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Doppler identified venous congestion in septic shock: protocol for an international, multi-centre prospective cohort study (Andromeda-VEXUS)

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ABSTRACT

Introduction Venous congestion is a pathophysiological state where high venous pressures cause organ oedema and dysfunction. Venous congestion is associated with worse outcomes, particularly acute kidney injury (AKI), for critically ill patients. Venous congestion can be measured by Doppler ultrasound at the bedside through interrogation of the inferior vena cava (IVC), hepatic vein (HV), portal vein (PV) and intrarenal veins (IRV). The objective of this study is to quantify the association between Doppler identified venous congestion and the need for renal replacement therapy (RRT) or death for patients with septic shock.

Methods and analysis This study is a prespecified substudy of the ANDROMEDA-SHOCK 2 (AS-2) randomised control trial (RCT) assessing haemodynamic resuscitation in septic shock and will enrol at least 350 patients across multiple sites. We will include adult patients within 4 hours of fulfilling septic shock definition according to Sepsis-3 consensus conference. Using Doppler ultrasound, physicians will interrogate the IVC, HV, PV and IRV 6–12 hours after randomisation. Study investigators will provide web-based educational sessions to ultrasound operators and adjudicate image acquisition and interpretation. The primary outcome will be RRT or death within 28 days of septic shock. We will assess the hazard of RRT or death as a function of venous congestion using a Cox proportional hazards model. Sub-distribution HRs will describe the hazard of RRT given the competing risk of death.

Ethics and dissemination We obtained ethics approval for the AS-2 RCT, including this observational substudy, from local ethics boards at all participating sites. We will report the findings of this study through open-access publication, presentation at international conferences, a coordinated dissemination strategy by investigators through social media, and an open-access workshop series in multiple languages.

Trial registration number NCT05057611.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ Prospective, multi-centre, multi-national study design.
⇒ Use of patient important outcomes including the need for renal replacement therapy or death.
⇒ Expert duplicate quality assurance of all study scans.
⇒ Heterogeneity of clinicians performing ultrasound scans.

INTRODUCTION

Despite advances in diagnosis and management, septic shock mortality remains as high as 30%–40%.[1] Septic shock is responsible for millions of deaths per year worldwide.[2] Early intravenous fluid (IVF) resuscitation, a cornerstone of septic shock management, can restore intravascular volume and augment cardiac output to improve end-organ perfusion. However, endothelial dysfunction, a defining characteristic of sepsis, causes fluid extravasation into the tissue. Mounting evidence suggests that such overzealous fluid administration results in interstitial oedema and iatrogenic organ injury.[3] The narrow therapeutic window for IVF administration in septic shock creates an urgent need to identify better physiological markers that can tailor haemodynamic resuscitation to individual patient physiology.

Venous congestion is a promising physiological marker that may be able to help direct the resuscitation of patients with septic shock. In venous congestion, pathogenic retrograde pressure from the right atrium impairs venous drainage from organs (eg, kidneys) resulting in organ oedema and dysfunction.[4–6] Venous congestion is an important haemodynamic

state for critically ill patients because it is associated with impaired organ function, particularly AKI.[6–9] While several processes, such as new or chronic cardiomyopathy, can predispose patients to venous congestion, excessive IVF administration is hypothesised to be an important iatrogenic cause.

Venous congestion of multiple organs can be readily measured in real-time at the bedside using Doppler ultrasonography. Venous congestion, determined by abnormal measurements or flows in the inferior vena cava (IVC), hepatic vein (HV), portal vein (PV) and intrarenal veins (IRV), has been associated with worsening AKI in patients post cardiac surgery, those with cardiorenal syndrome, and in a general medical-surgical intensive care unit (ICU) cohort.[4–8] What needs to be discovered is whether venous congestion is associated with worsening renal function in patients with septic shock.

The primary objective of this study is to quantify the association between venous congestion and the provision of renal replacement therapy (RRT) or death in a subpopulation of the ANDROMEDA-SHOCK 2 (AS-2) randomised controlled trial (RCT). In doing so, we seek to identify a promising physiological marker that can provide cues for the de-escalation of IVF administration and/or de-resuscitation. This study will also describe the epidemiology of venous congestion in patients with septic shock; evaluate the association between venous congestion and adverse clinical outcomes including AKI, the duration of organ-supporting therapies, and mortality; and assess the contribution of individual demographic and clinical parameters to the development of venous congestion.

METHODS

Study design and setting

This international multicentre, prospective, observational study will evaluate the association between venous congestion and the provision of RRT or death within 28 days in patients with septic shock. We will recruit patients from select centres participating in the AS-2 study, an RCT evaluating haemodynamic and perfusion-targeted resuscitation, compared with usual care, in patients with septic shock (online supplemental appendix 1) from January 2023 to January 2025 (or the completion of the AS-2 RCT).[10] Centres with clinicians that express interest in performing venous congestion ultrasound will participate in this study. One centre not involved in the AS-2 RCT will recruit patients in an observational capacity with identical eligibility procedures and the same study procedures as the control arm. Centres will be located worldwide in South America, Europe, North America and Asia.

Eligibility criteria

The inclusion criteria for this prospective observational study will be the same as the AS-2 inclusion criteria. We will enrol consecutive patients participating in the AS-2 RCT at the select venous congestion substudy centres who meet eligibility criteria. Eligible patients will be adults (≥18 years of age) who fulfil the septic shock definition according to the Sepsis-3 consensus conference, which includes the combination of suspected or confirmed infection, arterial lactate levels ≥2.0 mmol/L) and requirement of vasopressor support despite adequate initial fluid resuscitation.[11]

Similar to the AS-2 RCT, we will exclude patients if they have any of the following criteria: more than 4 hours have elapsed since diagnosis of septic shock, anticipated to undergo surgery, anticipated to start RRT during the 6-hour intervention period for the AS-2 study, active bleeding; those with limitations on resuscitation and/or medical therapy, Child B-C cirrhosis; underlying disease process with a life expectancy less than 90 days and/or the attending clinician deems aggressive resuscitation unsuitable; known pregnancy; concomitant severe acute respiratory distress syndrome; and patients in whom capillary refill time (CRT) cannot be accurately assessed. In addition to the AS-2 exclusion criteria above, our proposed study will exclude patients with any RRT (acute or chronic) at the time of eligibility assessment.

Ethics approval and informed consent

The original AS-2 protocol was approved by the Institutional Review Board (IRB) of each participating centre. Written informed consent will be obtained from a legal representative of all participants. The consent process for the AS-2 RCT encompasses all study activities associated with this observational substudy (eg, ultrasound measurements). One site that will not participate in the AS2-RCT will use a similar process to consent eligible patients to study procedures outlined in the usual care arm of the AS-2 RCT and procedures specific to our proposed observational study.

Data collection and sources

We will collect anonymised data using an electronic case report form (eCRF) on the Castor Electronic Data Capture or the Research Electronic Database Capture systems. Each patient will be assigned a unique study ID. We will capture variables such as demographics and baseline characteristics, prior comorbidities, the severity of illness, and physiological and haemodynamic data as per the AS-2 RCT parent study.[10] We will extract data from the electronic medical record and bedside patient chart. Study personnel will regularly check CRFs for completeness to reduce the frequency of missing data fields.

Outcomes

The primary outcome will be a composite of RRT or death within 28 days of presentation with septic shock. The primary endpoint will be time-to-initiation of RRT or death within 28 days. We will include the following secondary outcomes: RRT within 28 days of septic shock; all-cause mortality within 28 days, and 90 days after septic shock; development of new or worsening AKI within 7 days of septic shock; ventilator-free days (28 days);

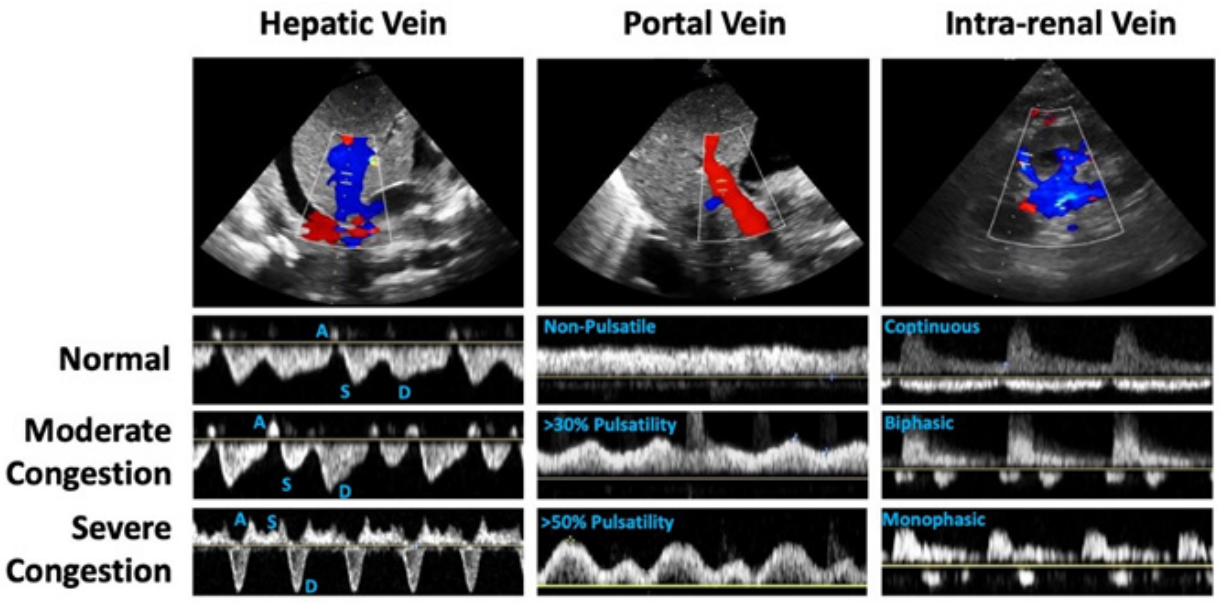

Figure 1 Doppler markers of venous congestion for the hepatic vein, porta vein and intrarenal veins.

vasopressor-free days (28 days); ICU free days (28 days); hospital free days (28 days) and vital support free days (28 days). Additional measurements will include: volume resuscitation (mL), net fluid balance (mL), the evolvement (change from initial to repeat) of CRT, evolvement of lactate levels, evolvement of central venous pressure, evolvement of central venous oxygen saturation, and evolvement of the central venous to arterial carbon dioxide difference at 72 hours. Online supplemental appendix 2 summarises the definitions of study outcomes.

Study procedures

Doppler ultrasound measurements

Members of the research team will perform Doppler ultrasonography to quantify the degree of venous congestion. We will perform a Doppler ultrasound between the 6-hour mark (once AS-2 RCT 6-hour resuscitative period ends) and 12 hours after enrolment. The venous congestion ultrasound interrogates four vessels: IVC, HV, PV and IRV (figures 1–3). The study protocol will require a curvilinear probe if available; however, a phased array probe can be used if a curvilinear probe is unavailable or unable to obtain a measurement. Ultrasound operators will acquire pulsed-wave (PW) Doppler measurements at an angle of insonation of less than 45%. We will record all Doppler measurements at end-expiration or during a breath hold. In addition, patients will undergo simultaneous ECG recording to ascertain the heart rhythm to time waveforms with the cardiac cycle. Study personnel will record heart rhythm, the use of positive pressure ventilation, and the patient respiratory rate at time of scan.

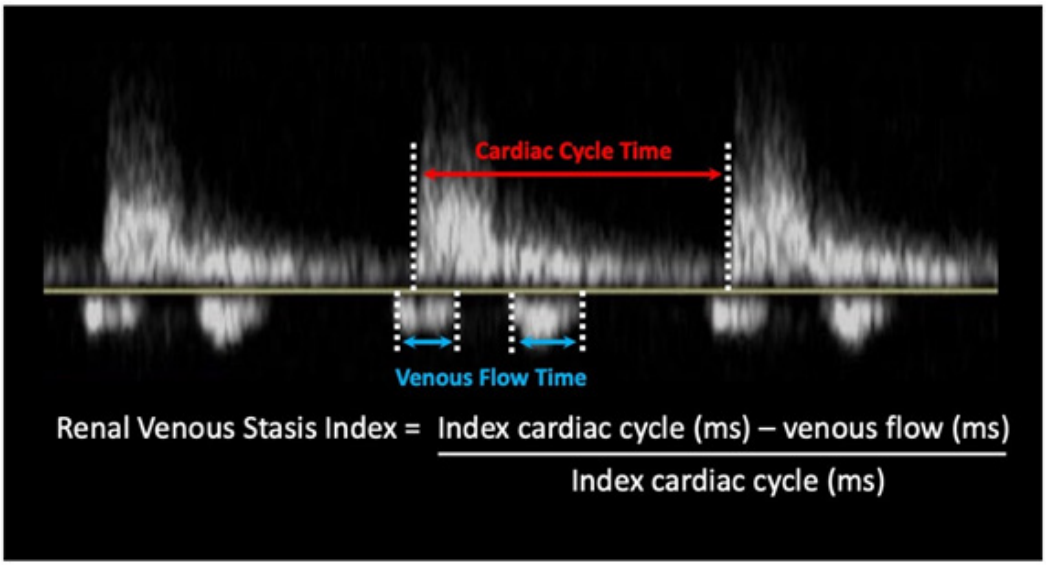

Figure 2 Renal venous stasis index for intrarenal veins Doppler.

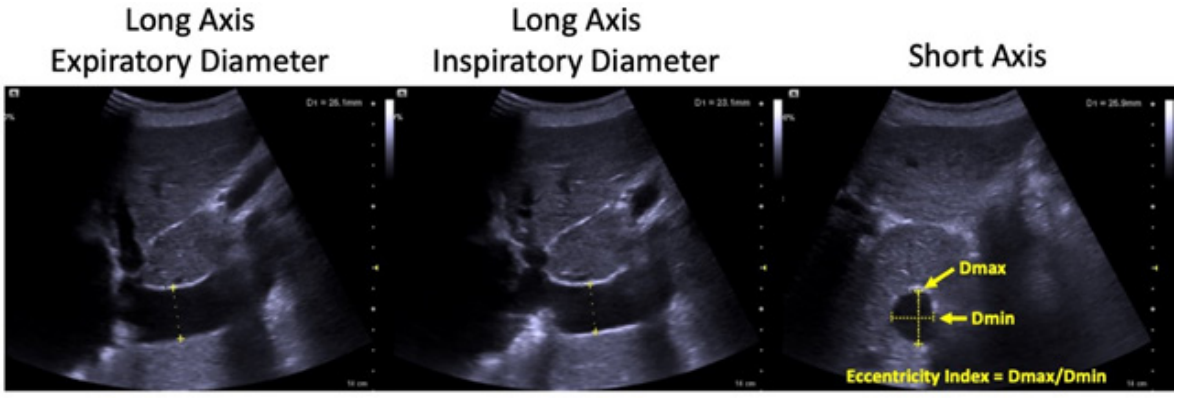

Figure 3 Inferior vena cava measurements in long and short axis.

Whenever possible, we will blind the treating team to the results of the venous congestion ultrasound by using an ultrasound operator not involved in patient care. Online supplemental appendix 3 provides the CRF.

IVC measurements

Ultrasound operators will measure the IVC in both long axis and short axis (figure 3). In long axis, we will record the maximum and minimum IVC diameter with respiration and calculate the IVC respirophasic variation ([Max–Min]/Max × 100%). In short axis, we will record the maximum and minimum dimensions of the IVC at end expiration, measured 1–2 cm inferior to the entrance of the HV into the IVC, and calculate an eccentricity index (longest dimension/shortest dimension).

Hepatic vein

Ultrasound operators will perform PW Doppler of the hepatic vein using a window from the mid-axillary line or around the midclavicular line in the right upper quadrant (RUQ). HV patterns will be classified and recorded as: continuous (washed out), systolic greater than diastolic (S>D, normal), systolic less than diastolic (S<D, abnormal), and systolic reversal (severely abnormal), or unable to obtain. We will also record the systolic and diastolic velocities.

Portal vein

Ultrasound operators will perform PW Doppler of the PV from the RUQ. Whenever possible, the main PV will be measured, however, the right PV is also acceptable. PV patterns include continuous (normal), or pulsatile. For pulsatile PVs, the pulsatility index (PI) will be calculated: ([PVmax – Pvmin]/PVmax × 100%). For non-pulsatile PVs, a value of 0% pulsatility will be applied. For PVs with reversal, a negative PVmin velocity will be used, yielding a PV pulsatility of >100%.

Intrarenal vein

Ultrasound operators will perform PW Doppler of the IRV from the RUQ. If the Doppler signal cannot be obtained from the RUQ, the left kidney will be imaged. IRV patterns include continuous (normal), pulsatile (mildly abnormal), biphasic (mildly abnormal) and monophasic (severely abnormal). Postprocessing analysis of the IRV Dopplers will calculate the renal venous stasis index (RVSI). The RVSI is the proportion of time spent in the cardiac cycle with no venous drainage visualised on Doppler. Values approaching 1 represent severe congestion (figure 2).

Training of ultrasound operators

Site Principal Investigators of the AS-2 trial will identify potential ultrasound operators that will acquire venous congestion data. Study investigators will then provide a 4-hour didactic session outlining the theoretical and technical components of the venous congestion measurements. Afterward, Point-of-care ultrasound (POCUS) operators will complete a 1-hour virtual webinar to discuss cases and answer specific questions. Next, we will require each ultrasound operator to demonstrate adequate acquisition and interpretation of the IVC, HV, PV and IRV on at least three non-study patients that will be reviewed by study investigators with feedback provided. Finally, each clinician will be required to complete a short online quiz to assess competency in acquisition and interpretation with a score of 80% required to pass.

Quality control

Ultrasound clips will be saved, anonymised, uploaded and reviewed by venous Doppler experts blinded to clinical information and other ultrasound measurements for quality assurance. Study investigators will review venous congestion scans for quality assurance of both the acquisition, and interpretation. We will assess the adequacy of acquisition for each scan in duplicate using a prespecified checklist (online supplemental appendix 4). The adequacy of interpretation will also be assessed, and in cases of disagreement between the expert reviewer and ultrasound operator, a third blinded expert will be used for adjudication with their interpretation included in the final analysis.

Cointerventions

Patients enrolled in our prospective observational study will also be coenrolled in the AS-2 RCT. Patients randomised to the intervention group will undergo

resuscitation based on a management algorithm outlined in online supplemental appendix 1. Patients' CRT will be assessed every hour over a 6-hour period. Patients with abnormal CRT will then receive vasoactive medications or IVFs based on their pulse pressure, diastolic blood pressure, fluid responsiveness and critical care echocardiography evaluation.

Patients randomised to the control group will be managed according to standard practices at the respective institutions. Standard practices at participating institutions will follow the general recommendations of the Surviving Sepsis Campaign Guidelines.[12] One centre that is not participating in the AS-2 RCT will follow the study procedures outlined in the control group. The AS-2 RCT study protocol provides a detailed outline of the study procedures.[10]

Statistical methods

We will report the study as per the Strengthening the Reporting of Observational Studies in Epidemiology guidelines.[13] We will present patient data and ultrasound measurements as means with SD, medians with IQR, or as counts and percentages, as appropriate. A p value of less than 0.05 will be statistically significant for all statistical comparisons. For all regression analyses, we will assess covariates for multicollinearity and evaluate the model fit. We will use imputations for missing data.[14]

Descriptive analyses

We will report measurements and Doppler waveform findings obtained from the IVC, HV, PV and IRV to describe the prevalence of venous congestion in patients with septic shock. HV Doppler findings will classify as either normal (systolic waveform greater than diastolic waveform), mildly abnormal (diastolic waveform greater than systolic waveform) or severely abnormal (systolic flow wave reversal). We will record PV findings as a continuous variable of the PI and IRV waveforms as normal (continuous monophasic), mildly abnormal (discontinuous biphasic flow) or severely abnormal (discontinuous monophasic flow).

Impact of venous congestion the provision of RRT or death

We will use a multilevel Cox proportional hazards model to evaluate the association between venous congestion and the composite of RRT or death within 28 days of presentation with septic shock. We will also characterise the impact of venous congestion on the incidence of RRT specifically. Given the competing risk of death, we will use the Fine and Gray model to derive sub-distribution HRs for both the provision of RRT and death.[15 16]

Regression analysis will employ multilevel modelling to adjust for clustering due to hospital sites. The independent variables will include age, sequential organ failure assessment (SOFA) score, Charlson comorbidity index, creatinine at admission, study arm and the degree of venous congestion quantified by Doppler ultrasound measurements. Biological plausibility and pre-existing literature highlight an association between the independent variable and the outcome of interest that guided the selection of covariates. We will evaluate all four measures of venous congestion for multicollinearity before including them in the model. The primary endpoint will be expressed as the hazard of RRT or death within 28 days of septic shock presentation given the degree of venous congestion. We will compare the probabilities of occurrence of RRT, and death over time between patients with and without venous congestion using cumulative incidence functions and Gray's test.

Impact of venous congestion on secondary clinical outcomes

We will use multilevel models to explore the association of venous congestion on the secondary outcomes. As with the main outcome, we will adjust our estimates for covariates that are associated with the outcome of interest. Logistic regression with mixed effects will explore the association between venous congestion on mortality at 28 days and 90 days as well as new or worsening AKI on day 7. Linear regression with mixed effects will explore the association between venous congestion and hospital and ICU-free days and days alive and free of organ-sustaining therapies.

Sample size

The primary outcome is RRT or death within 28 days of septic shock and the exposure of interest is venous congestion. It is expected that 20% of the study population will have a venous congestion. A sample of 350 eligible patients, of which 70 patients experience a venous congestion, will achieve 88% power at 0.05 level of significance (two-sided) to detect an HR of 2.0. The number of events to achieve this power is 130. The anticipated incidences of the primary outcome of RRT or death among patients with and without venous congestion are 45% and 35%, respectively. The HR is assumed to be constant over the study period in the Cox proportional hazard regression. In the regression model, besides venous congestion, age, SOFA score, Charlson comorbidity index, study arm and creatinine at the time of admission will be included. The exact relationship of these four covariates with venous congestion is unknown. Thus, the impact of including these four variables on the power could not be determined. However, the expected number of 130 events satisfies the rule of thumb of 20 events per variable.

Subgroup and sensitivity analyses

We will perform a subgroup analysis examining the association of venous congestion with the composite outcome of RRT or death in patients with or without any creatinine based kidney disease improving global outcomes AKI at the time of enrolment, those with pre-existing cardiomyopathy, and those with more severe illness (Acute Physiology and Chronic Health Evaluation II of greater than 25). We hypothesise that patients with AKI on admission, cardiomyopathy, and more severe illness will have a greater association between venous congestion

and developing RRT. In addition, we will perform sensitivity analysis including only centres where the treating clinicians are blinded to the venous congestion Dopplers measurements and in patients in whom ultrasound expert adjudicators deem the acquisition and interpretation to be of high quality.

Patient and public involvement

Patients or public were not involved in the design of this observational substudy of the AS-2 RCT.

Limitations and challenges

We anticipate several important challenges as we conduct this study. Although participating centres have experience measuring venous congestion using ultrasound, the validity of the study requires high-quality image acquisition and accurate interpretation of ultrasound measurements. To address this potential challenge, we have developed an onboarding process that provides didactic teaching with an evaluative component. Furthermore, images acquired from each site will be de-identified and reviewed for quality by study investigators. Another limitation is that echocardiography is not mandated for all patients as part of this substudy. Some patients will receive echocardiography as part of the AS-2 RCT, however, not performing this routinely will limit our ability to assess for echocardiographic contributors to venous congestion (eg, RV failure, tricuspid regurgitation). Because POCUS is widely available, this proposed study will be conducted across ICUs worldwide. To ensure external generalisability, multiple stakeholders reviewed our protocol to ensure it is pragmatic. Finally, we have not controlled for all potential confounders. We have not controlled for duration of hypotension, use of nephrotoxic medications or MAP variability. There are several reasons for this. The first is that given the pragmatic and international nature of the trial, not all of these variables are available to us. Additionally, we are trying to adhere to a 20:1 event rate to degree of freedom ratio for our multi-variable regression, which limits the number of variables we can include in our model. Our sample size unfortunately is constrained by the parent RCT we are recruiting under, which limits our ability to include these additional variables.

Ethics and dissemination

The original AS-2 protocol, and this substudy, were approved by the IRB of each participating centre. Onboarding new centres is a dynamic process with new sites being identified for inclusion into this substudy, but as of the time of publication of the manuscript the following centres have received ethics approval: the main ethics was obtained from the Ethical Scientific Committee of Chile SSMC, protocol number 666/2021. Additional sites include: Comité de Ética en Investigación del Antiguo Hospital Civil de Guadalajara 'Fray Antonio Alcalde', Mexico; Comité Ético Científico del Servicio de Salud Metropolitano Sur, Hospital Barros Luco, Chile; the standing committee for coordination of health and medical research, ministry of health, Kuwait; Comite De Etica De La Investigacion Con Medicamentos (CEIm) del Hospital Universitario de La Princesa, Madrid, Spain; Comité de Ética en Investigación Biomédica—Fundación Valle del Lili, Colombia. Written informed consent will be obtained from a legal representative of all participants with the consent form translated into different local languages. This observational substudy is part of the main trial.

Our knowledge translation plan will be to disseminate the results across several target audiences: (1) academic researchers, (2) healthcare providers and (3) POCUS educators. We will communicate the results of our study by publishing our findings in peer-reviewed journals, presenting our results at an international conference and disseminating key messages through various social media platforms. We will also host a free venous congestion webinar series in multiple languages that will be available for all healthcare providers worldwide. Our webinar series will be built on the same tools we developed for the study onboarding process (see the Training of ultrasound operators section).

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Competing interests AD has the following disclosures, however, none are relevant to this current research: CAE-Healthcare (2010) speaker bureau, (2020) KOL speaker bureau, Masimo (2017) speaker bureau, Edwards (2019) research (equipment grant) and supported by the Richard I. Kaufman Endowment Fund in Anesthesia and Critical Care (2015). EA has the following disclosures, however, it is not relevant or discussed in this current research: Speaker honoraria from EchoNous. The remaining authors have relevant conflict of interest to declare.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

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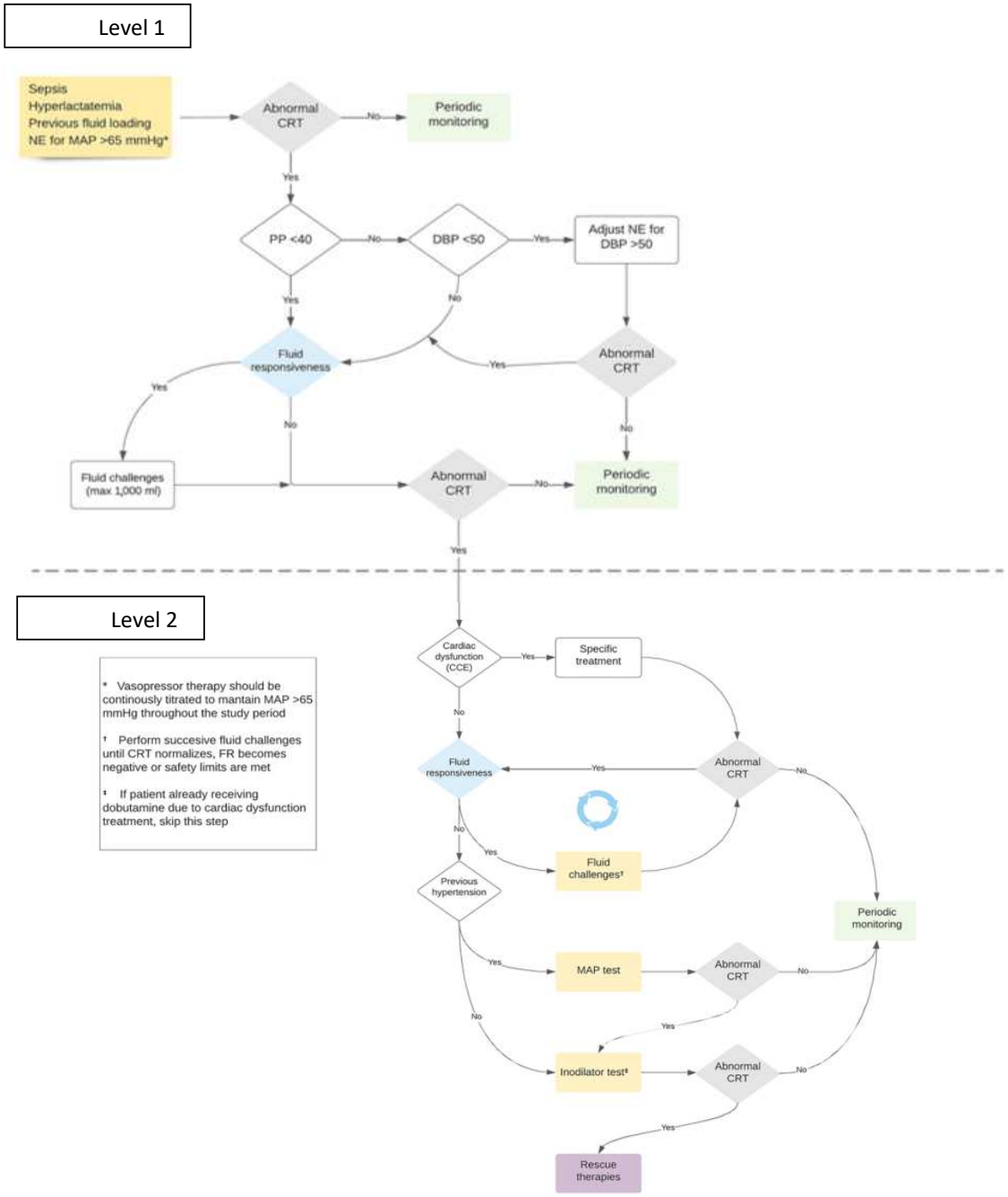
APPENDICES

Appendix 1: ANDROMEDA-SHOCK-2 Intervention Arm Protocol



Appendix 2: Definitions of outcomes

Outcome	Definition
Primary Outcome	
Renal replacement therapy or Death within 28 days	Renal replacement therapy will serve as the time-to-event endpoint and will be defined as the relative hazard of receiving renal replacement therapy at 28 days, censored for death. 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.
Secondary Outcomes	
New or worsening AKI at 7 days	Development of new or worsening acute kidney injury within 7 days will be defined by the creatinine-based kidney disease improving global outcomes (KDIGO) staging. For patients who on admission already have KDIGO stage 3 AKI (Cr 3x baseline or >= 353.6 umol/L), the initiation of renal replacement therapy (RRT) within 7 days will be classified as worsening AKI. If the patient dies, they will have been determined to meet the primary outcome. If a patient recovers renal function, they will still have been deemed to meet the primary outcome.
All-cause mortality (28 days)	Mortality by all causes within 28 after randomization
All-cause mortality (90 days)	Mortality by all causes within 90 after randomization
Ventilator free days (28 days),	Resolution of respiratory failure implies liberation from invasive mechanical ventilation for at least 48 hours. Patients who die within 28 days will have zero days counted for this variable, irrespective of ventilator status.
Vasopressor free days (28 days)	Resolution of cardiovascular failure implies complete stopping of vasopressor support for at least 24 consecutive hours. Patients who die within 28 days will have zero days counted for this variable, irrespective of vasopressor status.
ICU free days (28 days)	Number of days free from remaining in ICU (from randomization up to ICU discharge). Re-admission to ICU during follow-up period will be accounted for the original ICU length of stay only if occurred within the next week of ICU discharge and by a cause related with the original admission. Patients who die within 28 days will have zero days counted for this variable. The duration of ICU stay is determined by when the patient is deemed medically stable for transfer to ward, not when the transfer occurs, to account for hospital administrative delays.
Hospital free days (28 days	Number of days free from remaining hospitalization within 28 days. Patients who die within 28 days will have zero days counted for this variable, regardless of whether they are discharged from hospital.
Vital support free days (28 days)	The number of calendar days between randomization and 28 days 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.
Tertiary Outcomes (72 hours post enrollment)	
Volume resuscitation (mL)	The volume of fluids administered with resuscitative intention up to 72 hours from randomization
Net fluid balance (mL),	The volume of cumulated fluids during the first 72 hours from randomization
Evolvement of CRT	Evolvement of CRT within the first 72 hours after randomization
Evolvement of lactate levels	Evolvement of Arterial Lactate levels within the first 72 hours after randomization
Evolvement of central venous pressure	Evolvement of Central venous pressure within the first 72 hours after randomization
Evolvement of central venous oxygen saturation	Evolvement of central venous oxygen saturation within the first 72 hours after randomization
Evolvement of the central venous to arterial carbon dioxide difference	Evolvement of central venous to arterial carbon dioxide difference within the first 72 hours after randomization

Appendix 3: Case report form for venous congestion sub-study

Field	**Buttons**
Date and Time of Venous Congestion Ultrasound	Date/Time
Was the treating team blinded to the venous congestion ultrasound results?	Yes/No/Unknown
What was the cardiac rhythm at time of ultrasound?	Sinus Rhythm Atrial Fibrillation, Other (specify), Unknown
What was the respiratory rate of the patient at time of ultrasound?	Numerical Answer (breaths per min), Unknown
Was the patient receiving positive pressure ventilation (invasive or non-invasive) at the time of the ultrasound?	Invasive, Non-Invasive, None, Unknown
Inferior Vena Cava maximum diameter	Numerical Answer (mm), Cannot Complete
Inferior Vena Cava minimum diameter	Numerical Answer (mm), Cannot Complete
Inferior Vena Cava Maximum Diameter in SAX during expiration	Numerical Answer (mm), Cannot Complete
Inferior Vena Cava Minimum Diameter in SAX during expiration	Numerical Answer (mm), Cannot Complete
Hepatic Vein Doppler	Continuous (washout) Normal (S>D) Mildly Abnormal (S<D) Severely Abnormal (S wave reversal) Not visualized
Hepatic Vein Systolic Velocity (positive value if anterograde)	Numerical Answer (cm/s), Cannot Complete
Hepatic Vein Diastolic Velocity (positive value if anterograde)	Numerical Answer (cm/s), Cannot Complete
Portal Vein Pulsatility (Vmax – Vmin / Vmax) x 100%	Numerical Answer (%) No pulsatility Not visualized
Portal Vein Systolic Velocity (positive value if anterograde)	Numerical Answer (cm/s), Cannot Complete
Portal Vein Diastolic Velocity (positive value if anterograde)	Numerical Answer (cm/s), Cannot Complete
Renal Vein Doppler	Normal (continuous) Mildly Abnormal (biphasic) Severely Abnormal (monophasic) Not visualized

If invasive arterial measurements were performed during the 6 hour study protocol, which site was used?	Radial Femoral Brachial Axillary Other No invasive blood pressure monitoring
How many hours was the invasive arterial measurements used during the 6 hour study protocol? (Zero if not used)	Numerical Answer (hrs) Unknown

Appendix 4: Quality assurance case report form

Scan	Expert Assessment
IVC Long Axis: Is the image acquisition adequate? • IVC is correctly in-plane • IVC maximum and minimum diameter seen during both inspiration and expiration	Yes No IVC LAX Not Performed
IVC short Axis: Is the image acquisition adequate? • IVC in short axis is seen with the maximum and minimum diameters measured	Yes No IVC SAX Not Performed
HV: Is the image acquisition adequate? • PW placed on the HV • Angle of insonation $<45^0$ • ECG used	Yes No Unsure HV Not Performed
HV: Is the image interpretation adequate? • Correct interpretation of the HV pattern?	Yes No Unsure HV Not Performed
PV: Is the image acquisition adequate? • PW placed on the right or main PV • Angle of insonation $<45^0$ • ECG used	Yes No Unsure PV Not Performed
PV: Is the image interpretation adequate? • Correct measurement of the PV?	Yes No Unsure PV Not Performed
RV: Is the image acquisition adequate? • PW placed on the interlobar veins (not hilum) • Angle of insonation $<45^0$ • Venous tracing below baseline obtained	Yes No Unsure IRV Not Performed
RV: Is the image interpretation adequate? • Correct interpretation of the RV?	Yes No Unsure IRV Not Performed
What is the renal venous stasis index? (done using post processing)	Numerical answer Unable to obtain

	IRV not performed