Faecal microbiota transfusion for decolonization of multidrug resistant Enterobacteriaceae in renal transplant recipients (RESET): a pilot study.

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Primary Objective: To assess the efficacy and safety of faecal microbiota transfusion in female renal transplant recipients with intestinal carriage of extended-spectrum β-lactamase Enterobacteriaceae (ESBL-E) and/or carbapenemase producing…

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Bacterial infectious disorders
Study type	Interventional

Summary

ID

NL-OMON54672

Source
ToetsingOnline

Brief title
RESET

Condition

- Bacterial infectious disorders
- Urinary tract signs and symptoms

Synonym
intestinal carriage of multidrug resistant bacteria (Enterobacteriaceae)

Research involving
Human

Sponsors and support

Primary sponsor: Leids Universitair Medisch Centrum
Source(s) of monetary or material Support: Ministerie van OC&W,Vedanta Biosciences

Intervention

Keyword: Faecal microbiota transfusion (FMT), Multi drug resistant Enterobacteriaceae, Renal transplant recipients

Outcome measures

Primary outcome

Primary study parameters:

Frequency and magnitude of any adverse event within 1 month of faecal

microbiota transfusion, including infections. The occurrence of renal

transplant related adverse events (graft loss, biopsy-proven acute rejection,

doubling of serum creatinine) within 3 months after FMT.

Secondary outcome

Secondary / exploratory study parameters:

- Number of participants with intestinal carriage of MDRE after FMT (assessed

at 1 and 2 weeks and 1, 3 and 6 months after FMT).

- Number of participants with one or more MDRE infection(s) within 6 months

after FMT.

- Change (relative to baseline) in the microbiota composition during 6 months

of follow-up.

- Change in microbiome diversity, calculated by Shannon diversity index, during

6 months of follow-up.

- Prevalence of antibiotic resistance genes in faecal samples during 6 months

of follow up as determined by metagenomics.

Study description

Background summary

Colonization and infections with multidrug resistant Enterobacteriaecae (MDRE) are a major public health concern. Renal transplant patients are at increased risk of colonization with MDRE due to medications that modify their immune status, increased healthcare and antibiotic exposure, and surgical alteration of the urinary tract [Pinheiro 2010]. A recent review showed a colonization rate with extended-spectrum beta-lactamase producing Enterobacteriaecae (ESBL-E) of 24% among kidney transplant recipients [Alevizakos 2017]. Gastro-intestinal (GI) colonization with ESBL-E is associated with subsequent ESBL-E-infections. For example, GI colonization was associated with an approximately 12 time greater risk of developing an infection in liver transplant recipients [Bert et al 2012].
Infections in renal transplant patients caused by MDRE are both frequent and severe and leads to inferior outcomes and increased financials costs [Biehl LM 2016, Tumbarello 2014]. Treatment options in severe infection are limited and there is an emerging concern about the resulting overuse of reserve antibiotics like carbapenems exerting a selection pressure leading to the emerge of carbapenemase-producing microorganism [Vardakas 2012].
Thus, effective strategies for decolonization of MDR bacteria are urgently needed to reduce invasive infections, hospital admissions, the use of reserve antibiotics and to prevent transmission. In literature, different antibiotic decolonization regimens have been studied for MDRE-carriers in different patient populations [Huttner 2013, Rieg 2015]. The study by Rieg et al showed a 42% eradication rate (19/45 patients) after first line decolonization treatment with colistin low-dose, colistin high-dose or rifaximin in a heterogenous group of patients. The decolonization success rate for renal transplant patients was 26% (5/12 patients). However, follow-up showed that 7/13 patients (54%) with successful initial or salvage decolonization became recolonized within 3 months after post-treatment assessment. The study by Huttner et al showed no statistically significant difference between the placebo and intervention group (colistin plus neomycin) with the regard to the primary outcome of ESBL-carriage 28 days after the end of treatment.
Currently, effective decolonization strategies are lacking and targeted selective digestive decontamination seems to result in short term benefits only. Faecal microbial transplant (FMT) is the infusion of donor faeces into the gut with the aim of improving microbial diversity. FMT is an effective and accepted therapy to prevent recurrent Clostridium difficile infection [Van Nood 2013] and shows remarkable therapeutical potential in other intestinal [Pinn 2014, Paramsothy 2017, Anderson 2012] and extra-intestinal disorders [Vrieze

2012, Hornig 2013]. FMT appears also to be safe and effective in immunocompromised patients with recurrent Clostridium difficile infections [Kelly 2014].
For the first time in 2015, Lagier et al showed successful decolonization of an asymptomatic stool carriage of an OXA-48 carbapenemase-producing Klebsiella pneumoniae in a patient treated with oral colistin, gentamicin followed by FMT [Lagier 2015]. Since then, 8 case reports showed the potential effectiveness and safety of FMT for MDR bacterial decolonization, including the successfull eradication of intestinal ESBL-producing E.coli carriage in a kidney transplant patient with recurrent pyelonephritis with this organism[Magnes 2016]. A recent pilot study of FMT for patients with digestive tract colonization with carbapenem-resistant Enterobacteriaeceae (CRE) or vancomycin-resistant enterococci (VRE), showed clearance of carriage in 3 out of 8 patients three monhts after FMT [Davido 2017]. They were all CRE carriers and no VRE carrier was free of colonization. In this pilot study, the bacteria involved were heterogeneous, patients did not receive antibiotics prior to the FMT and solid organ transplant patients were excluded.
These case reports shows the potential effectiveness of FMT as an intervention of MDR bacterial decolonization, also in kidney transplant patients. The emerging evidence of FMT for MDR bacterial decolonization have created interest with several clinical trials underway. At this moment, none of those clinical trials have been published.
Because kidney transplant patient are especially at increased risk for colonization and infections with MDRE, we therefore purpose to perform this pilot trial. For the first time, this pilot trial with investigate the safety and efficacy of FMT to eradicate intestinal colonization with MDRE in renal transplant patients with a history of infection caused by these MDR bacteria.
We will use an uniform standardized protocol for oral gut decontamination regimen and standardized faecal suspension in a selected patient cohort, namely kidney organ transplant patients with intestinal carriage of MDRE and at least one documented infection by these organism within 6 months. Once the procedure has been established safe and there is a tendency to effectiveness, a larger efficacy trial will be performed.

Study objective

Primary Objective:
To assess the efficacy and safety of faecal microbiota transfusion in female renal transplant recipients with intestinal carriage of extended-spectrum β-lactamase Enterobacteriaceae (ESBL-E) and/or carbapenemase producing Enterobacteriaceae (CPE) with a history of infection caused by these bacteria.

Secondary Objectives:
To investigate the effect of faecal microbiota transfusion on intestinal colonization of ESBL-E and/or CPE and microbiota composition and diversity, and antibiotic resistance genes.
To assess the frequency of MDRE infections after combined oral gut

decontamination and faecal microbiota transfusion.

Study design

We will conduct a randomized open label clinical pilot trial. Twelve female renal transplant recipients with intestinal carriage of one of the target MDR organisms will be recruited from the department of Infectious Diseases and Nephrology of the Leiden University Medical Center and referring Dutch academic centers, after having had at least one documented infection by these bacteria within 6 months before enrolment.
Participating subjects will be randomly assigned (1:1) to the intervention (faecal microbiota transfusion) and control group. All subjects will receive the oral decontamination regimen.
Total follow up will be 6 months, in order to evaluate prolonged effects on microbiota, MDRE carriage after FMT and occurrence of (MDRE) infections during follow-up.

Intervention

Oral gut decontamination regimen polymixin/neomycine 500.000 IE/125 mg 4dd2 for 5 days, combined with nitrofurantoin (100 mg 2×/day) for 5 days if MDRE bacteriuria is present, followed by bowel lavage on day 6. Patients will receive Omeprazole 20 mg per os 1 dose on the evening of day 6 and on the morning of day 7. On day 7 200 ml of standardized faecal suspension will be infused through a nasoduodenal tube. FMT will be matched with regard to donor / recipient cytomegalovirus and Epstein-Barr virus serology.

Study burden and risks

In this trial efficacy and safety of infusion of faecal microbiota for decolonization of multidrug resistant Enterobacteriaceae (MDRE) in renal transplant recipients will be assessed.
Subjects participating in the study will receive a baseline evaluation with a blood sample (3 tubes of 3 ml for routine hematology, chemistry; additional 3 ml for serology only in previously CMV/EBV negative patients), examination of a sample of fresh faeces and urine. Furthermore, drug levels of the used immunosuppressants will be measured in dry blood spot specimens (DBS), collected by applying a few drops of blood, drawn by lancet from the finger onto a specially manufactured absorbent filter kit. These dry blood spot kits will be send to the laboratory by mail. This allows for the measurement of 4 time points at home and calculation of the area under the curve (AUC) of the relevant immunosuppressants.
All patients will use medication for oral gut decontamination, and 5 days of nitrofurantoin (or fosfomycin,) if MDRE bacteriuria is present, based on susceptibility pattern of the uropathogen. Patients may experience adverse events after taking these medications, such as liquid stools or mild nausea.

Patients allocated to the intervention group will receive bowel lavage with macrogol + electrolytes on day 6, and oral omeprazole on day 6 and 7. In the morning of day 7 a nasoduodenal tube will be placed in the radiology ward, using X-ray to conform correct placement. After infusion of fecal microbiota suspension, the patients will be monitored for 2 hours in the ward before being discharged. Short term, mild side effects are common directly after infusion of microbiota and consist of loose stools / diarrhea (~ 95%), abdominal cramps (~ 30%), belching (~ 20%) and constipation (~ 20%) [van Nood 2013]. Serious adverse events definitely related to FMT are very rare [Wang 2016].
Before the bowel lavage and FMT individual instructions will be given to each patient on the timing and use of medication, such as immunosupressants, diuretics and glucose regulating agents, to avoid complications such as reduced absorption of immunosupressants (potentially leading to rejection of the renal graft), hypoglycemia or hyponatremia. In case of persistent diarrhea possibly causing a reduction in the absorption of their immunosuppression, admission for the administration of intravenous preparations may be required. Drug levels of immunsuppressive drugs will be monitored after FMT, and dosage will be adapted accordingly.
Follow up consists of 5 outpatient clinic visits with collection of 5 samples of blood (3x 3ml, 1x9,5 ml, 1x6,5 ml; a total of 25 ml during 5 follow up visits), fresh faeces and urine. The dry blood spot measurements for AUC calculation will be repeated 3 times after FMT. Symptoms, treatment details, side effects and quality of life will be evaluated by standardized questionnaires obtained on each follow up visit.
We hypothesize that effective decolonization of MDRE can be achieved by infusion of donor faecal microbiota. Subjects will benefit from participation if decolonization is realized and difficult to treat infections with multidrug resistant bacteria can be prevented.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)

Inclusion criteria

In order to be eligible to participate in this study, a subject must meet all of the following criteria: 1. Competent renal transplant recipient aged 18 or above. 2. Intestinal carriage of extended-spectrum β-lactamase Enterobacteriaceae (ESBL-E) and/or carbapenemase producing Enterobacteriaceae (CPE) by rectal swab or stool culture tests (>=2x). 3. A history of >= 1 documented infection by these bacteria <6 months before enrolment. 4. Adequate understanding of the procedures of the study and agrees to abide strictly thereby. 5. Ability to communicate well with the investigators and availability attend all study visits. 6. Signed informed consent.

Exclusion criteria

1. Need for systemic antibiotics. 2. ICU admission at enrolment. 3. Creatinine clearance <30 ml/min. 4. (Planned) pregnancy during study. 5. Allergy / contraindication study drugs. 6. Recurrent aspirations / chronic dysphagia. 7. Recent intra-abdominal surgery. 8. A history of acute rejection within 6 months before enrolment. 9. Treatment with alemtuzumab within 6 months before enrolment. 10. Treatment with of eculizumab within 3 months before enrolment. 11. Clinical signs of active colitis / gastro-enteritis, including active infections (EBV /CMV / adenovirus / Clostridium difficile / chronic parasitic infection) or active inflammatory bowel disease. 12. Severe food allergy.

Study design

Design

Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)

Primary purpose: Prevention

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	09-04-2018
Enrollment:	12
Type:	Actual

Ethics review

Approved WMO

Date:	27-11-2017
Application type:	First submission
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

Approved WMO

Date:	15-08-2018
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

Approved WMO

Date:	11-03-2019
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

Approved WMO

Date:	21-03-2019
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
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Approved WMO Date:	24-02-2020
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
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Approved WMO Date:	02-02-2022
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
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Approved WMO Date:	06-09-2023
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
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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
CCMO	NL62209.058.17