Development of a new strategy to predict early sepsis

Published: 26-06-2018
Last updated: 12-04-2024

To validate and demonstrate reproducibility of the identified sepsis CR gene signature in participants from different age groups. The validation multicenter study will also lead to biomarker refinement of the original core set of 31 genes tailored...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Other condition
Study type	Observational invasive

Summary

ID

NL-OMON46603

Source
ToetsingOnline

Brief title
Sepsis Transcriptome

Condition

- Other condition
- Bacterial infectious disorders

Synonym
blood infection/poisoning, sepsis

Health condition

sepsis

Research involving
Human

Sponsors and support

Primary sponsor: Universitair Medisch Centrum Groningen
Source(s) of monetary or material Support: Ministerie van OC&W

Intervention

Keyword: Diagnosis, Prediction, Sepsis, Transcriptome

Outcome measures

Primary outcome

Molecular analysis

- CR gene expression (RNA) signature (e.g. measured by RNA sequencing and qPCR)

Disease severity

- Physician Diagnosis of sepsis

- 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

- Organ Failure Free Days

- 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)

- In-hospital mortality

- 28-day mortality

Demographic parameters, medication use, co-morbidity and functional status

- Demographic characteristics (i.e. age, sex)

- Smoking

- Known pregnancy

- Co-morbidity: Charlson comorbidity index

- Functional status: Barthel Index and WHO performance index

- Medication use

Secondary outcome

Molecular analysis:

- Genome analysis (e.g. measured by DNA sequencing, and PCR)

- Proteome analysis (e.g. measured by Olink proteomics and, ELISA)

Study description

Background summary

Sepsis is defined as a life-threatening organ dysfunction caused by a dysregulated host response to infection. It can affect people from all ages, causing significant rates of morbidity and mortality in Canada and across the world (Singer, 2016). Sepsis is also a leading cause of mortality in adulthood but especially in the elderly (Starr, 2014) and the Surviving Sepsis campaign has estimated that it causes around 5 million deaths annually.

Currently, microbiology diagnoses take at least 30 hours to obtain and clinicians are forced to treat empirically with antibiotics while waiting for results. In 30-50% of cases, these initial antibiotics are retrospectively recognized as inadequate. This is partly because *last line* antibiotics are not recommended as part of the initial therapy, since this would lead to an increase in the prevalence of organisms that are resistant to these crucial antibiotics. The current clinical diagnostic methods are not only variable and subjective (Rhee, 2016), but they are also insensitive: in half of septic patients a causative organism is never found. In our view, this approach to sepsis diagnosis and treatment is unacceptable as the risk of death increases by 8% each hour that inappropriate antibiotics are used.

Moreover, after the initial strong inflammatory response to primary infection, the next phase of illness in septic patients is profound immune suppression, that has been linked to a biological phenomenon known as endotoxin tolerance or cellular reprogramming (CR). Beeson (Beeson, 1946) first reported CR in 1946 as the abolition of the fever response of rabbits undergoing repeated daily injections of the same dose of typhoid vaccine. Subsequently, it was found that neutrophils and monocytes isolated from later-stage septic patients exhibited a state of hypo-responsiveness, including the absence of pro-inflammatory cytokine production and low levels of HLA-DR expression, and that these patients are classically unable to defend against secondary infections. Similarly, patients who survive acute septic shock have deficiencies in monocyte cell activation that persist for two weeks (or more). CR involves a suppressive effect induced by exposure to more than one dose of microbial signature molecules such as endotoxin/lipopolysaccharide (or the bacteria containing them). These molecules in single dose are potent inducers of inflammation. It was later found that repeated doses of several different microbial molecules that induce inflammation could lead to the same suppressive effects and so the phenomenon is more correctly termed cellular reprogramming (CR). Key aspects of the CR phenotype are: (i) an inability of cells to respond to related stimuli (immune amnesia) (Biswas, 2009), (ii) cross-tolerance to other bacterial signature molecules, and (iii) the long duration of the reprogrammed cells consistent with the long-term nature of sepsis.

In this phase of CR during sepsis, deadly secondary infections can occur becoming a driver of mortality rates but clinicians have had no means of identifying when immune suppression really occurs (Zhao, 2016) and after decades of research, clinicians have been unable to predict when a septic patient will transition to an immunosuppressed state that signals rapid clinical deterioration. In our effort to investigate this, we defined CR and inflammation signatures using transcriptomics on human volunteer peripheral blood mononuclear cells challenged either a single time (inflammatory) or twice (CR) with endotoxin (LPS) (Pena, 2011) respectively. In a follow up study, we demonstrated the strong presence of a gene expression signature of CR. Our conclusions were informed by both a meta-analysis of 592 patients, including both pediatric and adult sepsis cohorts, and by an initial single-blinded

observational clinical study in adult patients in the emergency ward (72 patients), at first clinical presentation. These observations are fundamental and novel. With this project, our main objective is to perform a validation phase with a larger cohort, in a multi-center, international study. The results of this study will have enormous implications in the management of sepsis, with respect to early diagnosis and prognosis, as well as supporting early application of appropriate therapies including antimicrobial and non-pharmaceutical (e.g. immunomodulatory) strategies. *

Study objective

To validate and demonstrate reproducibility of the identified sepsis CR gene signature in participants from different age groups. The validation multicenter study will also lead to biomarker refinement of the original core set of 31 genes tailored to each age group. To determine whether the CR gene signature is affected by variation in the genome (eg. polymorphisms) and whether changes in gene expression affect downstream protein levels, as transcription may be affected by epigenetic regulation. Not only will this approach allow to identify a genetic signature associated with sepsis, but it may also provide highly valuable information about the pathophysiology of sepsis.

Study design

This study is designed as a multicenter prospective cohort study, in which every center is expected to include 100 subjects. Transcriptome analysis performed on the blood sample collected upon presentation to the emergency department (ED) will be associated with clinical parameters of sepsis, which will be collected during ED stay and hospitalization.

Study groups:
- sepsis subjects (n = 1000, of which n = 100 will be included in the UMCG)
- surgical subjects (control group; n = 100, of which n = 10 will be included in the UMCG)
Note: study groups will be stratified upon analysis (see *Statistical analysis*).

Study phases:
1. signature refinement
2. signature validation
3. systems biology analysis of genetic signature

Note: each study phase has a specific objective; to answer these objectives, data and blood samples collected from both study groups will be analyzed in two phases. For the third phase, samples obtained from a subset of patients with sepsis (n = 50), subsequently admitted to the ED at the UMCG, will be used.

Study burden and risks

Study participants are asked to donate blood by means of a (minimally invasive) venapuncture during their stay at the ED at the same moment when blood is collected for routine examinations as part of standard care to limit the discomfort as much as possible for the study participant. Participants will not directly benefit from the results. However, the results may be of major relevance to increase the speed and accuracy of diagnosis in patients with sepsis.

Contacts

Public
Universitair Medisch Centrum Groningen

Hanzeplein 1
Groningen 9713 AV
NL
Scientific
Universitair Medisch Centrum Groningen

Hanzeplein 1
Groningen 9713 AV
NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

Study subjects (sepsis):
* Presenting to the Emergency Department (ED)
* Attending physician suspect sepsis based on at least 2 sign of SIRS criteria and suspicion of infection
* 19 years of age or greater;Surgical Subjects (control group):
* Having surgery
* 19 years of age or greater
* Subjects already undergoing blood collection during their hospital stay
* Non*emergency surgery subjects including ear/nose and throat cases, orthopedic surgery of the major
joints including hip, knee, ankle, shoulder, and wrist.

Exclusion criteria

* Patient is terminal (death anticipated in 12 hours)
* Subjects who are unable to obtain blood as a standard of care.
* Blood sample could not be taken within 24 hours of a physician first contact in the ED with the patient.

Study design

Design

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

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	06-08-2018
Enrollment:	100
Type:	Actual

Ethics review

Approved WMO Date:	26-06-2018
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	13-11-2018
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	NL65140.042.18