Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

Supplement to: Corl KA, Prodromou ML, Merchant RC, Gareen I, Marks SJ, Banerjeee D, Amass T, Abbasi AA, Delcompare C, Palmisciano A, , Aliotta J, Jay G, Levy M. The Restrictive Intravenous Fluid Trial in Severe Sepsis and Septic Shock (RIFTS): a Randomized Pilot Study

**Supplementary Appendix**

**The Restrictive Intravenous Fluid Trial in Severe Sepsis and Septic Shock (RIFTS): a Randomized Pilot Study**

**Table of Contents Page**

**List of Investigators**………..…………………………………………………………………………………….3

**Supplementary Methods**………………………………………….……………………………………………. 4

 Fluid Definitions…………...……………………….…………………..……..………………………......4

Inclusion and Exclusion Criteria…………...……………………….………...…………………………..5

Definition of Serious Adverse Events……………...…………….….…….…..…………………………..6

**Supplementary Table 1.** Resuscitative IV fluid administered in major sepsis trials …….....…….….……….....7

.

**Supplementary Table 2:** Initial and repeat lactate measurements……………………….………………………7

**Supplementary Table 3.** Clinical reasoning for patient cross over.......................................................................8

**Supplementary Table 4.** Mean IV fluid administered to study groups (ml): intention-to-treat analysis……......8

**Supplementary Table 5:** Median IV fluid administered to study groups (ml/kg): intention-to-treat analysis..…9

**Supplementary Table 6.** Mean IV fluid administered to study groups (ml/kg): per-protocol analysis….….…...9

**Supplementary Table 7.** Mean IV fluid administered to study groups (ml): per-protocol analysis…….....…..10

**Supplementary Table 8.** Study outcomes and adverse events: per-protocol analysis..………………...............10

**Supplementary Table 9:** Sensitivity analysis for all cause 30-day mortality…………....…….......………,,.....11

**Supplementary Table 10:** Norepinephrine dosing and incidence of an adjunct vasopressors, among participants requiring vasopressor support………………………………………………………………………12

**References**…………………………...…………………………………………………………………………..12

**List of Investigators**

Keith A. Corl, MD, ScM

Michael L. Prodromou, MD

Roland C. Merchant, MD, MPH, ScD

Ilana Gareen PhD

Sarah J. Marks MS

Jason Aliotta MD

Debasree Banerjee MD

Timothy Amass MD

Adeel A. Abbasi MD

Cesar Delcompare BS

Amy Palmisciano RN

Mitchell M. Levy, MD

The Department of Medicine, Division of Pulmonary Critical Care & Sleep; the Department of Emergency Medicine, Alpert Medical School of Brown University; The Providence Veterans Affairs Medical Center;

The Brown UniversitySchool of Public Health, all in Providence, RI; and the Department of Emergency Medicine Brigham and Women’s Hospital, Harvard Medical School, Boston, MA

**Supplemental Methods**

**RIFTS Fluid Definitions and Limitations**

Resuscitative IV fluid: 0.9% normal saline, Ringer’s lactate, or sodium bicarbonate in D5W bolus or continuous infusions extracted from the electronic medical record (EPIC, Verona, WI). Other balanced salt solutions such as PlasmLyte were not available at the study institutions and therefore not included in the trial. Fluids administered to maintain IV patency ( i.e. “keep vein open”) were not included.

Non-resuscitative IV fluid: all fluid administered with medications (antibiotics, vasopressors, paralytics, sedatives/hypnotics, analgesics, antiepileptic drugs, etc.) in volume of > 100 ml extracted from the electronic medical record.

Adjunct fluid: tube feeds, free water flushes and parenteral feeds where not recorded or included in the analysis.

Adjunct resuscitation products: Hetastarch usage was prohibited in either group.

**RIFTS Inclusion Criteria**

1. Patients with severe sepsis or septic shock, as defined by the Sepsis 2 International Consensus definitions:1

Temperature > 38°C or < 36°C, heart rate of > 90/min, respiratory rate of >20/min or PaCO2 <32 mmHg, white blood cell count > 12000/mm3 or < 4000/mm3 or >10% immature bands, with known or suspected infection at the time of enrollment. The worst value for each variable is used obtained between triage time zero and enrollment.

2. Since over 12% of patients ultimately diagnosed with sepsis do not meet SIRS criteria,2 SIRS negative patients may be enrolled if the treating attending physician clinically diagnoses severe sepsis or septic shock.

3. Severe sepsis or septic shock is defined as refractory hypotension or a lactic acid>4 mmol/L. Refractory hypotension is a systolic blood pressure (SBP)<90 mmHg or a mean arterial pressure (MAP)<65 mmHg for 15 minutes, following 1000 mL of IV fluid, or any blood pressure maintained by vasopressor administration.

**RIFTS Exclusion Criteria**

1. Patients who received >60 ml/kg of IV fluid resuscitation prior to randomization.

2. A primary ICU admitting diagnosis of: acute cerebral vascular event, acute coronary syndrome, acute pulmonary edema, status asthmaticus, active gastrointestinal bleeding, seizure, drug overdose, burn, trauma, requirement for immediate surgery, or undergoing extracorporeal membrane oxygenation.

3. An active fluid wasting process including: extensive diarrhea, diabetes insipidus, cerebral salt wasting, or an osmotic diuresis, or as indicated by the primary treating clinician.

4. A concurrent diagnosis of diabetic ketoacidosis, hyperosmolar non-ketotic hyperglycemia, or rhabdomyolysis, where large volume IV fluid resuscitation is standard care.

5. Required immediate surgery

6. Received extracorporeal membrane oxygenation (ECMO)

7. Time >24 hours since triage

8. Patients previously enrolled in the RIFTS trial

9. Age <18 years old

10. Pregnancy

11. Incarceration

12. Patients receiving comfort measures only/hospice care

**RIFTS Definition of Serious Adverse Events**

1. Myocardial Infarction (MI): An ST elevation or non-ST elevation MI diagnosed by the clinical team and evidenced by elevated biomarkers, electrocardiogram changes, and/or the clinical presentation.

2. Acute Kidney Injury: A doubling of the baseline admission creatinine.

3. Re-intubation: Any intubation following the first extubation during hospitalization. Not included were patient self extubations that required emergent re-intubation.

4. Disseminated intravascular coagulation: As diagnosed by the primary care team and evidenced by presence of schistocytes on the peripheral blood smear, elevated split fibrin products and a decreased fibrinogen.

5. Limb ischemia: As diagnosed by the primary care team and evidenced by antithrombotic treatment, open/percutaneous intervention, or amputation.

**Supplementary Table 1:** Resuscitative IV fluid administered in major sepsis trials

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Study**  | **Group** | **IV fluid ml/kg pre-randomization** | **IV fluid ml/kg****0 to 6 hours** | **IV fluid ml/kg****7 to 72 hours** | **Total IV fluid ml/kg** | **IV fluid****ml** | **60-day Mortality %** |
| **Rivers** | standard | NR | 43.8 | 132.5 | 167.0 | 13,358 | 56.9 |
| EGDT | NR | 62.2 | 107.8 | 168.0 | 13,443 | 44.3 |
| **ProCESS** | standard | 28.0 | 28.5 | 54.4 | 110.9 | 8,716 | 18.9 |
| EGDT | 30.5 | 35.1 | 55.7 | 118.8 | 9,507 | 21.0 |
| protocol  | 29.2 | 41.1 | 61.5 | 130.2 | 10,419 | 18.2 |
| **ARISE** | standard | 34.7 | 18.7 | 48.8 | 102.2 | 7,485 | 18.3 |
| EGDT | 34.6 | 21.1 | 48.7 | 104.4 | 7,670 | 16.9 |
| **ProMISe** | standard  | 24.5 | 27.8 | 52.7 | 97.6 | 7,809 | 28.8 |
| EGDT  | 23.6 | 25.2 | 54.6 | 98.0 | 7,836 | 28.7 |

Resuscitative fluid volume in ml/kg for Rivers, ProMISe and ProCESS are estimated based upon an average 80kg participant. IV fluid for time periods does not sum to total IV fluid because mean values are presented. 60-day mortality extracted from Kaplan Meier curves for ARISE and ProMISe. NR = not reported

**Supplementary Table 2:** Initial and repeat lactate measurements

|  |  |  |  |
| --- | --- | --- | --- |
| **Lactic acid level meq/L, median (IQR)**  | **Restrictive fluid group**(n=55) | **Usual care group**(n=54) | **P value** |
|  First measurementa | 2.0 (1.4, 3.7) | 3.0 (1.5, 5.3) | 0.07 |
| Second measurementb | 1.9 (1.1, 3.7) | 2.2 (1.5, 5.1) | 0.27 |

a Restrictive group missing one measurement, median (IQR) time from triage to first measurement for restrictive group 1 hour (0-1) and for usual care group 0 hours (0-1)

b Restrictive group missing 14 measurements and usual care group missing 7; median (IQR) for time to second measurement is 4 hours (2.5-6) for restrictive group and 4 hours (3-6) for usual care

**Supplementary Table 3:** Clinical reasoning for patient cross over (restrictive to usual care group)

|  |  |
| --- | --- |
| **Participant Number** | Reason for cross over |
| 3 | Rhabdomyolysis was discovered in the medical ICU. Clinical team administered IV fluid to treat this concomitant diagnosis.  |
| 19 | “Patient already on high dose vasopressors with runs of supraventricular tachycardia. Normal saline bolus given to see if we could avoid a higher levophed dose, ectopy, and the need for a third vasopressor.”  |
| 50 | “Patient has persistent shock, a high vasopressor requirement, oligouria, acute kidney injury, and a rising lactic acid level.” |
| 55 | Clostridium difficile infection discovered after randomization. Clinical team administered IV fluid for a fluid wasting process.  |
| 71 | “Patient arrived to the medial ICU with systolic blood pressures in the 50s. Following emergent intubation she required the addition of an epinephrine drip. Clinically the patient was extremely dry on exam.” |
| 80 | Patient required emergent surgery on day #2 for operative drainage of deep buttock abscess. IV fluid limit was exceeded in the intraoperative period.  |

For participants 19, 50, and 71 the clinical reasoning was obtained directly from the ICU attending of record by standardized form. For participants 3, 55, 80 the clinical reason for cross over was extracted from the electronic medical record.

**Supplementary Table 4:** Mean IV fluid administered to study groups (ml): intention-to-treat analysis

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Intervention**  | **Restrictive fluid group**(n=55) | **Usual care group**(n=54) | **Difference (95% CI)** | **P value** |
| ***Resuscitative IV fluid: mla*** |  |  |  |  |
| Prior to randomization  | 3074 ± 1101 | 3015 ± 1148 | -59 (-486 to 368) | 0.78 |
|  Randomization to 24 hoursb  | 665 ± 1119 | 1251 ± 1588 | 586 (62 to1109) | 0.03 |
|  Hours 24 to 48 | 299 ± 929 | 583 ± 970 | 284 (-78 to 647) | 0.12 |
|  Hours 48 to 72 | 111 ± 347 | 116 ± 377 | 5 (-135 to 144) | 0.95 |
| Total  | 4140 ± 1660 | 4963 ± 2362 | 823 (49 to 1597) | 0.04 |
| ***Non-resuscitative IV fluid and fluid totals*** |  |  |  |  |
|  Non-resuscitative IV fluid, ml/kgc | 2074 ± 1305 | 3065 ± 2637 | 991 (195 to 1787) | 0.02 |
|  Total all forms IV fluid, ml/kg | 6213 ± 2207 | 8027 ± 4120 | 1814 (562 to 3066) | 0.005 |

a ± indicates standard deviation

b Six participants (5 restrictive and 1 standard) were randomized after 24 hours, none received additional IV fluid during that time

c Non-resuscitative fluid includes all IV fluid administered with medications in volumes of >100ml

**Supplementary Table 5:** Median IV fluid administered to study groups (ml/kg): intention-to-treat analysis

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Intervention**  | **Restrictive fluid group**(n=49) | **Usual care group**(n=60) | **Difference (95% CI)** | **P value** |
| ***Resuscitative IV fluid: ml/kg (IQR)*** |  |  |  |  |
|  Prior to randomization  | 37.5 (23.7 to 42.9) | 35.4 (26.3 to 48.6) | -1.6 (-8.7 to 7.3 | 0.40 |
| Randomization to hour 24a | 0 (0 to 10.3) | 11.1 (0 to 23.0) | 10.7 (0 to 16.5) | 0.03 |
| Hours 24 to 48 | 0 (0 to 0) | 0 (0 to 13.2) | 0 (-5.4 to 13.7) | 0.04 |
| Hours 48 to 72 | 0 (0 to 0) | 0 (0 to 0) | 0 (0 to 0) | 0.86 |
|  Total  | 43.5 (32.6 to 55.8) | 54.8 (37.8 to 79.5) | 10.4 (-4.8 to 17.8) | 0.01 |
| ***Non-resuscitative IV fluid and fluid totals*** |  |  |  |  |
| Non-resuscitative IV fluid, ml/kgb | 19.7 (10.8 to 29.6) | 28.1 (17.5 to 45.8) | 8.8 (-0.4 to 18.0) | 0.01 |
| Total all forms IV fluid, ml/kg | 65.6 (50.8 to 82.4) | 83.9 (58.4 to 125.0) | 19.8 (-1.2 to 36.8) | 0.03 |

a Six participants (5 restrictive and 1 standard) were randomized after 24 hours, none received additional IV fluid during that time

b Non-resuscitative fluid includes all IV fluid administered with medications in volumes of >100ml

IQR = Intra quartile range

**Supplementary Table 6:** Mean IV fluid administered to study groups (ml/kg): per-protocol analysis

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Intervention**  | **Restrictive fluid group**(n=49) | **Usual care group**(n=60) | **Difference (95% CI)** | **P value** |
| ***Resuscitative IV fluid: ml/kga*** |  |  |  |  |
|  Prior to randomization  | 33.7 ± 13.4 | 36.7 ± 14.0 | 3.0 (-2.2 to 8.2) | 0.26 |
| Randomization to hour 24b | 5.5 ± 9.4 | 17.6 ± 22.3 | 12.1 (5.6 to 18.7) | 0.0004 |
| Hours 24 to 48 | 1.7 ± 5.1 | 8.2 ± 14.0 | 6.4 (2.5 to 10.4) | 0.002 |
| Hours 48 to 72 | 0.4 ± 1.7 | 2.3 ± 6.1 | 1.9 (0.2 to 3.6) | 0.03 |
| Total  | 41.2 ± 13.6 | 64.5 ± 32.7 | 23.3 (14.0 to 32.5) | <0.0001 |
| ***Non-resuscitative IV fluid and fluid totals*** |  |  |  |  |
| Non-resuscitative IV fluid, ml/kgc | 22.0 ± 15.7 | 37.6 ± 34.4 | 15.5 (5.6 to 25.4) | 0.003 |
| Total all forms IV fluid, ml/kg | 63.3 ± 22.2 | 102.1 ± 53.5 | 38.8 (23.6 to 53.9) | <0.0001 |

a ± indicates standard deviation

b Six participants (5 restrictive and 1 standard) were randomized after 24 hours, none received additional IV fluid during that time

c Non-resuscitative fluid includes all IV fluid administered with medications in volumes of >100ml

**Supplementary Table 7:** Mean IV fluid administered to study groups (ml): per-protocol analysis

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Intervention**  | **Restrictive fluid group**(n=49) | **Usual care group**(n=60) | **Difference (95% CI)**  | **P value** |
| ***Resuscitative IV fluid: mla*** |  |  |  |  |
|  Prior to randomization  | 3086 ± 1121 | 3011 ± 1126 | -76 (-505 to 353) | 0.73 |
| Randomization to Hour 24b | 3602 ± 1089 | 4325 ± 1854 | 798 (308 to 1289) | 0.002 |
| Hours 24 to 48 | 143 ± 433 | 689 ± 1180 | 546 (216 to 876) | 0.002 |
| Hours 48 to 72 | 42 ± 174 | 173 ± 455 | 132 (3 to 261) | 0.05 |
| Total  | 3785 ± 1167 | 5170 ± 2421 | 1384 (680 to 2088) | 0.0002 |
| ***Non-resuscitative IV fluid and fluid totals*** |  |  |  |  |
| Non-resuscitative IV fluid, ml/kgc | 2021 ± 1284 | 3008 ± 2544 | 987 (240 to 1735) | 0.01 |
| Total all forms IV fluid, ml/kg | 5807 ± 1819 | 8178 ± 3996 | 2371 (1147 to 3596) | <0.0001 |

a ± indicates standard deviation

b Six participants (5 restrictive and 1 standard) were randomized after 24 hours, none received additional IV fluid during that time

c Non-resuscitative fluid includes all IV fluid administered with medications in volumes of >100ml

**Supplementary Table 8:** Study outcomes and adverse events: per-protocol analysis

|  |  |  |  |
| --- | --- | --- | --- |
| **Outcome**  | **Restrictive fluid group**(n=49) | **Usual care group**(n=60) | **P value** |
| ***Death***: no./total (%) |  |  |  |
|  30-day mortality: primary outcome | 9/49 (18.4) | 15/60 (25.0) | 0.49 |
|  60-day mortality  | 12/49 (24.5) | 19/60 (30.0) | 0.67 |
| ***New organ failure***: n (%) |  |  |  |
| Cardiovascular – vasopressors for shock | 42/49 (85.7) | 48/60 (80.0) | 0.46 |
| Respiratory – new mechanical ventilationa | 12/47 (25.5) | 20/48 (35.6) | 0.29 |
| Renal – new hemodialysisb  | 0/42 (0) | 3/59 (5.1) | 0.26 |
| ***Duration of organ support***: median (IQR) |  |  |  |
| Vasopressor free daysc | 28 (27-29) | 28 (2.5-29) | 0.013 |
| Vasopressor hoursc | 16.3 (8.0 to 26.3) | 21.8 (10.0 to 57.5) | 0.06 |
| Ventilation free daysd  | 27.5 (0.5-28) | 13.5 (0-27.5) | 0.31 |
| Mechanical ventilation hoursd  | 16.6 (8.9 to 21.4) | 41.9 (21.5 to 143.6) | 0.01 |
| ***Use of hospital resources:*** median (IQR) |  |  |  |
| ICU length of stay hours | 53.5 (27.5 to 89.5) | 69.0 (26.3 to 110.8) | 0.44 |
| Hospital length of stay hours  | 191.5 (114.0 to 297.8) | 173.4 (94.8 to 270.3) | 0.54 |
| ***Electrolyte measurements:*** mean, SDe  |  |  |  |
| Change in chloride, mmol/L | 4.0 ± 3.9 | 5.4 ± 5.1 | 0.14 |
| Change in bicarbonate, mmol/L | 0.63 ± 3.8 | 1.1 ± 5.0 | 0.61 |
| ***Serious adverse events***: n (%) |  |  |  |
| Myocardial infarction  | 2 (4.1) | 1 (1.7) | 0.24 |
| Acute kidney injuryf  | 1 (2.0) | 1 (1.7) | >0.99 |
| Required re-intubation  | 1 (2.0) | 3 (5.0) | 0.63 |
| Disseminated intravascular coagulation | 0 (0) | 0 (0) |  |
| Limb ischemia  | 0 (0) | 0 (0) |  |

a Four participants with mechanical ventilation at baseline excluded

b Eight participants with dialysis at baseline excluded

c Includes the 90 participants who were on vasopressors, out of 30 days

d Includes the 30 participants with new mechanical ventilation, out of 30 days

e Includes only the participants alive at 72 hours, ± indicates standard deviation

f Defined as a doubling of creatinine from the first recorded value during the study period

**Supplementary Table 9:** Sensitivity analysis for all cause 30-day mortality

|  |  |  |
| --- | --- | --- |
|  | Intent-to-treat: OR (95% CI) | Per-protocol: OR (95% CI) |
|  | Unadjusted | Adjusted for CKD | Adjusted for CKD and non-resuscitative fluid | Unadjusted | Adjusted for CKD | Adjusted for CKD and non-resuscitative fluid |
| Treatment group (restrictive vs. usual care)  | 1.02(0.41 to 2.53) | 0.89(0.35 to 2.30) | 1.97 (0.67 to 5.75) | 1.48 (0.59 to 3.75) | 13.6 (0.53 to 3.53) | 1.24 (0.44 to 3.56) |

CI = confidence interval, CKD = chronic kidney disease, OR = odds ratio

**Supplementary Table 10:** Norepinephrine dosing and incidence of an adjunct vasopressors, among participants requiring vasopressor support

|  |  |  |  |
| --- | --- | --- | --- |
| **Vasopressor**  | **Restrictive fluid group**(n=55) | **Usual care group**(n=54) | **P value** |
| ***Norepinephrine dose (mg/kg/hr) median (IQR)*** |  |  |  |
|  Initiation dose independent of time | 0.059 (0.027-0.100) | 0.057 (0.026-0.074) | 0.44 |
| 6 hours | 0.051 (0-0.100) | 0.040 (0-0.090) | 0.47 |
| 12 hours  | 0.026 (0-0.068) | 0.035 (0-0.116) | 0.64 |
| 24 hours  | 0 (0-0.061) | 0 (0-0.045) | 0.57 |
| 36 hours  | 0 (0, 0) | 0 (0, 0.026) | 0.27 |
| 48 hours  | 0 (0, 0) | 0 (0, 0) | 0.16 |
| 72 hours  | 0 (0, 0) | 0 (0, 0) | 0.18 |
| ***Vasopressin (0.04 mg/hr) % patients receiving, n(%)*** |  |  |  |
|  6 hours | 2 (3.6) | 4 (7.4) | 0.44 |
|  12 hours  | 5 (9.1) | 8 (14.8) | 0.39 |
|  24 hours  | 2 (3.6) | 4 (7.4) | 0.44 |
|  36 hours  | 2 (3.6) | 3 (5.6) | 0.68 |
|  48 hours  | 1 (1.8) | 3 (5.6) | 0.36 |
|  72 hours  | 0 (0) | 2 (3.7) | 0.24 |
| ***Phenylephrine % patients receiving, n(%)*** |  |  |  |
|  6 hours | 1 (1.8) | 1 (1.9) | >0.99 |
|  12 hours  | 2 (3.6) | 3 (5.6) | 0.68 |
|  24 hours  | 2 (3.6) | 1 (1.9) | >0.99 |
|  36 hours  | 0 (0) | 0 (0) |  |
|  48 hours  | 0 (0) | 0 (0) |  |
|  72 hours  | 0 (0) | 1 (1.9) | 0.50 |

Epinephrine and dopamine both were used in 3 (2.7%) participants

**References**

1. Levy MM, Fink MP, Marshall JC, et al (2003) 2001 SCCM/ESICM/ACCP/ATS/SIS International Sepsis Definitions Conference. Crit Care Med 31:1250-6

2. Kaukonen KM, Bailey M, Pilcher D, Cooper DJ, Bellomo R (2015) Systemic inflammatory response syndrome criteria in defining severe sepsis. N Engl J Med 372:1629-38