The Pathophysiology of Disrupted Endothelial Barrier Integrity in Septic shock

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Ethical review	Approved WMO
Status	Will not start
Health condition type	Ancillary infectious topics
Study type	Observational invasive

Summary

ID

NL-OMON49036

Source
ToetsingOnline

Brief title
PEBSI

Condition

- Ancillary infectious topics

Synonym
blood poisoning, Septic shock

Research involving
Human

Sponsors and support

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

Intervention

Keyword: Endothelium, Permeability, Plasma, Sepsis

Outcome measures

Primary outcome

- Transendothelial electrical resistance (TER)

Electric Cell-substrate Impedance Sensing (ECIS) will be used to quantify endothelial barrier integrity.

Secondary outcome

- Endothelial barrier function

Transwell assays will be used to study endothelial permeability and microscopic techniques to study endothelial junction formation and linearity.

- Markers of endothelial activation and inflammation

- Demographic data: (admission)

Age, gender, specific reason for admission, medication use, comorbidities (acute, chronic)

- Clinical data:

Complete blood count, markers of biochemistry on inclusion day (as determined as part of standard care), APACHE II score, daily SOFA score, mechanical ventilation (yes/no), mechanical ventilation duration (days), occurrence of ARDS (yes/no), ARDS score, inotropic therapy (yes/no), duration of inotropic/vasopressor support, renal failure according to the RIFLE score

(yes/no), occurrence of DIC (yes/no), DIC score, anticoagulant use, site of infection, culture results, 30 day mortality, length of ICU stay (days), hospital length of stay (days), red blood cell units transfused, plasma units transfused, platelets units transfused

Study description

Background summary

Sepsis is a condition characterized by life-threatening organ dysfunction resulting from dysregulated host responses to infection. Septic shock is a subset of sepsis in which underlying circulatory, cellular and metabolic abnormalities are profound enough to substantially increase the risk of mortality. Mortality of septic shock is a staggering 40%, which is largely due to organ failure.

Sepsis is characterized by the presence of inflammatory-induced acute endothelial integrity loss. However, it is largely unknown which pathways are involved in mediating endothelial permeability. Increased endothelial permeability results in loss of fluids into the interstitium. Fluid deficiency is further aggravated by vasodilation, resulting in hypotensive and shocked states. Therefore, volume resuscitation with crystalloids is one of the key components of treating sepsis. However, the downside of resuscitation is the occurrence of edema. Most likely, fluid resuscitation results in an increased gradient of leakage over the permeable endothelium. Of note, compared to a liberal fluid balance, a restrictive fluid balance reduces the occurrence of organ failure. This poses a dilemma to the treatment of sepsis, as fluid therapy is both a cornerstone of therapy as well as a foe in the occurrence of organ failure, calling for alternative strategies. Plasma may be a candidate resuscitation fluid.

In trauma animal models, plasma was found to improve the condition of the glycocalyx lining the vessels walls, with improved endothelial barrier integrity, thereby preventing edema and organ failure. This finding prompts the question whether plasma is also effective in sepsis. In an animal model of sepsis, plasma transfusion improved survival compared to saline resuscitation and attenuated markers for inflammation and endothelial injury. Furthermore, we found that in sepsis patients, transfusion of plasma was associated with a decrease in levels of markers of endothelial activation, including von Willebrand Factor (vWF) antigen and syndecan-1 levels. To date, the mechanism behind this is unknown.

On a further note, not all plasma products may exert the same effects. In pediatric patients, use of solvent detergent (SD) plasma compared to fresh frozen plasma (FFP) was associated with improved survival which emphasizes that certain components in plasma mediate the protective effects on the endothelial barrier. The aim of this study is two-fold: to investigate mechanisms by which mechanisms sepsis induces endothelial barrier dysfunction and permeability and to investigate the effects of plasma and specific plasma components on the endothelial barrier function. This will be done ex vivo using blood samples from patients with septic shock in various models of endothelial barrier function.

Study objective

In this study we aim to investigate which pathways in septic patients exacerbate endothelial injury and dysfunction, furthermore do we want to investigate to what extent, and due to which components plasma transfusion can improve the endothelial dysfunction is sepsis.

Primary objective:
1. To identify mediators in sepsis that promote loss of endothelial cell function.

Secondary objectives:
2. To identify if plasma has protective/restorative effects on the endothelium in sepsis.
3. To identify components of plasma that mediate endothelial stabilization.
4. To identify differences in effect between different plasma products: SD plasma and FFP.

Study design

An observational cohort study will be conducted. in patients with (a suspicion of) septic shock that are admitted to the intensive care unit (ICU). Blood samples will be retrieved at 2 time points. The first blood sample will be retrieved within 12 hours of ICU admission . The second blood sample will be taken 7 days after admission or at the moment of ICU discharge, whichever comes first. Demographic and clinical data will be collected from EPIC. Blood samples will be stored at * 80 C° for further analyses.

Study burden and risks

The patient does not benefit from participation. The proposed study aims to find new and improved ways to restore and protect the endothelium in sepsis, which may benefit sepsis patients in the future. Risks of blood sampling from an arterial line are negligible and do not interfere with standard care.

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

- *18 years old

- Quick Sequential Organ Failure Assessment score (qSOFA score) *2 with suspicion of infection

- MAP < 65 mmHg and lactate > 2 mmol/L despite volume resuscitation, requiring vasopressors

- Inclusion within 12 hours after arriving on the Intensive Care Unit

Exclusion criteria

- Absence of informed consent

- No arterial catheter placement * 12 hours after arriving on the Intensive Care Unit

- Transfer from another hospital

Study design

Design

Study type: Observational invasive

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

Recruitment

NL

Recruitment status:	Will not start
Enrollment:	30
Type:	Anticipated

Ethics review

Approved WMO Date:	23-01-2020
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	30-03-2020
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	18-12-2020

Application type:	Amendment
Review commission:	METC Amsterdam UMC

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

ID: 21518
Source: NTR
Title:

In other registers

Register	ID
CCMO	NL70318.018.19
OMON	NL-OMON21518