Probiotics for the post-operative management of term neonates after gastrointestinal surgery (Protocol)

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# Table of Contents

<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>Header</td>
<td>1</td>
</tr>
<tr>
<td>Abstract</td>
<td>1</td>
</tr>
<tr>
<td>Background</td>
<td>2</td>
</tr>
<tr>
<td>Objectives</td>
<td>3</td>
</tr>
<tr>
<td>Methods</td>
<td>3</td>
</tr>
<tr>
<td>Acknowledgements</td>
<td>5</td>
</tr>
<tr>
<td>References</td>
<td>6</td>
</tr>
<tr>
<td>Appendices</td>
<td>7</td>
</tr>
<tr>
<td>What's New</td>
<td>7</td>
</tr>
<tr>
<td>Contributions of Authors</td>
<td>7</td>
</tr>
<tr>
<td>Declarations of Interest</td>
<td>7</td>
</tr>
<tr>
<td>Sources of Support</td>
<td>7</td>
</tr>
</tbody>
</table>
ABSTRACT

This is a protocol for a Cochrane Review (Intervention). The objectives are as follows:

The objective of this review is to evaluate the efficacy and safety of administering probiotics for the post-operative management of term neonates regarding the incidence of sepsis, mortality, time to full enteral feeds, duration of hospital stay and the intestinal microflora. We aim to evaluate benefits and harms with the use of probiotics in individual gastrointestinal pathologies and specific probiotic products, if sufficient data is available.
BACKGROUND

The intestinal microflora plays an important role in human health by providing a barrier against colonisation of pathogens, facilitating important metabolic functions, stimulating the development of the immune system and maintaining intestinal motility (Guarner 2001; Lundell 2011). There are a variety of dynamic host and environmental factors that play an important role in the development of intestinal microflora. It is apparent that gastrointestinal surgery has the potential to alter this complex ecosystem. A review article reported possible beneficial effects of probiotics in adults undergoing abdominal surgery, but recommended further research (Lundell 2011). In the article three randomised controlled studies reported improved intestinal microbial population, significantly decreased incidence of further infectious complications, and a shortened duration of postoperative hospital stay and the period needed for antibiotic administration in adults undergoing colorectal surgery (Lundell 2011). With this in mind, it is worthwhile to explore the potential benefits of probiotics in neonatal populations undergoing gastrointestinal surgery.

Description of the condition

Congenital defects of the abdominal wall and intestine, and less commonly acquired conditions such as necrotising enterocolitis, require surgical intervention in a term neonate. Most of these conditions are either diagnosed in the antenatal period or shortly after birth. Besides the surgical intervention, management of these conditions requires variable duration of inpatient stay, drug therapies and appropriate feeding practices. Neonates undergoing gastrointestinal surgery are susceptible to bacterial sepsis; Kessler 2009 reported that infants less than six months old with a median-term gestation had a postoperative sepsis rate of 6.9%. The infectious complications in the postoperative period may originate from the intestinal microflora, a phenomenon known as the 'gut origin of sepsis' hypothesis (Guarner 2001; Nieuwenhuijzen 1996). Postoperative sepsis occurs due to disruption of the gut barrier from surgical trauma, increased intestinal permeability, gut microbial imbalance and immunological compromise of the host (Correia 2012).

The fetal gut is sterile and development of the intestinal microflora begins immediately after birth (Ezaki 2012). The establishment of gut microflora is a complex process. Extrinsic factors such as bacterial load of the environment, medication and host-related factors such as anatomical development of the intestinal tract, peristalsis, immune responses, microbial interaction, and mucosal receptor could influence the acquisition of the intestinal microflora (Fanaro 2003). Systemic antibiotics are used in the postoperative period to prevent or manage infections. However, the use of antibiotics does have significant influences upon the intestinal colonisation pattern of the neonate (Fanaro 2003). Neonates treated with four weeks of intravenous ampicillin and gentamicin have been shown to have significantly diminished beneficial flora of Bifidobacteria and Lactobacillus when compared against control (Fouhy 2012). Furthermore, the potentially pathogenic Proteobacteria group, including Escherichia, Salmonella, Vibrio, Helicobacter and Yersinia were the dominant population in the intestinal flora (Fouhy 2012).

Delayed initiation of enteral feeding and variable lengths of management with total parenteral nutrition (TPN) are not uncommon in newborns undergoing surgery. A neonatal piglet model of TPN showed selective growth of mucolytic bacteria including Clostridium perfringens (Deplancke 2002). Parenteral nutrition and delayed oral feeding have been reported to be associated with delayed establishment of stable microflora, paucity of bacterial species and decreased numbers of anaerobes, particularly Bifidobacteria, in extremely low birth weight infants (Fanaro 2003). Bacterial adherence of pathogenic bacteria could potentially increase in response to luminal nutrient deprivation from enteral starvation (Bengmark 1998).

Description of the intervention

Probiotics are live microorganisms that, when administered in adequate amounts, confer a significant health benefit on the host (FAO/WHO Working Group 2002; Nair 2013). Commonly used probiotics include strains of Lactobacillus, Bifidobacterium, Streptococcus salivarius and Saccharomyces boulardii (Schanel 2016). The main functions of probiotics are related to increasing the intestinal motility, suppression of pathogenic microorganism activity, improved intestinal barrier function and modulation of the immune response (Correia 2012; Ezaki 2012; Schanel 2016). Different strains of probiotics may exert their effects by different mechanisms of action (Sherman 2009).

How the intervention might work

Beneficial effects of probiotics could be due to the following (Correia 2012; Jeppsson 2011; Nair 2013; Quigley 2006; Rolfe 2000):

- Probiotics may antagonise the pathogenic bacteria by:
  * Producing organic acids, hydrogen peroxide, bacteriocins and defensin (from Paneth cells);
  * Competing for substrate required for fermentation;
  * Inhibiting adherence of enteric pathogens to mucosal surfaces;
  * Enhancing secretion of mucus layer overlying the epithelial lining of the gut;
  * Obscuring receptor binding sites and directly binding to the pathogen;

- Probiotics have been reported to modulate immune function by increasing activity of the natural killer cells, inducing secretion of cytokine and immunoglobulin A and inhibiting nuclear factor-κB activation, interferon-γ, tumour necrosis factor-α, IL-12 and IL-10;

- The barrier integrity may well be promoted by alteration in mucus and chloride secretion, inhibition of pathogenic-induced alteration of epithelial permeability and regulation of enterocyte gene expression.

Probiotics may reduce the incidence of sepsis and make an impact on intestinal motility, thus reducing morbidity and mortality and improving enteral feeding in post-operative term neonates.

Why it is important to do this review

Review articles have reported potential roles of probiotics in many types of gastrointestinal surgery in adult populations (Correia 2012; Jeppsson 2011). Though the evidence exists for the role of probiotics in the preterm neonatal population on mortality and prevention of necrotising enterocolitis (AlFaleh 2014), the role of probiotics in term infants after abdominal surgery has not been appraised. Areas of concern with probiotic use are the risk of sepsis
from the probiotic strain itself and possible transfer of antimicrobial resistance from probiotic strains to more pathogenic bacteria in the intestinal microbiota (Boyle 2006).

**OBJECTIVES**

The objective of this review is to evaluate the efficacy and safety of administering probiotics for the post-operative management of term neonates regarding the incidence of sepsis, mortality, time to full enteral feeds, duration of hospital stay and the intestinal microflora. We aim to evaluate benefits and harms with the use of probiotics in individual gastrointestinal pathologies and specific probiotic products, if sufficient data is available.

**METHODS**

Criteria for considering studies for this review

Types of studies

Randomised, quasi-randomised and cluster randomised controlled trials will be eligible.

Types of participants

Infants born at or more than 37 weeks of gestation who had one or more episodes of gastrointestinal surgery within 28 days of birth and enrolled any time during the inpatient stay for the surgery will be eligible. Gastrointestinal surgery for the purpose of this review is any form of operative intervention that results from a gastrointestinal pathology. The control and experimental groups in the research study should differ only in the administration of probiotics at the time of inpatient stay for the surgery.

Types of interventions

Administration of probiotics is defined as administration of any probiotic product, during the inpatient stay for gastrointestinal surgery, orally without any restrictions on type, dosage and duration.

Types of outcome measures

**Primary outcomes**

- Proven infection (positive bacterial culture in cerebrospinal fluid, blood or urine);
- Sepsis (positive bacterial blood culture);
- Meningitis (positive bacterial culture in cerebrospinal fluid);
- All-cause neonatal mortality (28 days);
- Time to full enteral feeds in days

**Secondary outcomes**

- Duration of hospital admission in days;
- All-cause mortality prior to discharge from hospital;
- Pathogenic or non-pathogenic intestinal microflora (as defined by the studies included in this review), assessed any time during the study period by performing faecal culture.

Search methods for identification of studies

Electronic searches

We will search the Cochrane Central Register of Controlled Trials (CENTRAL) (Appendix 1), PubMed (Appendix 2), EMBASE (Appendix 3) and CINAHL (Appendix 4) databases.

We will impose no publication or language restrictions.

Searching other resources

We will search relevant clinical trials registers such as the World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) (http://www.who.int/ictrp/en/) and ClinicalTrials.gov (http://clinicaltrials.gov/) for completed but unpublished and ongoing trials. For abstracts published in the meetings of Pediatric Academic Societies, we will search at Abstracts2view from the year 2000 onwards (www.abstracts2view.com/pas/). We will contact pharmaceutical companies to obtain access to any unpublished trial data, should there be any.

Data collection and analysis

Selection of studies

Two review authors (WC, ET) will assess titles and abstracts retrieved from the search to determine their relevance concerning the Objectives and Criteria for considering studies for this review. We will manage disagreements through discussion. If not resolved, then one author (AT) will be the arbiter. We will enter all search results into Review Manager 5 (RevMan 2014).

Data extraction and management

Two review authors (WC, ET) will design a data extraction sheet for study reports, which will be pilot tested using sample studies and revised by the other authors (AT, WT). Onto this data extraction sheet, two authors (WC, ET) will independently extract and record key features of each study including details of the:

- Authors
- Date and place of publication
- Study design
- Inclusion and exclusion criteria
- Setting
- Summary of study participant characteristics
- Summary of intervention and control conditions
- Number of participants in each arm (including dropouts)
- Adverse events
- Outcome measurement and assessment time points
- Risk of bias
- Any relevant additional comments reported by the study authors

We will manage disagreements through discussion. If not resolved, then one author (AT) will be the arbiter. Any disagreements that cannot be resolved will be addressed by contacting the study author(s). If this is unsuccessful, the disagreement will be reported in the review. We will enter and present the data for each included study in a table in Review Manager 5 (RevMan 2014).
Assessment of risk of bias in included studies

Two review authors (WC, ET) will independently analyse each study as per Cochrane’s tool for assessing risk of bias (Higgins 2011). Bias in studies will be graded as low, high or unclear, for each of the following domains:

- Selection bias due to inadequacy of random sequence generation;
- Selection bias due to inadequate concealment of allocations prior to assignment;
- Performance bias due to inadequate blinding of participants and personnel to knowledge of the allocated interventions;
- Detection bias due to inadequate blinding of outcome assessors to knowledge of the allocated intervention;
- Attrition bias due to incompleteness of the outcome data;
- Reporting bias due to selective outcome reporting;
- Bias resulting from any other source, such as study being stopped early because of a data-dependent process, notable baseline imbalance, study funding from a profit-based organisation.

We will manage any disagreements through discussion, a deciding arbiter (AT) or both. We will present our assessment of risk of bias for the included studies in the ‘Risk of bias’ summary tables and graphs as generated through input into Review Manager 5 (RevMan 2014).

Measures of treatment effect

1. We will present treatment effect as risk difference (RD) and relative risk (RR) with 95% confidence intervals (CIs) for dichotomous variables. If the RD is statistically significant, we will calculate the number needed to treat for an additional beneficial outcome (NNTB) or number needed to treat for an additional harmful outcome (NNTH) for comparison against other treatments or no treatment (Higgins 2011).

2. We will present treatment effect as mean difference (MD) for continuous variables, if the same scale is used.

Unit of analysis issues

We envisage that the unit of analysis in our review will be the participant. Nonetheless:

1. If the unit of analysis is not the same as the unit of randomisation, such as in cluster-randomised trials, we plan to adjust for clustering by using the guidance given in the Cochrane Handbook for Systematic Reviews of Interventions (Higgins 2011);

2. In the event of repeated observations on the same study participant (such as episodes of sepsis), the data will be treated as dichotomous with each study participant counted once.

Dealing with missing data

We intend to contact the trial authors of the original studies when the missing data is considered to be ‘not missing at random’.

Assessment of heterogeneity

We will assess the included studies for heterogeneity through three successive steps to determine if they should be pooled with the rest of the included studies or considered separately:

1. Two review authors will independently analyse the included studies for their ‘face-value’ similarities; that is, for the extent of clinical diversity (participants, interventions and outcomes), and for methodological diversity (study design and risk of bias) (Higgins 2011).

2. We will assess the included studies for statistical heterogeneity using the Chi² test, with a P value of less than 0.10 being statistically significant (Higgins 2011).

3. We then intend to calculate the I² statistic with the thresholds for levels of heterogeneity being:
   - less than 25% – no heterogeneity;
   - 25% to 49% – low heterogeneity;
   - 50% to 74% – moderate heterogeneity;
   - 75% and above – high heterogeneity.

If moderate or high levels of heterogeneity are detected, we will explore the causes of heterogeneity among results of the studies by conducting subgroup analyses.

Assessment of reporting biases

If a sufficient number of studies (that is, greater than 10) have been pooled, we plan to use a funnel plot to inspect visually the risk of publication bias, whereby more pronounced asymmetry of the funnel plot may be indicative of a substantial overestimation of the intervention effect (Higgins 2011).

Data synthesis

We will synthesise the data using one of these two methods:

1. We will use the fixed-effect model, where the analysis will produce an estimate of the true effect.

2. Where cluster RCTs are included, we will use the generic inverse variance method (Higgins 2011).

Clinical heterogeneity will be identified by examining variability in the participants, choice of the probiotic product and outcomes of the studies included in the review. Two authors (AT and WT) will assess clinical heterogeneity and make a decision about pooling in meta-analysis.

If studies included in this review use different scales for continuous variables, then a standardised mean difference (SMD) will be used, where we will assess the impact of using the highest versus the lowest of the available standard deviations (SD) on the overall estimate of effect. If SDs are not reported, we will estimate the SD based on similar studies and use this in the meta-analysis (Higgins 2011).

Quality of evidence

We used the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach, as outlined in the GRADE Handbook (Schünemann 2013), to assess the quality of evidence for the following (clinically relevant) outcomes: proven infection (positive bacterial culture in cerebrospinal fluid, blood or urine); sepsis; meningitis; all-cause mortality prior to discharge from the hospital; time to full enteral feeds in days; duration of hospital admission in days; and intestinal microflora in study participants defined as pathological or not.

We considered evidence from randomised controlled trials as high quality but downgraded the evidence one level for serious (or two
levels for very serious) limitations based upon the following: design (risk of bias), consistency across studies, directness of the evidence, precision of estimates and presence of publication bias.

The GRADE approach results in an assessment of the quality of a body of evidence in one of 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 of effect.

Two authors independently assessed the quality of the evidence for each of the outcomes above. We used the GRADEpro Guideline Development Tool to create a ‘Summary of findings’ table to report the quality of the evidence. See Appendix 3 for more detail on the quality assessment of the evidence.

**Subgroup analysis and investigation of heterogeneity**

If sufficient data is available or heterogeneity exists, we intend to explore further the treatment effect in specific subgroups.

We will perform subgroup analyses (restricted to the primary comparisons) on the following:

1. Specific intestinal pathology, for example intestinal atresia or abdominal wall defect or NEC
2. Probiotic product (single microorganism or a combination), given the strain-specific effects
3. Type of feeding: breast milk versus formula

**Sensitivity analysis**

If sufficient data are available, we intend to perform sensitivity analyses:

1. In order to determine the impact of risk of bias on the overall effect estimate, we will add high risk of bias studies to low risk of bias studies and compare the results (Higgins 2011).
2. In order to determine the impact of heterogeneity on the overall estimate of effect, we will remove studies that contribute to heterogeneity from the analyses and compare the results (Higgins 2011)

**ACKNOWLEDGEMENTS**

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REFERENCES

Additional references

AlFaleh 2014

Bengmark 1998

Boyle 2006

Correia 2012

Deplancke 2002

Ezaki 2012

Fanaro 2003

FAO/WHO Working Group 2002

Fouhy 2012

Guaran 2001

Higgins 2011

Jeppsson 2011

Kessler 2009

Lundell 2011

Nair 2013

Nieuwenhuijzen 1996

Quigley 2006

RevMan 2014 [Computer program]

Rolfe 2000

Schanler 2016

Schünemann 2013
Appendix 1. CENTRAL search strategy
(probiotic OR lactobacillus OR bifidobacterium OR OR streptococcus thermophilus OR saccharomyces) AND (surgery OR surgical OR laparotomy OR anastomosis) AND (infant or newborn or neonate or neonatal)

Appendix 2. PubMed search strategy
(probiotic OR lactobacillus OR bifidobacterium OR OR streptococcus thermophilus OR saccharomyces) AND (surgery OR surgical OR laparotomy OR anastomosis) AND (infant, newborn[MeSH] OR newborn OR neonate OR neonatal or infant* or neonat*) AND (randomized controlled trial[pt] OR controlled clinical trial[pt] OR Clinical Trial[ptyp] OR randomized [tiab] OR placebo [tiab] OR clinical trials as topic [mesh: noexp] OR randomly [tiab] OR trial [ti]) NOT (animals [mh] NOT humans [mh])

Appendix 3. EMBASE search strategy
(probiotic OR lactobacillus OR bifidobacterium OR OR streptococcus thermophilus OR saccharomyces) AND (surgery OR surgical OR laparotomy OR anastomosis) AND (infant, new born or new born or neonate or neonatal or New born or infant* or neonat*) AND (human not animal) AND (randomized controlled trial or controlled clinical trial or randomized or placebo or clinical trials as topic or randomly or trial or clinical trial)

Appendix 4. CINAHL search strategy
(probiotic OR lactobacillus OR bifidobacterium OR OR streptococcus thermophilus OR saccharomyces) AND (surgery OR surgical OR laparotomy OR anastomosis) AND (infant, newborn OR newborn OR neonate OR neonatal OR Newborn OR infant* 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)

Appendix 5. Quality of the evidence assessment
In cases where we considered the risk of bias arising from inadequate concealment of allocation, randomized assignment, complete follow-up or blinded outcome assessment to reduce our confidence in the effect estimates, we downgraded the quality of evidence accordingly. We evaluated consistency by similarity of point estimates, extent of overlap of confidence intervals and statistical criteria including measurement of heterogeneity ($I^2$). We downgraded the quality of evidence when large and unexplained inconsistency across studies results was present (i.e. some studies suggest important benefit and others no effect or harm without a clinical explanation). We assessed precision according to the 95% confidence interval (CI) around the pooled estimation. When trials are conducted in populations other than the target population, we downgraded the quality of evidence because of indirectness.

**WHAT'S NEW**

<table>
<thead>
<tr>
<th>Date</th>
<th>Event</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>6 February 2017</td>
<td>Amended</td>
<td>Added external source of support</td>
</tr>
</tbody>
</table>

**CONTRIBUTIONS OF AUTHORS**
All authors contributed equally to the authorship of this protocol.

**DECLARATIONS OF INTEREST**
None of the authors have any conflicts of interest to declare.

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