Venous Excess Ultrasound (VEXUS)-Guided Fluid Management versus Usual Care in Patients with Septic Shock: A Pilot Randomized Controlled Trial

1. PROJECT SUMMARY

Septic shock is a common life-threatening condition caused by a dysregulated host response to infection that severely reduces blood pressure and organ perfusion. Fluids are an essential treatment for patients with septic shock, but when given in excess, can contribute to acute kidney failure and the need for renal replacement therapy (RRT). Unfortunately, nearly 70% of patients with septic shock will develop fluid overload during their ICU stay (1). Currently, we lack effective tools to prevent fluid-overload associated organ injury.

Venous Excess Ultrasound (VEXUS) method a point-of-care ultrasound (POCUS)-based tool, offers a non-invasive method to assess systemic venous congestion, an early marker of fluid overload. However, there is a lack of robust evidence, particularly from randomized controlled trials (RCTs), to determine whether VEXUS-guided fluid management can improve clinical outcomes in septic shock compared to usual care. In this pilot RCT, we will assess the feasibility of patient enrollment, delivery of the intervention (VEXUS-guided fluid therapy) and explore differences in physiologic (cumulative fluid balance) and patient-important (kidney failure, dialysis need, and mortality) outcomes.

2.0 KEY WORDS

Septic shock, ultrasound, venous congestion, pilot study, randomized controlled trial

3. BACKGROUND

3.1 Septic shock causes multi-organ failure and death

Septic shock, the most severe form of sepsis, causes hypotension that impairs oxygen delivery to crucial organs (2). Septic shock is a leading cause of intensive care unit (ICU) admissions, resulting in multi-organ failure and death in more than 40% of patients (3). Nearly 25% of patients will develop renal failure that requires renal replacement therapy (RRT) (4, 5). Excess intravenous (IV) fluid administration, due to resuscitation, is a **modifiable cause** of sepsis-induced renal failure.

3.2 Fluid overload may lead to renal failure and the need for RRT

IV fluid resuscitation is a cornerstone of septic shock treatment. However, current fluid administration practices cause fluid overload a high number of these patients and contribute to renal failure (6, 7). Excess IV fluids accumulate in the venous system and increase venous pressures, precipitating a pathologic state known as **venous congestion**. Venous congestion can then: 1. disrupt kidney blood vessels due to shear stress from distension (8); 2. push fluid out of vessels and into the interstitial space, causing the kidneys to swell in an enclosed space (9); and 3. impair oxygen delivery by reducing the arterial-to-venous perfusion pressure gradient (10). These mechanisms may explain why fluid overload is associated with increased risk of renal failure (by 5-fold), need for RRT, and mortality (11, 12).

3.3 We lack effect tools to prevent fluid overload-induced renal failure

Although there is no shortage of clinical tools for guiding fluid administration, none effectively prevent fluid overload. In the absence of effective tools, published guidelines continue to offer weak recommendations for the use of physical examination, radiographic tests, and dynamic measures of fluid responsiveness to guide fluid administration (13).

Existing tools fail to prevent potential iatrogenic harm from fluid overload. Physical examination and radiographic tests identify fluid overload (e.g., peripheral or pulmonary edema) **after excess fluid has accumulated** in the organs and caused injury (14). Dynamic measures of fluid responsiveness may fail to prevent fluid overload as patients can be simultaneously fluid-responsive and fluid overloaded (15, 16). Furthermore, based on a meta-analysis of randomized controlled trials (RCTs), dynamic measures of fluid responsiveness **do NOT** improve clinical outcomes in septic shock (17). Finally, static measures (central venous pressure), are also not sufficient because they are poor indicators of fluid status (18).

The lack of effective tools leaves clinical practice guidelines unable to offer a recommendation on the optimal fluid administration strategy after the initial IV fluid bolus (13). This gap in sepsis care subjects' patients to iatrogenic harm from current fluid administration practices.

3.4 Venous congestion, detected by Venous Excess Ultrasound (VEXUS), is an early marker of fluid overload

Venous congestion is an early physiologic marker of fluid overload that can warn clinicians before **renal failure** occurs (Figure 1)**.** Excess fluid administration increases venous pressures (section 3.2) and precipitates venous congestion. Venous congestion manifests as altered blood flow patterns in central veins, such as the hepatic, portal, and intra-renal veins.

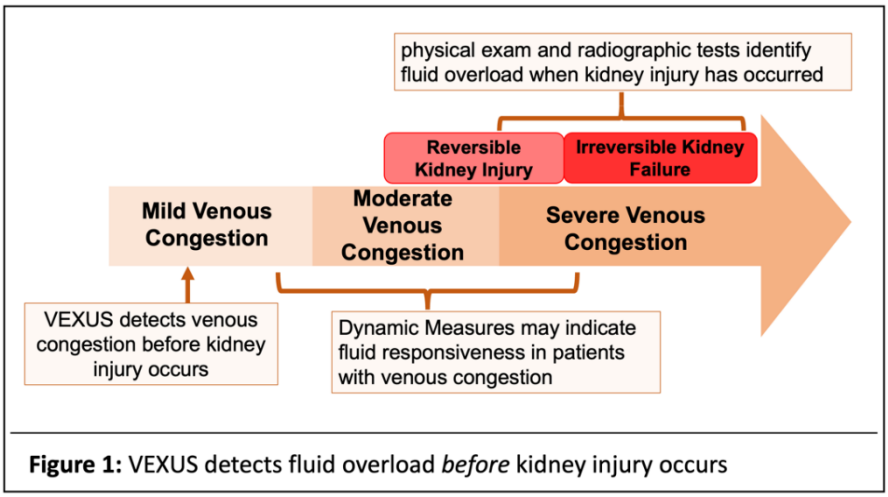

Figure 1: VEXUS detects fluid overload *before* kidney injury occurs

A novel, validated method called VEXUS allows us to detect venous congestion **earlier than current clinical and radiographic markers of fluid overload** (9). VEXUS uses pulse-wave Doppler to assess blood flow alterations in the hepatic, portal, and intra-renal veins to determine the severity of venous congestion (Figure 2). We can perform VEXUS using point-of-care ultrasound (POCUS); **a painless, non-invasive, safe, and equitable health technology that is widely available** in ICUs in low- to high-income settings.

VEXUS provides an objective, reproducible, and non-invasive assessment of venous congestion that can be readily scaled across ICUs worldwide. VEXUS can ***prevent*** renal failure from fluid overload by informing clinicians when to ***stop administering fluids*** (and rely on vasoactive agents to support hemodynamics) and when to ***remove fluid*** (using diuretics). Importantly, VEXUS can do this ***prior to fluid overload causing renal failure***, while accounting for differences in individual patient physiology and illness trajectory.

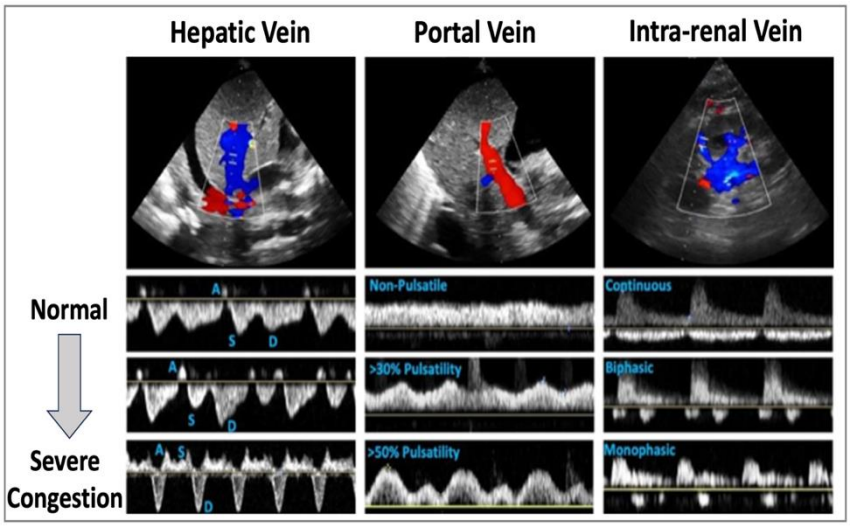

Figure 2: VEXUS uses pulse-wave Doppler to grade the

3.5 Venous congestion predicts renal failure in non-septic shock patients

We are conducting a systematic review to evaluate the impact of venous congestion on clinical outcomes. Although we identified no RCTs, several observational studies in non-septic shock patients suggest that fluid balance is correlated with venous congestion severity, and venous congestion, measured using VEXUS, is associated with renal failure (19-25). We completed the **first study** in patients with septic shock to explore the association between venous congestion and clinical outcomes.

In our **observational** study, venous congestion, measured using VEXUS, *may* be associated with RRT OR death (hazard ratio 3.4, 95% CI 0.9 to 11.9, p=0.06), but our results are limited by imprecision (26). **No RCT has evaluated the impact of VEXUS-guided fluid management on patient outcomes in septic shock.**

4.0 RATIONALE FOR OUR RCT

For decades, the primary treatment for patients with septic shock has involved the administration of large volumes of fluid, with the consequences of fluid overload receiving minimal consideration. Evidence on the harmful effects of fluid overload has now revealed that such resuscitation practices have likely resulted in iatrogenic renal failure and dialysis dependence. For over 10 years, we have engaged in academic discourse about the harmful effects of fluid overload. However, we have still not developed resuscitation strategies to prevent this iatrogenic injury, and the last 3 iterations of the Surviving Sepsis Guidelines have not changed their recommendations.

This paralysis is a consequence of existing research strategies focusing on the arterial system. We propose that venous system may be the answer to preventing the harmful effects of fluid overload. The VEXUS method provides a novel approach to fluid management by being the first reliable system to warn clinicians of the harmful effects before they occur.

We propose to conduct the first pilot RCT comparing VEXUS-guided management with usual care in patients with septic shock. This pilot RCT will determine the feasibility of a definitive multicenter RCT. VEXUS may finally end 10 years of academic discourse, resolve equipoise on the optimal fluid administration strategy after the initial fluid bolus, and renew current resuscitation practices to better serve our patients**.**

5.0 OBJECTIVES AND EXPECTED OUTCOMES

Objective 1: To determine the feasibility of a pilot multicenter RCT comparing VEXUS-guided fluid management versus standard care on days alive and free of RRT at 28 days in patients with septic shock. **Expected Outcome:** This pilot RCT will successfully demonstrate the feasibility of a multicenter RCT based on recruitment rate, retained consent rate, VEXUS scan completion rate, and protocol adherence.

Objective 2: To perform exploratory analyses on whether VEXUS-guided fluid management improves clinical outcomes (see project outcome evaluation metrics). **Expected Outcome:** VEXUS-guided fluid management will be associated with improved process/proximal (e.g., cumulative fluid balance) and patient-important (e.g., mortality) outcomes.

6.0 METHODOLOGY

6.1 Study Design/ Setting: Pragmatic, open-label, parallel-group, pilot RCT evaluating VEXUS-guided fluid management versus standard care in adult patients with septic shock.

6.2 Eligibility Criteria

6.2.1 Inclusion Criteria: 1. Adult patients (> 18 years); 2. Within 16 hours of meeting septic shock diagnosis based on following Sepsis-3 criteria (requirement for vasopressors to maintain organ perfusion, lactate > 2 mmol/L, suspected or confirmed infection); 3. Within 48 hours of ICU admission.

6.2.2 Exclusion Criteria: 1. Already receiving RRT; 2. Patients for whom a decision to initiate RRT has been made prior to study enrollment; 3. Patients who have limitations or restrictions on goals of care; 4. Active bleeding causing hemodynamic instability; 5. Veno-venous or veno-arterial extracorporeal membrane oxygenation; 6. Previously enrollment in study; 7. 10% or more of body surface area acute burn injury; 8. Suspected or confirmed liver cirrhosis; 9. Established allergy to sulfa drugs; 10. Patients receiving treatments that require continuous IV fluid infusions (e.g., diabetic ketoacidosis, diabetes insipidus); 11. Unable to measure fluid balance accurately; 12. Contra-indication to study recommended interventions (e.g., diuretics, inotropes); 13. Unable to perform VEXUS due to anatomical barriers (e.g., surgical dressings); 14. Unable to complete VEXUS scan during the resuscitation window; 15. Moderate to Severe Primary pathological Valvular Tricuspid Regurgitation; 16. Untreated Metabolic/biochemical findings (Hypokalemia [K+]< 3.0 mmol/L; metabolic alkalosis [Bicarbonate > 40 mmol/L and/or pH >

7.55], Hypomagnesemia [Mg2+] < 0.6, and Hypernatremia [Na+] > 155 mmol/L; 17. Previous liver resection or liver\renal transplantation or recent abdominal surgery; 18. Known IVC thrombosis; 19. Patients with left ventricular assisted device (LVAD) or intra-aortic balloon pump (IABP) or any mechanical circulatory support device; 20. Patients admitted for post cardiac arrest care; 21. Patient with UOP <5 cc\hr for >6 hours.

6.3 Randomization: Although blinding patients, investigators, and clinical personnel is not possible, we will blind data analysts (for objective 2 outcomes) and maintain allocation concealment. Research personnel will use a centralized system to randomize eligible patients (1:1 ratio) using undisclosed variable block sizes (2,4,6). An independent statistician will prepare the randomization schedule and stratify by study site.

6.4 Consent: We will employ a hybrid consent model that combines *a priori* consent, deferred consent, and waiver of consent approaches. This model utilizes a tiered approach to obtaining informed consent. *Tier 1:* we will attempt to obtain written informed consent from the participant whenever possible. If the participant is incapable of providing consent, we will seek written informed consent from their substitute decision maker (SDM). In cases where the SDM is not available in person, we will obtain consent via telephone. *Tier 2:* If the SDM cannot be reached by phone, we will enroll the participant based on deferral of informed consent, with the commitment to seek consent at the earliest available opportunity, either in person or by telephone. *Tier 3:* if we are unable to reach the SDM after two documented attempts or if the participant dies before consent can be obtained, we will invoke a waiver of informed consent and retain the collected data for analysis. This tiered approach ensures that we maximize opportunities for informed consent while allowing for the timely enrollment of critically ill patients in whom immediate intervention may be crucial.

6.5 Planned Interventions:

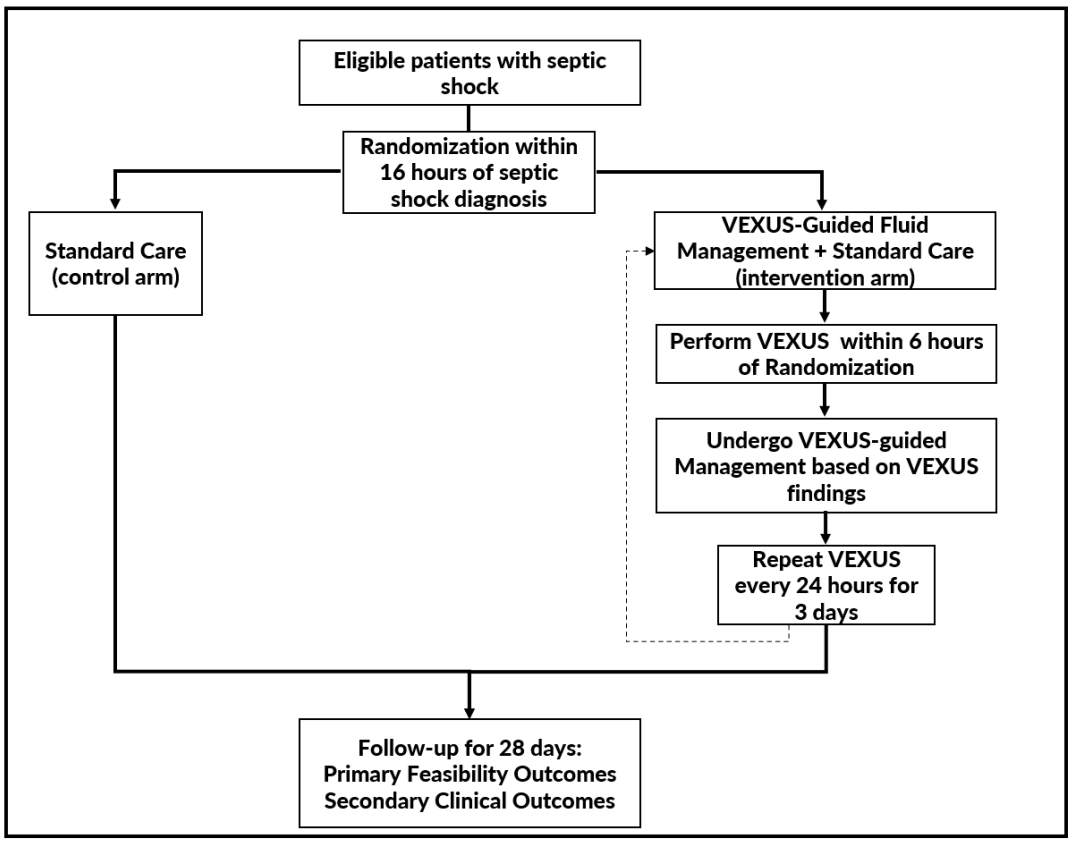

Figure 3: Overview of intervention and control arm procedures

6.5.1 Co-interventions for BOTH arms: We will provide all patients, regardless of group assignment, with the standard care according to the Surviving Sepsis Campaign guidelines (13). Both groups will receive fluid resuscitation, the recommended mean arterial pressure (MAP) target of ≥65 mmHg, early broad-spectrum antibiotics, source control when applicable, vasopressor support with norepinephrine as the first-line agent, stress-dose corticosteroids, early nutrition, and lung-protective mechanical ventilation when required. Clinicians may utilize hemodynamics assessment tools such as dynamic measures of fluid responsiveness and cardiac point-of-care ultrasound. The Surviving Sepsis Campaign guidelines endorse dynamic measures (due to a lack of alternatives), while forthcoming Society of Critical Care Medicine guidelines support adult critical care ultrasound in patients with septic shock.

6.5.2 Intervention arm: We sought input from academic and community physicians, patient partners, physiologists, and ultrasound experts to ensure study procedures and interventions are **internally valid, pragmatic, and acceptable** to practitioners. Expert ultrasound operators (already practicing at study sites) will perform VEXUS within 6 hours of randomization. Following the VEXUS protocol, operators will evaluate the Inferior Vena Cava and perform pulse-wave Doppler on the portal, hepatic, and intra-renal veins to determine the severity of venous congestion (9). The severity of venous congestion, based on VEXUS, will then guide the 24-hour fluid balance target and management decisions. Operators will repeat VEXUS every 24 hours for 3 days (or until ICU discharge or death if earlier), providing updated fluid balance targets and management decisions based on repeat VEXUS findings.

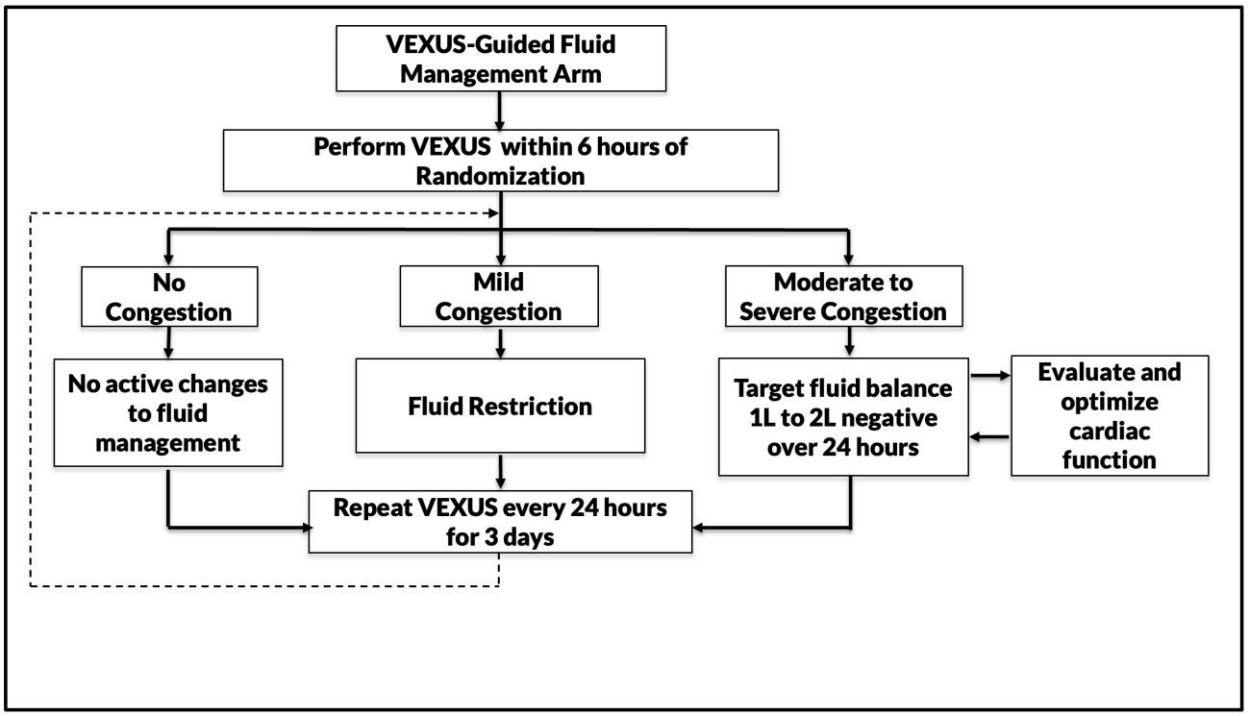

Figure 4: Overview of intervention arm procedures based on VEXUS findings

6.5.2.1 Ultrasound Operators: Ultrasound operators performing VEXUS will include either 1. Study Investigators with expertise in ultrasonography/VEXUS (J.B, R.P), or 2. Physicians in a dedicated point-of-care ultrasound (POCUS) fellowship at our institution (POCUS fellows). Study Investigators (J.B., R.P.) are critical care physicians with at least 3-6 months of dedicated POCUS training during fellowship and have served as POCUS instructors at national and international courses. Study Investigators perform VEXUS routinely and adjudicate VEXUS scans for other international prospective studies. POCUS fellows are acute care physicians undergoing 6-12 months of advanced ultrasonography training. They begin their fellowship with strong foundational expertise in POCUS. Although POCUS fellows are familiar with the VEXUS protocol, they will receive additional training from Study Investigators

with international expertise in VEXUS. The comprehensive training curriculum includes didactic sessions, hands-on instruction, and rigorous assessments. This educational model has proven effective in previous VEXUS studies and ensures standardized, high-quality VEXUS performance across all operators.

6.5.2.2 Acquisition of VEXUS: Participants randomized to the intervention arm will undergo VEXUS within 6 hours of randomization. We will follow a modified version of the published, validated VEXUS protocol.[8] VEXUS interrogates four vessels: Inferior Vena Cava (IVC), hepatic vein, portal vein (PV), and intra-renal vein. Operators will perform VEXUS with a curvilinear probe; however, a phased array probe may be used if a curvilinear probe is unavailable. Ultrasound operators will acquire pulse-wave (PW) Doppler measurements at an angle of insonation of less than 45 degrees. We will record all Doppler measurements at end-expiration or during a breath hold. In addition, participants will undergo simultaneous electrocardiogram recording to ascertain the heart rhythm and time waveforms with the cardiac cycle. *IVC Measurement:* Ultrasound operators will measure the IVC in the long and short axis and record the maximum and minimum IVC diameter within 2 cm of where the hepatic veins enter the IVC. *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. Hepatic patterns will be classified and recorded as: continuous (washed out), systolic greater than diastolic (S>D, normal), systolic less than diastolic (S<D, abnormal), 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 portal vein from the right upper quadrant. Whenever possible, the main portal vein will be measured, however, the right portal is also acceptable. Portal vein patterns include continuous (normal), or pulsatile. For pulsatile portal veins, operators will calculate the pulsatility index (PI): ([PVmax – Pvmin]/PVmax x 100%). *Intra-renal Vein:* Ultrasound operators will perform pulse wave Doppler of the intra-renal vein from the right upper quadrant. If the Doppler signal cannot be obtained from the right upper quadrant, the left kidney will be imaged. The intra-renal vein patterns include continuous (normal), pulsatile (mildly abnormal), biphasic (abnormal), and monophasic (severely abnormal). POCUS operators will store 6 second prospective clips of each view, including still images of the pulse-wave Doppler. QPath, a HIPAA compliant workflow manager for storing and reporting ultrasound scans, will archive the VEXUS scans and generate a report on the findings as well as the final VEXUS score.

6.5.2.3 Interpretation of VEXUS:
Defining venous congestion: In our study, we will assess manifestations of venous congestion using Doppler ultrasound of three central veins: hepatic, portal, and intra-renal. For the hepatic vein, we will consider an S wave amplitude less than the D wave or S wave reversal as abnormal. Portal vein abnormalities will be defined as pulsatility greater than or equal to 30% or flow reversal. For the intra-renal vein, we will classify bi-phasic or monophasic flow patterns as abnormal. Figure 5 provides an overview of venous Doppler profiles.

We will define venous congestion severity as follows:

a) No congestion: Normal Doppler patterns in the hepatic, portal, and renal veins.

b) Mild Congestion as: One mild Doppler abnormality in the hepatic, portal, or renal veins.

c) Moderate Congestion: Either $\geqslant$ 2 mild Doppler abnormalities **OR** $\geqslant$ 1 severe Doppler abnormality.

d) Severe Congestion: Either $\geqslant$ 2 severe Doppler abnormalities **OR** 1 severe and $\geqslant$ 1 mild Doppler abnormality

In situations where the renal veins cannot be adequately imaged, we will use an inferior vena cava sphericity index as a substitute criterion. An IVC sphericity index <0.6 indicates no intrarenal congestion, a sphericity index ⩾0.9 indicates severe intrarenal congestion, and values between 0.6 and 0.9 are indeterminate, requiring classification based on hepatic and portal findings alone. This approach allows for a comprehensive assessment of venous congestion while accounting for potential imaging challenges, thereby ensuring the robustness and applicability of our protocol across various clinical scenarios. We also estimate that 30% of patients in our trial will demonstrate moderate to severe venous congestion.

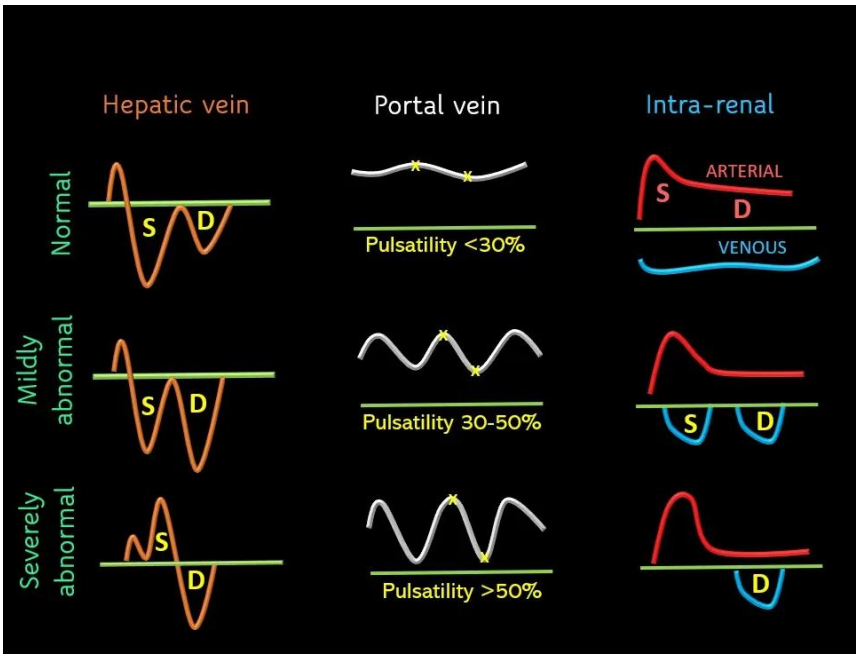

Figure 5: Overview venous Doppler profiles identified on VEXUS

6.5.2.4 Management of patients with no venous congestion on VEXUS: For patients without venous congestion (no abnormalities on VEXUS), we will advise no changes to fluid management over the subsequent 24 hour period. The clinical team may manage fluid administration at their discretion, utilizing hemodynamic assessment tools and/or relying on clinical judgement, physical examination, and radiographic tests.

6.5.2.5 Management of patients with mild venous congestion: For patients with mild venous congestion, our protocol will recommend a fluid restrictive strategy. We will restrict IV fluid boluses, reduce all maintenance fluids to the minimum requirements to keep veins open (TKVO), and administer medications in the smallest volume possible, using concentrated formulations when available (minimum required amounts). We will not restrict volume associated with nutrition or administration of blood products when clinically indicated. In patients who, based on the clinical team, are deemed to be hypotensive and hypo-perfused, we will recommend hemodynamic assessment, including fluid responsiveness assessment, followed by vasopressor challenge first (up titrate vasopressor infusion doses). If still required, we will permit rescue fluid boluses if certain criteria are met (see section 6.5.2.7).

6.5.2.6 Management of patients with moderate to severe venous congestion: We will implement several interventions to abrogate moderate to severe venous congestion. While the volume of IV fluid administered is an important cause of venous congestion in patients with septic shock, heart function and positive end expiratory pressure (PEEP) play an important role and/or confound the findings. To maximize our protocol's efficacy, in patients with moderate to severe venous congestion, we will also optimize PEEP (in mechanically ventilated patients) and heart function.

PEEP Optimization: For mechanically ventilated patients, we will recommend that the clinical team optimize PEEP settings based on established clinical practice tools, such as esophageal balloon measurements or ventilator pressure-volume curves.

Cardiac Function Optimization: Our protocol will require a limited cardiac evaluation, using POCUS, that aligns with basic critical care competency standards and existing standard of care practices for POCUS (27-29). POCUS operators will use a phase-array probe (1-5 MHz) to obtain standard views: parasternal long axis, parasternal short axis at the mid-cavity level, apical four- and five-chamber, and subcostal views. Acknowledging the nuances of right ventricular (RV) assessment, one or more of the following will indicate moderate to severe RV dysfunction: 1. tricuspid annular plane systolic excursion (TAPSE) < 17 mm, 2. severely dilated RV (RV > LV size), 3. interventricular septal shift, and 4. RV S prime < 10.5 cm/second. For LV assessment, operators will estimate systolic function using the eyeball method in at least two views with adequate endocardial resolution. An ejection fraction of < 40% indicates moderate to severe systolic left ventricular (LV) dysfunction. In addition, operators will obtain the Left Ventricular Outflow Tract (LVOT) Velocity Time Integral (VTI), a pragmatic and widely accepted surrogate measure of stroke volume. As with the VEXUS scan, POCUS operators will store 6 second prospective clips of each view, including still images of LVOT VTI.

In patients with reduced stroke volume (VTI <18 cm) due to either moderate to severe left ventricular dysfunction (ejection fraction < 40% based on the eyeball method) or right ventricular dysfunction (TAPSE < 17 mm, RV greater than LV size, interventricular septal shift, or RV S prime < 10.5 cm/second), our protocol will recommend initiating an inotrope. The choice of inotrope agent will be at the discretion of the clinical team. This treatment aligns with current standards of care for septic shock patients exhibiting moderate to severely reduced cardiac function, where inotropic support is routinely administered for patients in shock (Surviving Sepsis Campaign guidelines) (12). For patients with reduced stroke volume and RV dysfunction, our protocol will *suggest*: 1. reducing positive end-expiratory pressure to the lowest and safest setting in mechanically ventilated patients, guided by clinical judgement, esophageal balloon, or pressure volume tools, 2. initiating a pulmonary artery vasodilator (e.g., epoprostanol or nitric oxide), 3. restoring sinus rhythm in patients with atrioventricular synchrony.

In rare settings patients exhibit normal stroke volume and pulmonary hypertension, our protocol *suggests*: 1. reducing positive end-expiratory pressure to the lowest and safest setting in mechanically ventilated patients, guided by clinical judgement, esophageal balloon, or pressure volume tools, 2. initiating a pulmonary artery vasodilator (e.g., epoprostanol or nitric oxide), 3. initiating an inotrope, and 4. restoring sinus rhythm in patients with atrioventricular synchrony. Figure 6 summarizes management strategies based on ultrasound findings.

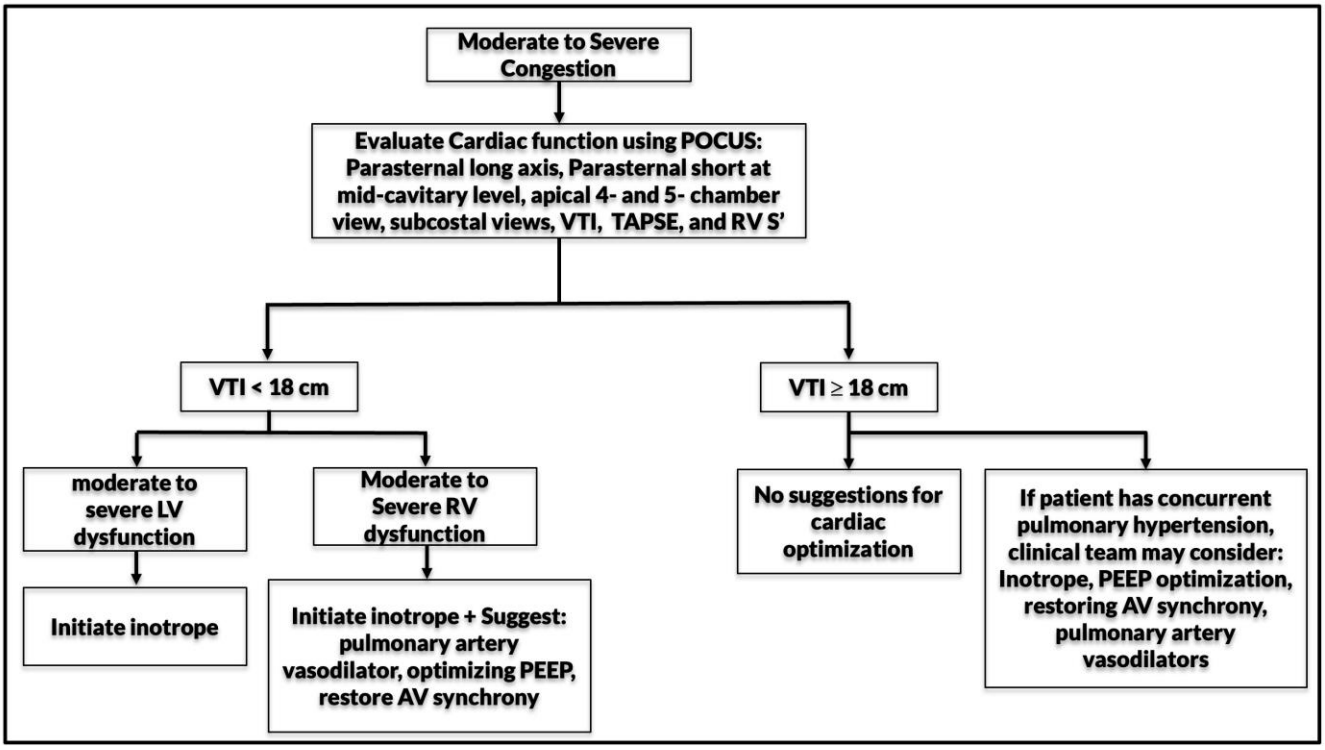

Figure 6: Overview cardiac optimization strategy for patients with moderate to severe congestion

Fluid Management Strategy: Our protocol will implement a more definitive fluid management strategy to reduce the fluid balance in patients with moderate to severe venous congestion. We will achieve fluid balance targets by: 1. Restricting IV fluid boluses; 2. Minimizing IV fluid intake (e.g., administering medications in minimum permitted volumes, reducing maintenance fluids to only keep veins open); 3. Administering diuretics (e.g., Furosemide).

For patients with moderate to severe venous congestion, the 24-hour target fluid balance will be -1 to -2L negative. The clinical team will check the fluid balance every 6 hours to ensure the fluid balance targets are met. Fluid balance is routinely collected as part of clinical care and reported in the electronic medical record. Depending on the 6-hour fluid balance values, our protocol will provide guidance on fluid management targets (**Figure 7**). To maintain internal validity while remaining pragmatic, our protocol provides flexible options that reflect current multimodal diuretics administration practice (e.g., choice of furosemide infusion versus bolus) and will mandate diuretic administration only if the 6-hour fluid balance suggests that, given the current trajectory, patients will not achieve the 24-hour target. As with patients with mild venous congestion, we will permit rescue fluid boluses if certain conditions are met (see section 6.2.5.7).

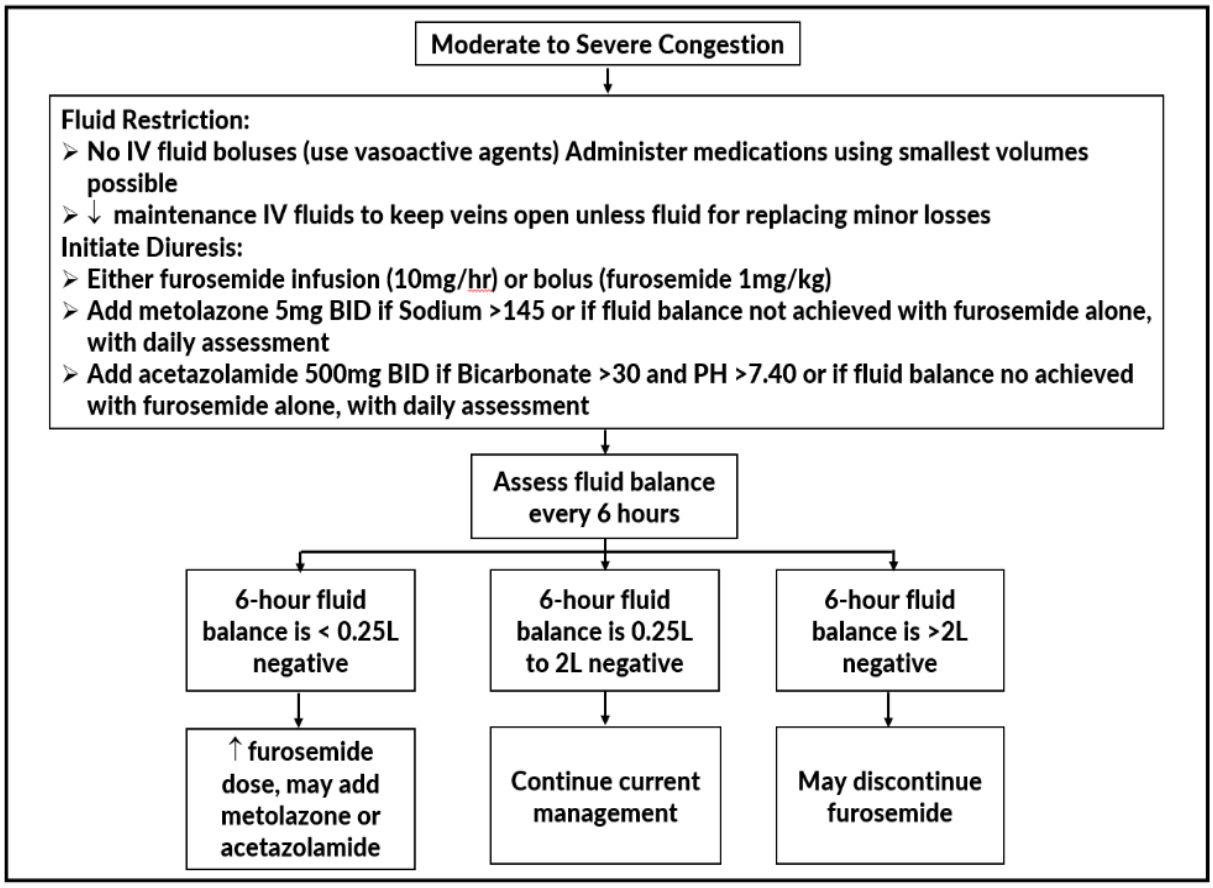

Figure 7: Overview fluid management strategy for patients with moderate to severe congestion

Monitoring procedures for patients: As part of the standard of care, all patients receive hemodynamic monitoring (invasive via arterial line or frequent non-invasive blood pressure cuff readings, cardiac monitoring using three electrocardiogram leads), hourly intake and urine output measurements, continuous oxygen saturation monitoring, and bloodwork every 4 to 6 hours. This will allow the clinical team to titrate interventions safely and judiciously without precipitating adverse effects.

Stopping criteria for diuretics: Because nearly 70% of patients develop fluid overload (6), most patients with septic shock undergo de-resuscitation and active fluid removal using diuretics during their ICU stay. As part of the standard of care, all patients will undergo routine surveillance of urine output (on an hourly basis in the vast majority of cases), serum electrolytes (every 4 to 6 hours), serum creatinine (every 12 to 24 hours), and acid/base balance (every 4 to 6 hours). If patients develop Hypernatremia (Na > 155), alkalemia due to metabolic alkalosis (pH > 7.55), Hypomagnesemia (Mg < 60), then we will withhold diuretic administration until biochemical derangements are corrected. We anticipate the risk of such derangements to be low because patients will undergo frequent blood work monitoring and patients undergoing diuresis are placed on electrolyte replacement protocols.

With respect to potential acute kidney injury due to diuretics, we will defer to the clinical team's judgment for diuretic cessation and not pre-specify creatinine, urine output, or Acute Kidney Injury Stage criteria for withholding diuretics. This pragmatic approach acknowledges the multifactorial nature of AKI in septic shock and aligns with current practice where patients with AKI often receive diuretics. Notably, observational data suggest venous congestion associates with AKI and dialysis requirement, underscoring the potential benefit of diuretics to alleviate venous congestion and improve kidney function (20-22).

6.5.2.7 Rescue fluid boluses: In patients with **mild venous congestion or worse** who exhibit signs of **hypotension and/or hypoperfusion**, clinicians should follow standard practice and conduct a **hemodynamic evaluation with fluid responsiveness assessment**. A **rescue fluid bolus of 500 mL of normal saline or Ringer's lactate over 10–15 minutes** may be administered under the following conditions:

1. The patient is deemed **fluid responsive AND** meets **one or more** of the following criteria:
    - (a) **Severe hypotension**: systolic blood pressure <70 mmHg or MAP <50 mmHg.
    - (b) **Refractory hypotension**: systolic blood pressure <90 mmHg or MAP <65 mmHg, **despite receiving norepinephrine (or equivalent vasopressor) at >0.3 mcg/kg/min**.
    - (c) **Plasma lactate ≥4 mmol/L** and rising after 2 hours of maintaining MAP >65 mmHg with vasopressor infusion.
    - (d) **Capillary refill time >3 sec** after 2 hours of maintaining MAP >65 mmHg with vasopressor infusion.
2. The treating team determines that administering a fluid bolus is in the patient's best interest, even if the above criteria are not fully met.

Patients requiring fluid for **baseline intake** (e.g., medication carrier volume, enteral feeding) or replacing **minor documented losses** (e.g., drains, diarrhea) should be managed by **titrating maintenance infusions to the minimum required volume**. All other fluids should be administered **to keep veins open** (**TKVO) rates** rather than as boluses.

All patients who receive a rescue fluid bolus should be **reassessed 30–60 minutes after administration** to evaluate for improvement in perfusion and early signs of volume intolerance.

6.5.2.8 Duration of intervention period: Every 24 hours for 3 days (or until ICU discharge or death if earlier), patients will undergo VEXUS to determine the fluid balance target. We chose a 3-day window for monitoring/intervention because it encompasses a period when fluid overload arises while remaining pragmatic. Furthermore, our observational study demonstrated that the peak cumulative incidence of either deaths or RRT initiation occurred within the first 3-5 days of septic shock diagnosis (30).

6.5.3 Control arm: Patients in the control arm will receive standard care for septic shock based on the Surviving Sepsis Campaign guidelines (13). Although VEXUS is **NOT permitted** during the first 28 days, patients may receive heart/lung POCUS for shock management. This approach is aligned with POCUS guidelines currently in development.

6.5.4 Data Collection Methods: Trained research personnel will collect data on the REDCap platform at prespecified time points. At baseline, we will record demographics and baseline characteristics (e.g., age, sex, height, weight), comorbidities (Charlson Comorbiditiy Index), Sequential Organ Failure Assessment (SOFA) score, source of infection, time from septic shock diagnosis to randomization, baseline biochemical data, organ sustaining therapies, and co-interventions administered. We will document physiologic and hemodynamic data (e.g., heart rate, mean arterial pressure, vasopressor doses expressed as norepinephrine equivalents, fluid balance) starting from baseline (time of randomization), followed by hourly for the first 6 hours, then at 12, 24, 48, 72, 96, and 120 hours. Once-daily data collection also includes SOFA score, mechanical ventilation parameters, laboratory data, such as complete blood count, liver and renal function tests, biochemistry, lactate, cardiac biomarkers, coagulation profile (e.g., INR/PTT), and inflammatory markers (e.g., CRP). We will collect data on co-interventions (e.g., corticosteroids, diuretics) during the 3-day intervention period and hemodynamic assessment tools utilized. In the intervention arm, we will document VEXUS scan details, including timing, frequency, and quality ratings of each score. We will also collect data on other point-of-care ultrasound findings for both arms. Finally, we will also collect data on feasibility outcomes, process outcomes, adverse events, and clinical outcomes.

6.6 Outcomes:

6.6.1 Primary Feasibility Outcomes: Our primary outcomes focus on determining the feasibility of implementing this pilot RCT nationwide. Key feasibility outcomes include recruitment rate, consent rate, and protocol adherence.

Recruitment rate: Number of participants enrolled during the recruitment period who successfully complete study procedures and follow-up. Target: 1 patient/hospital/month.

Consent rate: The total number of eligible participants consented divided by the total number of eligible participants approached for consent. Target: ≥80%**.**

VEXUS scan completion rate: For VEXUS protocol adherence, we will calculate the number of participants who successfully underwent VEXUS scan and, if applicable, cardiac evaluation, divided by the total number of participants randomized to the Intervention arm. A successful VEXUS and Cardiac evaluation entails acquiring adequate quality images for interpretation and providing conclusive assessments venous congestion and cardiac function. Study Investigators (J.B., R.P.) will grade image acquisition and interpretation quality. The target for VEXUS scan completion rate: ≥80%.

Protocol adherence: *Intervention arm:* For fluid balance adherence, we will calculate the proportion of participants who achieved the protocol-specified fluid balance targets on days 1 to 3, divided by the total number of participants in the intervention arm. This metric will account for participants who withdraw or deviate from the protocol. To assess adherence to inotrope initiation based on POCUS findings, we will determine the percentage of participants who received inotropes when indicated by POCUS results, as per protocol guidelines, divided by the total number of participants with POCUS findings warranting inotrope initiation. *Control arm:* The number of participants in the control arm who do NOT receive a VEXUS scan during the 28-day study period (or until ICU discharge or death) divided by the total number randomized to this arm. Target: ≥80%.

6.6.2 Process outcomes: We will quantify daily differences in cumulative fluid balance, diuretic use, vasoactive agents/dosages, inotrope administration, renal function, lactate, and changes in severity of illness score on days 1 to 5.

6.6.3 Adverse events: We will focus adverse event data collection on potential risks associated with the interventions. While the risk is extremely low, we will document electrolyte and metabolic abnormalities attributed to diuresis (e.g., hypokalemia < 3.0 mmol/L; hyponatremia <130 mmol/L, or hypernatremia > 155 mmol/L, metabolic alkalosis pH>7.55 or bicarbonate >40 mmol/L, and hypomagnesemia < 0.6 mmol/L) hypotension episodes (defined as MAP < 60 mmHg for 5 minutes or more), hypotension episodes requiring intervention (greater than 20% increase in vasopressor requirements from baseline or need for fluid bolus), acute kidney injury, and tachyarrhythmias.

All study interventions fall within the spectrum of the standard of care. We expect the serious adverse event risks to be low because: 1. Electrolytes are monitored every 4 to 6 hours as part of routine care in the ICU, 2. Clinicians routinely prescribe diuretics for de-resuscitation in critically ill patients, and when administered as continuous infusions, these medications typically induce gradual fluid removal, minimizing the risk of abrupt hemodynamic changes, 3. Inotrope administration, due to the cardiac evaluation, would occur as part of the standard of care (regardless of study participation), 4. Patients are on cardiac monitors and undergo invasive hemodynamic monitoring (via arterial line) as part of the standard of care.

6.6.4 Secondary Outcomes: We will collect data on 28-day and 90-day mortality, days alive and free of vasoactive medications, mechanical ventilation, and RRT at 28 days, and ICU and Hospital length of stay.

6.7 Loss to follow-up: If this pilot RCT demonstrates feasibility, we anticipate the primary outcome for our future larger RCT will be 28-day mortality. We expect less than 3% loss to follow-up for this outcome. This estimate is supported by local studies in patients with septic shock and RCTs in patients septic shock that reported >99% follow-up for 28-day mortality (31, 32).

6.8 Statistical Analysis: A PhD biostatistician developed the statistical analysis plan and will conduct data analyses according to the intention-to-treat principle. *Primary outcome:* We will report recruitment rate as participants/month and protocol adherence, consent, and POCUS screening rate as proportions (count [%]) with 95% CI. *Secondary Outcomes (Process Outcomes, Serious Adverse Events, and Clinical Outcomes):* If we meet our feasibility targets without requiring a protocol change, we will transition the pilot into the larger RCT without analyzing secondary outcomes (process, adverse events, and clinical) by study arms (i.e. vanguard trial). Instead, we will only report secondary outcomes in aggregate. If we require a protocol change for the future RCT, we will analyze secondary outcomes by study arm as follows: we will present the data as mean and standard deviation for normally distributed continuous variables, and as median and interquartile range for skewed distributions. We will present categorical data as absolute and relative frequencies (n and %). We will compare baseline characteristics between the two groups using Fisher's exact test or Chi-Square ($\chi 2$) for categorical covariates, and Mann-Whitney U test or Kruskal-Wallis for continuous covariates. We will perform bivariate logistic regression models to determine which variables are associated with 28-day mortality. We will report odds ratios as point estimates with 95% CI. We will conduct all statistical analyses using R-4.4.1 (The R Foundation for Statistical Computing, Austria, Vienna, 2023). We will define statistical significance as a two-tailed $p < 0.05$ for all tests.

6.9 Subgroup analysis: Although our pilot RCT will not be powered for subgroup analyses, subgroups of interest for the larger RCT include sex, prior history of cardiac dysfunction, and whether patients are deemed to be fluid-responsive at the time of randomization.

6.10 Sample Size Estimation: We would deem this study feasible if protocol adherence rate is ≥80%. Assuming that VEXUS scan and protocol adherence rate is 90%, permitting a margin of error of 10%, and a drop-out/missing data rate of no more than 10%, enrolling 40 patients/arm will afford us 95% confidence that the true proportion of patients will meet our feasibility targets with a lower bound of 80%, achieving the desired level of precision around our feasibility outcomes (33).

$$\propto = \frac{1-CI_{95\%}}{2} = 0.025, \text{ and } Z_{\propto} = 1.960$$

$$0.10 = Z_{\propto} \sqrt{\frac{p\,(1-p)}{N}}$$

$$0.10 = 1.962 \sqrt{\frac{0.0\,(1-0.10)}{N}}$$

$$0.10 = 1.962 \sqrt{\frac{0.09}{N}}$$

$$0.051^2 = \frac{0.09}{N}$$

$$0.0026 = \frac{0.09}{N}$$

$$N = 35$$

Assuming an upper limit of 10% for patient drop-out/missing data:

$$N = \frac{35}{1-0.1}$$

$$N \sim 40$$

Therefore, we anticipate requiring 40 participants per arm.

Data Sharing:

We will share data between this study and the ESTABLISH (Early Severe Illness Translational Biology Informatics in Humans) registry. This arrangement ensures that study procedures and data collection activities common to both studies will not be duplicated.
Similarly, participants enrolled in another Critical Care point-of-care ultrasound study, or those who have undergone similar study procedures in other studies, will have their data and outcome measures (e.g., baseline characteristics, ultrasound measures, ICU length of stay) shared between the studies.

6.11 Proposed mechanisms for protecting against sources of bias: *Bias arising from the randomization process:* An independent statistician will generate a random allocation sequence, concealed by a central randomization system. *Bias due to deviations from intended interventions:* Although blinding patients and healthcare providers is not feasible due to the nature of the intervention, we will implement clear protocols and specify acceptable co-interventions to prevent the imbalance of non-protocol interventions between groups. We will carefully document all co-interventions, including diuretic and inotrope administration, adjunctive therapies, and POCUS scans performed. Research personnel will conduct routine protocol adherence checks. *Bias due to missing outcome data:* A quality assurance specialist (C.H) will routinely review case report forms to minimize missing data. Furthermore, we will conduct all analyses based on the intention-to-treat principle. If necessary, we will conduct best-case, worst-case sensitivity analyses. *Bias in measurement of the outcome:* We defined our outcomes to maintain objectivity. Two assessors will independently adjudicate primary feasibility outcomes. *Bias in selection of the reported results:* We will pre-register our RCT before commencement. We will report all pre-specified outcomes regardless of the results, report all analysis plan deviations, and adhere to the CONSORT reporting guidelines (34).

7.0 Knowledge Translation Plan: Our integrated Knowledge Translation (KT) strategy aims to generate awareness for our pilot RCT and galvanize hospital sites to participate in our future larger multicenter RCT. We will target five audiences: 1. Patients, 2. Researchers, 3. Critical care doctors, 4. Nephrologists, and 5. Point-of-care ultrasound (POCUS) users. We will employ the following KT strategies: **1. Early stakeholder integration:** We invited members from our five target audiences to provide input on study design to increase acceptability**. 2. Social media** (e.g., X [formerly Twitter], Instagram). We will relay our messages through the accounts of our co-investigators, patient partners, Knowledge User partners (@ArgaizR:16.7k followers; @katiewiskar:6.5k followers; @Andromedashock: 6.1k followers; @RPrager:11.7k followers; @LHSCCanada:9.2k followers) and KT specialists affiliated with the Canadian Critical Care Trials Group (@CCCTG:1.6k followers). **3. Conference presentations** (e.g., Canadian Critical Care Forums). We will also share our results with POCUS educators at national ultrasound courses. **4. Publications:** We will submit our work to high-impact open-access journals to reach a broad international readership.

8.0 Trial Coordination and Governance: London Health Sciences Center Research Inc. (coordinating center) will oversee project management, trial set-up, site initiation, and REDCap database design. Our coordinating center has the expertise required to successfully complete this pilot study. Since this is a pilot RCT and given the low risks to participants, we will not establish a formal Data Safety and Monitoring Committee. However, a Trial Steering Committee – comprised of the principal investigators, co-investigators, an independent clinician, and statistician, and patient representatives – will oversee trial conduct, recruitment, protocol adherence, and safety concerns. The committee will review serious adverse events, should they arise, and report to the Western University Research Ethics Board. In addition, Study investigators will review patients randomized to the intervention arm and approach the clinical teams for concerns. If concerns arise, the Trial Steering Committee will undertake a comprehensive review of the study procedures.

10. Ethical Considerations

10.1 Risks to Participants: The primary risks associated with VEXUS-guided fluid management are related to the administration of associated interventions. With respect to VEXUS and critical care echocardiography, there are no risks associated with ultrasound as it is radiation-free and non-invasive.

In patients with clinically apparent venous congestion, our protocol will result in fluid restriction, diuresis, and, depending on the cardiac evaluation, initiation of inotropic support. The potential risks associated with fluid restriction and diuresis include hypotension, acute kidney injury, metabolic and electrolyte abnormalities (e.g., hypokalemia, hypo- or hypernatremia, metabolic alkalosis, and hypomagnesemia). The potential risks associated with inotropic agents include tachyarrhythmias. We utilized data from trials that reflect our patient population and those with similar study procedures. The PI (J.B) calculated absolute risk differences as these are more directly relevant to patients.

First, administration of inotropes in this study context falls directly in line with the Surviving Sepsis Campaign guidelines, as we would be administering them to patients with septic shock, cardiac dysfunction, and in those with reduced cardiac output. Moreover, the choice of inotropic agent would be left to the clinical team.

Indirect data exists on the risks associated with fluid restriction based on two clinical trials comparing restrictive versus liberal fluid administration in patients with septic shock In both trials, the risks of adverse events was no different between intervention and control arms. In the CLOVER Trial, the risk of any serious adverse event in the fluid restriction group was 2.7% (21/782 patients), while in the liberal fluid group, 2.4% (19/781 patients). The absolute risk difference was 0.25% (95% CI -1.3 to 1.82%). In the CLASSIC Trial, the serious adverse event rate was 29.4% (221/751 patients) in the intervention group and 30.8% (238/772 patients) in the control group. The risk difference was -1.4% (95% CI -6 to 3.2)

Indirect data also exists on the risks associated with active de-resuscitation/diuresis. Although no studies exist in patients with septic shock, the RADAR-2 trial compared active de-resuscitation with standard care in a broad cohort of critically ill patients. In the intervention group, the risk of serious adverse events was 6.7% (6/89 patients) and 5.6% (5/90 patients) in the control group. The absolute risk difference was 1.2% (95% CI -5.9 to 8.2). With respect to acute kidney injury, the risk in the intervention arm was 4.5% (4/89 patients) and 5.6% (5/90 patients) in the control arm. The absolute risk difference was -1.1% (95% CI -7.5 to 5.3). Notable non-serious adverse events included hypernatremia, occurring in 14.4% of patients (13/89 patients) in the intervention arm and 8.9% of patients in the control arm. The risk difference is not statistically significant (risk difference 6%, 95% CI -0.04 to 15). Other non-serious adverse events included metabolic alkalosis, occurring in 10% in intervention arm patients (10/90 patients), and in 0% of patients in control arm (0/90 patients). The risk difference was 10% (95% CI 4 to 16).

While RADAR-2 demonstrated an acceptably low risk profile, our proposed trial incorporates several key modifications that further mitigate potential risks. Therefore, we expect the risks in our study to be substantially lower. First, every patient in RADAR-2 underwent de-resuscitation with a target negative fluid balance of 1 to 3L/day. Unlike RADAR-2, Our trial will only require de-resuscitation for patients who exhibit moderate to severe congestion (estimated to be 30%), targeting -1 to -2L daly fluid balance. Second, the RADAR-2 trial immediately mandated the administration of furosemide, indapamide, and spironolactone simultaneously, which likely increased the risk of metabolic abnormalities seen. Third, RADAR-2 mandated interventions for 5 days, while our trial requires interventions for 3 days. These important modifications further reduce the risks associated with our trial.

We have also implemented several safeguards to protect participants. First, we developed clear, cautious protocols for fluid restriction and diuresis to prevent adverse effects. Second, study personnel will closely monitor patients and remain accessible to guide clinical teams should adverse events occur. Third, patients in our trial undergo routine monitoring for potential adverse events as part of the standard of care (see 6.5.2.6 section on monitoring and stopping criteria for diuretics). Unlike previous trials, our RCT tailors diuresis and fluid restriction based on patient physiology, specifically using VEXUS-guided assessment, rather than applying interventions indiscriminately. Fifth, the interventions we propose in this RCT are already administered to patients and within the spectrum of standard of care. Therefore, study procedures are familiar to the clinical team.

10.1 Benefits to participants: we do not expect immediate benefits to participants.

10.2 Compensation to participants: We will not compensate participants who enroll in this study.

10.3 Co-enrollment: we will place no restriction on co-enrollment with other studies

10.4 Privacy and Confidentiality: Database and patient confidentiality will be respected as per the Personal Information Protection and Electronic Documents Act of Canada. All study investigators have completed their local centers' privacy and confidentiality educational programs and are up to date with the Tri-Council Policy Statement regarding the Ethical Conduct for Research Involving Humans. The master list that links all study participants to their unique REDCap study ID will be password protected and stored in the coordinating centre's secure cloud server (Microsoft Teams), behind the hospital's firewall. POCUS data will be stored on QPath, a HIPAA compliant workflow manager for storing and reporting ultrasound scans.

10.5 Conflicts of Interest: Co-Investigators have no conflicts of interest to declare.

References

1. Espinosa-Almanza CJ, Sanabria-Rodríguez O, Riaño-Forero I, Toro-Trujillo E. Fluid overload in patients with septic shock and lactate clearance as a therapeutic goal: a retrospective cohort study. Rev Bras Ter Intensiva. 2020;32(1):99-107.
2. Vincent JL. Clinical sepsis and septic shock--definition, diagnosis and management principles. Langenbecks Arch Surg. 2008;393(6):817-24.
3. Farrah K, McIntyre L, Doig CJ, Talarico R, Taljaard M, Krahn M, et al. Sepsis-Associated Mortality, Resource Use, and Healthcare Costs: A Propensity-Matched Cohort Study. Crit Care Med. 2021;49(2):215-27.
4. Hernández G, Ospina-Tascón GA, Damiani LP, Estenssoro E, Dubin A, Hurtado J, et al. Effect of a Resuscitation Strategy Targeting Peripheral Perfusion Status vs Serum Lactate Levels on 28-Day Mortality Among Patients With Septic Shock: The ANDROMEDA-SHOCK Randomized Clinical Trial. JAMA. 2019;321(7):654-64.
5. Peters E, Antonelli M, Wittebole X, Nanchal R, François B, Sakr Y, et al. A worldwide multicentre evaluation of the influence of deterioration or improvement of acute kidney injury on clinical outcome in critically ill patients with and without sepsis at ICU admission: results from The Intensive Care Over Nations audit. Crit Care. 2018;22(1):188.
6. Espinosa-Almanza CJ, Sanabria-Rodríguez O, Riaño-Forero I, Toro-Trujillo E. Fluid overload in patients with septic shock and lactate clearance as a therapeutic goal: a retrospective cohort study. Rev Bras Ter Intensiva. 2020;32(1):99-107.
7. Marik P, Bellomo R. A rational approach to fluid therapy in sepsis. Br J Anaesth. 2016;116(3):339-49.
8. Ganda A, Onat D, Demmer RT, Wan E, Vittorio TJ, Sabbah HN, et al. Venous congestion and endothelial cell activation in acute decompensated heart failure. Curr Heart Fail Rep. 2010;7(2):66-74.
9. Beaubien-Souligny W, Rola P, Haycock K, Bouchard J, Lamarche Y, Spiegel R, et al. Quantifying systemic congestion with Point-Of-Care ultrasound: development of the venous excess ultrasound grading system. Ultrasound J. 2020;12(1):16.
10. Tamayo-Gutierrez A, Ibrahim HN. The Kidney in Heart Failure: The Role of Venous Congestion. Methodist Debakey Cardiovasc J. 2022;18(4):4-10.
11. Claure-Del Granado R, Mehta RL. Fluid overload in the ICU: evaluation and management. BMC Nephrol. 2016;17(1):109.
12. Messmer AS, Zingg C, Muller M, Gerber JL, Schefold JC, Pfortmueller CA. Fluid Overload and Mortality in Adult Critical Care Patients-A Systematic Review and Meta-Analysis of Observational Studies. Crit Care Med. 2020;48(12):1862-70.

13. Evans L, Rhodes A, Alhazzani W, Antonelli M, Coopersmith CM, French C, et al. Surviving Sepsis Campaign: International Guidelines for Management of Sepsis and Septic Shock 2021. Crit Care Med. 2021;49(11):e1063-e143.
14. Rola P, Miralles-Aguiar F, Argaiz E, Beaubien-Souligny W, Haycock K, Karimov T, et al. Clinical applications of the venous excess ultrasound (VExUS) score: conceptual review and case series. Ultrasound J. 2021;13(1):32.
15. Kattan E, Castro R, Miralles-Aguiar F, Hernandez G, Rola P. The emerging concept of fluid tolerance: A position paper. J Crit Care. 2022;71:154070.
16. Kenny JS. Assessing Fluid Intolerance with Doppler Ultrasonography: A Physiological Framework. Med Sci (Basel). 2022;10(1).
17. Ehrman RR, Gallien JZ, Smith RK, Akers KG, Malik AN, Harrison NE, et al. Resuscitation Guided by Volume Responsiveness Does Not Reduce Mortality in Sepsis: A Meta-Analysis. Crit Care Explor. 2019;1(5):e0015.
18. Marik PE, Baram M, Vahid B. Does central venous pressure predict fluid responsiveness? A systematic review of the literature and the tale of seven mares. Chest. 2008;134(1):172-8.
19. Beaubien-Souligny W, Benkreira A, Robillard P, Bouabdallaoui N, Chasse M, Desjardins G, et al. Alterations in Portal Vein Flow and Intrarenal Venous Flow Are Associated With Acute Kidney Injury After Cardiac Surgery: A Prospective Observational Cohort Study. J Am Heart Assoc. 2018;7(19):e009961.
20. Spiegel R, Teeter W, Sullivan S, Tupchong K, Mohammed N, Sutherland M, et al. The use of venous Doppler to predict adverse kidney events in a general ICU cohort. Critical Care. 2020;24(1):615.
21. Eke C, Szabó A, Nagy Á, Párkányi B, Kertai MD, Fazekas L, et al. Association between Preoperative Retrograde Hepatic Vein Flow and Acute Kidney Injury after Cardiac Surgery. Diagnostics. 2022;12(3):699.
22. Wiersema R, Kaufmann T, van der Veen HN, de Haas RJ, Franssen CFM, Koeze J, et al. Diagnostic accuracy of arterial and venous renal Doppler assessment for acute kidney injury in critically ill patients: A prospective study. Journal of Critical Care. 2020;59:57-62.
23. Hermansen JL, Pettey G, Sørensen HT, Nel S, Tsabedze N, Hørlyck A, et al. Perioperative Doppler measurements of renal perfusion are associated with acute kidney injury in patients undergoing cardiac surgery. Scientific Reports. 2021;11(1):19738.
24. Pettey G, Hermansen JL, Nel S, Moutlana HJ, Muteba M, Juhl-Olsen P, et al. Ultrasound Hepatic Vein Ratios Are Associated With the Development of Acute Kidney Injury After Cardiac Surgery. Journal of Cardiothoracic and Vascular Anesthesia. 2022;36(5):1326-35.
25. Bhardwaj V, Vikneswaran G, Rola P, Raju S, Bhat RS, Jayakumar A, et al. Combination of Inferior Vena Cava Diameter, Hepatic Venous Flow, and Portal Vein Pulsatility Index: Venous Excess Ultrasound Score (VEXUS Score) in Predicting Acute Kidney Injury in Patients with Cardiorenal Syndrome: A Prospective Cohort Study. Indian J Crit Care Med. 2020;24(9):783-9.
26. Prager R, Arntfield R, Wong MYS, Ball I, Lewis K, Rochwerg B, et al. Doppler identified venous congestion in septic shock: a pilot prospective observational study. Canadian Journal of Anesthesia. 2024; 71(5):640-649.
27. Rajamani A, Galarza L, Sanfilippo F, Wong A, Goffi A, Tuinman P, et al. Criteria, Processes, and Determination of Competence in Basic Critical Care Echocardiography Training: A Delphi Process Consensus Statement by the Learning Ultrasound in Critical Care (LUCC) Initiative. CHEST. 2022;161(2):492-503.

28. Millington SJ, Goffi A, Arntfield RT. Critical care echocardiography: a certification pathway for advanced users. Canadian Journal of Anesthesia/Journal canadien d'anesthésie. 2018;65(4):345-9.
29. ICU ERToEi. International consensus statement on training standards for advanced critical care echocardiography. Intensive Care Med. 2014;40(5):654-66.
30. Prager R, Arntfield R, Wong MYS, Ball I, Lewis K, Rochwerg B, et al. Venous congestion in septic shock quantified with point-of-care ultrasound: a pilot prospective multicentre cohort study. Canadian Journal of Anesthesia/Journal canadien d'anesthésie. 2024;71(5):640-9.
31. Kakihana Y, Nishida O, Taniguchi T, Okajima M, Morimatsu H, Ogura H, et al. Efficacy and safety of landiolol, an ultra-short-acting β1-selective antagonist, for treatment of sepsis-related tachyarrhythmia (J-Land 3S): a multicentre, open-label, randomised controlled trial. The Lancet Respiratory Medicine. 2020;8(9):863-72.
32. Whitehouse T, Hossain A, Perkins GD, Gordon AC, Bion J, Young D, et al. Landiolol and organ failure in patients with septic shock: the STRESS-L randomized clinical trial. Jama. 2023;330(17):1641-52.
33. Thabane L, Ma J, Chu R, Cheng J, Ismaila A, Rios LP, et al. A tutorial on pilot studies: the what, why and how. BMC Medical Research Methodology. 2010;10(1):1.
34. Schulz KF, Altman DG, Moher D. CONSORT 2010 statement: updated guidelines for reporting parallel group randomized trials. Ann Intern Med. 2010;152(11):726-32.