Hemodynamic Phenotype-Based, Capillary Refill Time-Targeted Resuscitation In Early Septic Shock: The ANDROMEDA-SHOCK-2 Randomized Clinical Trial (A2)

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To test if a CRT-targeted resuscitation based on clinical hemodynamic phenotyping can improve a hierarchical clinical outcome - mortality, time to cessation of vital organ support, and length of hospital stay, all within 28 days - in septic shock...

Ethical review	Approved WMO
Status	Pending
Health condition type	Other condition
Study type	Interventional

Summary

ID

NL-OMON51438

Source
ToetsingOnline

Brief title
ANDROMEDA-SHOCK-2 (A2)

Condition

- Other condition
- Infections - pathogen unspecified

Synonym
Circulatory failure in sepsis

Health condition

circulatory shock

Research involving
Human

Sponsors and support

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

Intervention

Keyword: Capillary refill time, Early Resuscitation, Peripheral Perfusion, Septic Shock

Outcome measures

Primary outcome

The hierarchical composite of all-cause mortality within 28 days, time to cessation of vital support (truncated at 28 days) and length of hospital stay (truncated at 28 days).

Secondary outcome

Mortality by all causes at 28 days following randomization

Vital support free days within 28 days following randomization

The number of calendar days between randomization and 28 days later that the patient is alive and with no requirement of cardiovascular, respiratory and renal support. Patients who die within 28 days will have zero days counted for this variable, irrespective of vital support status.

Resolution of cardiovascular failure implies complete stopping of vasopressor support for at least 24 consecutive hours. Resolution of respiratory failure implies extubation/liberation from mechanical ventilation for at least 48 hours. Resolution of renal failure implies liberation of renal replacement therapy for at least 72 hours in those receiving continuous replacement modalities and at least 5 days for those receiving intermittent ones.

Length of hospital stay at 28 days following randomization.

Number of days remaining hospitalized (from randomization up to hospital

discharge), truncated at day 28.

Study description

Background summary

Septic shock is associated with a high mortality risk related to progressive tissue hypoperfusion. Over-resuscitation, particularly when inducing fluid overload, might contribute to a worse outcome. Fluid overload more likely occurs when fluids are administered to fluid unresponsive patients, but also when inappropriate resuscitation goals are pursued. A robust body of evidence confirms that abnormal peripheral perfusion after initial or advanced resuscitation is associated with increased morbidity and mortality. In the ANDROMEDA-SHOCK study capillary refill time (CRT)-targeted resuscitation was safe and associated with lower mortality (34.9% vs. 43.4%), beneficial effects on organ dysfunction, and less intensity of treatment. From a clinical point of view, many patients despite been fluid loaded in pre- ICU settings, are still fluid responsive and may benefit from further administration of fluid boluses. Patients that present with very low diastolic arterial pressures (DAP) reflecting profound vasodilatation are unlikely to benefit from fluid administration as first line treatment. Recent data suggest that these patients may benefit from early norepinephrine (NE). Continued fluid administration is unlikely to correct vascular tone and increases the risk of fluid overload. In addition, a recent echocardiography-based study confirms that a relevant myocardial dysfunction is present in a significant number of patients, and that several cardiovascular phenotypes with a potentially different therapeutic approach may be recognized. Eventually, to assess basic universally available clinical hemodynamic signals such as pulse pressure (PP) and DAP may allow clinicians to individualize initial management avoiding the classic approach to continue to administer fluids to all septic shock patients.

Study objective

To test if a CRT-targeted resuscitation based on clinical hemodynamic phenotyping can improve a hierarchical clinical outcome - mortality, time to cessation of vital organ support, and length of hospital stay, all within 28 days - in septic shock patients as compared to usual care

Study design

Multicenter, open-label, randomized controlled trial conducted under supervision of an independent Data Safety Monitoring Board (DSMB). Recruited patients will be randomized to intervention arm (CRT-P) or usual care (UC).

Intervention

Recruited patients will be randomized to intervention arm (CRT-P) or usual care (UC).

Usual Care (UC) group:
Patients allocated to the UC group will be managed by the clinical staff according to usual practice at their sites including following general recommendations of the Surviving Sepsis Campaign to avoid extremes of clinical practice.

Intervention arm group (CRT-P):
Intervention in this group will follow the therapeutic algorithm as described in Figure 1 in the protocol.
In short, interventions included in the algorithm are:
• Fluid Responsiveness (FR) assessment using standard procedures
• Fluid boluses (500 ml of crystalloids or 5% albumin) administered in 30 min intervals, and repeated as needed if capillary refill time (CRT) is still abnormal
• Transthoracic Echocardiography to rule out significant cardiac dysfunction
• Titration of dose of noradrenaline to achieve a MAP >65 mmHg and a diastolic arterial pressure >= 50 mmHg.

Study burden and risks

The suspected benefit is that survival rate in the treatment group can be improved with fluids resuscitation guided by changes in capillary refill time (CRT). There is no additional risk for patients concerning the measurements of peripheral perfusion, pulse pressure and transthoracic echocardiography as all these techniques are noninvasive and harmless.
A refractory shock may occur in the event a patient does not respond to initial therapy and patient may fail to correct CRT after the whole algorithm procedures. On this circumstances, rescue therapies will be considered by the attending physician, but these will not be standardized since the protocol is interrupted at that point, although monitoring and registration during the 6h intervention period and thereafter continue until the end of the study.

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 (>= 18 years) with septic shock according to Sepsis-3 consensus conference. Septic shock is defined as suspected or confirmed infection, the presence of increased lactate levels and the requirements for the administration of a vasopressor to maintain blood pressure following a fluid load of at least 1000mL in 1h.

Exclusion criteria

•More than 4 hours since septic shock diagnosis,
•Anticipated surgery or acute hemodialysis procedure to start during the 6h intervention period
•Active bleeding,
•Do not resuscitate status,
•Child B-C Cirrhosis
•Underlying disease process with a life expectancy < 90 days and/or the

attending clinician deems aggressive resuscitation unsuitable
•Refractory shock (high risk of death within 24h)
•Pregnancy
•Concomitant severe acute respiratory distress syndrome
•Patients in whom CRT cannot be accurately assessed.

Study design

Design

Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)

Primary purpose: Diagnostic

Recruitment

NL

Recruitment status:	Pending
Start date (anticipated):	01-02-2023
Enrollment:	25
Type:	Anticipated

Ethics review

Approved WMO

Date:	08-03-2023
Application type:	First submission
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
ClinicalTrials.gov	NCT05057611
CCMO	NL79805.078.22