Long-term effects of renal mitochondrial vitality in severe infections and sepsis

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Primary ObjectiveThe primary objective of the current project is to study the association between biomarkers for renal mitochondrial damage in sepsis with the change in renal function and mortality after sepsis.Secondary Objective(s)The secondary…

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

Summary

ID

NL-OMON47415

Source
ToetsingOnline

Brief title
LONGEVITIES

Condition

- Bacterial infectious disorders
- Renal disorders (excl nephropathies)

Synonym
blood poisoning, sepsis

Research involving
Human

Sponsors and support

Primary sponsor: Universitair Medisch Centrum Groningen
Source(s) of monetary or material Support: Nierstichting

Intervention

Keyword: kidney, mitochondria, mitochondrial DNA, sepsis

Outcome measures

Primary outcome

In order to answer the primary objective, the following parameters will be

measured in the group *hospitalized with infection*:

Estimation of renal an systemic mitochondrial damage

- Biomarkers for mitochondrial damage in plasma, urinary exosomes and urine

- MtDNA copy number in plasma and urine

- Oxidation of mtDNA in urinary exosomes and urine

- MtDNA damage in urinary exosomes and urine

Estimation of renal function

- Serum creatinine level

- Albumin/creatinine-ratio in urine

- Estimated glomerular filtration rate (eGFR, MDRD-4 (44, 45))

- CKD (classified according to the KDIGO criteria (44, 45))

Mortality

- In-hospital mortality

- Long-term mortality

Estimation of delirium (only in aged individuals)

- Confusion assessment method (CAM) score within 24 hours and at day 4

Peripheral immune cells (functional status assessed by surface markers; only in aged individuals)

- monocyte functional status and number (CD14/CD16)
- NK-cell functional status and number (CD56)
- T-cell functional status and number (CD3/CD45RO/CCR-7/CD27)
- B-cell functional status and number (CD19)

The following parameters will be measured in the group *matched control subjects*:

Estimation of renal an systemic mitochondrial damage:

- Biomarkers for mitochondrial damage in plasma, urinary exosomes and urine
- MtDNA copy number in plasma and urine
- Oxidation of mtDNA in urinary exosomes and urine
- MtDNA damage in urinary exosomes and urine

Estimation of renal function:

- Serum creatinine level
- Albumin/creatinine-ratio in urine
- Estimated glomerular filtration rate (eGFR, MDRD-4 (44, 45))
- CKD (classified according to the KDIGO criteria (44, 45))

In addition to these parameters that will be collected to answer the primary study objectives, the following parameters will be collected in all subjects, from both groups:

- Demographic characteristics (i.e. age, sex)
- Smoking
- Known pregnancy
- Medication use
- Cardiovascular and renal risk factors: hypertension, hyperlipidemia, hyperglycemia/diabetes mellitus, heart failure, chronic kidney disease, family history

Secondary outcome

In addition to the parameters that will be already collected to answer the primary study objectives, the following will be collected in the group *hospitalized with infection*:

Measurement of serum cytokine levels (only in aged individuals)

- The following cytokine levels will be measured: IL-1β, IL-6, TNF-α, IL-8, IL-10, IFN-α, IFN-β, IL-1RA, granzyme B, myeloperoxidase (MPO), IP-10 (CXCL10), PAI-1, IL12p40, tPA, paraoxonase-1, glycA and E-selectin.

Measurement of cardiovascular events, co-morbidity, quality of life and functional status

- Co-morbidity: Charlson comorbidity index
- Functional status: Barthel Index, Lawton's Instrumental Activities of Daily

Living (IADL), Short Physical Performance Battery and WHO-performance score

- Quality of Life: EuroQol 5D 3L (EQ-5D-3L)

Measurement of disease severity

- Biomarkers of disease severity

- Presumed source of infection

- Treatment parameters

- Vital signs at presentation, and after 3 hours

- Clinical impression score at presentation, and after 3 hours

- MEDS score at presentation, and after 3 hours

- SOFA score at presentation, and after 3 hours

- APACHE-II score at presentation, and after 3 hours

- PIRO score at presentation, and after 3 hours

- Vital signs at presentation, and after 3 hours

- In-hospital mortality

- Admittance to the ICU

- Length of stay at ICU

- Length of hospital stay

- Progression to septic shock (i.e. persistent hypotension despite adequate fluid resuscitation)

Study description

Background summary

Sepsis accounts for 2% of all hospital admissions, can lead to multiple organ dysfunction syndrome (MODS) and is the leading cause of death among patients admitted to the intensive care unit (ICU) with a mortality rate of 20-30% (1). In addition, survivors of sepsis are at major risk for (fatal) cardiovascular events, with a 3-year mortality rate as high as 47% after hospital discharge (2). Despite the high mortality during and after sepsis, the pathogenesis remains poorly understood and therapy is limited to fighting the causative agents by administrating antibiotics and supply supportive care in the ICU (1, 3). Acute kidney injury (AKI) is in most cases caused by sepsis and is the strongest predictor of both short- and long-term survival after sepsis (1, 4-8). The occurrence of AKI during sepsis is not only associated with failure of other organs and an increased mortality risk during sepsis, but is also strongly associated with the risk for chronic kidney disease (CKD) and long-term mortality after sepsis (5-9). The pathophysiology of sepsis-associated AKI is complex and not fully elucidated. The kidneys contain a large number of mitochondria to support the relatively high ATP-demand (10-12). Mitochondrial dysfunction, leading to impaired ATP-production, while free radical formation is increased, is emerging as a key process in the pathophysiology of sepsis-associated AKI (6, 13). The importance of mitochondria in sepsis is supported by the observation that ATP levels are profoundly reduced in sepsis and that biomarkers for mitochondrial dysfunction and reduced anti-oxidant defense are associated with poor survival (14, 15). Furthermore, clinical signs of organ failure do not correlate with histological signs of tissue injury or inflammation in patients with sepsis, although intracellular levels of ATP are profoundly reduced in organ failure (Aslan and van Meurs, unpublished data) (13, 16, 17). Interestingly, administration of mitochondria targeted antioxidants limits renal mitochondrial dysfunction, attenuates sepsis-induced AKI and improves survival in a murine model of sepsis (18). Remarkably, not only does renal mitochondrial dysfunction seem to be involved in the pathogenesis of local injury in the kidney, it may also play a role in the induction of organ injury during sepsis, through the generation of free radicals and the release of damage associated molecular patterns (DAMPs) from damaged mitochondria and injured cells, as well as the production of pro-inflammatory cytokines (1, 3, 6, 19). Moreover, free radicals can damage renal mtDNA (20) and thereby permanently affect mitochondrial function, analogue to the process of aging (21-23). Indeed, mitochondrial function is not restored after survival from sepsis and leads to impaired long-term muscle function in mice (24). However, it is not known whether renal mtDNA damage induced by sepsis may explain the relatively high incidence of CKD and mortality among sepsis survivors. Analogue to the process of aging, sepsis is associated with oxidative damage to mtDNA, which may lead to respiratory chain dysfunction (20-23). In aged individuals, damage to mtDNA is associated with CKD and important co-morbidities such as diabetes mellitus type 2, and cardiovascular diseases (21-23). Furthermore, biomarkers for a reduced mitochondrial function, including inactivation of complex IV in peripheral blood mononuclear cells, increased free radical formation and reduced levels of mtDNA in blood are associated with the development of CKD (12, 29). Whether a

similar correlation between mitochondrial function and CKD exists among sepsis survivors remain to be unraveled. Potentially, oxidative stress during sepsis induces a comparable aged mitochondrial phenotype and thereby increases the risk of CKD, cardiovascular events, aging-related diseases and mortality after survival from sepsis. Thus, mitochondrial dysfunction plays a central role in the pathophysiology of AKI during sepsis, which is in turn associated with increased in-hospital and long-term mortality, as well as an increased risk of CKD among survivors. In this project, we will analyze whether the induction of damage to (renal) mitochondria during sepsis increases the risk of CKD and long-term mortality among sepsis survivors.

Study objective

Primary Objective
The primary objective of the current project is to study the association between biomarkers for renal mitochondrial damage in sepsis with the change in renal function and mortality after sepsis.

Secondary Objective(s)
The secondary objectives of the current project are:
- to study the association between biomarkers for renal mitochondrial damage in sepsis with the occurrence of cardiovascular events, co-morbidity, quality of life and functional status after sepsis.
- to study the association between sepsis severity and the induction of renal and systemic mitochondrial damage.
- to study the association between sepsis severity and the induction of renal and systemic DNA damage.
- to study the association between systemic mitochondrial damage in sepsis with (change in) renal function, cardiovascular/renal risk factors, cardiovascular events, co-morbidity, quality of life, health/functional status and mortality after sepsis.
- to study the association between sepsis severity and the (change in) renal function, cardiovascular/renal risk factors, cardiovascular events, co-morbidity, quality of life, functional status and mortality after sepsis.
In addition, the following objectives will be studied in aged individuals (i.e. > 65 years old):
- to study whether delirious patients demonstrate an aberrant functional status and number of circulating immune cells compared to patients that do not develop delirium following sepsis.
- to study the association between peripheral cytokine levels and delirium following sepsis
- to study the association between the occurrence of delirium during sepsis with the occurrence of cardiovascular events, co-morbidity, quality of life, functional status and mortality after sepsis.

Study design

This study is designed as a prospective cohort study with a follow-up of 2 year on the emergency department. The aim of the project is to study whether sepsis leads to mitochondrial damage, which may in turn explain the increased cardiovascular morbidity and mortality among sepsis survivors. Therefore, patients who will be hospitalized with an infection, will be included in our study. A control group consist of healthy subjects from the PREVEND study, matched according to age, sex and renal function consisting of patients who presented with an infection to the ED will be included as controls (Figure 2). The study is performed as a pilot study, since there is insufficient data available about the surrogate markers for mitochondrial (DNA) damage biomarkers that will be measured to perform a power analysis. This pilot study will gather the data required to make a power analysis for a larger subsequent study. Next to the values of the surrogate markers for mitochondrial (DNA) damage, this study will also record various other parameters for the purpose of statistical analysis. These parameters will be used to detect correlations or confounding factors. The parameters are described in the following sections and will (where possible) be extracted from the subject*s medical record.

Study groups
1. hospitalized with infection (n = 100)
2. matched control subjects (n = 100)

Note: the control subjects will be matched according to age, sex and renal function (KDIGO CKD class) from PREVEND.
*

Study burden and risks

Study participants will be asked to donate blood through a (minimally invasive) venapuncture and to donate urine at two different times during their stay in the hospital, as well as at three different times during the outpatient visits after hospital discharge. The collection of blood samples will be combined as much as possible with the collection of blood for normal routine clinical samples, in order to limit discomfort as as much as possible. To collect blood / urine during follow-up, and potentially also for the second time point (depending on the time of discharge from the hospital), the study participant have to travel to our center. Study participants may benefit from participation in the trial by the additional clinical follow-up and treatment of potential risk factors for (fatal) cardiovascular and renal diseases.

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

- Adult patients, aged between 18 and 85 years
- Clinical suspicion of a pulmonary or urinary tract infection

Exclusion criteria

- Congenital mitochondrial diseases
- Renal transplant recipients
- Patients on renal replacement therapy
- Hepatic failure (Child Pugh C)
- Hepatorenal syndrome

Study design

Design

Study type:	Observational invasive
Intervention model:	Other
Allocation:	Non-randomized controlled trial
Masking:	Open (masking not used)

Primary purpose: Basic science

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	10-10-2017
Enrollment:	100
Type:	Actual

Ethics review

Approved WMO Date:	29-05-2017
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	20-12-2017
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	05-02-2018
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	31-08-2018
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	11-12-2018
Application type:	Amendment

Review commission: METC Universitair Medisch Centrum Groningen (Groningen)

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	NL60061.042.16