AssessmeNT of the Incidence of Clostridium difficile Infections in hospitalized Patients on Antibiotic TrEatment

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Primary objective:To determine the incidence of Clostridium difficile infection (CDI) in hospitalized patients aged * 50 years old and receiving oral or intravenous fluoroquinolones, cephalosporins, penicillins + beta-lactamase inhibitors,...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Gastrointestinal infections
Study type	Observational non invasive

Summary

ID

NL-OMON42976

Source
ToetsingOnline

Brief title
ANTICIPATE

Condition

- Gastrointestinal infections
- Bacterial infectious disorders

Synonym
Clostridium difficile infection; diarrhea caused by the bacterium Clostridium difficile

Research involving
Human

Sponsors and support

Primary sponsor: Universitair Medisch Centrum Utrecht
Source(s) of monetary or material Support: DaVolterra, Parijs,Europese subsidie IMI (50%) + DaVolterra (50%)

Intervention

Keyword: antibiotics, Clostridium difficile, microbiota

Outcome measures

Primary outcome

Incidence of CDI within 28 days of initiation of antibiotic treatment.

Secondary outcome

Secondary endpoints:

1. Incidence of CDI within 90 days of antibiotic treatment initiation.

2. Incidence of AAD within 28 days of antibiotic treatment initiation.

3. Incidence of AAD within 90 days of antibiotic treatment initiation.

4. Incidence of CDI and AAD 28 and 90 days after antibiotic treatment initiation by class of antibiotics.

5. Incidence of CDI and AAD 28 and 90 days after antibiotic treatment initiation by C. difficile colonization status at the start of antibiotic treatment.

6. Time from the start of antibiotic treatment to occurrence of CDI.

7. Incidence of CDI in patients with previous CDI.

8. Bacterial diversity of the intestinal microbiome, as assessed by the Shannon diversity index using 16S rRNA gene profiling, at the start of antibiotic treatment in patients developing CDI, patients developing AAD (including CDI), patients developing non-CDI AAD, and non-diarrheic patients.

9. Change from baseline to day 6 of bacterial diversity and composition of the intestinal microbiome as assessed respectively by the Shannon diversity index and the Spearman rank correlation coefficient of the relative abundance of OTUs between the start of the antibiotic treatment and day 6 measured by 16S rRNA gene sequencing, by antibiotic class.
10. 3-3-indoxyl sulfate levels in urine at the start of antibiotic treatment in patients developing CDI, patients developing AAD (including CDI), patients developing non-CDI AAD, and non-diarrheic patients.
11. Relationship between 3-3-indoxyl sulfate levels in urine and bacterial diversity and composition of the intestinal microbiome, both at the start of antibiotic treatment and at day 6.

Exploratory endpoints:
1. Number and proportion of study sites/hospitals which included patients in the present study within the desired time window, overall and by country.
2. Number and proportion of study sites/hospitals able to collect the required information on study outcomes (occurrence of AAD/CDI) during hospitalisation and after discharge from hospital, overall and by country.
3. Description of the identified potential bottlenecks for successful execution of the DAV132 RCT, overall and by country.
4. Antibiotic consumption, length of stay in hospital, length of stay in ICU, and mortality in patients with CDI compared to patients not developing CDI, overall and by country.

5. Estimated costs of CDI management, overall and by country.

Study description

Background summary

During or after antibiotic treatment, antibiotic residues impair the intestinal microbiota (gut flora) and lead to adverse effects such as the emergence of bacterial resistance or the occurrence antibiotic-associated diarrhoea (AAD) including antibiotic-induced C. difficile infection (CDI). The spread of resistant Gram-negative bacteria and the increasing number and severity of CDI are considered as worldwide public health threats.
Da Volterra is a biotechnology company developing a novel product, DAV132 (a medical device in Europe), intended to prevent these antibiotic adverse effects. Da Volterra is planning to carry out a phase 2-3 randomized controlled trial (RCT) of DAV132 in the prevention of antibiotic-induced CDI. The RCT will involve hospitalized patients aged *50 years old and treated with predefined antibiotic classes known to increase the risk of CDI. The incidence of CDI in this population is unknown, yet, incidence is an important determinant for the required sample size.
Therefore, the main objective of the current study is to assess CDI incidence in patients *50 years of age treated with predefined antibiotic classes.
In addition, to optimise the target population of the DAV132 RCT, the effect of the predefined antibiotic agents on the intestinal microbiota will be assessed. Furthermore, biomarkers predictive of CDI occurrence might help identify patients at high risk for the disease, which could further optimise the RCT. No validated biomarkers have been described in the literature yet. Assessment of potential biomarkers is another aim of the present study.

Study objective

Primary objective:
To determine the incidence of Clostridium difficile infection (CDI) in hospitalized patients aged * 50 years old and receiving oral or intravenous fluoroquinolones, cephalosporins, penicillins + beta-lactamase inhibitors, carbapenems, and/or clindamycin.

Secondary objectives
1. To determine the incidence of antibiotic-associated diarrhoea (AAD, including CDI).
2. To quantify the predictive value of asymptomatic carriage of toxin-producing C. difficile at the start of antibiotic treatment for the occurrence of CDI/AAD.
3. To determine the incidence of CDI in patients with previous CDI.
4. To assess if bacterial diversity of the intestinal microbiome at the start

of antibiotic treatment predicts the occurrence of CDI/AAD.
5. To determine the changes of intestinal microbiome bacterial diversity and composition induced, by antibiotic class.
6. To assess if 3-indoxyl sulfate levels in urine at the start of antibiotic treatment predict the occurrence of CDI/AAD.
7. To quantify the correlation between 3-indoxyl sulfate levels in urine and the disruption of the intestinal microbiome at the start of and during antibiotic treatment.

Exploratory objectives
In preparation of a phase II/III RCT of DAV132 the following exploratory objectives are specified:
1. To determine the capability of study sites/hospitals to include patients in the present study within the desired time window.
2. To determine the ability of study sites/hospitals to collect the required information on study outcomes (occurrence of AAD/CDI) during hospitalisation and after discharge from hospital.
3. To identify and describe potential bottlenecks (and solutions) for successful execution of the RCT.
4. To characterize the outcome of CDI.
5. To evaluate the cost of CDI management.

Study design

European multicenter, hospital-based, prospective, observational cohort study.

Study burden and risks

Burden: collection of three rectal swabs at two time points. Collection of two urine samples at two time points. Collection of stool sample in case of diarrhea. Completion of the patient diary containing three yes/no questions daily for 90 days.
Risk: temporary uncomfortable feeling from the rectal swabs.
Benefit: there is no direct benefit for patients to participate in the study.
Group relatedness: the subject of investigation is related to the study population in that all patients treated with antibiotics are at risk of developing Clostridium difficile infections.

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

1. Male or female hospitalized patient.
2. Aged >< = 50 years old.
3. Initiation of intravenous or oral treatment with intended duration *5 days (*1 day for clindamycin) with at least one of the following antibiotic classes, or treatment scheduled within the next 72 hours:
- Third or fourth generation cephalosporins
- Fluoroquinolones
- Penicillins +beta-lactamase inhibitors
- Clindamycin
- Carbapenems
4. Written informed consent provided prior to inclusion.

Exclusion criteria

1. Ongoing antibiotic treatment with one of the above classes initiated >6 hours before inclusion into the study.
2. ICU admission at the time of inclusion or anticipated admission within 48h.
3. Suspected or diagnosed CDI, ongoing treatment for CDI, or diarrhoea at the time of

inclusion.
4. Subject has been included into this study previously.
5. Patient treated with probiotics to prevent CDI.
6. Patient with any social or logistical condition which in the opinion of the investigator may interfere with the conduct of the study, such as incapacity to well understand, not willing to collaborate, or cannot easily be contacted after discharge.
7. Subject deprived of liberty by judicial or administrative decision.

Study design

Design

Study type: Observational non invasive

Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Basic science

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	07-12-2016
Enrollment:	50
Type:	Actual

Ethics review

Approved WMO

Date:	21-09-2016
Application type:	First submission
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
ClinicalTrials.gov	NCT02896244
CCMO	NL57769.041.16