SUPPLEMENT
TRIAL PROTOCOL AND STATISTICAL ANALYSIS PLAN
ANDROMEDA-SHOCK STUDY

This supplement contains the following items

S1. Original protocol and statement about changes
S2. Original statistical analysis plan and statement about changes

S1. THE ANDROMEDA-SHOCK STUDY PROTOCOL

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The ANDROMEDA-SHOCK STUDY PROTOCOL was accepted for publication by Annals of Intensive Care on April 12, 2018 and is accessible on (https://www.ncbi.nlm.nih.gov/pubmed/29687277).

The trial protocol (version 1.0 from December, 2016) was submitted and published, is registered with ClinicalTrials.gov (NCT03078712), and was approved by the Institutional Review Boards (IRB) of all the participant centers.

No amendment was performed to the Study Protocol since the IRB approval of the first version of the study.

Abbreviations

APACHE: Acute Physiology and Chronic Health Evaluation

AKI: acute kidney injury

CRT: capillary refill time

CVP: central venous pressure

DSMC: Data Safety Monitoring Committee

ED: emergency department

HR: heart rate

IRB: Institutional Review Board

ICU: intensive care unit

LTR: lactate-targeted resuscitation

MAP: mean arterial pressure

MV: mechanical ventilation

NE: norepinephrine

PLR: passive leg raising

P(cv-a) CO_2: central venous-arterial pCO_2 gradient

PPTR: peripheral perfusion-targeted resuscitation

PPV: pulse pressure variation

RRT: renal replacement therapy

$ScvO_2$: central venous oxygen saturation

SOFA: Sequential Organ Failure Assessment

SVV: stroke volume variation

SCC: Study Coordinating Center

SSC: Surviving Sepsis campaign

A. Background

Septic shock is a highly lethal condition associated with a mortality risk of 30 to 60% [1,2]. It is currently the most frequent cause of death in the intensive care unit (ICU) as we demonstrated in a recent Chilean prevalence study [3]. Several pathogenic factors such as hypovolemia, myocardial depression, vasoplegia, and microcirculatory abnormalities can induce progressive tissue hypoperfusion in severe cases [4]. In this context, persistent hyperlactatemia has been traditionally considered as the hallmark of ongoing tissue hypoxia during septic shock [4], and therefore lactate normalization is recommended as a resuscitation target by recent guidelines [5].

Pathophysiologic determinants of persistent hyperlactatemia

The physiologic basis of lactate generation or clearance during septic shock has been matter of active research [4]. Hypovolemia-induced hypoperfusion is probably the predominant pathogenic mechanism during the early phase [4]. Some patients resolve acute circulatory dysfunction and clear lactate after initial fluid resuscitation, while others evolve into a persistent circulatory dysfunction with hyperlactatemia [4]. Several mechanisms have been associated to persistent hyperlactatemia besides hypoperfusion, and recent literature has highlighted the role of sustained hyperadrenergia with increased muscle aerobic glycolysis (known as stress hyperlactatemia) [6], and of impaired hepatic lactate clearance [7].

We have explored the significance and potential determinants of hyperlactatemia in a series of clinical physiological studies performed over the last 15 years [7-18]. These studies have addressed the three most relevant pathogenic factors involved in persistent hyperlactatemia: overt or occult hypoperfusion, hyperadrenergic state and impaired hepatic clearance. The complexity of this subject is also highlighted by a more recent study where we demonstrated that lactate decrease during successful septic shock resuscitation exhibits a biphasic pattern, an early rapid decrease in parallel to normalization of more flow-sensitive variables (see below), followed by a slower recovery thereafter [18]. The latter eventually related to non-flow dependent mechanisms such as hyperadrenergic state and/or delayed hepatic clearance [4, 7,17,18].

Persistent hyperlactatemia after initial resuscitation is particularly difficult to interpret as suggested by the extensive research summarized above [4]. Optimizing systemic blood flow might reverse ongoing hypoperfusion, a potential source of anaerobic lactate generation. Under this perspective, some of the pathogenic factors involved in hyperlactatemia are potentially flow-sensitive, and others are not. Distinction between the two scenarios could strongly impact further resuscitation. If persistent hyperlactatemia is caused by non-hypoperfusion-related mechanisms, then sustained efforts aimed at increasing cardiac output could lead to detrimental effects of excessive fluids or inotropes, a fact now well demonstrated in the literature [4]. The decision of when to consider that a patient has been fully resuscitated and as a consequence stop further interventions is a milestone, and appears as highly relevant since the results of a number of recent studies have increased awareness about the risk of fluid overload and/or of vasopressors and inodilators such as pulmonary edema, increased intraabdominal hypertension, acute kidney injury, delayed weaning, arrhythmias, hepatosplanchnic or myocardial ischemia, among other problems [19,20]. By these means, over-resuscitation could eventually increase morbidity and/or mortality [4,19,20].

Is hyperlactatemia a valid resuscitation target in septic shock?

Not surprisingly, lactate clearance or normalization is used worldwide as resuscitation targets. Indeed, the Surviving Sepsis Campaign (SSC), the most ambitious and global collaboration in critical care, has proposed to focus septic shock resuscitation on normalizing macrohemodynamic parameters and lactate [5]. SSC guidelines are followed in many countries and adherence to recommended management bundles have been reported to be associated to improved survival, although the role of each individual component is not clear [5]. Lactate clearance, defined by a change of lactate levels between two time-points, and expressed as a 10-20% hourly lactate

reduction [21], or a decrease of at least 10% in 6h during early resuscitation [21] has been related to survival, and tested as a goal in two important studies with conflicting results [22,23].

However, there are several unresolved aspects and concerns about the role of lactate as an appropriate resuscitation target. First, it is not clear if selecting lactate clearance versus lactate normalization as resuscitation goals is equivalent, but more importantly, if this decision leads to similar timely resolution of tissue hypoperfusion or hypoxia. Second, since non-hypoperfusion related causes of hyperlactatemia might predominate in an unknown number of patients, this could lead to over-resuscitation in at least some of them as stated above. Third, the dynamics of recovery of lactate might exhibit a biphasic pattern and therefore, the real-time response of lactate to fluid challenges could be not straightforward depending on the hypoperfusion context [18,24]. Some survivors might even normalize lactate only after 24h of evolution [18]. Therefore, to explore other potential resuscitation targets appears as mandatory.

Potential alternative resuscitation targets in septic shock

A foremost priority is to rule out ongoing hypoperfusion in septic shock patients under active resuscitation. We recently proposed that a simultaneous analysis of central venous O_2 saturation ($ScvO_2$), central venous-arterial pCO_2 gradient ($P(cv\text{-}a)CO_2$), and peripheral perfusion as assessed by capillary refill time (CRT), mottling score or central-to-toe temperature differences, might be helpful in suggesting a hypoperfusion context for patients with or without hyperlactatemia [4]. From a theoretical point of view, these three easily assessable perfusion-related variables offer an important advantage over lactate as potential resuscitation targets in septic shock patients: they are clearly flow-sensitive and exhibit much faster dynamics of recovery after systemic blood flow optimization. In other words, these parameters might clear in minutes in fluid-responsive patients as compared to lactate, which sometimes takes hours to recover. We demonstrated this by analyzing the dynamics of recovery of these parameters in a cohort of ultimately surviving septic shock patients. $ScvO_2$, $P(cv\text{-}a)CO_2$ and CRT where already normal in almost 70% of the patients after 2h of fluid resuscitation, as compared with only 15% in the case of lactate [18].

However, there are also certain drawbacks for some of these perfusion-related flow-sensitive parameters. $ScvO_2$ is a complex physiological variable. It was widely used until recently as the resuscitation goal in critically ill patients [5], although several limitations may preclude a straightforward interpretation of its changes [4]. For instance, normal or even supranormal $ScvO_2$ values do not rule-out global or regional tissue hypoxia for several reasons that have been highlighted elsewhere, but that include severe microcirculatory derangements impairing tissue O_2 extraction capabilities [4]. Vallee et al found persistent abnormal $P(cv\text{-}a)CO_2$ values in 50% of septic shock patients who had already achieved normal $ScvO_2$ values after initial resuscitation [25]. Nevertheless, in some hyperdynamic states a high efferent venous blood flow could be sufficient to wash out the global CO_2 generation from hypoperfused tissues; thus, $Pcv\text{-}aCO_2$ could be normal despite the presence of tissue hypoxia [16]. Another problem for these two variables is that they necessarily require a central venous catheterization to be assessed, a task that might be complex to perform in resource-limited settings or emergency departments. Therefore, peripheral perfusion appears as the most appropriate, alternative resuscitation target in septic shock patients.

Peripheral perfusion as a potential resuscitation target in septic shock patients

The skin territory lacks auto-regulatory flow control, and therefore sympathetic activation impairs skin perfusion during circulatory dysfunction [26], a process that could be evaluated by peripheral perfusion assessment. Indeed, peripheral perfusion can be easily evaluated in many ways at bedside [26] and, therefore, could be a valuable monitoring tool in any setting. The presence of a cold clammy skin, mottling or CRT are frequently described as indications to initiate fluid resuscitation in patients with sepsis-related acute circulatory dysfunction [26]

The concept of CRT, the most relevant parameter, is based on this assumption. It was proposed initially in trauma patients but some negative studies that found no correlation with systemic

hemodynamics precluded further research on this variable [26]. More recently however, Lima et al found that abnormal peripheral perfusion is associated with hyperlactatemia and organ dysfunctions in critically ill patients [26]. Other authors confirmed this finding and built up a robust body of evidence supporting the strong prognostic value of abnormal peripheral perfusion in the ICU context [26].

We observed that CRT was the first parameter to be normalized in a cohort of septic shock patients and this predicted lactate normalization at 24h and survival [8]. Moreover, some recent clinical data suggest that targeting peripheral perfusion during septic shock resuscitation might improve outcome [27]. van Genderen et al performed a randomized controlled trial comparing two resuscitation protocols; one targeted at normal peripheral perfusion and the other to standard management in thirty critically ill patients [27]. The study demonstrated that targeting peripheral perfusion is safe, and associated with less fluid administration and organ dysfunctions. Therefore, a parameter like CRT with a rapid-response time could be very useful to test the response to treatments with strong physiologic impact such as fluid loading, especially at the emergency department or in resource-limited settings. In a prospective study performed in a cohort of 100 patients just admitted to the emergency room, we found that patients exhibiting a normal CRT after initial fluid loading had a hospital mortality of less than 10% as compared to 55% in patients with abnormal values [28].

How can fluid loading and resuscitation improve peripheral perfusion? There is an intricate relationship between macrohemodynamics and peripheral perfusion. Both are affected by hypovolemia and tend to improve in parallel in fluid-responsive patients. Their relative changes, though, are not well correlated. The beneficial effects of fluids and vasoactive drugs may be explained by an increase in cardiac output or perfusion pressure, a decrease in the neurohumoral response to hypovolemia, and eventually by direct effects at the microcirculatory level [4, 29]. Whatever the mechanism, normalization of peripheral perfusion parameters appears to indicate a successful reversal of initial circulatory dysfunction.

There are some data that suggest that vasopressor adjustment and/or inodilators could induce favorable effects on peripheral perfusion or microcirculation under certain circumstances [30-35]. Jhanji et al demonstrated that increasing mean arterial pressure (MAP) to 90 mmHg with norepinephrine (NE) doses up to 0.41 mcg/kg/min improved cutaneous oxygenation and microvascular red blood cell flux in a cohort of septic shock patients [30]. The same group obtained similar results in another cohort of postoperative patients after major abdominal surgery but with an intervention consisting in stroke volume optimization with fluid challenges and an inodilator (dopexamine) in fixed dose [31]. Dubin et al demonstrated that rising MAP to 85 mmHg with incremental doses of NE up to 0.74 mcg/kg/min improved sublingual microcirculatory flow in septic shock patients with the worst microcirculation at baseline [32]. Dobutamine in fixed doses of 5 mcg/kg/min improved sublingual microcirculatory flow in another cohort of septic shock patients [33]. On the other hand, active vasodilation with nitroglycerine induced a clear improvement of peripheral perfusion parameters in a group of shock patients, despite a mean fall in MAP of 14 mmHg [34]. Based on these findings and other data, it was proposed that permisive hypotension could eventually improve microcirculatory driving-pressure in patients with acute circulatory failure [35]. In summary, it appears that pharmacological therapies aimed at improving peripheral perfusion might be individually tailored but could imply increasing or lowering vasopressors and MAP, inodilators or pure vasodilators according to the clinical context.

More recently Brunauer et al, added another important piece of information after performing a pilot study in 30 septic shock patients subjected to early resuscitation [36]. In this study, CRT and skin mottling were correlated with the pulsatility index, a sonographic surrogate of vascular tone, of visceral organs. This means that improvement in peripheral perfusion might move in parallel with improvement in hepatosplanchnic perfusion, eventually explaining the good prognosis associated with recovery of CRT and other related parameters [36].

Using peripheral perfusion to target resuscitation in septic shock has also several potential drawbacks. First, there is some degree of subjectivity and inter-observer variability in some of the

parameters used to assess it such as CRT and mottling. Second, it cannot be evaluated in some settings such as dark skin patients. Third, and more importantly, the corpus of evidence that supports that improvement of peripheral perfusion is associated with resolution of profound tissue or microcirculatory hypoperfusion, or hypoxia is still scanty.

However, the excellent prognosis associated with CRT recovery, the rapid-response time to fluid loading, the simplicity of its assessment, its availability in limited resource settings, and recent data suggesting that it might change in parallel to perfusion of physiologically more relevant territories such as the hepatosplanchnic region [36] constitute a strong fundament to promote studies evaluating its usefulness to guide resuscitation in septic shock patients.

Why to compare peripheral perfusion with lactate as targets for septic shock resuscitation?

Potential differences between peripheral perfusion and lactate as targets for fluid resuscitation are outlined in table 1. Summarizing the theoretical background stated above, it is plausible that normalization of peripheral perfusion as compared to normalization or a rapid decrease (>20%/2h) of lactate might be associated with less fluid resuscitation and secondarily less positive 24h fluid balances. Eventually, less positive fluid balances might be associated with less organ dysfunctions. In addition, peripheral perfusion targeted-resuscitation might be also associated with less vasopressor load and inodilator use thus preventing other set of potential complications such as hepatosplanchnic hypoperfusion, arrhythmias or myocardial ischemia. At the end, this could result in less mortality for a combination of the previous reasons.

B. Project outline

Hypothesis

Peripheral perfusion guided resuscitation in septic shock is associated with lower mortality, less organ dysfunctions, less mechanical ventilation (MV), less vasopressor load, and less renal replacement therapies than a lactate-targeted resuscitation strategy.

Design

Multicenter, open-label randomized controlled study, conducted under supervision of an independent Data Safety Monitoring Committee (DSMC).

Main Objective

To test if peripheral perfusion targeted resuscitation in septic shock is associated with lower 28-day mortality than a lactate targeted resuscitation.

Primary Outcome

All-cause 28-day mortality

Secondary and tertiary outcomes

Need of MV

Need of renal replacement therapies (RRT)

Days free of MV, vasopressors and RRT in 28-days

Sequential Organ Failure Assessment (SOFA) [37] at 8, 24, 48 and 72h

Acute kidney injury (AKI) [38]

Intra-abdominal hypertension

Resuscitation fluids at 8h

Fluid balances at 8, 24, 48 and 72h

All-cause hospital and 90-day mortality

ICU and hospital length of stay

I. Patients

Inclusion Criteria

Adult patients (≥18 years) will be screened for the following inclusion criteria:

Septic shock diagnosed at ICU admission according to the Sepsis-3 Consensus Conference [39]. In short, they correspond to septic patients with hypotension requiring NE to maintain a MAP of ≥ 65 mmHg, and serum lactate levels > 2 mmol/l after initial fluid resuscitation with at least 20/ml kg in one hour.

Exclusion Criteria

1. Pregnancy
2. Anticipated surgery or dialysis procedure during the first 8h after septic shock diagnosis
3. Do-not-resuscitate status
4. Child B or C liver cirrhosis
5. Active bleeding
6. Acute hematological malignancy
7. Severe concomitant acute respiratory distress syndrome
8. More than 4h after officially meeting septic shock criteria

II. Randomization

Recruited patients will be randomized to a peripheral perfusion-targeted resuscitation (PPTR) with a goal of normalizing CRT, or a lactate-targeted resuscitation (LTR) with a goal of either normalizing lactate or achieving a >20% decrease per hour during the 8h study period (Figure 1).

A randomization sequence with an allocation of 1:1 will be generated by a computer program. Study-group assignment will be performed by means of randomized permuted blocks of eight. Allocation concealment will be maintained by means of central randomization.

Investigators at the sites will call a representative of the Study Coordinating Center (SCC) available 24 hours a day, 7 days a week, through a dedicated phone number. The group to which the patient is allocated will only be disclosed after the information is checked and recorded. Such a measure

prevents the investigator and the medical team from predicting to which treatment group the patient will be allocated.

III. Assessments

Baseline

Demographics, comorbidities, acute physiology and chronic health evaluation (APACHE) II [40], sepsis source and treatment.

pre-ICU resuscitation and fluid balance.

SOFA + AKI criteria.

Hemodynamics: heart rate, systolic blood pressure, diastolic blood pressure, MAP, central venous pressure (CVP), dynamic predictors of fluid responsiveness, intraabdominal pressure, NE dose, diuresis.

Perfusion: lactate, ScvO2, P(cv-a)CO2, hemoglobin, central venous and arterial blood gases, CRT, mottling score.

Evolution

SOFA and AKI criteria at 8, 24, 48 and 72h

Hemodynamics hourly up to 8h

Fluid administration and balance at 8, 24, 48 y 72h

Complete perfusion assessment when the targeted parameter is normalized and then at 8, 24, 48 and 72h

Register of vasoactive drugs and dobutamine/milrinone use

Register of MV and RRT

Source control re-analysis at 4h

Adjuvant therapies: high-volume hemofiltration, vasopressin, epinephrine, steroids, others

Echocardiography recommended at least once during the study period

Follow-up till 28 days for use of MV, RRT and vasopressors

All-cause mortality at hospital discharge, 28 and 90 days

Cause of death

IV. Principles of general management

Sepsis source identification and treatment should be pursued as a priority of first line treatment. A central venous catheter and an arterial line will be inserted in all, and the use of a pulmonary artery catheter or a pulse contour continuous cardiac output device is recommended for patients with a past medical history of heart failure or with concomitant acute respiratory distress syndrome.

Echocardiography will be performed routinely as soon as possible after admission to evaluate basal cardiac function and repeated as necessary to aid in assessing preload status through inferior vena cava distensibility when necessary.

NE will be the vasopressor of choice and adjusted to a MAP ≥ 65 mmHg in all patients.

Hemoglobin concentrations will be maintained at 8 g/dl or higher to optimize arterial O2 content. Mechanical ventilation settings will be adjusted according to current recommendation. Rescue therapies such as epinephrine, vasopressin analogues, steroids or different blood purification techniques like high-volume hemofiltration will be decided following usual practice of the involved centers in patients evolving with refractory septic shock.

C. Study protocol

A sequential approach to resuscitation will be followed in both groups as shown in Figure 2 and in Figure S1.

Time 0 is the starting point when after randomization, a central venous catheter and an arterial line are in place, and the basal measurements are performed including hemodynamics and blood sampling.

The study period will be of 8 hours. After this, attending intensivists may continue to treat patients according to their usual practice or department protocol.

I. Tests and Procedures during the study period

Capillary refill time assessment

CRT will be measured by applying firm pressure to the ventral surface of the right index finger distal phalanx with a glass microscope slide. The pressure will be increased until the skin is blank and then maintained for 10 seconds. The time for return of the normal skin color will be registered with a chronometer, and > 3 seconds is defined as abnormal.

Lactate measurements

A normal serum lactate value is defined as less then 2 mmol/l. Lactate will be assessed with the technique more easily available for each center, including arterial serum levels point-of-care or common gas analyzers at the central lab, or capillary levels with lactate scout strips.

Fluid responsiveness

This is the first step [41]. Fluid responsiveness will be assessed with a structured approach as detailed in Figure 3. Basically, dynamic predictors will be evaluated depending on the patient background status.

In sedated and adapted mechanically ventilated patients without arrhythmias, pulse pressure variation (PPV) or stroke volume variation (SVV) will be used as first choice. A fluid responsive status is established with values ≥ 13% and 10%, respectively. If negative, PPV and SVV will be reassessed after transiently increasing tidal volume to 8 ml/kg (one minute). An increase >3.5% and 2.5% in PPV or SVV, respectively will be considered as fluid responsive.

In patients with arrhythmia, the preferred tests will be the end expiratory occlusion test with a 15 sec pause (> pulse pressure >5% considered as positive), or echocardiography assessing inferior vena cava distensibility index (>15% considered as positive) [41].

In spontaneous breathing patients or non-sedated patients under MV, a passive leg rising (PLR) maneuver will performed with an early increase (<1min) in pulse pressure being >10% considered as fluid responsive. If this is not obtained, and to rule out a false negative response, the maneuver will be repeated assessing aortic velocity time integral with echocardiography before and after PLR with a >15% increase in this variable accepted as indicating fluid responsiveness [41].

Fluid Challenge

In fluid-responsive patients the first resuscitation step is to administer a fluid bolus of 500 ml of crystalloids every 30 min until CRT is normalized in PPTR, or dynamic predictors becomes negative in LTR. Fluid responsiveness and CVP will be assessed before and after each bolus in both groups.

Safety measures during fluid challenges

CVP and fluid responsiveness will be reevaluated after any fluid challenge. If CVP increases <5 mmHg and the patient is still fluid responsive, another fluid bolus will be administered and so on while the goal is not reached.

If CVP increases ≥ 5 mmHg or a state of fluid unresponsiveness is reached, fluids will be stopped, and the patient will be moved to the next step.

Vasopressor test

In fluid unresponsive patients with persistent abnormal CRT or with a still abnormal lactate that decreased <20%/2h, a vasopressor test will be performed.

In previously hypertensive patients, MAP will be increased to the range of 80-85 mmHg by transiently rising NE doses. CRT and lactate will be rechecked (CRT at 1 hour and lactate at 2 hours). If CRT is normal in the group A, or lactate normalizes or decreases >20% in group B, resuscitation will be stopped, and NE dose maintained. If not, NE will be reduced to the pre-test doses, and the protocol moves to the next step.

In all the other patients, MAP will be maintained at the 65 mmHg level by decreasing NE doses.

Use of inodilators

Dobutamine 5 mcg/kg/min or milrinone 0.25 mcg/kg/min in fixed doses will be started, and CRT or lactate rechecked (CRT at 1 hour and lactate at 2 hours). If the goals are not reached, drugs will be discontinued and no further action will be taken during the study period, except rechecking fluid responsiveness every hour and restarting fluid challenges if patients resumes a fluid responsive status. In responders to inodilators (same as with the vasopressor test), the drug will be continued throughout the study period.

As a safety measure, inodilators will be stopped if heart rate increases >15%, or arrhythmias, ischemia or hypotension develop.

Group A. Management of peripheral perfusion-targeted resuscitation.

In this group, the goal is to normalize CRT by following the next steps in the given order:

1. Assessment of fluid responsiveness

2. Fluid challenges until CRT is normal, the patient is fluid unresponsive or a safety measure is met

3. Vasopressor test

4. Inodilator test

As a safety measure, resuscitation will be stopped even with normal CRT, only in the presence of stable macrohemodynamics as demonstrated by heart rate <120 BPM, and stable MAP with no increase in vasopressors during the last hour.

After CRT normalization at any step, CRT will be reassessed hourly during the study period. At any point, if CRT turns abnormal the resuscitation sequence will be restarted.

Group B. Management of lactate-targeted resuscitation.

In this group the goal is to normalize lactate levels or get a decrease rate of at least 20% in 2 hours, by following the next steps in the proposed order, always reevaluating lactate at 2-hours intervals.

1. Assessment of fluid responsiveness

2. Fluid challenges until patients get a fluid unresponsive state or a safety CVP limit is reached during the 2-hour intervals between lactate assessments.

3. Vasopressor test

4. Inodilators

Lactate will be assessed every two hours during the 8-hours study period. If after obtaining the lactate goal, lactate gets abnormal again or the decrease rate turns <20% in 2 hours at any of the following 2-hour controls during the study period, the resuscitation sequence will be restarted.

D. Other aspects

Safety measures

The protocol can be stopped at any moment for safety considerations during the 8-h study period if the attending intensivist considers that the patient has developed unexpected and severe complications or evolves into refractory shock, conditions that under his judgment require liberalization of management. This action must be reported on the case report form, and the patient will be followed up with major outcomes, and included in the intention-to-treat analysis. Specific safety measures for fluid administration, vasopressor test and inodilator use are specified above.

Suspected unexpected serious adverse reactions (SUSAR)

Any adverse event that occurs in a clinical trial subject, which is assessed by the study investigator as being unexpected, serious and as having a reasonable possibility of a causal relationship with the study procedure will be reported. Reports of these reactions are subject to expedited submission to health authorities. SUSAR's will be analyzed by the SCC and DSMC.

Blinding

Since the intervention will be administered to critically ill patients (mostly sedated), blinding of these patients is not necessary. Because this is a non-pharmacological intervention, blinding of the medical team is not feasible.

Quality control

Several procedures will assure data quality, including (1) all investigators will attend a training session before the start of the study to standardize procedures, including data collection (2) the investigators may contact the SCC to solve issues or problems that may arise; (3) case report forms provided by the centers will be subjected to various checks by members of the SCC for missing data, plausible, possible or non-permitted value ranges, and logic checks on a weekly basis. (4) centers will be notified of the inconsistencies or missing data as queries and asked to correct them; (5) the SCC will review detailed reports on screening, enrollment, follow-up, inconsistencies and completeness of data. Immediate actions will follow to solve problems that arise; (6) only after the case report forms are cleared by the SCC, data will be entered in the final electronic database by the data digitizer***.***

Ethical aspects

Each investigator center will submit the study protocol to its Institutional Review Board (IRB). The study will start only after being approved by the IRB. Written informed consent will be obtained from a legal representative of all participants. This study follows local and international declarations.

Trial organization and management

A team based on the Departmento de Medicina Intensiva, Facultad de Medicina of the Pontificia Universidad Católica, Chile, will manage the trial on a day-to-day basis. The SCC is comprised by the chief and co-chair investigators, four project managers, a statistician and a data digitizer. The statistician is based on the Research Institute HCor, São Paulo, Brazil.

The responsibilities of the SCC include: 1. Planning and conducting the study designing the protocol; designing the case report form; designing the operation guide; managing and controlling data quality; designing, testing and maintaining the electronic database; data quality control; assisting the steering committee; 2. Managing the research centers selecting and training the research centers; helping the centers prepare a regulatory report to be submitted to the IRBs and assisting the centers with the submission; monitoring recruitment rates and the actions to increase recruitment; monitoring follow-up and implementing actions to prevent follow-up losses; auditing; sending study materials to the research centers; producing a monthly study newsletter; developing supporting material for the study.

Trial Steering Committee

The Trial Steering Committee is responsible for the overall study supervision, assisting in developing the study protocol and preparing the final manuscript. All other study committees report to this committee. Its members are investigators trained in designing and conducting randomized clinical trials in critically ill patients.

Data Safety Monitoring Committee

The DSMC is set up with independent epidemiologists and intensivists that supervises the trial. It also might provide recommendations for the SCC of continuing the study as planned or discontinuing the recruitment based on evidence that the intervention causes increased mortality in the experimental group (PPTR) as compared to the control group (LTR). Interim analyses will be conducted after recruitment of the first 100 patients and at 75% of the sample. In addition, the DSMC will discuss and potentially recommend a re-estimation of the sample size according to the interim analysis after recruitment of 75% of the patients.

Study centers

The study centers for ANDROMEDA-SHOCK were selected through a rigorous process. This started with a survey of professional and technical resources as well as processes of care. Centers were contacted trying to make this process representative across public, private and university hospitals, different countries and cultures, and hospital size.

At the end, 34 centers were selected and all applied for ethical approval, leaving finally 28 active centers. Details of the investigators and centers are provided in the Supplementary Appendix.

Funding

The study will be funded by the Departmento de Medicina Intensiva, Facultad de Medicina, Pontificia Universidad Católica, Chile.

E. Sample size

Mortality in patients with increased lactate levels in circulatory dysfunction has been shown to exceed 40% [22]. In addition, several studies have shown that abnormal peripheral perfusion is associated with a mortality exceeding 40% [28, 42].

We will enroll 420 patients. With these sample size the study will have 90% power to detect a reduction in 28-day mortality from 45% to 30%, at a significance level of 5%, considering time-to-event analysis. We considered a decrease of 15% in mortality to have a direct clinical implementation effect. Similar effects on mortality have been shown in early resuscitation studies. In addition, limiting fluid administration in patients with septic shock and normal peripheral perfusion has been shown to decrease organ failure, which is the leading cause of death in these patients [22, 27].

Considering a smaller decrease in mortality (e.g. 10%), this sample size would only have 57% power to detect benefit. Therefore, we will use an adaptive approach that will allow for a sample-size re-estimation at the interim analysis when 75% of the sample has been recruited. The sample-size re-estimation will be conducted by the DSMC if the effect size observed in the interim analysis is between 10% and <15% absolute reduction in mortality [43].

F. Statistical analysis plan

A detailed statistical analysis plan will be prepared before proceeding to patient enrolment. The essential characteristics of this statistical analysis plan are described on S2 file.

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Table 1. Strengths and drawbacks of peripheral perfusion and lactate as endpoints of fluid resuscitation

	Peripheral Perfusion	**Lactate**
Prognostic factor	++	+++
Demonstrated association with profound tissue hypoperfusion	+	+++
Specificity as a marker of tissue hypoperfusion	++	+
Real-time assessment of response to fluids	+++	+
Availability	+++	+
Simplicity	+++	+
Faster dynamics of recovery	+++	+

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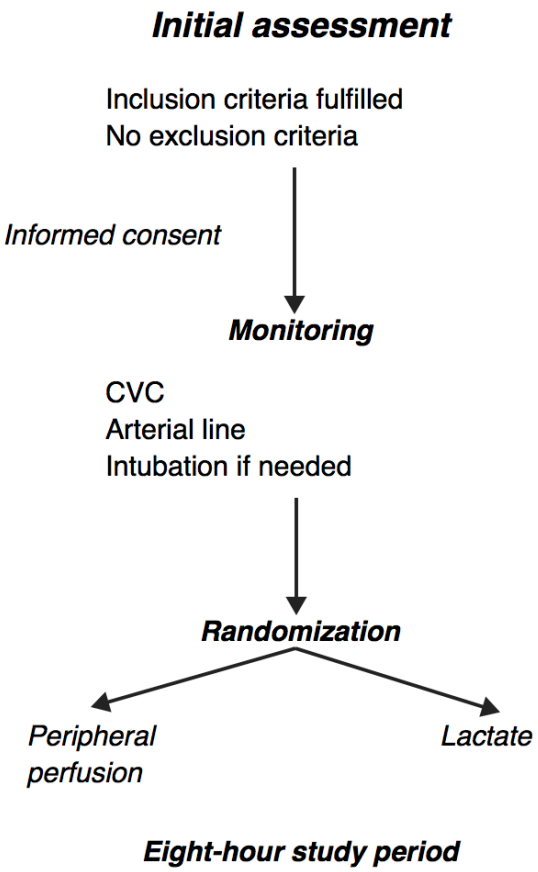
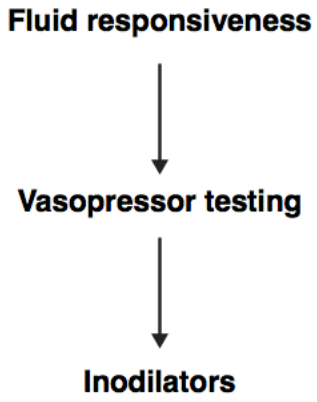


Figure 1. Pre-randomization phase assessments and interventions.



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661 **Figure 2. Sequential approach to optimize resuscitation based on perfusion goals.**

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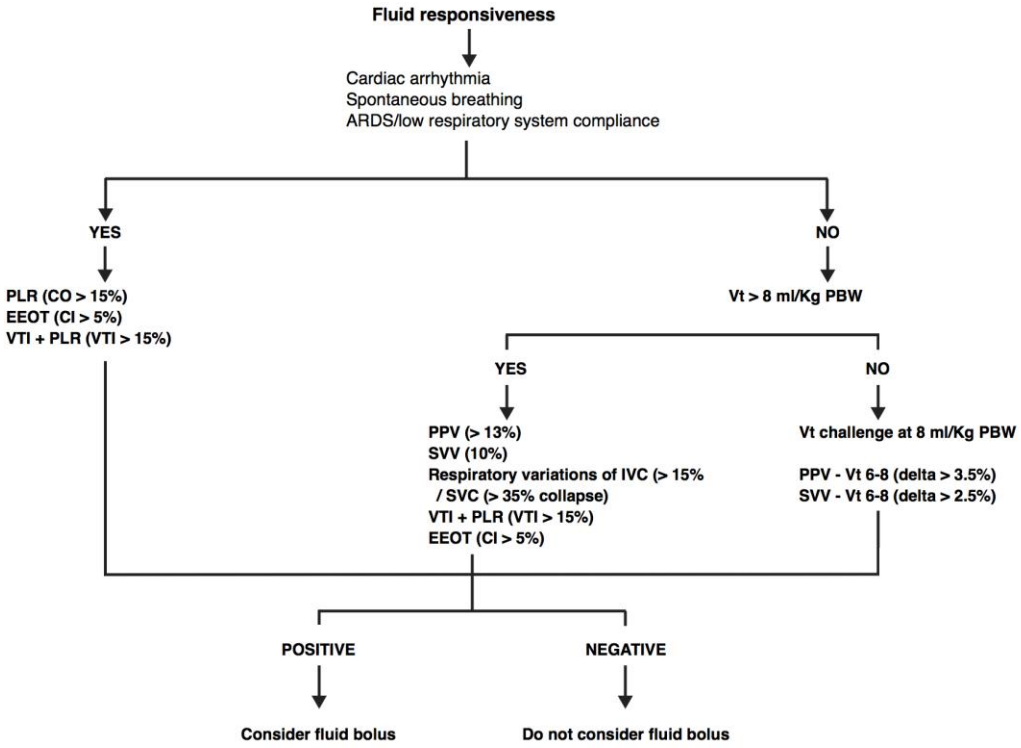

Figure 3. Assessment of fluid responsiveness during the study period.

ARDS acute respiratory distress syndrome; PLR passive leg rising; CO cardiac output; EEOT end-expiratory occlusion test; CI cardiac index; VTI velocity time integral; Vt tidal volume, PBW predicted body weight; PPV pulse pressure variation; SVV stroke volume variation, IVC inferior vena cava; SVC superior vena cava

S2. THE ANDROMEDA-SHOCK STUDY STATISTICAL ANALYSIS PLAN

The Statistical Analysis Plan was accepted for publication by RBTI on May 11, 2018 and is accessible on (https://www.ncbi.nlm.nih.gov/pubmed/30066731)
The Statistical Analysis Plan was developed following appropriate guidelines [1] prior to locking the trial database and starting analyses.
The trial protocol (version 1.0 from December, 2016) was submitted and published, is registered with ClinicalTrials.gov (NCT03078712), and was approved by the Institutional Review Boards (IRB) of all the participant centers.
No amendment was performed to the statistical analysis plan since the IRB approval of the first version of the study.

Abbreviations

APACHE: Acute Physiology and Chronic Health Evaluation

CRT: capillary refill time

DSMC: Data Safety Monitoring Committee

ICU: intensive care unit

LTR: lactate-targeted resuscitation

PPTR: peripheral perfusion-targeted resuscitation

SOFA: Sequential Organ Failure Assessment

Framework

The design of the study is aimed at demonstrating superiority of peripheral perfusion targeted resuscitation (PPTR) over lactate targeted resuscitation (LTR) in terms of 28-day mortality and other secondary and tertiary outcomes.

Sample size calculation

Mortality in patients with increased lactate levels in circulatory dysfunction might exceed 40% [2]. Furthermore, an abnormal peripheral perfusion is associated with mortality greater than 40% as well, whereas a normal capillary refill time (CRT) in the early phase of septic shock has been linked to mortality lower than 10% [3]. We anticipate a mortality within 28-days of 45% in the LTR group of our trial as suggested by the Sepsis-3 Consensus Conference [2].

A total sample size of 210 per group (420 patients in total) is expected to provide approximately 90% power to detect a reduction in in 28-day mortality from 45% to 30%, analyzing the data using the intention-to-treat principle, with a two-sided alpha level of 5%. A 15% reduction in mortality (33% relative risk reduction) has important clinical value and was observed in earlier resuscitation studies [4]. In addition, this effect size is plausible because limiting fluid administration has been shown to decrease organ failure, one of the main determinants of death in septic patients [5].

Nevertheless, we used an adaptive approach [6], that would allow for a sample-size re-estimation at a pre-planned interim analysis, after recruiting 75% of the total sample. The sample-size re-estimation was supposed to be conducted by the independent Data Safety Monitoring Committee (DSMC) only if the size effect observed in the interim analysis is between 10% and 15% absolute reduction in mortality (promising zone), favoring PPTR over LTR [6]. In the interim analysis, a favorable zone was defined as an absolute difference >15% (conditional power >90%), and an unfavorable zone, as an absolute difference <10% (conditional power <61%).

We calculate operational characteristics of this this strategy conducting simulations with 200 studies. Without adaptation, conditional power for the promising zone is between 61% and 90%. In case the study interim analysis felt in the promising zone, adapting sample size up to 840 patients would increase conditional power. Considering a true effect size of 15%, probability of “landing” on promising zone is 22% and mean conditional power would increase to >90%. Considering a true effect size of 10%, probability of “falling” on the promising zone is 40% and mean conditional power would increase to >80%.

This interim analysis was performed in February 2nd, 2018, and the DSMC recommended to continue the trial with no modifications.

Statistical interim analyses

Interim analyses were conducted after the inclusion of the first 100 patients and at 75% of the sample size (300 patients). Only the independent DSMC had access to results of those analyses. The DSMC is comprised by 5 experienced intensivists and trialists, and 1 senior statistician. The DSMC established no *a priori* statistical stopping guidance according to efficacy, safety or futility. The DSMC recommended that the trial should continue without alterations after those analyses.

Timing of final analysis

All outcomes will be analyzed simultaneously after we have completed the 90-day follow-up of all patients and the database has been locked.

Timing of outcome assessments

We will assess outcomes at 8, 24, 48, and 72 hours; at hospital discharge; and at 28 and 90 days,

Statistical principles

Confidence intervals and P values

We will present 95% confidence intervals for effect estimates on all primary and secondary outcomes. All hypothesis tests will be two-sided with α of 5%. We will not adjust P-values and

confidence intervals for analyses of primary or secondary outcomes. Therefore, all results for secondary outcomes should be interpreted as exploratory.

Adherence and protocol deviations

We will report the numbers and percentages of non-adherence to randomly allocated treatment.

Protocol deviations will be assessed and registered by the local coordinators at each center. Major deviations or violations are defined as wrong inclusion (misjudgment of inclusion or exclusion criteria) or inadequate resuscitation procedures during the study period.

Analysis populations

All analyses will be conducted according to the intention-to-treat principle.

Analysis

Outcome definitions

The primary outcome is all-cause mortality within 28 days.

The secondary outcomes are:

- All-cause mortality within 90 days.
- Mechanical ventilation-free days during the first 28 days after randomization.
- All type of renal replacement therapy-free days during the first 28 days after randomization.
- Vasopressor-free days during the first 28 days after randomization.
- Organ dysfunction assessed with the Sepsis-related Organ Failure Assessment (SOFA) [7] score at 72 hours after randomization
- Intensive care unit (ICU) and hospital lengths of stay, truncated at 90 days.

The tertiary exploratory outcomes are:

- Total resuscitation fluids in the first 8 and 24 hours after randomization.
- Total fluid balance in the first 8, 24, 48 and 72 hours.
- Occurrence of intra-abdominal hypertension during the first 72 hours after randomization (%), when measured by the attending physician, at his/her discretion when intra-abdominal hypertension is suspected.
- Use of renal replacement therapy (%) within 28 days.
- In-hospital mortality, truncated at 90 days.

Analysis methods

Continuous distribution will be assessed by visual inspection of histograms and D'Agostino-Pearson's normality tests. Variables will be expressed as counts and percentages, mean and standard deviation (SD), or median and interquartile range (IQR), whenever appropriate. Linear mixed models for continuous variables will be carried out where Gaussian error distribution applies to account for the repeated measurements on the same patient. Binary variables will be tested using logistic mixed regression models and continuous variables with non-symmetrical distributions, such as lactate and mottling score, will use the distribution that better fits the data.

The effect of PPTR versus LTR on the primary outcome will be analyzed by means of Cox proportional hazards models, with adjustment for 5 pre-specified baseline covariates: APACHE II score [8], SOFA score, lactate level, CRT and source of infection, as fixed (individual-level) effects. Results will be reported as hazard ratios with 95% confidence intervals (CI) and P-values. Kaplan Meier curves will be presented.

Effects on secondary and tertiary outcomes will be presented as hazard ratio for 90-day all-cause mortality and renal replacement therapy within 28 days, or risk difference for all other binary outcomes, along with 95% CI and P-values (calculated with Fisher’s exact tests). The effect on 90-

day all-cause mortality and the need of renal replacement therapy within 28 days will be assessed with Cox-proportional hazard model, without adjustment for baseline covariates.

The effect of both therapies on mechanical ventilation-free days, renal replacement therapy-free days and vasopressors-free days within 28 days will be analyzed with generalized linear models using the distribution that best fits the data (possibly truncated Poisson distribution). The impact on organ dysfunction at 72 hours (measured by SOFA) will be calculated with generalized linear models with the distribution that better fits the data, adjusting for baseline SOFA. Effects on other continuous outcomes, such as ICU or hospital length of stay, amount or resuscitation fluids, fluid balance, will also be calculated with generalized linear models with the distribution that better fits the data (normal, gamma, inverse Gaussian, or other), without adjustment for covariates.

Subgroup analysis

We will use Cox proportional hazards adjusted for baseline covariates (same as main analysis) to assess interactions between treatment effect and the following prespecified subgroups:

a) Patients with lactate > 4.0 mmol/L versus equal or lower than 4 mmol/L

b) Patients without a confirmed source of infection (as this could increase the translation of the study to other critically ill) versus those with confirmed source of infection.

c) Patients with APACHE II lower versus equal or higher than 25.

d) Patients with SOFA score lower versus equal or higher than 10.

e) Patients with a more than 10% difference in lactate levels between the very first one measured and the baseline when starting the study.

Sensitivity analysis

We will assess the effect of PPTR compared to LTR on 28-day mortality using a frailty Cox model with site as random effect and adjustment for the same baseline co-variates as in the main analysis (APACHE II score, SOFA score, lactate level, CRT and source of infection).

Harms

The primary, secondary and tertiary outcomes are intended to reflect potential harms resulting from the PPTR versus LTR approach for managing septic shock.

Missing data

Primary outcome (28-day mortality) will be treated as time-to-event outcome and reported as Cox proportional hazard models; patients with loss of follow up will be censored in the last contact. We will use multiple imputation methods to assess treatment effect on the primary outcome in cases without follow-up information. As a sensitivity analysis, we will also assess the effect on the primary outcome using complete case data.

Statistical software

Analyses will be performed using the R (R Core Team, 2017, Vienna, Austria) software.

Conclusion

In accordance with best trial practices, statistical analysis plan and data management plan are herein reported before the database is locked, and previously to the beginning of the analyses.

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