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[Intervention Review]

Enteral lactoferrin for the treatment of sepsis and necrotizing enterocolitis in neonates

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ABSTRACT

Background

Neonatal sepsis and necrotizing enterocolitis (NEC) cause significant neonatal mortality and morbidity despite appropriate antibiotic therapy. Enhancing host defense and modulating inflammation by using lactoferrin as an adjunct to antibiotics in the treatment of sepsis, NEC, or both, may improve clinical outcomes.

Objectives

The primary objective was to assess safety and efficacy of oral lactoferrin as an adjunct to antibiotics in the treatment of neonates with suspected or confirmed sepsis, NEC, or both.

Search methods

We used the standard search strategy of Cochrane Neonatal to search the Cochrane Central Register of Controlled Trials (CENTRAL 2018, Issue 9), MEDLINE via PubMed, PREMEDLINE, (1966 to 20 September 2018) Embase (1980 to 20 September 2018), and CINAHL (1982 to 20 September 2018). We also searched clinical trial databases, conference proceedings, the reference lists of retrieved articles and clinical trials, and the authors' personal files.

Selection criteria

We included randomized or quasi-randomized controlled trials evaluating enteral lactoferrin (at any dose or duration), used as an adjunct to antibiotic therapy, compared with antibiotic therapy alone (with or without placebo) or other adjuncts to antibiotic therapy to treat neonates at any gestational age up to 44 weeks' postmenstrual age with confirmed or suspected sepsis or necrotizing enterocolitis (Bell's Stage II or III).

Data collection and analysis

We used the standardized methods of Cochrane Neonatal for conducting a systematic review and for assessing the methodological quality of studies (neonatal.cochrane.org/en/index.html). The titles and the abstracts of studies identified by the search strategy were independently assessed by the two review authors and full text versions were obtained for assessment if necessary. Forms were designed to record trial inclusion/exclusion and data extraction. We used the GRADE approach to assess the quality of evidence.

Main results

We did not identify any eligible trials evaluating lactoferrin for the treatment of neonatal sepsis or NEC.

Authors' conclusions

Implications for practice: currently there is no evidence to support or refute the use of enteral lactoferrin, as an adjunct to antibiotic therapy, for the treatment of neonatal sepsis or necrotizing enterocolitis.

Implications for research: given the lack of efficacy of enteral lactoferrin for preventing late-onset sepsis and necrotizing enterocolitis, evaluation of enteral lactoferrin as an adjunctive agent for treatment of sepsis or necrotizing enterocolitis does not appear to be a research priority.

PLAIN LANGUAGE SUMMARY

Enteral lactoferrin for the treatment of sepsis and necrotizing enterocolitis in neonates

Review question

Is lactoferrin supplementation, along with antibiotics, effective and safe for babies with sepsis and necrotizing enterocolitis?

Background

Newborn babies, especially those born preterm, are at risk from infections in the blood (sepsis), gastrointestinal inflammation and injury (necrotizing enterocolitis), or both these conditions. A number of babies with sepsis or necrotizing enterocolitis die or suffer from long-term brain and lung damage, despite treatment with antibiotics. Lactoferrin, a substance normally present in human milk, may be effective against infections and gastrointestinal injury.

Study characteristics

We searched for studies that used lactoferrin supplementation feeds to treat babies with infection or gastrointestinal injury.

Key results

We did not find any studies on lactoferrin supplementation with antibiotics in treating babies with sepsis and necrotizing enterocolitis. It is unlikely that lactoferrin will be used for treatment of infection or intestinal inflammation in preterm babies because it has not been found effective to prevent these illnesses. During infection and intestinal problems feeds are usually not given. We do not recommend studies be done in the future to address this issue.

Quality of evidence

This could not be assessed as no eligible studies were identified.

BACKGROUND

Description of the condition

Neonatal sepsis is the most common cause of neonatal deaths worldwide (Lawn 2006). The incidence of neonatal sepsis in the high-income countries is reported to be between one and four cases per 1000 live births (Stoll 2004b). In low- and middle-income countries, the rate of neonatal sepsis is significantly higher (6.5 to 38 per 1000 live hospital births) (Zaidi 2005). Sepsis is a particular problem in very low birth weight (VLBW) infants (those with a birth weight of less than 1500 g); early-onset sepsis (sepsis in infants of less than 72 hours of life) occurs in about 1.5% of VLBW infants, and late-onset sepsis in about 21% (Stoll 2002; Stoll 2005). Infections due to *Staphylococcus* and *Candida* species are among the common infections in the neonate. Mortality and morbidity (including patent ductus arteriosus, prolonged ventilation, prolonged need for intravascular access, bronchopulmonary dysplasia, necrotizing enterocolitis and length of hospital stay) are significantly increased in infected infants. In a large cohort study of infants born weighing less than 1000 g, infected infants had significantly higher incidence of adverse neurodevelopmental outcomes at follow-up when compared to uninfected infants (Stoll 2004a).

Necrotizing enterocolitis (NEC) occurs in 1% to 5% of admissions to the neonatal intensive care unit (Lin 2006). The most consistent risk factors are prematurity and low birth weight. Factors that contribute to the development of NEC include gastrointestinal immaturity, enteral feeding (especially formula feeding), presence of bacteria and inflammation in the gastrointestinal tract (Lin 2006). Host-pathogen interactions trigger inflammation in the gastrointestinal tract, which may contribute to the pathogenesis of NEC and septic shock (Blackwell 1997; Neish 2004). NEC significantly increases mortality (attributable mortality of 15% to 30%) and morbidity (including surgery in 20% to 40% of infants and neurodevelopmental delay) (Bell 1978; Lin 2006; Stoll 2004a).

Mortality and morbidity due to sepsis and NEC remain high despite the use of potent antimicrobial agents (Stoll 2005; Stoll 2002). Increased use of antimicrobials has led to the emergence of antibiotic-resistant strains of bacteria (Levy 1998). Adverse pulmonary and neurodevelopmental outcomes after sepsis or NEC may be due to inflammatory injury (Adams-Chapman 2006; Speer 1999). Agents that modulate inflammation or enhance host defenses (or both) may have great potential to improve the outcomes of infants with neonatal sepsis or NEC.

Description of the intervention

The glycoprotein lactoferrin is a component of the innate immune response. It is found in significant concentrations in human colostrum and in lower concentrations in human milk, tears, saliva, seminal fluid and secondary granules of neutrophils. Lactoferrin has broad-spectrum antimicrobial activity against bacteria, fungi, viruses and protozoa, resulting either from its ability to sequester iron or to a direct effect on microbial cell membranes (Valenti 2005). Proteolysis of lactoferrin under acidic conditions (as would occur in the stomach or in the phagolysosomes of neutrophils) yields peptides called lactoferricins that have enhanced antimicrobial activity (Gifford 2005).

How the intervention might work

Lactoferrin inhibits the growth of *Staphylococcus epidermidis* and *Candida albicans* in vitro (Valenti 2005). It reduces the minimum inhibitory concentrations of vancomycin against *S. epidermidis* and antifungal agents such as azoles and amphotericin against *Candida* (Kuipers 1999; Leitch 1999). Lactoferrin and lactoferrin-derived peptides are highly effective against antibiotic-resistant *Klebsiella* and *S. aureus* in vitro (Nibbering 2001). Lactoferrin has wide ranging immuno-modulating effects (Legrand 2016).

Lactoferrin is effective in animal models of systemic and intestinal infection. In transgenic mice over-expressing lactoferrin, there is enhanced clearance of *S. aureus* infection and a reduction in arthritis, septicemia and mortality (Guillen 2002). In a rabbit model of *S. flexneri* enteritis, lactoferrin treatment in doses equal to that present in human colostrum protects against intestinal inflammation (Gomez 2002). The systemic effects of oral lactoferrin are generally thought to be indirect and probably initiated by contact with intestinal epithelial cells and gut-associated lymphoid tissues (GALT). Lactoferrin modulates cytokine or chemokine production (or both) by the GALT cells, which then enter the systemic circulation and influence circulating leukocytes (Bellamy 1992; Tomita 2002). Lactoferrin and other similar products in milk (prebiotics) create an environment for the growth of beneficial bacteria in the gastrointestinal tract, reducing colonization with pathogenic bacteria. The fact that intestinal receptors for lactoferrin have been demonstrated, and that lactoferrin has the ability to modulate intestinal cell differentiation and proliferation (Buccigrossi 2007), makes lactoferrin a promising agent in NEC.

In adult humans, oral recombinant human lactoferrin has been found to be safe and well tolerated. Oral lactoferrin has shown promise as an anti-tumor agent (Hayes 2006). Oral lactoferrin has been shown to reduce viremia in chronic hepatitis C infection (Iwasa 2002; Tanaka 1999). In patients with acute myeloid leukemia and neutropenia, lactoferrin has been found to reduce the incidence, duration and severity of bacteremia due to enteric pathogens (Trumpler 1989). To date, no significant adverse effects have been reported in either animal or human studies.

Lactoferrin provides significant potential benefit for preterm infants, including antimicrobial and immunomodulatory effects and promotion of neurodevelopment (Manzoni 2016; Ochoa 2017). Systematic reviews on probiotics in preterm infants have reported decreased NEC and mortality (Alfaleh 2014; Dermyshe 2017). Lactoferrin has been reported to act synergistically with probiotic strains of bacteria, enhancing their growth and inhibiting intestinal pathogens (Chen 2017; Tian 2010).

Why it is important to do this review

The potential beneficial effects, and lack of reported adverse effects, make lactoferrin a promising agent for the treatment of neonatal sepsis and NEC. This review evaluates the role of enteral lactoferrin in the treatment of neonatal sepsis and NEC.

OBJECTIVES

Primary objectives

To assess safety and efficacy of enteral lactoferrin, used as an adjunct to antibiotic therapy, in the treatment of neonates with suspected or confirmed sepsis.

To assess safety and efficacy of enteral lactoferrin, used as an adjunct to antibiotic therapy, in the treatment of neonates with necrotizing enterocolitis.

Efficacy will be addressed by evaluating duration of positive pressure ventilation, development of chronic lung disease (CLD), necrotizing enterocolitis (NEC) and periventricular leukomalacia (PVL), length of hospital stay in survivors to discharge, and adverse neurological outcome, at two years of age or later.

Safety will be addressed by evaluating for adverse effects of enteral lactoferrin in the treatment of neonatal sepsis and NEC.

METHODS

Criteria for considering studies for this review

Types of studies

We evaluated randomized or quasi-randomized controlled trials for inclusion in our review.

Types of participants

For treatment of sepsis: neonates (at any gestational age up to 44 weeks' postmenstrual age) with confirmed or suspected sepsis, who are on antibiotics.

For the treatment of NEC: neonates (at any gestational age up to 44 weeks' postmenstrual age) with NEC (Bell's Stage II or III), who are on antibiotics.

Confirmed sepsis is defined as clinical signs and symptoms consistent with infection and microbiologically proven with a positive blood culture, cerebro-spinal fluid culture, urine culture (obtained by a suprapubic tap) or culture from a normally sterile site (e.g. pleural fluid, peritoneal fluid or autopsy specimens) for bacteria or fungi.

Suspected sepsis is defined as clinical signs and symptoms consistent with sepsis, without isolation of a causative organism.

Types of interventions

Enteral lactoferrin at any dosage or duration, used as adjunct to antibiotics to treat suspected or confirmed neonatal sepsis or NEC (or both), compared with placebo, no intervention, or other adjuncts to antibiotics.

Types of outcome measures

Primary outcomes

All-cause mortality during hospital stay and at 28 days.

Secondary outcomes

1. Neurological outcome at two years of age or more (neurodevelopmental outcome assessed by a validated test).

2. Chronic lung disease (CLD) in survivors (CLD is defined as oxygen requirement at 36 weeks' postmenstrual age or at hospital discharge).
3. Adverse outcomes directly attributable to oral lactoferrin: increased gastric residuals (gastric aspirate greater than 10% of oral feed), vomiting and other gastrointestinal disturbances during hospital stay.
4. Periventricular leukomalacia (PVL, defined as necrosis of brain white matter in a characteristic distribution, i.e. in the white matter dorsal and lateral to the external angles of lateral ventricles involving particularly the centrum semiovale, optic and acoustic radiations and diagnosed by magnetic resonance imaging (MRI) or as periventricular cystic lesions by cranial ultrasound) (Volpe 1995) at discharge or at neurodevelopmental follow-up.
5. Duration of assisted ventilation through an endotracheal tube during hospital stay (days).
6. Necrotizing enterocolitis (NEC) (definite NEC and perforated NEC, Bell's stage II or III) (Bell 1978) during hospital stay (outcome for infants enrolled with sepsis).
7. Length of hospital stay for survivors to discharge (days).

Search methods for identification of studies

We used the criteria and standard methods of Cochrane and Cochrane Neonatal (see the Cochrane Neonatal [search strategy](#) for specialized register).

Electronic searches

We updated our comprehensive search of the Cochrane Central Register of Controlled Trials (CENTRAL 2018, Issue 9) in the Cochrane Library; MEDLINE via PubMed (1966 to 20 September 2018); Embase (1980 to 20 September 2018); and CINAHL (1982 to 20 September 2018), using the following search terms: (sepsis, septicemia, septic, NEWC, necrotizing enterocolitis, lactoferrin, talactoferrin), plus database-specific limiters for randomized controlled trials and neonates (see [Appendix 1](#) for the full search strategies for each database). We also searched abstracts of conferences proceedings of Pediatric Academic Societies (American Pediatric Society, Society for Pediatric Research and European Society for Pediatric Research), from 1990 to 20 September 2018, from the journals *Pediatric Research* and *Abstracts Online*. We contacted authors who have published in this field, for possible unpublished articles. We did not apply language restrictions.

We searched clinical trials registries for ongoing or recently completed trials ([ClinicalTrials.gov](#); the World Health Organization's [International Trials Registry](#) and Platform, and the [ISRCTN Registry](#)).

Searching other resources

We also searched the reference lists of any articles selected for inclusion in this review in order to identify additional relevant articles.

Data collection and analysis

We followed the standard methods of Cochrane Neonatal for conducting a systematic review (neonatal.cochrane.org/resources-review-authors).

Selection of studies

The titles and the abstracts of studies identified by the search strategy were independently assessed by the two review authors for eligibility of inclusion in this review. If this could not be done reliably by title and abstract, then the full text versions were obtained for assessment. Any differences were resolved by mutual discussion and consultation with a third party.

Data extraction and management

We planned to obtain the full text versions of eligible studies for quality assessment. Forms were designed for trial inclusion/exclusion, data extraction and for requesting additional published information from authors of the original reports. Should we identify eligible studies in future updates of this review, the two review authors will perform data extraction independently, using specifically designed paper forms. The extracted data will be compared for any differences; if noted, differences will then be resolved by discussion.

Assessment of risk of bias in included studies

The two review authors (MP and SA) planned to independently assess the risk of bias (low, high, or unclear) of all included trials using the Cochrane 'Risk of bias' tool (Higgins 2011) for the following domains.

1. Sequence generation (selection bias)
2. Allocation concealment (selection bias)
3. Blinding of participants and personnel (performance bias)
4. Blinding of outcome assessment (detection bias)
5. Incomplete outcome data (attrition bias)
6. Selective reporting (reporting bias)
7. Any other bias

Any disagreements would have been resolved by discussion or by a third assessor. See [Appendix 2](#) for a more detailed description of how we would have assessed risk of bias for each domain.

Measures of treatment effect

We planned to perform statistical analyses according to the recommendations of Cochrane Neonatal. All infants randomized would have been analyzed on 'an intention to treat basis' irrespective of whether they received their allocated treatment completely. We would have analyzed treatment effects in the individual trials. We planned to use the statistical package Review Manager 5 (RevMan 5), provided by the Cochrane. We would have reported relative risk (RR) and risk difference (RD) with 95% confidence intervals (CIs) for dichotomous outcomes, and mean differences for continuous outcomes. If there was a statistically significant reduction in RD, then we would have calculated the number needed to treat for an additional beneficial outcome (NNTB).

Unit of analysis issues

The unit of analysis will be the participating infant in individually randomized trials, and an infant will be considered only once in the analysis. The participating neonatal unit or section of a neonatal unit or hospital will be the unit of analysis in cluster-randomised trials. We will analyze them using an estimate of the intracluster correlation coefficient (ICC) derived from the trial (if possible),

or from a similar trial or from a study with a similar population as described in Section 16.3.6 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2017). If we use ICCs from a similar trial or from a study with a similar population, we will report this and conduct a sensitivity analysis to investigate the effect of variation in the ICC.

If we identify both cluster-randomised trials and individually randomized trials, we will only combine the results from both if there is little heterogeneity between the study designs, and the interaction between the effect of the intervention and the choice of randomisation unit is considered to be unlikely.

We will acknowledge any possible heterogeneity in the randomisation unit and perform a sensitivity analysis to investigate possible effects of the randomisation unit.

Dealing with missing data

Where data are missing, and cannot be derived as described, we planned to approach the analysis as follows:

- We planned to contact the original study investigators to request the missing data
- Where possible, we planned to impute missing standard deviations (SDs) using the coefficient of variation (CV) or calculate from other available statistics including standard errors, confidence intervals, t values and P values
- If the data were assumed to be missing at random, we planned to analyse the data without imputing any missing values
- If this could not be assumed then we planned to impute the missing outcomes with replacement values assuming all to have a poor outcome and conduct sensitivity analyses to assess any changes in the direction or magnitude of effect resulting from data imputation

Assessment of heterogeneity

We planned to estimate the treatment effects of individual trials and examine heterogeneity between trials by inspecting the forest plots and quantifying the impact of heterogeneity using the I^2 statistic. We would have graded the degree of heterogeneity as low ($> 25\%$), moderate ($> 50\%$) or high ($> 75\%$). If we detected statistical heterogeneity, we would have explored the possible causes (for example, differences in study quality, participants, intervention regimens, or outcome assessments), using post hoc subgroup analyses.

Assessment of reporting biases

We planned to assess reporting bias by comparing the stated primary outcomes and secondary outcomes and reported outcomes. Where study protocols were available, we planned to compare these to the full publications to determine the likelihood of reporting bias. Studies using the interventions in a potentially eligible infant population but not reporting on any of the primary and secondary outcomes would be documented in the "Characteristics of included studies" tables. We planned to use the funnel plots to screen for publication bias where there were sufficient number of studies (> 10) reporting the same outcome. If publication bias was suggested by a significant asymmetry of the funnel plot on visual assessment, we planned to incorporate this in our assessment of quality of evidence.

Data synthesis

If eligible studies were identified, we would have performed the meta-analysis using Review Manager 5 software ([RevMan 5](#)). For estimates of typical RR and RD, we would have used the Mantel-Haenszel method. For measured quantities, we would have used the inverse variance method. All meta-analyses would have been performed using the fixed-effect model.

Quality of the evidence

We would have used the GRADE approach, as outlined in the [GRADE Handbook](#) ([Schünemann 2013](#)), to assess the quality of evidence for the following clinically relevant outcomes: all-cause mortality, neurological outcome at two years of age or more, CLD, PVL, duration of assisted ventilation and length of hospital stay.

Two review authors (MP and SA) would have independently assessed the quality of evidence for each of the outcomes above. We consider evidence from RCTs as high quality but would have downgraded the evidence by one level for serious (or two levels for very serious) limitations based upon the following: design (risk of bias), consistency across studies, directness of evidence, precision of estimates, and presence of publication bias. We planned to use the [GRADEpro Guideline Development Tool](#) ([GRADEpro GDT](#)) to create a 'Summary of findings' table to report the quality of evidence.

The GRADE approach yields an assessment of the quality of a body of evidence using one of the following four grades.

1. High: we are very confident that the true effect lies close to that of the estimate of the effect.
2. Moderate: we are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
3. Low: our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect.
4. Very low: we have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate.

Subgroup analysis and investigation of heterogeneity

We planned to perform separate comparisons for the following interventions when data were available.

1. Enteral lactoferrin for the treatment of sepsis
 - a. Enteral lactoferrin treatment as an adjunct to antibiotics versus antibiotics (with or without placebo).
 - b. Enteral lactoferrin treatment as an adjunct to antibiotics versus antibiotics with other adjuncts (intravenous immunoglobulin, granulocyte colony stimulating factor,

granulocyte macrophage colony stimulating factor and pentoxifylline).

2. Enteral lactoferrin for the treatment of NEC
 - a. Enteral lactoferrin treatment as an adjunct to antibiotics versus antibiotics (with or without placebo).
 - b. Enteral lactoferrin treatment as an adjunct to antibiotics versus antibiotics with other adjuncts (intravenous immunoglobulin, granulocyte colony stimulating factor, granulocyte macrophage colony stimulating factor and pentoxifylline).

Key subgroups of participants would have been based on the following characteristics.

1. Gestational age
 - a. Preterm neonates (born before 37 completed weeks' gestation)
 - b. Term infants (born at or after 37 completed weeks' gestation)
2. Birth weight
 - a. Very low birth weight infants (birth weight less than 1500 g)
 - b. Extremely low birth weight infants (birth weight less than 1000 g)
3. Time of onset of sepsis
 - a. Early-onset sepsis (sepsis at 72 hours of life or less)
 - b. Late-onset sepsis (sepsis at more than 72 hours of life)
4. Type of sepsis
 - a. Neonates with suspected sepsis
 - b. Neonates with confirmed sepsis
 - c. Neonates with confirmed gram-negative sepsis
 - d. Neonates with confirmed gram-positive sepsis
 - e. Neonates with confirmed fungal sepsis

Sensitivity analysis

We planned to present results of the sensitivity analyses only if these are significantly different from the primary results. We planned to perform sensitivity analyses in the following situations.

- If there was unexplained moderate to high heterogeneity, we planned to explore this by removing the outlying study/studies causing heterogeneity (if feasible).
- If a study with high risk of (material) bias was included in the meta-analysis of an outcome where the other studies had low risk of bias, we planned to remove the study with high risk of bias.

RESULTS

Description of studies

Our search strategy did not identify any trials that were eligible for inclusion, nor did it identify any relevant ongoing trials ([Figure 1](#)).

Figure 1. Study flow diagram of updated search in September 2018

There is one excluded study, which we disregarded as it was not conducted in neonates ([Zavaleta 2007](#)); see [Characteristics of excluded studies](#). This double-blind randomized controlled study enrolled 140 Peruvian children aged 5 to 33 months who had acute diarrhea. Children were randomized to one of three oral rehydrating solutions (ORS): WHO-ORS (glucose-based ORS, $n = 47$); rice-based ORS ($n = 45$); or rice-based ORS with added lactoferrin and lysozyme derived from recombinant rice (Lf/Lz-R-ORS; $n = 48$). Intake of ORS and stool output was monitored for 14 days. Children who received Lf/Lz-R-ORS had significantly decreased duration of diarrhea (3.67 days versus 5.21 days, $P = 0.05$) and were more likely to achieve a solid stool at 48 hours when compared to the other two groups combined (85% versus 69%, $P = 0.04$).

Risk of bias in included studies

It was not possible to assess risk of bias, as there were no eligible trials.

Effects of interventions

It was not possible to calculate the effects of interventions, as there were no eligible trials.

DISCUSSION

Summary of main results

There were no eligible randomized or quasi-randomized trials using enteral lactoferrin as an adjunct to antibiotics in the treatment of neonatal sepsis or necrotizing enterocolitis. We also did not identify any ongoing trials that were potentially eligible for inclusion on completion. The reason for dearth of studies evaluating treatment of lactoferrin may be that feeds are often discontinued in sick preterm infants with sepsis or NEC and it might be difficult to perform randomized studies of lactoferrin treatment in this vulnerable population.

Potential biases in the review process

We strove to decrease biases in the review process. Both the review authors performed the literature search using an inclusive search strategy and combined the results. We did not identify any trials that met our inclusion criteria. We could not evaluate the completeness or quality of evidence due to lack of eligible trials.

Agreements and disagreements with other studies or reviews

We did not identify any other review that summarized evidence on enteral lactoferrin for treatment of sepsis or necrotizing enterocolitis in neonates or infants. We identified two trials that were performed in adults with sepsis; they had contrasting results ([Guntapalli 2013](#); [Vincent 2015](#)). In a double-blind, randomized, placebo-controlled study of talactoferrin alfa (human recombinant lactoferrin), Guntapalli and colleagues randomized 194 patients

who were aged 18 years or more in the first 24 hours of severe sepsis, who were able to take medication by mouth or feeding tube and were on antibiotics. Investigators reported a 12.5% absolute and 46.5% relative reduction in 28-day mortality, and this reduction was retained at six months. The drug was well tolerated, with a safety profile similar to that of placebo ([Guntapalli 2013](#)). In another randomized controlled trial, Vincent and co-investigators assessed the safety and efficacy of talactoferrin alfa in adults with severe sepsis ([Vincent 2015](#)). The study was terminated after 305 patients (153 in the talactoferrin group and 152 in the placebo group), because of futility and safety concerns identified by the Data and Safety Monitoring Board. Twenty-eight-day mortality was higher in talactoferrin-treated patients than placebo-treated patients (24.8% versus 17.8% $P = 0.117$) and the difference may be explained by a higher proportion of shock in the lactoferrin group (31.4%, versus 20.2% in the placebo group). No difference in mortality was seen in patients without shock (10.4% in the talactoferrin group, versus 12.5% in the placebo group; $P = 0.806$). However, the in-hospital and three-month mortality rates were significantly higher in talactoferrin-treated patients compared to those given placebo (28.1% versus 17.8%, and 30.1% versus 20.4%, respectively). No increased adverse effects were noted in the lactoferrin group. One trial in children with diarrhea found oral rehydration solution containing human recombinant lactoferrin and lysozyme expressed in rice had a significant impact on the duration of diarrhea (3.67 days versus 5.21 days, $P = 0.05$) and the percentage of children having a solid stool in 48 hours (85% versus 69%, $P = 0.04$) compared to oral rehydration solutions not containing lactoferrin or lysozyme in children who had acute diarrhea ([Zavaleta 2007](#)).

AUTHORS' CONCLUSIONS

Implications for practice

There is no evidence to support or refute the use of enteral lactoferrin for the treatment of neonatal sepsis or necrotizing enterocolitis, or both, as an adjunct to antibiotics.

Implications for research

Currently, given the lack of efficacy of enteral lactoferrin for preventing late-onset sepsis and necrotizing enterocolitis, evaluation of enteral lactoferrin as an adjunctive agent for treatment of sepsis or necrotizing enterocolitis does not appear to be a research priority.

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The methods section of this protocol is based on a standard template used by Cochrane Neonatal.

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CHARACTERISTICS OF STUDIES

Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
Zavaleta 2007	Participants were not neonates but were children aged 5 to 33 months with acute diarrhea.

APPENDICES

Appendix 1. Cochrane Neonatal standard search strategy

Search strategy for MEDLINE and PREMEDLINE.

```
# 1 explode 'sepsis' [all subheadings in MIME, MJME]
# 2 sepsis or septicemia
# 3 septic
# 4 NEC
# 5 'necrotizing enterocolitis'
# 6 # 1 or # 2 or # 3 or # 4 or # 5
# 7 explode 'infant - newborn' [all subheadings in MIME, MJME]
# 8 Neonat*
# 9 Newborn*
# 10 # 7 or # 8 or # 9
# 11 # 6 and # 10
# 12 'lactoferrin' [all subheadings on MIME, MJME]
# 13 Talactoferrin
# 14 # 10 or # 11
# 15 # 9 and # 12
```

PubMed: ((infant, newborn[MeSH] OR newborn*[TIAB] OR "new born"[TIAB] OR "new borns"[TIAB] OR "newly born"[TIAB] OR baby*[TIAB] OR babies*[TIAB] OR premature[TIAB] OR prematurity[TIAB] OR preterm[TIAB] OR "pre term"[TIAB] OR "low birth weight"[TIAB] OR "low birthweight"[TIAB] OR VLBW[TIAB] OR LBW[TIAB] OR infan*[TIAB] OR neonat*[TIAB]) AND (randomized controlled trial [pt] OR controlled clinical trial [pt] OR randomized [tiab] OR placebo [tiab] OR drug therapy [sh] OR randomly [tiab] OR trial [tiab] OR groups [tiab]) NOT (animals [mh] NOT humans [mh]))

Embase:

```
#1 (infant, newborn or newborn or neonate or neonatal or premature or very low birth weight or low birth weight or VLBW or LBW or Newborn or infan* or neonat*).mp
```

#2 exp infant

#3 (#1 OR #2)

#4 (human not animal) .mp

#5 (randomized controlled trial or controlled clinical trial or randomized or placebo or clinical trials as topic or randomly or trial or clinical trial).mp

#6 (#3 and #4 and #5)

CINAHL: (infant, newborn OR newborn OR neonate OR neonatal OR premature OR low birth weight OR VLBW OR LBW or Newborn or infan* or neonat*) AND (randomized controlled trial OR controlled clinical trial OR randomized OR placebo OR clinical trials as topic OR randomly OR trial OR PT clinical trial)

CENTRAL: infant or infants or infantile or infancy or newborn* or "new born" or "new borns" or "newly born" or neonat* or baby* or babies or premature or prematures or prematurity or preterm or preterms or "pre term" or premies or "low birth weight" or "low birthweight" or VLBW or LBW or ELBW or NICU

Appendix 2. Risk of bias tool

'Risk of bias' tool

1. Sequence generation (checking for possible selection bias). Was the allocation sequence adequately generated?

For each included study, we would have categorized the method used to generate the allocation sequence as:

- low risk (any truly random process, e.g. random number table; computer random number generator);
- high risk (any non-random process, e.g. odd or even date of birth; hospital or clinic record number); or
- unclear risk.

2. Allocation concealment (checking for possible selection bias). Was allocation adequately concealed?

For each included study, we would have categorized the method used to conceal the allocation sequence as:

- low risk (e.g. telephone or central randomization; consecutively numbered sealed opaque envelopes);
- high risk (open random allocation; unsealed or non-opaque envelopes, alternation; date of birth); or
- unclear risk.

3. Blinding of participants and personnel (checking for possible performance bias). Was knowledge of the allocated intervention adequately prevented during the study?

For each included study, we would have categorized the methods used to blind study participants and personnel from knowledge of which intervention a participant received. Blinding would have been assessed separately for different outcomes or class of outcomes, and classed as:

- low risk, high risk or unclear risk for participants; and
- low risk, high risk or unclear risk for personnel.

4. Blinding of outcome assessment (checking for possible detection bias). Was knowledge of the allocated intervention adequately prevented at the time of outcome assessment?

For each included study, we would have categorized the methods used to blind outcome assessment. Blinding would have been assessed separately for different outcomes or class of outcomes. We would have categorized the methods as:

- low risk for outcome assessors;
- high risk for outcome assessors; or
- unclear risk for outcome assessors.

5. Incomplete outcome data (checking for possible attrition bias through withdrawals, dropouts, protocol deviations). Were incomplete outcome data adequately addressed?

For each included study and for each outcome, we would have described the completeness of data including attrition and exclusions from the analysis. We would have noted whether attrition and exclusions were reported, the numbers included in the analysis at each stage (compared with the total randomized participants), reasons for attrition or exclusion where reported, and whether missing data were balanced across groups or were related to outcomes. Where sufficient information was reported or supplied by the trial authors, we would have re-included missing data in the analyses. We planned to categorize the methods as:

- low risk (< 20% missing data);
- high risk ($\geq$ 20% missing data); or
- unclear risk.

6. Selective reporting bias. Are reports of the study free of suggestion of selective outcome reporting?

For each included study, we would have described how we investigated the possibility of selective outcome reporting bias and what we found. For studies in which study protocols were published in advance, we would have compared prespecified outcomes versus outcomes eventually reported in the published results. If the study protocol was not published in advance, we planned to contact study authors to gain access to the study protocol. We would have assessed the methods as:

- low risk (where it is clear that all of the study's prespecified outcomes and all expected outcomes of interest to the review have been reported);
- high risk (where not all the study's prespecified outcomes have been reported; one or more reported primary outcomes were not prespecified outcomes of interest and are reported incompletely and so cannot be used; study fails to include results of a key outcome that would have been expected to have been reported); or
- unclear risk.

7. Other sources of bias. Was the study apparently free of other problems that could put it at a high risk of bias?

For each included study, we would have described any important concerns we had about other possible sources of bias (for example, whether there was a potential source of bias related to the specific study design or whether the trial was stopped early due to some data-dependent process). We planned to assess whether each study was free of other problems that could put it at risk of bias as:

- low risk;
- high risk; or
- unclear risk.

If needed, we would have explored the impact of the level of bias through undertaking sensitivity analyses.

WHAT'S NEW

Date	Event	Description
16 January 2019	New citation required but conclusions have not changed	Minor revisions to the review but conclusions unchanged. New additional references added.
16 January 2019	New search has been performed	This updates the review 'Oral lactoferrin for the treatment of sepsis and necrotizing enterocolitis in neonates', published in the <i>Cochrane Database of Systematic Reviews</i> (Pammi 2011). The literature search was conducted on 20 September 2018. No new studies were found.

HISTORY

Protocol first published: Issue 2, 2008
Review first published: Issue 1, 2009

Date	Event	Description
8 July 2011	New search has been performed	Updated search in July 2011 did not identify any new trials for inclusion in the review.
8 July 2011	New citation required but conclusions have not changed	No change to conclusions.
7 December 2010	Amended	Contact details updated.

CONTRIBUTIONS OF AUTHORS

Mohan Pammi wrote the text of the protocol and the review; formulated the search strategy and performed the literature search; and is the corresponding author.

Steve Abrams performed the literature search; assisted in writing the protocol and review; and assisted in incorporating peer reviewers' comments.

DECLARATIONS OF INTEREST

Human recombinant lactoferrin for Dr Pammi's laboratory research was donated by Agennix Inc.

SOURCES OF SUPPORT

Internal sources

- None, Other.

External sources

- Vermont Oxford Network, USA.

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DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We added methods to the following sections: Unit of analysis issues, Dealing with missing data, Assessment of reporting biases, and Sensitivity analysis.

INDEX TERMS

Medical Subject Headings (MeSH)

Anti-Bacterial Agents [therapeutic use]; Enterocolitis, Necrotizing [*drug therapy]; Infant, Premature; Lactoferrin [administration & dosage] [*therapeutic use]; Neonatal Sepsis [*drug therapy]; Probiotics [therapeutic use]; Randomized Controlled Trials as Topic; Treatment Outcome

MeSH check words

Humans; Infant, Newborn