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Establishing the role gut bacteria play in promoting intestinal rehabilitation amongst children with early onset short bowel syndrome

Submission date 21/11/2022	**Recruitment status** No longer recruiting	[_] Prospectively registered [X] Protocol
Registration date 18/04/2024	**Overall study status** Completed	[_] Statistical analysis plan [_] Results
Last Edited 20/12/2024	**Condition category** Digestive System	[_] Individual participant data [_] Record updated in last year

Plain English summary of protocol

Background and study aims
Short bowel syndrome (SBS) is where the bowel is too short to absorb enough nutrients and fluids to sustain health. The commonest childhood cause is major surgery for gut malformation or inflammation in babies. Providing nutrition and fluid (parenteral nutrition [PN]) through a plastic catheter in a child's large vein is life-saving but associated with serious complications and has a high economic and social cost. Most children eventually manage to come off PN - a process called intestinal rehabilitation (IR) but this can take several years. Gut bacteria have important roles in maintaining health. Children with SBS have different bacteria present and they function differently compared to healthy individuals. Children with SBS are at higher risk of infections and receive more antibiotics, which could alter the balance of bacteria in the gut. The researchers predict that gut bacteria have an important role in IR in SBS in children.

Who can participate?
Children with SBS will be invited to participate from specialist centres in Newcastle, London, and Birmingham

What does the study involve?
The study will invite participants to provide samples and permit sharing of pseudo-anonymised clinical data. Then genetic technologies will be used to analyse the gut bacteria in stool, comparing results with clinical outcomes. Additional samples will be taken if a child receives antibiotics or has any significant changes to their diet as these factors may change gut bacteria. When children undergo a medically-indicated procedure requiring samples of the gut to be taken, these will be analysed to investigate gut surface bacteria which may be different to that in stool, and also important. We will study markers of gut function (in blood and urine samples) in relation to IR. This project may reveal important relationships between gut bacteria and IR that may help clinicians to understand why some patients achieve IR more quickly.

What are the possible benefits and risks of participating?
Participants are not likely to gain a specific benefit from being in the study other than that gained by all research participants. The study is observational. The only additional burden is the

collection of stool and urine samples. We do not perceive risk from this as parents routinely handle their infants' nappies, and where children are old enough to provide their own samples again we perceive no additional risk. Clinic visits are frequent in this patient group and study participation alone will not involve additional visits.

Where is the study run from?
Department of Paediatric Gastroenterology, Great North Children's Hospital (UK)

When is the study starting and how long is it expected to run for?
September 2021 to September 2025

Who is funding the study?
Newcastle Hospitals Charity (UK)

Who is the main contact?
Jemma Cleminson, jemma.cleminson@newcastle.ac.uk (UK)

Contact information

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Principal investigator

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Additional identifiers

Clinical Trials Information System (CTIS)
Nil known

Integrated Research Application System (IRAS)
306100

Protocol serial number
NuTH R&D 10013, IRAS 306100

Study information

Scientific Title
Gut microbiota and intestinal rehabilitation: a prospective childhood cohort longitudinal study of short bowel syndrome (The MIRACLS Study)

Acronym
The MIRACLS Study

Study objectives
The gut microbiota differs between children with short bowel syndrome who do and do not achieve intestinal rehabilitation. Temporal changes in gut microbiota composition and function are the major predictors of successful intestinal rehabilitation amongst children with early onset short bowel syndrome.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approved 28/11/2022, East Midlands - Nottingham 2 Research Ethics Committee (Meeting held by video-conference via Zoom; +44 (0)207 104 8169, (0)2071048035, (0)20 71048016; nottingham2.rec@hra.nhs.uk), ref: 22/EM/0233

Study design
Multicentre observational cohort study

Primary study design
Observational

Study type(s)
Other

Health condition(s) or problem(s) studied
Children with early onset short bowel syndrome

Interventions
The proposed multi-centre prospective study will recruit children with early onset short bowel syndrome. Participants will be asked to provide non-invasive stool samples at 3 monthly intervals (for the study of the microbiota and metabolome) and urine samples once per year (to study I-FABP), usually coinciding with routine clinical appointments, as well as an additional blood test once per year (for plasma citrulline), when they have routine clinically indicated blood tests. If the participant requires a clinically indicated gastrointestinal endoscopy, and if appropriate pre-procedural consents are in place, up to two additional small samples will be requested for analysis of the gut microbiota. If a patient requires a surgical procedure on the gut, a small sample of the resected tissue margin will be requested for analysis of the gut microbiota using the techniques described. Patients will be studied for up to a 3-year period, depending on the stage of gut health and intestinal rehabilitation at recruitment. It is, therefore, expected that most participants will be studied for 2 years. Additional stool samples will be collected following courses of antibiotics, following changes in antibiotic therapy amongst children on long-term treatments or after significant changes in food type. This study is completed once all samples have been obtained and analysed. Following this, where appropriate permissions and informed consents are in place, residual samples will be stored in the Great North Neonatal Biobank, hosted by Newcastle University, for future research (HTA licence no. 12534, Ethics approval 15/NE/0334, IRAS 161883).

Intervention Type
Other

Primary outcome(s)
Gut bacterial structural and functional profile in routinely collected stool samples in relation to intestinal rehabilitation measured using genetic sequencing techniques (16S rRNA sequencing and shotgun metagenomic sequencing) approximately every 3 months

Key secondary outcome(s))
1. Achieving intestinal rehabilitation (weaning off parenteral nutrition (PN) to full enteral feeds for >28 days)
2. Proportion of PN as total nutritional intake measured as a percentage (based on Kcal/kg/day PN as a proportion of daily estimated energy intake) using information obtained from patient medical records at routine PN clinical team reviews at 3 monthly intervals
3. Presence of adverse PN-associated clinical outcomes (culture-confirmed central line-associated bloodstream infection, intestinal failure associated liver disease, catheter-related thrombosis), obtained from patient medical records at 3 monthly intervals
4. Quality of life measured using the Pediatric Quality of Life (PedsQL) questionnaire after recruitment (baseline) and at the end of the study period

Completion date

01/09/2025

Eligibility

Key inclusion criteria
Group 1: Prospective recruitment of infants born within the study period from 4 weeks post-term with parenteral nutrition-dependent intestinal failure due to short bowel syndrome
Group 2: Any child already on parenteral nutrition and meets criteria for group 1 in the year before the study commences
Group 3: Children who had short bowel syndrome but have successfully achieved intestinal rehabilitation in the year before the study commences

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Child

Sex
All

Total final enrolment
23

Key exclusion criteria
Informed consent not provided

Date of first enrolment
01/12/2022

Date of final enrolment
21/10/2024

Locations

Countries of recruitment
United Kingdom

England

Study participating centre
Great North Children's Hospital
Institute of Translational and Clinical Research
Paediatric Immunology Dept c/o Ward 3
C/o: Professor Andrew Gennery

Newcastle upon Tyne
United Kingdom
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Study participating centre
Birmingham Women's and Children's Hospital
Department of Paediatric Gastroenterology
Steelhouse Lane
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Study participating centre
Great Ormond Street Hospital
Department of Paediatric Gastroenterology
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Sponsor information

Organisation
Newcastle upon Tyne Hospitals NHS Foundation Trust

ROR
https://ror.org/05p40t847

Funder(s)

Funder type
Charity

Funder Name
Newcastle Hospitals Charity

Results and Publications

Individual participant data (IPD) sharing plan

Suitability for sharing:
Link-anonymised clinical information and 'omic' data is suitable for sharing as results will be anonymised and scientific results will benefit patients and will be of scientific and clinical interest to relevant parties outside of Newcastle University.

Discovery by potential users of the research data:
Datasets, including null and negative findings, will be archived with supporting documentation into appropriate data repositories, including the European Nucleotide Archive. The data will be assigned a persistent identifier (i.e. DOI) to ensure the data is findable on its own but the DOI can also be included in project outputs, including publications, to detail how and where the data can be accessed. In addition, a data collection will be created in data.ncl, Newcastle's repository, to bring together all the archived datasets in one place. Metadata records will be created in data.ncl for datasets archived elsewhere to allow a user to see all the data outputs in on place. Moreover, the collection will be assigned a DOI to allow the record to be findable and citable.

Governance of access:
The datasets will be made openly available under a Creative Commons license to ensure credit is given when the data is reused and access provided for at least ten years. Metadata, summary level data, and related documents will be freely accessible on the NIH dbGaP (Database of Genotype and Phenotype) website. Individual-level data are accessible via Controlled Access application.

The study team's exclusive use of the data:
At points of research publication and on project completion, data will be deposited into a variety of data repositories suitable for research.

Restrictions or delays to sharing, with planned actions to limit such restrictions:
Data will be made available within six months of project completion (or at the time of publication if this is earlier), which is standard practice within this field, allowing time for further data analysis and preparation of data for sharing, providing ethical approvals and consents are in place.

Regulation of responsibilities of users:
Access to patient identifiable information for research purposes will only be permitted for the applicant and supervisory team. Collaborators at other institutions will be able to access clinical information on their own patients in accordance to Good Medical Practice guidance. All research team members will be able to access the electronic database. For external researchers, managed access procedures will be made available on request and processed on a case-by-case basis, requiring completion of a data request form and signed Data Transfer Agreement stating that they will not make any attempt to identify participants, among other requirements.

IPD sharing plan summary

Stored in publicly available repository, Available on request, Published as a supplement to the results publication

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Protocol file	version 3.3	30/08/2022	28/11/2022	No	No