Dose individualization of Antibiotics in ICU patients: to TDM or not to TDM and the effects on outcome (DOLPHIN-trial)

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The aim of this trial is to evaluate a new early dosage adjustment strategy (TDM) of beta-lactam and fluoroquinolones in adult ICU patients to achieve the adequate pharmacodynamic targets (PDT), compared to the usual treatment strategy.

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Hepatobiliary neoplasms malignant and unspecified
Study type	Interventional

Summary

ID

NL-OMON55835

Source
ToetsingOnline

Brief title
DOLPHIN

Condition

- Hepatobiliary neoplasms malignant and unspecified

Synonym
critically ill patients, Infection

Research involving
Human

Sponsors and support

Primary sponsor: Erasmus MC, Universitair Medisch Centrum Rotterdam
Source(s) of monetary or material Support: MRace

Intervention

Keyword: Antibiotics, ICU, Pharmacokinetics, Pharmaodynamics, TDM

Outcome measures

Primary outcome

The primary outcome parameter is the length of ICU stay (LOS).

The cohort COVID-19 patients are analysed as a separate subpopulation. Furthermore, to rule out any additional effects of continuous infusion on the endpoints, we will also consider this population as a separate cohort. This applies to all endpoints, and for primary endpoint the difference in achieving the pharmacodynamics targets (delta target attainment) is determined instead of the LOS in the both the COVID-19 and continuous infusion cohorts. The LOS is determined in both cohorts, but is reported as a secondary outcome measure.

The target for continuous infusion is increased from 100% *T> MICECOFF to 100% *T> 4xMICECOFF, with the dose reduction threshold for intermittent and continuous infusion being equal (10xMICECOFF).

Secondary outcome

Secondary aims are to show that active TDM results in improved clinical outcome, increased cost-effectiveness, better quality of life.
Clinical outcomes are 28-day mortality, decrease in SOFA (sequential organ failure assessment score), and hospital stay. Cost-effectiveness will be determined intramural and extramural and using appropriate health * economic analysis. Furthermore, the number of antibiotic days, use of other antibiotics,

and decrease in CRP and procalcitonin will be registered. At last, major side effects will be reported.

Quality of life will be measured 6 months after ICU stay, as a proxy for post-ICU syndrome.

Amendment April 2020 secondary outcome measures:

* Change from baseline in white blood cell and differential count [T=0-28]. From routine blood tests.

* Time to first negative in 2019 novel Corona virus RT-PCR test [T=0-28]. From routine swabs tests.

Study description

Background summary

Emerging evidence supports the importance of optimized antibiotics exposure in intensive care unit (ICU) patients, while evidence based antibiotic dosing in ICU patients in clinical practice is limited. Changes in pharmacokinetic (PK) parameters of antibiotics in subpopulations of critically ill patient have been defined in previous studies. However, there are no data from studies assessing whether the issues identified in a controlled research environment correspond to clinical practice. Assessment is essential in order to determine whether actions, such as the use of therapeutic drug monitoring (TDM), are required to change our existing antibiotic prescribing practices in ICU patients. The potential benefits of a TDM-based approach include a better outcome because of more appropriate antibiotic concentrations, but also less resistance development and avoidance of toxicity. It is most commonly used when the PK and therefore the optimal dose of a drug for an individual patient are difficult to predict. In clinical practice, this approach has been routinely used for many years for vancomycin and aminoglycosides. However, expansion of this practice to cephalosporin and fluoroquinolone antibiotics, which are frequently used to treat infections in critically ill patients, has not been widely tested as a routine intervention. This is very unfortunate, because the contemporary antibiotic dosing is debatable in severely ill patients as most dosing references have been derived from studies that do not consider the occurrence

of pathophysiological changes in critical illness.

Study objective

The aim of this trial is to evaluate a new early dosage adjustment strategy (TDM) of beta-lactam and fluoroquinolones in adult ICU patients to achieve the adequate pharmacodynamic targets (PDT), compared to the usual treatment strategy.

Study design

The design is a multicenter, prospective, randomised trial: active TDM versus non-TDM group of beta-lactam and fluoroquinolone antibiotics.

Intervention

Antibiotic start dosing will occur as deemed by the ICU clinician and/or infectious disease clinician and the local dosing practices. Assigned interventions in the active TDM group: dosage of beta-lactam and fluoroquinolone antibiotics will be adjusted according to serum concentrations. In the non-TDM (control) group samples of serum concentrations of beta-lactam and fluoroquinolone will be collected for comparison. The antibiotic concentrations in the control group will be measured in bulk later and blinded for the ICU clinician and/or infectious disease clinician.

Study burden and risks

With the exception of blood collection, there is no discomfort associated with participation in this study. Risks are moderate and the burden is minimal.

Contacts

Public
Erasmus MC, Universitair Medisch Centrum Rotterdam

's Gravendijkwal 230
Rotterdam 3000 CA
NL
Scientific
Erasmus MC, Universitair Medisch Centrum Rotterdam

's Gravendijkwal 230
Rotterdam 3000 CA
NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

All patients admitted to the adult general ICU wards and given standard of care intravenous therapy of the target antibiotic are screened for participating in trial.

Patients will be admitted to the cohorts based upon the following three cohorts:
1. Main cohort (COVID-19 Negative, No continuous infusion)
2. COVID-19 cohort (including continuous infusion)
3. Continuous infusion cohort (COVID-19 Negative)

Antibiotic initiation based on clinical suspicion of infection and/or cultured pathogens susceptible to the target drugs, initial dosage prescription, and duration of therapy are at the discretion of the attending physician. , In order to be eligible to participate in this study, a subject must also meet all of the following criteria:
* *18 years of age
* Receiving intravenous antibiotic therapy of the target drugs (including continuous infusion)
* Treatment should be aimed for at least 2 days.
* Written informed consent has been obtained from the patient or their legally authorized representative.

Exclusion criteria

A potential subject who meets any of the following criteria will be excluded from participation in this study:
* Pregnancy
* Patient already enrolled in this trial

* Antibiotic cessation before sampling
* Medium care and burn wound patients admitted to the ICU
* Patients receiving target antibiotics only as prophylaxis within the context of Selective Digestive tract Decontamination (SDD)

Study design

Design

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):	19-10-2018
Enrollment:	562
Type:	Actual

Ethics review

Approved WMO Date:	06-03-2018
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	09-03-2018
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

Approved WMO Date:	31-07-2018
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	07-02-2019
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	21-03-2019
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	15-04-2019
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	25-06-2019
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	10-12-2019
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	30-04-2020
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	19-05-2020
Application type:	Amendment

Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	30-11-2020
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	02-03-2021
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
EudraCT	EUCTR2017-004677-14-NL
CCMO	NL64070.078.17

Study results

Date completed:	28-02-2022
Actual enrolment:	486