Antibiotic exposure at the infection site in periprosthetic joint infections

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To develop a pharmacokinetic (PK) model for the relationship between dosage, blood concentration and infection site concentration, estimating covariates to determine differences in antibiotic concentrations in synovial fluid, synovial tissue and...

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

Summary

ID

NL-OMON54617

Source
ToetsingOnline

Brief title
ASTERICS

Condition

- Bacterial infectious disorders

Synonym
infection at the site of the prosthesis, Periprosthetic joint infections

Research involving
Human

Sponsors and support

Primary sponsor: Erasmus MC, Universitair Medisch Centrum Rotterdam
Source(s) of monetary or material Support: Ministerie van OC&W,afh van te krijgen subsidie;wordt nu geworven

Intervention

Keyword: Antibiotics, Exposure, Periprosthetic joint infection, Target site concentration

Outcome measures

Primary outcome

PK/PD indices are calculated. The treatment drug Minimal Inhibitory Concentration (MIC) for the isolated pathogen and the free (unbound) drug exposure value are used to calculate pharmacodynamic indices. Epidemiological cut-off value (ECOFF) and MIC data for the expected bacteria will be used.

Secondary outcome

- PK/PD model to evaluate the relation between antibiotic dosage, blood- and infection site concentration (estimating covariates) for the different antibiotics of interest and knee versus hip.

- Differences in target site concentration of the antibiotics between THA and TKA patients suffering from PJI.

- The number and type of drug-related adverse events occurring during the antimicrobial treatment.

- Differences in target site concentration and antibiotic exposure (measured in concentration with respect to the MIC of the bacteria) between patients treated with the antibiotic therapy applied during the two-stage arthroplasty exchange and patients treated with the former in combination with an antibiotic-loaded spacer.

- Duration of antibiotic elution from antibiotic-loaded spacers.

Study description

Background summary

Prosthetic joint infections (PJI, periprosthetic infection) is a serious complication of joint replacement surgery, leading to prosthesis failure. The standard treatment of PJI consists of a one-stage two-stage arthroplasty exchange, which includes a six-weeks course of orally and intravenously administered antimicrobial therapy. In practice, antibiotic regimens and the therapeutic efficacy are optimized by measuring concentrations in plasma. However, through this method it remains unclear whether effective concentrations of the antibiotics have reached the site of PJI, although adequate target site concentrations are important to achieve effective eradication of the micro-organism causing the PJI. Furthermore, antibiotic concentrations vary depending on individual patient characteristics such as body mass, renal function and bowel absorption. Additionally, the comparison of studies on the penetration of surgical prophylactic antibiotics in bone and joint tissue indicates a large variation in the antibiotic concentrations at the target site in extremities, making antibiotic dosage recommendations supported by limited evidence. Despite these insights, knowledge is lacking regarding the target site concentrations of the antibiotics, administered as part of the one-stage or two-stage arthroplasty exchange, with respect to the dosage and plasma concentrations. The overall aim of this proposed study is to gain insight into the target attainment of the administered antibiotics during the two-stage arthroplasty exchange, in order to determine the efficacy in relation to the minimal inhibitory concentration (MIC) of the pathogen causing the infection. Additionally, by comparing the target site concentrations of orally and intravenously (IV) administered antibiotics we can determine whether a need exists per patient for both oral and IV administration of antibiotics, or if one route of administration is sufficient enough.

Study objective

To develop a pharmacokinetic (PK) model for the relationship between dosage, blood concentration and infection site concentration, estimating covariates to determine differences in antibiotic concentrations in synovial fluid, synovial tissue and bone between different types of antibiotics and knee versus hip.

Study design

Cross-sectional observational study

Study burden and risks

This study is relevant since effective concentrations of the applied

antibiotics at the site PJI are of importance for not only the optimization of the treatment efficacy, but also to decrease the incidence of unnecessary antibiotic-related adverse events. Patients have to undergo study related procedures which are minimally invasive; risks and burdens associated with participation are minimized by combining them with procedures for standard care, as much as possible. Therefore, only undergoing venous blood sampling and joint punctures for collecting synovial fluid outside of the surgeries can be considered invasive and a burden for the patient. To reduce the extend of the burden on the patients these joint punctures will be combined with the periodic hospital visitations of the patients after prosthesis extraction; if not possible additional hospital visits will be necessary and unavoidable. Adverse events of joint punctures may include pain, bleeding, bruising and joint swelling; however, these events are rare making joint punctures a well-tolerated procedure. The individual patients participating in this study have no direct benefits. The possible risks associated with the study are outweighed by its benefits for the study population.

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

- Age >= 18 years.
- Written informed consent has been obtained from the patient or their legally authorized representative.
- Suffering from periprosthetic (hip or knee) joint infections and therefore treated with one of the following antibiotics as part of the one-stage wo-stage arthroplasty exchange:
IV: vancomycin, flucloxacillin or cefuroxime
Oral: flucloxacillin, clindamycin or co-trimoxazole or ciprofloxacine
- Patients undergoing a two-stage implant exchange of hip or knee with or without antibiotic free interval prior to re-implantation.
- Able and willing to undergo joint punctures and venous blood sampling during and, in case of an antibiotic free interval, at the end of the six-weeks antibiotic treatment.

Exclusion criteria

- Unable to draw samples for study purposes; Except when a patient received a vancomycin-loaded spacer, then they will remain included.
- Language barriers.
- The use of the target antibiotics at the start of study participation (and therefore at the start of the antibiotic treatment as part of the two-stage arthroplasty exchange).
- The use of drugs interacting with the target antibiotics.

Study design

Design

Study type: Observational invasive

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

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	06-10-2020
Enrollment:	120
Type:	Actual

Ethics review

Approved WMO Date:	25-05-2020
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	10-03-2021
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	29-11-2022
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	27-06-2023
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	09-01-2024
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

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	NL72038.078.19