Crystalloids Liberal or Vasopressors Early Resuscitation During Sepsis

ACRONYM: CLOVERS

PROTOCOL CO-CHAIRS:

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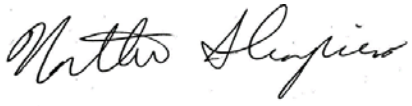

07/12/19

INVESTIGATOR SIGNATURE ***DATE***

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07/22/19

INVESTIGATOR SIGNATURE ***DATE***

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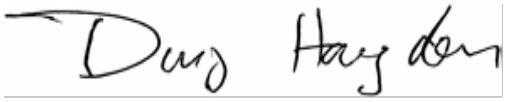

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Contents

1. Trial Summary

1.1 Title

Crystalloids **L**iberal **O**r **V**asopressors **E**arly **R**esuscitation in **S**epsis **(CLOVERS)**

1.2 Objective

Primary Objective: To determine the impact of a restrictive fluids strategy (vasopressors first followed by rescue fluids) as compared to a liberal fluid strategy (fluids first followed by rescue vasopressors) on 90-day in-hospital mortality in patients with sepsis-induced hypotension.

1.3 Hypothesis

Primary Hypothesis: Restrictive (vs liberal) fluid treatment strategy during the first 24 hours of resuscitation for sepsis-induced hypotension will reduce 90-day in-hospital mortality.

1.4 Study Design

Study Design: Multicenter, prospective, phase 3 randomized non-blinded interventional trial of fluid treatment strategies in the first 24 hours for patients with sepsis-induced hypotension.

1. We will emphasize early screening and protocol initiation, and enroll a maximum of 2320 patients with suspected sepsis-induced hypotension.
   - ✓ All patients will receive at least 1 liter of fluids prior to meeting study inclusion criteria (and no more than 3 liters prior to randomization).
   - ✓ Patients will be enrolled within 4 hours of meeting study inclusion criteria
   - ✓ Any type of isotonic crystalloid (normal saline, ringers lactate, or a balanced solution such as plasmalyte) is permitted.

2. Restrictive Fluids (Early Vasopressors) Group
   - ✓ Norepinephrine will be used as preferred vasopressor and titrated to achieve mean arterial pressure (MAP) between 65 mmHg and 75 mmHg
   - ✓ “Rescue fluids” may be administered as 500ml boluses if predefined rescue criteria are met

3. Liberal Fluids (Fluids First) Group (See Protocol Schema Appendix A)
   - ✓ Additional 2 liter intravenous fluid bolus upon enrollment
   - ✓ Administer 500ml fluid boluses for fluid triggers until 5 liters administered or development of clinical signs of acute volume overload develop
   - ✓ “Rescue vasopressors” may be administered after 5 liters of fluid, for development of acute volume overload, or if other predefined rescue criteria are met

4. Other care
   - ✓ Other elements of care (e.g. antibiotics, ventilation strategies, etc.) will be recommended to reflect current "best-practice" where feasible and appropriate

1.5 Inclusion Criteria

1. Age ≥ 18 years
2. A suspected or confirmed infection (broadly defined as administration or planned administration of antibiotics)
3. Sepsis-induced hypotension defined as systolic blood pressure < 100 mmHg or MAP < 65 mmHg after a minimum of at least 1 liter of fluid (*Fluids inclusive of pre-hospital fluids; blood pressure must be below any known or reported pre-morbid baseline).

1.6 Exclusion Criteria

1. More than 4 hours elapsed since meeting inclusion criteria or 24 hours elapsed since admission to the hospital
2. Patient already received 3 liters of intravenous fluid (includes prehospital volumes)
3. Unable to obtain informed consent
4. Known pregnancy
5. Hypotension suspected to be due to non-sepsis cause (e.g. hemorrhagic shock)
6. Blood pressure is at known or reported baseline level
7. Severe Volume Depletion from an acute condition other than sepsis.
   In the judgment of the treating physician, the patient has an acute condition other than sepsis causing (or indicative) of *severe volume depletion;
   Examples include: Diabetic ketoacidosis, high volume vomiting or diarrhea, hypersomolar hyperglycemic state, and nonexertional hyperthermia (heat stroke); severe is defined by the need for substantial intravenous fluid administration as part of routine clinical care
8. Pulmonary edema or clinical signs of new fluid overload (e.g. bilateral crackles, new oxygen requirement, new peripheral edema, fluid overload on chest x-ray)
9. Treating physician unwilling to give additional fluids as directed by the liberal protocol
10. Treating physician unwilling to use vasopressors as directed by the restrictive protocol.
11. Current or imminent decision to withhold most/all life-sustaining treatment; this **does not** exclude those patients committed to full support except cardiopulmonary resuscitation
12. Immediate surgical intervention planned such that study procedures could not be followed
13. Prior enrollment in this study

1.7 Randomization and Initiation Time Window

All patients must be enrolled and randomized within 4 hours of meeting inclusion criteria. Patients may become eligible in the ED, hospital ward, or ICU.

1.8 Primary Endpoint

The primary outcome is all-cause mortality prior to discharge home before day 90.

1.9 Secondary Endpoints

1. 28-day organ support free days (alive and without mechanical ventilation, new renal replacement or vasopressors; vasopressors prior to 48 hours excluded)
2. 28-day ventilator free days
3. 28-day renal replacement free days (new renal replacement therapy)
4. 28-day vasopressor free days (vasopressors prior to 48 hours excluded)
5. 28-day ICU free days
6. 28-day hospital free days to discharge home
7. Initiation of mechanical ventilation to day 28
8. Initiation of renal replacement therapy to day 28
9. Change in creatinine-based KDIGO stage between baseline and 72 hours
10. Change in SOFA score between baseline and 72 hours
11. 90-day all-cause mortality
12. Development of ARDS within 7 days
13. New onset atrial or ventricular arrhythmia to day 28
14. Additional secondary safety endpoints:
    a. New intubation through day seven
    b. New mechanical ventilation through day seven
    c. Ventricular arrhythmias in first 24 hours
    d. New renal replacement therapy through day seven
    e. New ARDS through day seven
    f. ICU admission through day seven
    g. Central venous line insertion through day three
    h. Vasopressor infusion through peripheral venous catheter
    i. Line complications of central venous catheter placement
    j. Line complications
    k. More than three line complications among patients with a line complication
    l. Site extravasation to day 28 from peripheral venous catheter infusion
    m. New ventilation and oxygen us in first 24 hours
    n. Adverse events

1.10 Process of Care Metrics

Process of Care Metrics: We will assess whether the proposed intervention has effectively altered care as intended by measuring:

1. Total intravenous fluids administered over initial 6 hours
2. Total intravenous fluids administered over initial 24 hours
3. Proportion receiving vasopressors and timing of vasopressor initiation within 24-hour study period

4. Total fluids administered prior to initiation of vasopressors

1.11 Sample Size/Interim Monitoring

1. Randomization 1:1; two-sided alpha 0.05.
   A total of 2320 patients are needed to detect a 4.5% absolute mortality difference between treatment groups with 90% power assuming 15% mortality in the liberal fluids group. The principal analysis will be intent-to-treat, based upon randomization assignment.
2. There will be a protocol feasibility assessment phase at the approximately100-patient mark, and then after approximately100 enrolled patients are available after any protocol changes for 2 more evaluation assessments. Aggregate data blinded to outcomes will be used to assess patient accrual, treatment protocol compliance, and separation of intravenous fluid and/or vasopressor administration. Protocol adjustments may be made at each of these patient marks to optimize the protocol. The study may be halted during the feasibility assessment phase for failure to meet pre-specified stopping guidelines
3. Trial progress will be evaluated by an independent Data and Safety Monitoring Board (DSMB) to determine whether the study should stop for superiority of either the liberal or restrictive fluid strategies; or, for projected trial futility. (See Appendix B) There will be two interim analyses and a final analysis conducted when approximately each successive 1/3 of the patients have been enrolled.

2. Endpoints

2.1 Primary Outcome

The primary outcome is all-cause mortality prior to discharge home before day 90. “Home” is defined as a patient’s place of residence prior to enrollment. Thus, if a patient is discharged to a location that is different from the place of residence prior to enrollment (e.g. rehabilitation facility or hospice) then the patient will be followed until they return to their original location, 90 days, or death, whichever comes first.

2.2 Secondary Outcomes

1. **28-Day Organ Support Free Days**
   Organ support free days is defined as a patient being alive and without assisted breathing, new renal replacement therapy, or vasopressors (beyond 48 hours). Patients will be followed for use of organ support to death, hospital discharge or study day 27, whichever comes first. Any day that a patient is alive and without organ support will represent days alive and free of organ support. Since there will be a bias in the protocols to place patients on vasopressors in the restrictive group, vasopressor use prior to 48 hours will be excluded from this calculation for both groups.

2. **28-day Ventilator Free Days (VFDs)**

   VFDs depend on both duration of ventilation and mortality through study day 28. In participants who survive 28 days, VFD is defined as 28 minus duration of ventilation. Duration of ventilation is counted from the first study day of assisted breathing through the last day of assisted breathing provided the last day is prior to day 28. Otherwise, it is counted from the first study day of assisted breathing through day 28. For participants discharged with assisted ventilation (e.g., to LTAC facility) prior to day 28, a phone call will be required to assess ventilator and vital status at day 28. Participants discharged prior to day 28 on unassisted breathing will be assumed to remain on unassisted breathing through day 28. Isolated periods of ventilation briefer than 24 hours for surgical procedures and ventilation solely for sleep disordered breathing do not count towards duration of ventilation. In participants who never require assisted breathing, duration of ventilation is zero. Participants who do not survive 28 days will be assigned zero VFD. VFD is undefined in participants with chronic/home mechanical ventilation (except solely for sleep disordered breathing) and they will be excluded from this analysis.

3. **28-day Renal Replacement Therapy Free Days**

   Renal replacement free days to day 28 are defined as the number of calendar days between randomization and 28 days later that the patient is alive and without renal replacement therapy. We also follow the “last off” method. Patients who died prior to day 28 and those who receive renal replacement therapy for the entire first 28 days are assigned zero renal replacement free days.

4. **28-day Vasopressor Free Days**

   Vasopressor free days to day 28 are defined as the number of calendar days between day 2 (eligibility starting 48 hours post randomization) and 26 days later that the patient is alive and without the use of vasopressor therapy. We also followed the “last off” method. Patients who died prior to day 28 and those who receive vasopressor therapy for the entire first 28 days are assigned zero vasopressor free days.

5. **28-day ICU free days**

   ICU free days to day 28 are defined as the number of days spent alive out of the ICU to day 28.

6. **28-day hospital free days**
   Hospital free days to day 28 are defined as 28 days minus the number of days from randomization to discharge home. If a patient has not been discharged home prior to study day 28 or dies prior to day 28, hospital free days will be zero. Patients transferred to another hospital or other health care facility will be followed to day 28 to assess this endpoint.

7. Initiation of mechanical ventilation to day 28

Patients who receive invasive mechanical ventilation via endotracheal or tracheostomy tube, except those intubated solely for a procedure and extubated within 24 hours, through to study day 28 meet this endpoint. Non-invasive mechanical ventilation will not be included as an outcome. This is a binary outcome.

8. Initiation of renal replacement to day 28

Patients who receive (new) renal replacement therapy through day 28 will meet this endpoint. Patients with chronic renal replacement therapy initiated prior to the current sepsis illness will not be eligible to meet this endpoint.

9. Change in creatinine-based KDIGO stage between baseline and 72 hours

Renal function will be assessed using the KDIGO staging system (serum creatinine criteria only; not urine output) between baseline and 72 hours to assess for de novo acute kidney injury (AKI) (e.g., meeting criteria for AKI by KDIGO criteria) or worsening AKI (e.g., increasing severity). Due to the potential influence of treatment assignment on urine output, as well as the potential for inaccurate urine output data in patients without indwelling urinary catheters, we will use only the KDIGO creatinine criteria. Patients on chronic renal replacement therapy will not be eligible for this endpoint determination.

10. Change in SOFA score between baseline and 72 hours

We will calculate the SOFA score upon enrollment and at 72 hours using clinically available data. If a value is not available at baseline, it will be assumed to be normal. At the 72 hours assessment, if a value is missing then we will carry forward the closet previously known value. If a patient is intubated or heavily sedated at either 0 or 72 hours, the GCS will be omitted when calculating the change in score. If a patient was on renal replacement therapy prior to presentation, then the renal dysfunction component to the SOFA score will be omitted as well.

11. 90-day all-cause mortality

We will contact patients at day 90 to ascertain their survival status. This will be done by telephone contact with the patient or family members as well as a review of medical records and publicly available data sources. We will use the national death index as a final check for patient with whom we are unable to confirm their vital status through other means.

12. Development of ARDS within 7 days

We will determine the presence and severity of ARDS for each day of mechanical ventilation to day 7 using the following approach: for each ventilator day, if an ABG is available between 2:00 AM and 8:00 AM, measure P/F (PaO2, FiO2 and PEEP) for all ABGs during this time window daily to day 7. Or, for ventilator days that no ABG available between 2:00 AM and 8:00 AM, determine lowest imputed P/F from measured S/F (SpO2, FiO2, and PEEP).

For participants with P/F <300 or imputed P/F <300, FiO2 ≥40%, and PEEP ≥5 cm H2O, determine if hypoxemia is valid, acute, and not fully explained by CHF or fluid overload. If yes, local investigators will review the first CXR (or CT) performed on each ventilated day with valid P/F or imputed P/F <300 (to day 7). If no chest imaging studies are present that day, site investigators may review available imaging one day before or after to determine if ARDS imaging criteria met. ARDS imaging criteria are met if the images are consistent with ARDS (bilateral opacities not fully explained by effusions, lobar/lung collapse, or nodules). If equivocal, the reviewing investigator will adjudicate with additional investigators.

13. **Supraventricular/ventricular tachycardia (SVT/VT) or new onset atrial fibrillation/flutter (AF) to day 28**

The occurrence of one or more episodes (sustained for more than 1 minute for SVT and AF, > 15 seconds for VT) during through day 28 will be recorded.

2.3 Process of Care Metrics

1. Total intravenous fluids administered over first 6 hours after randomization
2. The total amount of intravenous fluids or blood products of any type administered from pre-randomization to 6 hours after randomization.
3. Total intravenous fluids administered over 24 hours after randomization
4. The total amount of intravenous fluids or blood products of any type administered from pre-randomization to 24 hours after randomization.
5. Proportion receiving vasopressors and timing of vasopressor initiation within 24-hour study period
    a. Proportion of patients receiving vasopressors within 24 hours will be calculated. Additionally, among patients who received vasopressors, the duration of time elapsed from randomization until the time of initiation of vasopressor medications within 24-hour protocol period will be recorded.
6. Total fluids administered prior to initiation of vasopressors
    a. This process of care metric will assess the amount of fluids administered prior to the first receipt of vasopressors. (patients on vasopressors prior to randomization excluded from this metric)
7. Proportion of patients receiving two or more liters of fluid in the first six hours.
8. Administration of first and second liter of fluid infusion in liberal arm
    a. This process of care metric will summarize frequency of use of second liter and reasons for use or declining use.

3. Subgroups for Secondary Analysis

1. Patients receiving chronic dialysis
2. Patients with history of chronic heart failure (as documented in past medical history)
3. Patients with qualifying SBP < 90 mmHG versus 90-100 mmHG at randomization

4. Patients age > 65 years of age
5. Patients with a clinically confirmed infection as a cause of hypotension at study enrollment (as assessed by the investigator using records available throughout hospitalization)
6. Patients with pneumonia as the etiology of sepsis
7. Stratification by SOFA score quartiles on enrollment
8. Patients enrolled in the ED (vs. wards or ICU)
9. Use of cardiac ultrasound or other hemodynamic monitoring techniques (yes or no; defined in Section 5.3)
10. Patient with a history of hypertension (as documented in past medical history or by the prescription of chronic medications)
11. Patients enrolled prior to and following the protocol change regarding required or optional use of the second liter of fluid infusion in the liberal treatment arm.

As per NIH guidelines we will also do secondary analysis by sex, ethnicity, and race.

4. Baseline Characteristics

1. Demographics – Age, Gender, Ethnicity, Race
2. Primary source of infection
3. Co-Morbidities – Charlson, BMI, Pre-hospital level of care
4. Location at time of randomization
5. Illness severity – SOFA (Total and components), mechanical ventilation, ARDS, total pre-randomization fluid input, vasopressor use and infusion rate prior to and at randomization, vital signs, WBC, lactate

5. Statistical Methods

Primary Outcome

The primary outcome is intention-to-treat 90-day all cause in-hospital mortality, where in-hospital includes both study and discharge hospitals (i.e. transfer hospitals or LTAC). Subjects who are discharged home (defined as residence prior to admission) prior to day 90 will be assumed to be alive at day 90. Analysis of the primary outcome will be based on the Kaplan Meier day 90 mortality point estimates with all patients who are discharged home or still alive at day 90 censored at day 91, which is beyond the last possible day of death. The day 90 mortality estimates in the two treatment groups will be compared by a Z-test using Greenwood's standard error (Kalbfleisch, J. D. and Prentice, R. L. (1980), *The Statistical Analysis of Failure Time Data*, New York: John Wiley & Sons.).

If there is no loss to follow up then the primary outcome will compared between treatment groups on the risk difference scale using a generalized linear model with a binomial distribution function and identity link function.

The hypothesis regarding the primary outcome is a two-sided superiority hypothesis.

Secondary Outcomes

Continuous secondary outcomes will be compared between treatment groups using a t-test.

Categorical secondary outcomes will be compared between treatment groups using a Chi-square or Fisher's exact test as appropriate to the sparseness of the data.

The analysis is intention to treat and significance testing will be two-tailed at alpha = 0.05 with no adjustment made for multiple comparisons.

Process of Care Metrics

The analysis of the process of care metrics will be similar to that of the secondary outcomes.

The analysis is intention to treat and significance testing will be two-tailed at alpha = 0.05 with no adjustment made for multiple comparisons.

Adverse Events

Adverse events will be analyzed using weighted Poisson regression with non-serious events weighted by one and serious events weighted by two. Events rather than patients will be the unit of analysis. Adverse events will be grouped and analyzed separately by MeDRA system organ classes.

The analysis is intention to treat and significance testing will be two-tailed at alpha = 0.05 with no adjustment made for multiple comparisons.

On Study Variables

The analysis of pre-specified and systematically collected on study variables will be similar to that of the secondary outcomes. Variables that are measured daily will be compared between treatment groups on each study day with no adjustment made for multiple comparisons.

The analysis is intention to treat and significance testing will be two-tailed at alpha = 0.05.

Secondary Analysis by Subgroups

The secondary analysis of the primary and secondary outcomes by subgroups will use the same methods as the primary except that the statistical models will be augmented with subgroup and subgroup by treatment interaction terms.

The analysis is intention to treat and significance testing will be two-tailed at alpha = 0.05 with no adjustment made for multiple comparisons.

Missing Data

Analysis is based on all available data with no imputation of missing data; except in the case of selected derived variables, for example SOFA variables.

Null Hypothesis

The causal clinical effect of treatment on outcomes defined only in patients who are on study is complicated by potential case mix imbalance between treatment groups due to differential recovery and survivorship bias. However, the proposed statistical methods for these outcomes maintain the correct comparison-wise Type I error rate under the global null of no treatment effect whatsoever on any subject.