in a –20 °C freezer on the neonatal intensive care unit before transfer to central laboratories, where they were stored in a –80 °C freezer until analysis. Local research teams collected the date of the sample along with data on receipt of antibiotics, probiotics and antifungal treatment. This was combined with data collected by the Clinical Trials Unit for the ELFIN trial at the National Perinatal Epidemiology Unit, Oxford, which included demographic data, receipt of milk, parenteral nutrition and clinical outcomes. These included the occurrence of confirmed late-onset sepsis and necrotising enterocolitis in accordance with robust, internationally agreed case definitions and were confirmed at blinded end-point review committee. Samples were anonymised and data linked using unique study numbers.

To determine the impact of disease, the stool and/or urine samples collected up to 7 days before disease onset from infants developing necrotising enterocolitis or late-onset sepsis were identified. A matched healthy control infant of similar gestational age from the same neonatal intensive care unit, with samples at a similar postnatal age, was then identified. This enabled a comparison between samples from a group of infants before the onset of necrotising enterocolitis or late-onset sepsis and samples from a well-matched group of healthy infants. To explore the actions of lactoferrin affecting the gut, we identified infants who did not develop confirmed necrotising enterocolitis or late-onset sepsis and noted the ELFIN intervention trial group (lactoferrin or placebo). Many of the healthy infants who matched to a healthy infant from the other trial group were healthy twins because they were well matched for the key variables (i.e. neonatal intensive care unit site, gestation and postnatal age). In addition, twins have multiple similar exposures that may affect gut bacteria and function, such as the in utero environment, mode of delivery, type of milk and possibly similar genetic features. Because disease is more common in the most preterm infants, we also specifically identified healthy,

well-sampled, extremely preterm singleton infants of < 28 weeks' gestation who did not develop necrotising enterocolitis or late-onset sepsis. This resulted in healthy infants randomly allocated to lactoferrin or placebo, some of whom had been selected as healthy controls (for cases of necrotising enterocolitis and late-onset sepsis) and others who were selected on the basis of demographic factors, so that we analysed samples from every neonatal intensive care unit and included as broad a range of gestational ages as possible.

Stool samples for which both microbiomic and metabolomic analyses were required were removed from freezers in randomised batches, transferred to a laminar flow hood and split into aliquots using a sterile scalpel. This meant that data from the 16S analysis and metabolomic analysis were from the same stool sample. Previous studies may have used different samples that could have been collected hours or days apart. A sample-splitting negative control accompanied each batch of samples split for both gas chromatography–mass spectrometry and liquid chromatography–mass spectrometry analysis. Deoxyribonucleic acid extractions were performed in batches, and each contained an extraction kit negative and one blank to enable inclusion of a sequencing negative during library preparation protocol. Following isolation of sample deoxyribonucleic acid, all samples were sealed and stored at –80 °C until sequencing library preparation.

Faecal and/or urine samples for gas chromatography–mass spectrometry and liquid chromatography–mass spectrometry analyses were transferred frozen to the University of Liverpool and the University of Birmingham, respectively. Faecal samples for gas chromatography–mass spectrometry analyses were weighed and aliquots were transferred to glass headspace vials with magnetic caps in a hood. During aliquoting, an empty vial (air blank) remained unsealed in the hood to collect circulating air, which was analysed alongside the samples. Volatile organic compound analysis was performed using an established gas chromatography–mass spectrometry system.

The liquid chromatography–mass spectrometry analysis used ultra high-performance liquid chromatography–mass spectrometry analysis and represented the untargeted metabolomic profiling element of the project, which aimed to detect small molecules that represent the functional products of cellular processes. Frozen faecal samples were weighed, homogenised, dried and analysed. Quality control was ensured throughout and blank samples were analysed. Putative annotation of metabolites or metabolite groups was performed by applying standardised workflows.

Tissue samples from preterm infants, who had undergone surgery for necrotising enterocolitis, and from age- and gestation-matched control groups with limited intestinal inflammation, were identified. For each infant, three histologically defined microanatomical zones within the resection specimen were identified: 'healthy resection margin'; 'transition zone', showing architectural distortion and inflammation without overt necrosis; and 'necrosis'. Immunohistochemistry was performed on tissue sections and each antibody was optimised for intestinal tissue.

Results

We recruited 479 preterm infants from 13 neonatal intensive care units, of whom 239 received lactoferrin and 240 received placebo. Neonatal intensive care units recruited a mean of 37 infants each; 145 (30.2%) infants were from multiple pregnancies, 270 (56.3%) infants were born by caesarean section and 113 (23.6%) infants had prolonged rupture of the membranes. The mean ± standard deviation birthweight was 1120 ± 358 g and the mean gestation was 28.4 ± 2.3 weeks. Eighty-one infants (16.9%) had at least one confirmed episode of late-onset sepsis and 13 infants had two or more episodes. The first episode of late-onset sepsis occurred at a median age of 12 days (range 3–52 days). Sixteen infants with confirmed late-onset sepsis also had a confirmed episode of necrotising enterocolitis. In total, 30 infants (6.3%) had at least one confirmed episode of necrotising enterocolitis.

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A total of 33,331 samples of sufficient volume, matching labelling and containment criteria were collected from 467 infants from 13 neonatal intensive care units and were transferred to Northumbria University. We analysed 20 confirmed cases of necrotising enterocolitis (mean gestation 26.5 ± 2.0 weeks), 51 confirmed cases of late-onset sepsis (mean gestation 26.1 ± 2.1 weeks) and six infants who died but did not have confirmed necrotising enterocolitis or late-onset sepsis (mean gestation 25.5 ± 2.1 weeks). We selected healthy controls matched on gestation and postnatal age for each case of disease, along with additional well-sampled healthy infants. This resulted in 201 infants who underwent 16S ribonucleic acid bacterial analysis, with an overall mean birthweight of 1015 ± 331 g and mean gestation of 26.0 ± 1.8 weeks. Blinding to study group was maintained throughout. Overall, 1274 samples were selected for 16S ribonucleic acid analysis from 201 infants, of whom 97 infants received lactoferrin and 104 received placebo. For the metabolomic analyses, informative samples from disease cases and healthy matched controls were identified, along with samples from healthy infants to explore the impact of lactoferrin over the duration of neonatal intensive care unit stay. Stool samples were split, where possible, to enable concurrent analysis using gas chromatography–mass spectrometry and/or liquid chromatography–mass spectrometry. In addition, urine samples were also analysed using liquid chromatography–mass spectrometry and separate samples were assayed for intestinal fatty acid-binding protein.

The greatest change in the relative bacterial abundance over time was observed in *Staphylococcus*, which decreased from 42% at aged 7–9 days to only 2% at aged 30–60 days ($p < 0.001$). This reduction in the relative abundance of *Staphylococcus* spp. was paralleled by an increase in the relative abundance of *Veillonella* spp. (4–12%; $p < 0.001$) and Enterobacteriaceae (13–32%; $p = 0.002$). Shannon diversity showed an initial reduction between aged 0–6 days and aged 7–9 days, but an upwards trend in alpha-diversity thereafter that was similar in both trial groups. Small but significant differences in community composition were observed between samples in each ELFIN trial group by comparing weighted Bray–Curtis dissimilarity ($R^2 = 0.005$; $p = 0.04$). Bacterial genera contributing to differences in community structure were identified by comparing mean relative abundance across the two ELFIN trial groups. The results of the pairwise Kruskal–Wallis test with false discovery rate correction identified three genera, namely *Staphylococcus* ($p < 0.01$), *Haemophilus* ($p < 0.01$) and *Lactobacillus* ($p = 0.01$), with greater mean relative abundance in the placebo group than in the lactoferrin group.

Gas chromatography–mass spectrometry analysis showed that 43% of the variance in volatile organic compounds was determined by the individual infant ($p < 0.001$), 9.6% was neonatal intensive care unit site ($p = 0.02$) and 6.7% was postnatal age ($p = 0.005$). The ELFIN trial group had no detectable impact on the volatile organic compound profile and only very limited impact on the metabolome, as determined by liquid chromatography–mass spectrometry: only two metabolite peaks were significant after correction for multiple testing. By contrast, liquid chromatography–mass spectrometry showed significant metabolite differences between necrotising enterocolitis or late-onset sepsis and healthy controls. In total, 394 metabolite peaks were statistically significant in urine and 75 metabolite peaks were statistically significant in faeces, following correction for multiple testing. Urinary intestinal fatty acid-binding protein levels were raised immediately prior to some cases of necrotising enterocolitis and late-onset sepsis, although there was considerable variability between cases.

Resected gut tissue analysis was initially performed using tissue samples from 13 preterm infants, of whom four were recruited to the ELFIN trial or Speed of Increasing milk Feeds Trial (SIFT), six were other preterm infants, and three had spontaneous intestinal perforation and provided control (non-inflamed) tissue. The analysis first determined transcriptomic array quality control data, and infants with tissue samples with poor-quality control were excluded from subsequent analysis. The comparison of transitional zone tissue with necrosis tissue revealed two transcripts that were relatively increased in the necrosis tissue; both proteins associated with these transcripts have roles in metabolic cellular activity, including pro-inflammatory monocyte/macrophage function. The comparison of matched necrotic tissue with healthy resection margins revealed 82 significantly differentially expressed genes (fold change of > 2). This identified multiple innate immune proteins or pathways, including

granulocyte/neutrophil chemotaxis, neutrophil activation and macrophage activation. Multiple genes in the *IL1* family were upregulated, including *IL1*α, *IL1*β, *IRAK3* and *IL1R2*. Coupled with this, the increased expression of genes encoding IκBα, *TNFAIP3* and *MMP-1* implicates a dominant innate myeloid mechanism driving inflammation during necrotising enterocolitis. Consistent with this, gene expression analysis did not identify adaptive T-cell responses as associated with necrosis.

Discussion and conclusions

We successfully conducted a large mechanistic study across multiple hospital sites and collected > 30,000 samples from 479 infants in 13 neonatal intensive care units, which meant that we could carefully select informative samples for analysis. We used state-of-the-art techniques and showed that early stool samples were dominated by *Staphylococcus* spp., which was also the dominant organism causing late-onset sepsis. However, although lactoferrin significantly decreased the level of *Staphylococcus* and other key species, the impact was much smaller than that of other clinical variables, such as infant age or hospital site. This is in keeping with the results of the ELFIN trial, which showed no reduction in late-onset sepsis or necrotising enterocolitis. We observed minimal, if any, impact of lactoferrin on the metabolome, which is in keeping with our microbiomic data. We also noted that many cases of late-onset sepsis occurred after a relatively short duration of lactoferrin exposure. However, we saw significant changes in the stool and urinary metabolome in cases preceding late-onset sepsis or necrotising enterocolitis, which provide metabolic targets for future mechanistic study and biomarker discovery. Immunohistochemistry and gene expression analyses identified multiple inflammatory pathways leading to necrotising enterocolitis and showed that use of NHS pathology archive tissue is feasible in the context of a randomised controlled trial. Most parents gave consent for biobanking of residual samples, which will be stored in the Newcastle University biobank.

Trial registration

This trial is registered as ISRCTN12554594.

Funding

This project was funded by the Efficacy and Mechanism Evaluation (EME) programme, a Medical Research Council (MRC) and National Institute for Health Research (NIHR) partnership. This will be published in full in *Efficacy and Mechanism Evaluation*; Vol. 8, No. 14. See the NIHR Journals Library website for further project information.

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Efficacy and Mechanism Evaluation

ISSN 2050-4365 (Print)

ISSN 2050-4373 (Online)

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The EME programme is funded by the Medical Research Council (MRC) and the National Institute for Health Research (NIHR), with contributions from the Chief Scientist Office (CSO) in Scotland and National Institute for Social Care and Health Research (NISCHR) in Wales and the Health and Social Care Research and Development (HSC R&D), Public Health Agency in Northern Ireland.

This report

The research reported in this issue of the journal was funded by the EME programme as project number 13/122/02. The contractual start date was in February 2016. The final report began editorial review in February 2020 and was accepted for publication in December 2020. The authors have been wholly responsible for all data collection, analysis and interpretation, and for writing up their work. The EME editors and production house have tried to ensure the accuracy of the authors' report and would like to thank the reviewers for their constructive comments on the final report document. However, they do not accept liability for damages or losses arising from material published in this report.

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