Toddlers receiving synbiotics after antibiotics

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To investigate the effect of a cows-milk-based formula supplemented with synbiotics from t=0 to t=21, t=42 and t=84 days after amoxicillin or amoxicillin/clavulanic acid treatment in toddlers aged 1, 2 and 3 years old on: - change in proportion of...

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Gastrointestinal signs and symptoms
Study type	Interventional

Summary

ID

NL-OMON52353

Source
ToetsingOnline

Brief title
TOBBI trial

Condition

- Gastrointestinal signs and symptoms
- Bacterial infectious disorders

Synonym
Antibiotic use for bacterial infections

Research involving
Human

Sponsors and support

Primary sponsor: Wageningen Universiteit
Source(s) of monetary or material Support: Nutricia,TKI-agrifood

Intervention

Keyword: antibiotics, microbiota, synbiotics, toddlers

Outcome measures

Primary outcome

- Proportion of all species belonging to the genus Bifidobacterium out of total species, at t=0, t=21, t=42 and t=84 days, based on qPCR, ITS and 16s rDNA sequencing data.

- Composition of all species belonging to the genus Bifidobacterium at t=0, t=21, t=42 and t=84 days, based on qPCR, ITS and 16s rDNA sequencing data.

Secondary outcome

1.

a. Proportion of bifidobacteria by qPCR at t=0, t=7, t= 14, t=28, t=35, t=49, t=56, t=63, t=70, t=77 and t=84 days;.

b. Total microbiota composition by 16s rDNA sequencing at t=0,t=21, t=42 and t=84 days;

c. Faecal pH and short-chain fatty acid (SCFA) levels of faecal samples at t=0 to t=21, t=42 and t=84 days;

d. Stool characteristics: consistency and frequency as reported in a weekly diary using modified Bristol Stool Form Scale;

e. Gastrointestinal symptoms, deviating from normal, as documented in a weekly diary.

2. The proportion and composition of bifidobacteria and total microbiota composition in the intervention- and control group compared to the age matched group.

Other endpoints

1. The amount of study product and cow*s milk consumed for compliance, as reported in the diary;

2. Habitual dietary intake assessed with an FFQ of participants and its association with proportion bifidobacteria at 42 and 84 days;

3. Habitual dietary intake assessed with an FFQ of the participants and its association with microbiota composition at 42 and 84 days;

4. Habitual dietary intake assessed with an FFQ of the participants and its association with stool characteristics at 42 and 84 days.

Explorative study endpoints

• Total microbiota composition, bifidobacteria specific ITS sequence, faecal pH and SCFA composition, at all timepoints;

• Total microbiota composition and bifidobacteria specific ITS sequence at t=0 to t=21, t=42 and t=84 days assessed per breastfeeding duration group (e.g. no breastfeeding, breastfeeding up to 3, 6, 9 or 12 months after birth).

Study description

Background summary

The microbiota refers to a diverse ecosystem of bacteria, archaea, viruses and fungi that reside in and on our body, such as in our gastrointestinal-tract (GI-tract). This gut microbiota is of great importance for human health and the stability and composition of the gut microbiota plays a vital role in health and wellbeing throughout life from as early as birth, or even before that. Oral antibiotics have been used effectively to treat many bacterial infections in humans. However, the use of antibiotics has many direct and indirect health consequences. Directly it can lead to diarrhoea, skin rashes, nausea and fungal

infections. In addition, it is posited that microbiota disruptions, as caused by antibiotic use, can have long-lasting effects such as the development of diseases e.g. asthma, allergies, eczema, diabetes and gut related diseases such as inflammatory bowel disease.
There are multiple options by which the microbiota can be helped to recover after big changes like after the use of antibiotics. One of these options are synbiotics, they have the properties of both probiotics and prebiotics and were created to overcome difficulties such as survival of the probiotic in the GI-tract. The synbiotic product used in this study was specifically selected based on its safety record and previous positive effects in toddlers and infants on higher bifidobacteria proportions.

Study objective

To investigate the effect of a cows-milk-based formula supplemented with synbiotics from t=0 to t=21, t=42 and t=84 days after amoxicillin or amoxicillin/clavulanic acid treatment in toddlers aged 1, 2 and 3 years old on:
- change in proportion of species belonging to the genus Bifidobacterium out of total species
- change in composition of species belonging to the genus Bifidobacterium

Study design

A randomized study in 126 children with a duration of 12 weeks, of which 6 weeks of intervention (cows-milk-based formula supplemented with synbiotics) or control (cow's milk) followed by 6 weeks of run-out.
In addition, there will be an age-matched group (n=40) to assess a normal microbiota composition in children who have not received antibiotics.

Intervention

Participants will be randomized to the intervention or control group. The intervention group will be asked to replace 2 cups of regular milk with 2 cups of cows-milk-based formula supplemented with synbiotics (Bifidobacterium breve M-16V with scGOS / lcFOS) per day, and drink this for 6 weeks. The ideal intake is 2 x 120 mL per day. The maximum intake is 500 mL per day. In the run-out period during the last 6 weeks, participants will drink as normal.

The control group will continue to drink regular milk as they normally do (standard care).

Study burden and risks

The cows-milk-based formula supplemented with synbiotics used in this study is commercially available in France, Poland, Czech Republic and Slovakia and produced in the Netherlands under the name CESARBIOTIK. Because of the long

safety record in children and presence in the gut microbiota, especially in breastfed infants, Bifidobacterium breve M-16V is considered safe for consumption. Moreover, the Food and Drug Administration (FDA) has a list of Generally Recognized As Safe (GRAS) probiotics for the use in infant and toddler formula, that includes Bifidobacterium breve M-16V, for which no adverse events were reported. Therefore no side effects are expected. Only non-invasive study procedures are included in the study. The YCF supplemented with synbiotics may help speed up the recovery of the bifidobacteria composition in toddlers after treatment with antibiotics.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Children (2-11 years)
Babies and toddlers (28 days-23 months)

Inclusion criteria

1. Written informed consent obtained from both caregivers;

2. Caregivers are willing to comply with the requirements of the study;
3. Aged 1 to 4 years old at the time of enrollment;
4. Drinks cow*s milk (non-fat, semi-skimmed or full fat) regularly;
5. Received a prescription for amoxicillin or amoxicillin / clavulanic acid*.
* There are no restrictions on use of any (other) antibiotics earlier in life.

Exclusion criteria

1. Any gastro-intestinal (GI) complaints, known structural GI abnormalities, or previous GI surgery;
2. Clinically significant cardiac, vascular, liver, pulmonary, psychiatric disorders, severe renal insufficiency, human immunodeficiency virus infection, acquired immunodeficiency syndrome, hepatitis B or C or abnormalities of haematology, urinalysis, or blood biochemistry;
3. Known to have an allergy or intolerance to any of the ingredients in the study- or control product, including lactose and cow*s milk protein;
4. Is receiving breastmilk, or has received breastmilk in the last 7 days before start of antibiotic treatment.

Study design

Design

Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Prevention

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	29-09-2022
Enrollment:	166
Type:	Actual

Medical products/devices used

Registration:	No

Ethics review

Approved WMO Date:	26-05-2021
Application type:	First submission
Review commission:	METC NedMec
Approved WMO Date:	28-06-2022
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	23-07-2024
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

ID: 20358
Source: NTR
Title:

In other registers

Register	ID
CCMO	NL75975.081.20
Other	NL8996