A randomized controlled multicenter trial of a five day course of oral colistin and neomycin followed by restoration of the gut microbiota using fecal transplantation to eradicate intestinal carriage of extended spectrum beta-lactamase or carbapenemase-producing Enterobacteriaceae in high-risk patients

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The purpose of this study is to evaluate the efficacy of two antibiotics (neomycin sulfate and colistin sulfate), followed by fecal bacteria therapy , to multidrug - resistant bacteria (E - ESBL and EPC) to be eradicated from the intestine.

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Gastrointestinal infections
Study type	Interventional

Summary

ID

NL-OMON43965

Source
ToetsingOnline

Brief title
RGNOSIS WP3

Condition

- Gastrointestinal infections
- Bacterial infectious disorders

Synonym
ESBL-E infections; Infections of the gastrointestinal tract with antibiotic resitant bacteria

Research involving
Human

Sponsors and support

Primary sponsor: Prof. Stephan Harbarth; Hôpitaux Universitaires de Genève (HUG)
Source(s) of monetary or material Support: Europese Unie

Intervention

Keyword: fecal, microbiota, transplantation

Outcome measures

Primary outcome

The purpose of fecal bacteriotherapie is the restoration of the microbial

ecology by a healthy intestinal bacterial flora .

Secondary outcome

Not applicable.

Study description

Background summary

The intestinal flora is made up of many different types of bacteria that line the entire large bowel. These bacteria allow the proper functioning of the body and are partly eliminated in the stool. A change in diet, an illness, antibiotics or other drugs may in some people, change the number of bacteria (decrease or increase) and cause the emergence of antibiotic-resistant bacteria (called multidrug-resistant bacteria). Thus, it can happen that those who are colonized with multi-resistant bacteria, develop an infection with these bacteria from their own digestive tract and need to be treated with antibiotics. In this situation, some families of antibiotics may be ineffective.

In the context of a scientific research program, we will conduct a clinical study consisting of two phases.

* The first phase involves collecting stool containing no multidrug-resistant bacteria or other infectious agents from voluntary, healthy, qualified donors. This is the stage in which we invite you to participate.
* The second phase is to administer the processed stool of healthy volunteers to patients colonized with multidrug-resistant bacteria qualifying as recipients. The second phase, called fecal bacteriotherapy (FB) is an innovative medical technology that has demonstrated its ability to eliminate pathogenic bacteria such as Clostridium difficile from the digestive tract with great efficacy. FB aims to restore the microbial ecology by reintroducing a healthy bacterial flora (in this case, yours) via a nasogastric tube. Donor stools will be used to replace the multidrug-resistant bacteria in the digestive tract of recipients, specifically extended-spectrum betalactamase (ESBL-E) or carbapenemase producing Enterobacteriaceae (CPE).

Study objective

The purpose of this study is to evaluate the efficacy of two antibiotics (neomycin sulfate and colistin sulfate), followed by fecal bacteria therapy , to multidrug - resistant bacteria (E - ESBL and EPC) to be eradicated from the intestine.

Study design

A randomized , controlled multicentre trial .

Intervention

* "Control" group : patients assigned to the control group will receive no special treatment during this study. This is the usual standard for the treatment of patients colonized with ESBL -E and CRE .
* " Intervention " group : patients will be assigned to the intervention group asked for 5 days to take two antibiotics (4 tablets colistin sulfate and neomycin sulphate per day), followed by fecal bacteriotherapie .

Study burden and risks

For donors and patients : The collection of blood can be accompanied by pain and a hematoma may occur at the site of the puncture. It is possible that participation in this study reveals that a patient or donor has a dissease if which he or she is not aware of.

For patients:
* neomycin can cause gastrointestinal symptoms such as nausea, into the rectum. Vomiting, diarrhea and pain Neurological side effects, such as dizziness, hearing loss, tinnitus and twitching are rarely seen
* Colistin sulphate may cause intestinal problems, such as nausea , vomiting,

decreased appetite, diarrhea and rare allergic reactions such as skin rash, hives and itching.
* Omeprazole may cause headaches and gastrointestinal symptoms such as nausea, vomiting, bloating , abdominal pain , diarrhea or constipation.
* Placing a nasogastric tube can be experienced by the patient as painful. The insertion can damage the nasal mucosa and cause a nosebleed. An incorrect positioning of the probe is another rare occurrence risk and can lead to pneumonia or infections of the mediastinum (the region of the chest which lies between the two lungs).
* Fecal bacteriotherapie may cause gastrointestinal symptoms . The duration of these symptoms is usually limited to a few days (diarrhea , constipation , abdominal pain , abdominal cramps , bloating) .
* Despite careful selection and examination of the donor stool it is impossible to conclude with certainty that an unrecognized infectious disease , which is present at the donor is transferred to you via fecal bacteriotherapie . There is the possibility for a theoretical risk for the occurrence of autoimmune diseases or metabolic diseases (eg . Diabetes) in conjunction with fecal bacteriotherapie .
* It can not be excluded that there are other risks that hitherto unknown exist.
* Chest X-ray: while taking the X-ray, you will be exposed to a small amount ionising radiation. There is a small change that the used radiation could lead to health damage.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

For patients:
- Adult patients (18 years at date of inclusion)
- Documented intestinal carriage of ESBL-E and / or CRE by stool culture at baseline (visit 0).
- IF COLONIZED WITH ESBL-E ONLY (WITHOUT CRE): At least one episode of symptomatic infection with ESBL-E requiring systemic antibiotic therapy within the last 180 days before date of inclusion (based on the last day of antibiotic therapy for that infection).;For donors:
- Be aged between 18 and 60 years.
- Be in good health without comorbidities or significant past medical history.
- Have a normal body weight (body mass index between 20 and 25 kg/m2).
- Have a normal macroscopic appearance of stool.
- Have a normal stool frequency (1-3x/day).

Exclusion criteria

For patients:
- Pregnancy or planned pregnancy.
- Breastfeeding.
- Difficult / impossible follow-up.
- Allergy or other contraindication to one of the study drugs.
- Anatomic contraindication to the placement of a nasogastric tube.
- Recurrent aspirations.
- Resistance to colistin (defined as MIC > 2 mg/l) of any of the ESBL-E or CRE strains isolated at baseline.
- Estimated life expectancy < 6 months.
- Treatment with any systemic antibiotic on the day of inclusion.
- Severe immunodeficieny.
* Systemic chemotherapy *30 days from baseline or planned chemotherapy within the next 6 months.
* Human Immunodeficiency Virus (HIV) with CD4 count < 250/mcl.
* Prolonged use of steroids (prednisone equivalent * 60 mg per day for > = 30 days) or other immunosuppressive medications.

* neutropenia with absolute neutrophil count < 1000/*L.
* Solid organ transplant recipient.
* Hematopoeitic stem cell transplant recepients.
* Other causes of severe immunodeficiency.
- Hospitalization in an Intensive Care Unit.
- Estimated glomerular filtration rate (CKD-EPI) < 15 ml/min/1.73m2.
- Severe food allergy (anaphylaxis, urticaria).;For donors:
- Not have an acute or chronic digestive disorder.
- Not have a risk behavior for infectious diseases (eg recent change of sexual partner, homosexual intercourse, drug use etc.).
- Not be affected by a chronic disease.
- Not be under long-term treatment.
- Not have had an acute illness or fever in the last 4 weeks.
- Not have stayed in a tropical zone in the last three months or have lived in tropics for many years.
- Not have taken antibiotics in the last 6 months.
- Not have received a tattoo, piercing etc. in the last 6 months.
- Not have undergone a gastroscopy or colonoscopy within the last 6 months.
- Not have received blood products in the past 12 months.
- Not have a history of typhoid fever.
- Not have been hospitalized aborad in the last 12 months.
- Not have stayed in the UK for more than six months between 1980 and 1996.

Study design

Design

Study phase:	2
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	22-09-2015

Enrollment:	26
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Diarönt® mono
Generic name:	Colistinsulfate
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Neomycin sulfate
Generic name:	Neomycin sulfate
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Omeprazol-Actavis
Generic name:	Omeprazol
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	27-11-2014
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	22-04-2015
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	26-05-2015
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	25-08-2015
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)

Approved WMO Date:	16-09-2015
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	23-05-2016
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	21-07-2016
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

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR2014-003727-22-NL
ClinicalTrials.gov	NCT02472600
CCMO	NL51282.041.14