Improved quality of life in children with intestinal failure – a randomised controlled intervention trial

Improved quality of life in children with intestinal failure.

Research questions and hypotheses, theoretical approach and methodology
We hypothesize that prebiotics will improve QoL in children with intestinal failure (IF) by reducing bacterial overgrowth and hence restore the microbiota towards a healthier gut**.**

Primary aim:

- Determine whether prebiotics improves QoL (primary endpoint) in IF children.

Secondary aims:

- Study changes in microbiota and production of short chain fatty acids (secondary endpoints).
- Explore effects of prebiotics on GI-symptoms, changes in tolerance for enteral nutrition and need for antibiotic treatment.

Overview
The project consists of two work packages (WPs): Effect of prebiotics on microbiota (WP1) and Effect of prebiotics on quality of life (WP2), as illustrated in figure 3. The main study (WP2) is a randomised controlled trial.

Setting: Paediatric patients with IF are routinely followed at Oslo University Hospital (OUH) by a multidisciplinary team with expertise in the treatment of IF. Patients will be identified through this team and recruited by research workers (PhD student/research assistant).

Patients: Patients aged 1 to 18 years that fit one of the inclusion criteria will be invited to participate in the study by letter.
Inclusion criteria are:

- Diagnosed with congenital malformations or diseases requiring intestinal surgery leading to short bowel syndrome.
  or
- Diagnosed with conditions and diseases leading to IF.
  and
- Treated with parenteral nutrition for a periode of >3months

Exclusion criteria:

- Children in need of temporary advanced nutrition intervention due to illness, e.g. infections.
- Children with temporary malfunctioning gut due to advanced medical treatment, for example cancer treatment or transplantation

WP1. Effect of Prebiotics on microbiota (proof of concept).
The short-time effects of prebiotics on microbiota will be evaluated in an open 4-week intervention, to establish a proof of concept.

- **Task 1.1 Recruitment of participants**
  The patients will be recruited in connection with routine follow-ups at OUH.
- **Task 1.2 Run-in period**
  To ensure that the participants have a stable microbiota prior to the intervention we will use a run-in period before the intervention. Data collected at the start of the run-in are: QoL, Stool sample, stool consistency and use of antibiotics. Any hospital admissions or need for antibiotics during the run-in period will be recorded.

- **Task 1.3 Intervention**
  Data collected before and after the intervention include: QoL, stool sample, blood samples, nutritional intake (diet, enteral and intravenous nutrition), stool consistency and use of antibiotics . Participants are provided with sachets of prebiotics to ingest daily for 4 weeks of Phase 1 intervention. The dosage will be prescribed according to weight. The patients are then invited to the hospital for a follow-up of phase 1.

WP2 Effect of Prebiotics on Quality of Health

T2.1 Randomisation of participants from Phase 1
Participants will be randomised into two groups after completing Phase 1. One group will continue to use prebiotics (Stimulance), while the other group will not receive any intervention. Microbiota is known to return to its habitual flora within few weeks after short-term intervention. The group without prebiotic treatment will therefore act as a control group.

T2.2 Intervention Phase 2
The participants in the intervention group continues with prebiotics (Stimulance) for another 6 months. The dosage will be adjusted if necessary, pending the observations in Phase 1. Data collected at the end of the intervention include: QoL, stool sample, blood samples, nutritional intake (diet, enteral and intravenous nutrition), stool consistency and use of antibiotics. We will compare the intervention group with the control group. In addition, the intervention group will serve as their own control before and after the intervention with prebiotics. The study design is useful to account for the inter-individual make-up of the microbiota that contributes to a large portion of variability between subjects.

Endpoint:
Primary endpoint will be QoL score compared between the two groups at 6-months follow-up. QoL will be scored using two published and validated questionnaires: PedsQL 4.0 and PedsQL 3.0 Gastrointestinal Symptoms Scales (PedsQL GI). Scoring will be done at run-in, before and after phase 1 and at the end of phase 2. This enables us to study changes between the two groups (primary endpoint) and changes within the subjects before and after intervention with prebiotics.

Secondary endpoint will include changes in the microbiota measured indirectly by the production of SFCAs, the microbiota composition and diversity. In addition, relevant clinical outcomes will be obtained and analysed.

Methods:

- Stool samples will be collected using a provided stool collection kit with written instructions for the participant/parents. The sample will be collected in a tube and stored at home in the freezer in a specialised container until pick-up or hospital visit. The samples will be analysed for SCFA and total organic acid content using HPLC, while microbiota will be analysed in faecal samples using established techniques (16S rRNA amplicon sequencing and reduced metagenome sequencing). Faecal inflammation biomarkers will also be analysed. The main effect of the intervention on the microbiota will be tested based on crude alpha and beta diversity indices but we will also apply advanced multivariate methods.

- Diet will be recorded before and after phase 1 and at the end of phase 2:
  - Repeated 24 hr recall (2 days). Nutritional analysis will be done by use of the software DietistPro, which is implemented and used by dieticians at OUH, as well as in the other Nordic countries (www.kostdata.se/nb/dietistnet/dietist-net-pro).
  - Questionnaire to collect data on the use of nutritional supplements, vitamin- and mineral supplements, food avoidance, food allergies, food intolerances, enteral and intravenous nutrition.

- Clinical data (blood samples, GI-function, anthropometric data and other medical information) will be collected at run-in, before and after phase 1 and at the end of phase 2.

Outcomes and measurements

Outcome	Measurements
PRIMARY	
Quality of life	QoL questionnaires: PedsQL and PedsQL Gastrointestinal symptoms scale
SECONDARY	
Faeces	SCFA (HPLC), Organic Acids (HPLC), Microbiota composition (16S rRNA amplicon sequencing and reduced metagenome sequencing), inflammation markers (calprotectin)
Blood samples:	Biomarkers of intestinal leakage (albumin, Lipopolysaccharide-binding protein, citrulline) Biomarkers of intestinal absorption (iron status, vitamin status) Infection and inflammatory parameters (CRP, ESR, full blood count)
Nutritional record	Nutrient intake from food, drink, feeding tube (enteral nutrition), intravenous nutrition and supplements
Clinical status:	Anthropometrics: Weight, height, BMI GI-Function: stool frequency and consistency (Bristol Stool Scale) Electronic patient record: Diagnosis, medical complications, antibiotic treatment

Ethical considerations:

The intervention is a limited time supplementation with prebiotics. The product (Stimulance©) is approved for enteral use and is not expected to do any harm to the participants. However, any adverse events will be recorded. The project is approved by the Regional Ethical Committee (REK), nr 170851. The project will be registered at Helsenorge.no and Clinicaltrials.gov.