Short-course aminoglycosides as adjunctive treatment in adults with sepsis

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

Summary

ID

NL-OMON53650

Source
ToetsingOnline

Brief title
SAGA

Condition

- Bacterial infectious disorders

Synonym
infection, sepsis

Research involving
Human

Sponsors and support

Primary sponsor: Universitair Medisch Centrum Utrecht
Source(s) of monetary or material Support: NWO;KNAW;ZonMW

Intervention

Keyword: Aminoglycosides, Cephalosporins, Mortality, Sepsis

Outcome measures

Primary outcome

30-day all-cause mortality

Secondary outcome

Main study:

• Duration of intravenous antibiotic treatment in calendar days and hours

• Time to switch to oral treatment in calendar days and hours

• Duration of hospitalization in calendar days

• ICU admission, length of ICU stay, mechanical ventilation

• ICU admission in patients who are not directly admitted to the ICU

• Complications during hospital admission possibly related to the disease or treatment.

• Nephrotoxicity requiring dialysis

• Hospital re-admission within 30 days of initial hospitalization

• Failure of treatment

Active Follow-up subset:

• Quality of life

• 1 year mortality

• Duration of absenteeism

• Health care cost per quality-adjusted life year

• Societal costs per quality-adjusted life year

• Nephrotoxicity according to the The Kidney Disease: Improving Global Outcomes (KDIGO) criteria. For criteria see chapter 7.2.1.

• Recovery of renal function in patients with acute renal failure.

• Subjective hearing loss

PKPD subset:

- To define the association between attained PK/PD index of empirical sepsis treatment with cefuroxime, ceftriaxone, gentamicin and/or tobramycin in the first 48 hours of treatment and 30-day mortality and other clinical outcomes such as renal toxicity and length of hospital stay in patients with community-onset sepsis

- To define population pharmacokinetic characteristics of cefuroxime, ceftriaxone, gentamicin and tobramycin in patients with community-onset sepsis, including risk factors for not reaching the PK/PD target, in order to design future trials on optimized empirical antibiotic dosing in sepsis

- To assess and compare attained PK/PD indices of patients sepsis empirically treated with cefuroxime plus aminoglycoside versus ceftriaxone or cefuroxime monotherapy and their association with 30-day mortality.

- To assess and compare attained PK/PD indices of patients empirically treated with gentamicin versus tobramycin and their association with 30-day mortality.

Study description

Background summary

In the Netherlands, there is large variation in the empirical antibiotic treatment of sepsis, especially regarding the adjunctive short-term treatment with aminoglycosides added to the widely used beta-lactam antibiotics. In a recent multicenter observational study of684 patients with Gram-negative bacteremia we found large heterogeneity in the use of aminoglycosides (gentamicin or tobramycin)across seven hospitals.(Deelen et al, submitted) Proportions of patients receiving aminoglycosides added to beta-lactam antibiotics ranged from 11% to 49% per hospital. Over 80% of these infections concerned community-onset infections. In a multivariable model, *hospital* was by far the most important determinant of aminoglycoside prescription, and explained variation five times better than sepsis severity (the second most important determinant of aminoglycoside prescription).

The hypothesized added value of aminoglycosides results from a presumed more rapid clearance of bacteremia, synergistic activity with beta-lactams due to acting on two different targets, and increased probability of appropriate empirical antibiotic therapy (defined as treatment that covers the pathogen based on its in vitro susceptibility to antibiotics). Appropriateness of empirical antibiotic therapy is becoming less certain due to growing antibiotic resistance. In the Netherlands, aminoglycosides are often combined with second generation cephalosporins (usually cefuroxime), while the usual alternative strategy is monotherapy with a 3rd generation cephalosporins (usually ceftriaxone). The combination of a 2nd generation cephalosporin with an aminoglycoside provides a better coverage of S. aureus and better coverage of ESBL+ gram-negative bacteria. Indeed, in the aforementioned study of patients with Gram-negative bacteremia, the proportion of inappropriate empirical treatment was 14.8% among patients not receiving an aminoglycoside and 1.9% among those receiving both beta-lactam and aminoglycoside antibiotics. However, this was not associated with a better outcome. In fact, the adjusted odds ratio for day-30 mortality was 1.39 (95% CI 0.78-2.48) among patients receiving aminoglycosides, with the point estimate pointing towards higher mortality for patients that had received aminoglycosides.(Deelen et al) The apparent lack of benefit is in line with results from a previous observational study in the ICU setting in the Netherlands. Several studies on this topic have been performed in other countries. Naturally, observational studies suffer from potential residual confounding by indication, for which some included intermediates as confounders in their analysis, and others used a limited set of confounders, impeding direct causal interpretation. The few trials performed in this population are of limited size and mostly studied prolonged use of aminoglycosides. Yet, the results of these studies, together with the observed large heterogeneity between hospitals in the Netherlands, justify a randomized trial to determine the true effect of adding aminoglycosides to a beta-lactam antibiotic on patient-relevant clinical outcomes and healthcare efficiency in sepsis patients. The need of trials to determine the benefit of combination therapy has also been expressed by an international consensus committee on the research priorities in the management, epidemiology, outcome and underlying causes of sepsis and septic shock.

The most important risks associated with aminoglycosides are nephrotoxicity (sometimes requiring dialysis) and ototoxicity. Incidences of acute kidney injury (AKI) in sepsis patients treated with aminoglycosides range from 14% to 46%, depending on the population studied and the definition of AKI. There are two RCTs and six comparative observational studies assessing AKI incidence in sepsis patients treated or not treated with aminoglycosides which yielded heterogeneous results. E.g. a propensity score-matched cohort study of patients with bacteremia found no association between gentamicin and nephrotoxicity with an OR 0.90(95% CI 0.68-1.20; point estimate in favor of gentamicin). Another study, among patients with severe sepsis or septic shock in the ICU, found an adjusted OR for renal failure days of 1.39 (95% CI 1.00-1.94).(1) The risk of aminoglycoside-induced nephrotoxicity might be reduced by therapeutic drug monitoring (TDM) which is not always well described in these studies. Among the RCTs, one was too small to be conclusive, and the other adult patients with serious hospital-acquired infections found a small increased risk of 3% in patients treated with aminoglycosides. The literature on ototoxicity with short-term once-daily dosed aminoglycosides is muchless abundant. In a meta-analysis comparing beta-lactam monotherapy to once-daily aminoglycosides added to beta-lactams,ototoxicity outcomes were found to be not well reported and could, therefore, not be analyzed. To the best of our knowledge, noobservational studies have compared ototoxicity rates between regimens with or without aminoglycosides. There is some indirectevidence to suggest that the ototoxicity risk induced by short-course aminoglycosides is limited. Aminoglycoside-induced nephrotoxicity is usually reversible, ototoxicity is often permanent, and both increase patients* morbidity and health care costs, for instance because of a temporary need of renal replacement therapy in some patients.

The Dutch sepsis guideline does not recommend in favor or against the use of aminoglycosides due to the lack of evidence, but instead states that *the decision should be guided by local etiology and resistance data.* Obviously, aminoglycosides should be withheld if there is no added value. Colloquially it should be recommended if there is a clear positive risk-benefit balance. There areno trials on the effectiveness of short-course aminoglycosides adjunctive to beta-lactams in sepsis and it is not possible to answer this research question with existing observational data, as there is strong indication bias which cannot be fully corrected for. The heterogeneity in antibiotic treatment in sepsis patients in the Netherlands calls for a well-designed study to determine which strategy has the best risk-benefit balance.

Study objective

The objective of the proposed study is to determine the effectiveness, safety and cost-effectiveness of a strategy of cefuroxime combined with short course treatment with aminoglycosides compared to a strategy of ceftriaxone monotherapy in patients with sepsis presenting to the emergency room (ER) and admitted to the hospital. We hypothesize that the ceftriaxone monotherapy

strategy is non-inferior for mortality. Yet, we will design the analysis such that we can also test whether cefuroxime + aminoglycosideis superior (i.e. we will use a two-sided alpha). For nephrotoxicity we will test the hypothesis that a strategy of ceftriaxone monotherapy is superior to a strategy of cefuroxime combined with short course aminoglycosides.

A secondary aim is to determine whether there is a difference in nephrotoxicity between gentamicin and tobramycin. Here the null-hypothesis is that there is no difference in nephrotoxicity and the alternative hypothesis is that tobramycin is less nephrotoxic compared to gentamicin.

Study design

We will preform a cluster-randomized cross-over trial. During two consecutive periods of 12 months, hospitals will be randomized to alternating antibiotic policies for patients admitted with sepsis. The antibiotic policy serves as the preferred empiric treatment of sepsis during the 12 month-period. This implies that treating physicians may deviate from the policy if considered clinically indicated and that patients with treatment deviation will be included in the intention-to-treat analysis. In total 10 hospitals will participate in the study. We will ensure that a representative number of academic and non-academic hospitals are included to obtain a representative sepsis population.

By including 3,140 patients, the trial is large enough to statistically demonstrate or rule out a 5% absolute reduction in mortality risk,while taking into account possible deviations from the assigned treatment and clustering per hospital.

In a 1/3 of the patients (active follow-up subset) we will determine the quality of life and costs after discharge during one year. We will also actively look at nephrotoxicity by means of 1 vena puncture 10 days after admission. In a small group, an extra veni puncture will be necessary. This will be in the patients with acute kidney injury without recovery 10 days after admission or on discharge. Ototoxicity is also examined by a questionnaire. For the PK / PD part we want to include 900 patients. These can be patients from the active follow-up subset, but can also be participants from the main study only. Here, residual material is used to determine the PK / PD (blood taken in the first 48 hours of admission). The positive blood cultures will also be saved to determine the MIC.

The planned duration of the project is 4.5 years. The proposed project is feasible and will provide important information to improvethe health outcomes of patients with sepsis or to avoid unnecessary health loss and costs.

Intervention

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Study burden and risks

Since both treatments are currently standard care in this patient population (depending on which hospital you are admitted to), there is a negligible risk in terms of treatment. Additional blood draws in the active follow-up subset may present a risk of pain during blood collection and possible hematoma.

For the active follow-up subset, there are 3 questionnaires that must be completed. This takes between 10-30 minutes and consists of low-impact questions such as: how does the patient feel, has the patient been admitted or visited a doctor and is there hearing loss.

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) Age >= 18 years
2) Presenting to the ER
3) Suspicion of bacterial infection of unknown origin, primary suspected urinary origin or primary suspected abdominal origin.
4) National Early Warning Score (NEWS) >= 5.
5) Requiring intravenous antibiotic treatment and hospitalization.

Exclusion criteria

1) Working diagnosis at the ED of pneumonia (even if other foci are mentioned in the differential diagnosis).
2) Chemotherapy induced neutropenia as this is considered a separate entity in the guidelines.
3) History of renal transplantation or pre-existing renal failure defined as a GFR < 30, due to a relative contra-indication for aminoglycosides.
4) Allergy for cephalosporins or aminoglycosides, known prior to the start of antibiotic treatment.
5) Pre-existing hearing impairment known at the moment of presentation in the ER.
6) History of heart-, lung or liver transplantation.
7) Known myasthenia or botulism.
8) A patient who has had an indwelling catheter for a prolonged period or was catheterized intermittently, because of the recommended empirical treatment including an aminoglycoside according to the SWAB guidelines.
9) Use of the medication cyclosporine, cisplatin, neuromuscular acting muscle relaxants, oral neomycin and oral paromomycin due to relative contra-indication for aminoglycosides.
10) Known colonization with a 3rd generation cephalosporin resistant bacterium including Pseudomonas, relevant in the context of the infection the patient is admitted with.

Study design

Design

Study type:	Interventional
Intervention model:	Other
Allocation:	Randomized controlled trial

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

Recruitment

NL

Recruitment status:	Completed
Start date (anticipated):	25-05-2022
Enrollment:	3140
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Ceftriaxone
Generic name:	Ceftriaxone
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Cefuroxime
Generic name:	Cefuroxime
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Gentamicine
Generic name:	Gentamicine
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Tobramycine
Generic name:	Tobramycine
Registration:	Yes - NL intended use

Ethics review

Approved WMO

Date:	24-03-2022
Application type:	First submission

Review commission:	METC NedMec
Approved WMO Date:	26-04-2022
Application type:	First submission
Review commission:	METC NedMec
Approved WMO Date:	02-08-2022
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	13-08-2022
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	02-12-2022
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	15-02-2023
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	25-02-2023
Application type:	Amendment
Review commission:	METC NedMec

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	EUCTR2021-001840-83-NL
CCMO	NL80310.041.22
Other	NL9429

Study results

Date completed: 31-05-2023

Actual enrolment: 472

Summary results
Trial ended prematurely