Advances in Critical Care Nephrology & Acute Kidney Injury

Dinna N. Cruz, MD, MPH, FASN
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University of California, San Diego, CA
DISCLOSURES

• Alere – honorarium as speaker
• Estor – travel sponsorship as speaker
• Spectral – UCSD is a study site for the EUPHRATES
Outline

• Resuscitation in sepsis
• BP targets
• AKI, CKD, & RRT modality
• *Follow-up of AKI*
Clinical case

- 51/WM, h/o HTN, remote IVDU brought into ED by ambulance after 3 days of worsening LLQ abdominal pain, nausea, vomiting, diarrhea, weakness. No fevers or chills. His symptoms acutely worsened today and he became confused, then lost consciousness. His wife called 911 and paramedics found him unresponsive, hypotensive, and hypoglycemic (POC glu 22). Unable to get IV access, pt was given glucagon en route.

- Upon arrival to ED, pt being ventilated with BVM, not responsive to painful stimuli. Pt was intubated.

- Outpt meds: lisinopril, nifedipine, MVI, tramadol prn
• SBP in 70s HR 106 Wt 60 kg SpO2 initially 80s T 96
• PE remarkable for:
  – Distended abdomen, involuntary guarding in right upper and lower quadrants with left side soft, minimal BS; hands and feet cool, no c/c/e
• Labs remarkable for:
  – WBC 22.2, Seg 60 B 23, Hb 11.7, plt 259
  – Na 131 K 5.2 HCO3 20 BUN 20 Cr 0.8
  – Alk 153 ALT 426 AST 721 alb 3.3 TB 0.4
  – Lactate 6 mmol/l
• Non-contrast CT head: no IC pathology
• CXR: Lungs are clear.

• Non-contrast abd CT scan remarkable for:
  – diffusely fluid filled bowel from the duodenum to the rectum with some loops of small bowel dilated
  – multiple pockets of gas particularly within the ileum
  – probable dilated common bile duct which may be due to increased pressure in the duodenum

• Impression: **Septic shock** likely GI source, possible bowel ischemia
Septic Shock

• Surviving Sepsis Campaign:
  – Step 1: Adequate resuscitation
• Septic patients often initially require significant fluid resuscitation
• Appropriate and timely resuscitation is a cornerstone of management

• Starches have fallen out of favor in the ICU
Hydroxyethyl Starch or Saline for Fluid Resuscitation in Intensive Care

CONCLUSIONS
In patients in the ICU, there was no significant difference in 90-day mortality between patients resuscitated with 6% HES (130/0.4) or saline. However, more patients who received resuscitation with HES were treated with renal-replacement therapy. (Funded by the National Health and Medical Research Council of Australia and others; CHEST ClinicalTrials.gov number, NCT00935168.)

Hydroxyethyl Starch 130/0.42 versus Ringer’s Acetate in Severe Sepsis

CONCLUSIONS
Patients with severe sepsis assigned to fluid resuscitation with HES 130/0.42 had an increased risk of death at day 90 and were more likely to require renal-replacement therapy, as compared with those receiving Ringer’s acetate. (Funded by the Danish Research Council and others; 6S ClinicalTrials.gov number, NCT00962156.)
Which fluid will you use for resuscitation?

A. Normal saline
B. Lactated ringers
C. Plasmalyte
D. Isotonic fluid containing sodium bicarbonate
E. Albumin
F. Other
# IV Fluid Composition

<table>
<thead>
<tr>
<th></th>
<th>NS</th>
<th>LR</th>
<th>Hartmann solution</th>
<th>Plasmalyte</th>
<th>“Half half” 0.45S + NaHCO3 75 meq/L</th>
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<tbody>
<tr>
<td><strong>pH</strong></td>
<td>5.5</td>
<td>6.5</td>
<td>6.5</td>
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<tr>
<td><strong>Na</strong></td>
<td>154</td>
<td>130</td>
<td>131</td>
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<tr>
<td><strong>K</strong></td>
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<td>4</td>
<td>5</td>
<td>5</td>
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<tr>
<td><strong>Cl</strong></td>
<td>154</td>
<td>109</td>
<td>111</td>
<td>98</td>
<td>77</td>
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<tr>
<td><strong>Lactate</strong></td>
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<td><strong>Acetate</strong></td>
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<td><strong>Gluconate</strong></td>
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<td><strong>Ca</strong></td>
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<td>2.7</td>
<td>2</td>
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Co-administration of blood with LR is a listed contraindication by the Amer Asso of Blood Banks, and on FDA package inserts.
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Co-administration of blood with LR is a listed contraindication by the Amer Asso of Blood Banks, and on FDA package inserts.
Association Between the Choice of IV Crystalloid and In-Hospital Mortality Among Critically Ill Adults With Sepsis*

Karthik Raghunathan, MD, MPH1,2; Andrew Shaw, MB, FRCA, FFICM, FCCM1; Brian Nathanson, PhD3; Til Stürmer, MD, PhD4; Alan Brookhart, PhD4; Mihaela S. Stefan, MD5; Soko Setoguchi, MD, DrPH6; Chris Beadles, MD, PhD7; Peter K. Lindenauer, MD, MSc7

- Retrospective cohort study with propensity matching
  - 53,448 pts with sepsis, treated with vasopressors and crystalloids in an ICU by hospital day 2 (6.4% received balanced fluids)

Matched cohort:
- 3365 pts who received only NS vs 3365 pts who received various %s of balanced solutions
3.4% lower mortality for every 10% increase in proportion of balanced fluids
• Conclusion: Resuscitation with balanced fluids was associated with a lower risk of mortality
Association Between a Chloride-Liberal vs Chloride-Restrictive Intravenous Fluid Administration Strategy and Kidney Injury in Critically Ill Adults

Before/after study
Free use of Cl-rich fluids x 6 mos
Phase out, then
Use of Cl-rich fluids restricted to specific conditions x 6 mos (i.e. using more of “balanced solutions”)

Table 2. Composition of Trial Fluids

<table>
<thead>
<tr>
<th></th>
<th>0.9% Saline</th>
<th>Hartmann</th>
<th>4% Gelatin</th>
<th>Plasma-Lyte 148</th>
<th>Albumin</th>
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<tr>
<td>Sodium</td>
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<td>129</td>
<td>154</td>
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<td>0</td>
<td>0</td>
<td>6.4</td>
</tr>
</tbody>
</table>

All concentrations in mmol/L.
Association Between a Chloride-Liberal vs Chloride-Restrictive Intravenous Fluid Administration Strategy and Kidney Injury in Critically Ill Adults

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<th>Plasma-Lyte 148</th>
<th>Albumin 4%</th>
<th>Albumin 20%</th>
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<td>6.4</td>
<td>32</td>
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</table>

*All concentrations in mmol/L.*

Before/after study:
Free use of Cl-rich fluids x 6 mos
Phase out, then
Use of Cl-rich fluids restricted to specific conditions x 6 mos

Table 3. Incidence of Acute Kidney Injury Stratified by Risk, Injury, Failure, Loss, and End-Stage (RIFLE) Serum Creatinine Criteria

<table>
<thead>
<tr>
<th></th>
<th>Cc (n = 760)</th>
<th>Cl (n = 773)</th>
<th>d</th>
<th>p Value</th>
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</thead>
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<tr>
<td>RIFLE class</td>
<td>Cl-liberal</td>
<td>Cl-restrictive</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Risk</td>
<td>71 (9.0) [7.2-11.0]</td>
<td>57 (7.4) [5.5-9.0]</td>
<td>.16</td>
<td></td>
</tr>
<tr>
<td>Injury</td>
<td>48 (6.3) [4.5-8.1]</td>
<td>23 (3.0) [1.8-4.2]</td>
<td>.002</td>
<td></td>
</tr>
<tr>
<td>Failure</td>
<td>57 (7.5) [5.6-9.0]</td>
<td>42 (5.4) [3.8-7.1]</td>
<td>.10</td>
<td></td>
</tr>
<tr>
<td>Injury and failure</td>
<td>105 (14) [11-16]</td>
<td>65 (8.4) [6.4-10.0]</td>
<td>&lt;.001</td>
<td></td>
</tr>
</tbody>
</table>

*The control period was from February 18 through August 17, 2008, and the intervention period was from February 18 through August 17, 2009.*
Figure 1. Development of Stage 2 or 3 Acute Kidney Injury (AKI) While in the Intensive Care Unit (ICU)

Cl-restrictive (balanced sol)

Cl-liberal

Figure 2. Renal Replacement Therapy (RRT) in the Intensive Care Unit (ICU)

Cl-restrictive (balanced sol)

Cl-liberal

Stage 2 or 3 defined according to the Kidney Disease: Improving Global Outcomes clinical practice guideline.
Major Complications, Mortality, and Resource Utilization After Open Abdominal Surgery

0.9% Saline Compared to Plasma-Lyte

Andrew D. Shaw, MB, FRCA, FCCM,* Sean M. Bagshaw, MD,† Stuart L. Goldstein, MD,‡ Lynette A. Scherer, MD,§ Michael Duan, MS,|| Carol R. Schermer, MD,¶ and John A. Kellum, MD#

MAJOR OPEN ABDOMINAL SURGERY
467,131 CASES

EXCLUDE 110,325 PATIENTS WHO RECEIVED CALCIUM CONTAINING BALANCED FLUID

RECEIVED BALANCED FLUID (PLASMA-LYTE)
DURING HOSPITALIZATION
9905 CASES

RECEIVED 0.9% SALINE DURING HOSPITALIZATION
346901 CASES

RECEIVED BALANCED FLUID ON PROCEDURE DATE
8285 CASES

RECEIVED 0.9% SALINE ON PROCEDURE DATE
262904 CASES

ONLY BALANCED FLUID ON PROCEDURE DATE
926 CASES

ONLY 0.9% SALINE ON PROCEDURE DATE
30994 CASES

3:1 PROPENSITY MATCH

BALANCED FLUID COHORT
926 CASES

0.9% SALINE COHORT
2778 CASES
FIGURE 2. Odds ratios and 95% confidence intervals for pre-specified clinical outcomes.

FIGURE 3. Interventions related to metabolic acidosis diagnosis and management.
Potential mechanism

- Hyperchloremia inhibits proximal tubule Cl reabsorption → increase Cl delivery to distal nephron → negative feedback to afferent renal vessels to decrease flow
  - In animal models: shown to lead to ↓ renal artery blood flow, ↓ GFR
Chloride anion concentration as a determinant of renal vascular responsiveness to vasoconstrictor agents

Caroline P. Quilley, Yu-Shi R. Lin & John C. McGiff

- Isolated rat kidneys perfused with high and low Cl solutions
- Compare response to vasoconstrictor agents

![Graph showing vasoconstrictor response](image)

**Figure 1** Representative trace showing dose-dependent changes in perfusion pressure of the rat isolated kidney following bolus injections of angiotensin II during perfusion with Krebs-Henseleit buffer gassed with 95% O₂, 5% CO₂, 37°C containing high chloride (117 mM, a) low chloride (97 mM, b), when 20 mM NaCl was substituted with sodium acetate and, during reperfusion with high chloride (c).
Use of Cl-rich solutions is associated with:

- Hyperchloremia, lower bicarb, incomplete correction of base deficit
- Higher mortality
- More AKI
- Adverse effects on intrarenal hemodynamics

Use of “balanced” solutions may be preferable
You have opted to use balanced solutions.
Now, how will you resuscitate the patient?

A. Early goal-directed therapy
B. As per Surviving Sepsis Campaign guidelines
C. Based on CVP
D. Based on blood pressure
E. A & B are the same thing, and that’s what I will do
Figure 1: The Surviving Sepsis Campaign Care Bundles.

**Surviving Sepsis Campaign Bundles**

**TO BE COMPLETED WITHIN 3 HOURS:**
1) Measure lactate level
2) Obtain blood cultures prior to administration of antibiotics
3) Administer broad spectrum antibiotics
4) Administer 30 mL/kg crystalloid for hypotension or lactate ≥4 mmol/L

**TO BE COMPLETED WITHIN 6 HOURS:**
5) Apply vasopressors (for hypotension that does not respond to initial fluid resuscitation) to maintain a mean arterial pressure (MAP) ≥65 mm Hg
6) In the event of persistent arterial hypotension despite volume resuscitation (septic shock) or initial lactate ≥4 mmol/L (36 mg/dL):
   - Measure central venous pressure (CVP)*
   - Measure central venous oxygen saturation (Scvo₂)*
7) Remeasure lactate if initial lactate was elevated*

*Targets for quantitative resuscitation included in the guidelines are CVP of ≥8 mm Hg, Scvo₂ of ≥70%, and normalization of lactate.
A Randomized Trial of Protocol-Based Care for Early Septic Shock

The ProCESS Investigators*


Goal-Directed Resuscitation for Patients with Early Septic Shock

The ARISE Investigators and the ANZICS Clinical Trials Group*


Trial of Early, Goal-Directed Resuscitation for Septic Shock

Paul R. Mouncey, M.Sc., Tiffany M. Osborn, M.D., G. Sarah Power, M.Sc., David A. Harrison, Ph.D., M. Zia Sadique, Ph.D., Richard D. Grieve, Ph.D., Rahi Jahan, B.A., Sheila E. Harvey, Ph.D., Derek Bell, M.D., Julian F. Bion, M.D., Timothy J. Coats, M.D., Mervyn Singer, M.D., J. Duncan Young, D.M., and Kathryn M. Rowan, Ph.D., for the ProMISE Trial Investigators*

• In Rivers’ trial (NEJM 2001), mortality in patients with early septic shock was markedly lower in those treated according to a 6-hour protocol of early goal-directed therapy (EGDT)
  – intravenous fluids
  – vasopressors
  – inotropes
  – blood transfusions
• Adjusted to reach central hemodynamic targets using ScvO2 CVC, compared to those receiving usual care.
• ProCESS, ARISE and PROMISE trials to determine whether these findings were generalizable and whether all aspects of the protocol were necessary.
  – PROCESS (USA): 60-day hospital mortality
  – ARISE(Australia-NZ): 90-day all cause mortality
  – PROMISE (UK): 90-day all cause mortality
A Randomized Trial of Protocol-Based Care for Early Septic Shock

The ProCESS Investigators

N Engl J Med 370;18:1683

Protocolized Care for Early Septic Shock (ProCESS) trial
Goal-Directed Resuscitation for Patients with Early Septic Shock

The ARISE Investigators and the ANZICS Clinical Trials Group®

**Figure**

Panel A shows Kaplan–Meier estimates of the probability of death at 90 days for patients with septic shock receiving either early goal-directed therapy (EGDT) or usual care. The figure compares the survival rates between the two groups, with the blue line representing EGDT and the red line representing usual care. The survival rates are depicted over 90 days, with the x-axis showing days since randomization and the y-axis showing the probability of survival.
Trial of Early, Goal-Directed Resuscitation for Septic Shock

Adjusted hazard ratio, 0.94 (0.79–1.11); P=0.46
P=0.63 by log-rank test

No. at Risk

<table>
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<tr>
<th></th>
<th>EGDT</th>
<th>492</th>
<th>470</th>
<th>461</th>
<th>449</th>
<th>445</th>
<th>440</th>
</tr>
</thead>
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<tr>
<td>Usual care</td>
<td>626</td>
<td>487</td>
<td>469</td>
<td>464</td>
<td>448</td>
<td>445</td>
<td>439</td>
</tr>
</tbody>
</table>
• Conclusions:
  
  – EGDT, as compared with usual resuscitation practice, did not decrease mortality among patients presenting to the emergency department with early septic shock.
  
  – The findings suggest that the value of incorporating EGDT into international guidelines as a standard of care is questionable.
Updated Bundles in Response to New Evidence

With publication of 3 trials (2,3,4) that do not demonstrate superiority of required use of a central venous catheter (CVC) to monitor central venous pressure (CVP) and central venous oxygen saturation (ScvO₂) in all patients with septic shock who have received timely antibiotics and fluid resuscitation compared with controls or in all patients with lactate >4 mmol/L, the SSC Executive Committee has revised the improvement bundles as follows:

TO BE COMPLETED WITHIN 3 HOURS OF TIME OF PRESENTATION*:

1. Measure lactate level
2. Obtain blood cultures prior to administration of antibiotics
3. Administer broad spectrum antibiotics
4. Administer 30ml/kg crystalloid for hypotension or lactate ≥4mmol/L

* “Time of presentation” is defined as the time of triage in the emergency department or, if presenting from another care venue, from the earliest chart annotation consistent with all elements of severe sepsis or septic shock ascertained through chart review.

TO BE COMPLETED WITHIN 6 HOURS OF TIME OF PRESENTATION:

5. Apply vasopressors (for hypotension that does not respond to initial fluid resuscitation) to maintain a mean arterial pressure (MAP) ≥65mmHg
6. In the event of persistent hypotension after initial fluid administration (MAP < 65 mm Hg) or if initial lactate was ≥4 mmol/L, re-assess volume status and tissue perfusion and document findings according to Table 1.
7. Re-measure lactate if initial lactate elevated.
Clinical case (cont’d)

• ED course: Central line, intubation, resuscitation with 6L NS, glucose, insulin, tx to ICU
• Pan-cultured
• Antibiotics after cultures obtained (within 1 hour of presentation): Vanc/zosyn, ceftriaxone, metronidazole
• Pt cont to be hypotensive to 70s, started on norepi 30, phenylephrine 50.
• GI & Surgery have been consulted
The patient is now in your ICU. What BP are you aiming for?

MAP >=65
• Multicenter, open-label RCT
• Randomly assigned 776 patients with septic shock to undergo resuscitation with MAP target of:
  80 to 85 mm Hg (high-target group)
  65 to 70 mm Hg (low-target group)
• Primary end point - mortality at day 28
# High versus Low Blood-Pressure Target in Patients with Septic Shock

*N Eng J Med* 2014; 370:1583-1593

Pierre Asfar, M.D., Ph.D., Ferhat Meziani, M.D., Ph.D., Jean-François Hamel, M.D., Fabien Grelon, M.D., Bruno Megarbane, M.D., Ph.D., Nadia Anguel, M.D., Jean-Paul Mira, M.D., Ph.D., Pierre-François Dequin, M.D., Ph.D., Soizic Gergaud, M.D., Nicolas Weiss, M.D., Ph.D., François Legay, M.D., Yves Le Tulzo, M.D., Ph.D., Marie Conrad, M.D., René Robert, M.D., Ph.D., Frédéric Gonzalez, M.D., Christophe Guitton, M.D., Ph.D., Fabienne Tamion, M.D., Ph.D., Jean-Marie Tonnelier, M.D., Pierre Guezennec, M.D., Thierry Van Der Linden, M.D., Antoine Vieillard-Baron, M.D., Ph.D., Eric Mariotte, M.D., Gaël Pradel, M.D., Olivier Lesieur, M.D., Jean-Damien Ricard, M.D., Ph.D., Fabien Hervé, M.D., Damien Du Cheyron, M.D., Ph.D., Claude Guerin, M.D., Ph.D., Alain Mercat, M.D., Ph.D., Jean-Louis Teboul, M.D., Ph.D., and Peter Radermacher, M.D., Ph.D. for the SEPSISPAM Investigators*

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*Additional investigators in the Sepsis and Mean Arterial Pressure (SEPSISPAM) trial are listed in the Supplementary Appendix, available at NEJM.org.*

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## ABSTRACT

**Background**

The Surviving Sepsis Campaign recommends targeting a mean arterial pressure of at least 65 mm Hg during initial resuscitation of patients with septic shock. However, whether this blood-pressure target is more or less effective than a higher target is unknown.

**Methods**

In a multicenter, open-label trial, we randomly assigned 776 patients with septic shock to undergo resuscitation with a mean arterial pressure target of either 80 to 85 mm Hg (high-target group) or 65 to 70 mm Hg (low-target group). The primary end point was mortality at day 28.

**Results**

At 28 days, there was no significant between-group difference in mortality, with deaths reported in 142 of 388 patients in the high-target group (36.6%) and 132 of 388 patients in the low-target group (34.0%) (hazard ratio in the high-target group, 1.07; 95% confidence interval [CI], 0.84 to 1.38; *P* = 0.57). There was also no significant difference in mortality at 90 days, with 170 deaths (43.8%) and 164 deaths (42.3%), respectively (hazard ratio, 1.04; 95% CI, 0.83 to 1.30; *P* = 0.74). The occurrence of serious adverse events did not differ significantly between the two groups (74 events [19.1%] and 69 events [17.8%], respectively; *P* = 0.64). However, the incidence of newly diagnosed atrial fibrillation was higher in the high-target group than in the low-target group. Among patients with chronic hypertension, those in the high-target group required less renal-replacement therapy than did those in the low-target group, but such therapy was not associated with a difference in mortality.

**Conclusions**

Targeting a mean arterial pressure of 80 to 85 mm Hg, as compared with 65 to 70 mm Hg, in patients with septic shock undergoing resuscitation did not result in significant differences in mortality at either 28 or 90 days. (Funded by the French Ministry of Health; SEPSISPAM ClinicalTrials.gov number, NCT01149278.)

---

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Low-Target</th>
<th>High-Target</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Vasoactive infusions no (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Norepinephrine</td>
<td>368 (94.8%)</td>
<td>373 (96.1%)</td>
</tr>
<tr>
<td>Epinephrine</td>
<td>20 (5.2%)</td>
<td>15 (3.9%)</td>
</tr>
<tr>
<td>Dobutamine</td>
<td>21 (5.4%)</td>
<td>16 (4.1%)</td>
</tr>
<tr>
<td><strong>Median vasopressor dose</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Norepinephrine</td>
<td>0.35 (0.20-0.61)</td>
<td>0.40 (0.20-0.62)</td>
</tr>
<tr>
<td>Epinephrine</td>
<td>0.23 (0.17-0.32)</td>
<td>0.22 (0.13-0.64)</td>
</tr>
<tr>
<td>Mechanical ventilation</td>
<td>286 (73.7%)</td>
<td>308 (79.4%)</td>
</tr>
<tr>
<td>PaO2/FiO2 ratio</td>
<td>198 ± 120</td>
<td>199 ± 126</td>
</tr>
<tr>
<td>Acute Kidney Injury</td>
<td>188 (48.7%)</td>
<td>173 (45.1%)</td>
</tr>
<tr>
<td>Serum creatinine</td>
<td>1.96 ± 1.39</td>
<td>1.93 ± 1.47</td>
</tr>
</tbody>
</table>
In a multicenter, open-label trial, we randomly assigned 776 patients with septic shock to undergo resuscitation with a mean arterial pressure target of either 80 to 85 mm Hg (high-target group) or 65 to 70 mm Hg (low-target group). The primary end point was mortality at day 28. Targeting a mean arterial pressure of 80 to 85 mm Hg, in patients with septic shock undergoing resuscitation did not result in reductions of 20 percentage points, as compared with 65 to 70 mm Hg (low-target group). However, given the small number of deaths reported in previous multicenter trials ranging from 25 to 57% were reported. Hence, the anticipated risk reduction in our study was close to the risk reductions tested in other studies, although it was in line with the results in the Surviving Sepsis Campaign. The New England Journal of Medicine recommends targeting a mean arterial pressure of 80 to 85 mm Hg, in patients with septic shock undergoing resuscitation did not result in reductions of 20 percentage points, as compared with 65 to 70 mm Hg (low-target group).

The incidence of newly diagnosed atrial fibrillation was higher in the high-target group (74 events [19.1%] and 69 events [17.8%], respectively; P = 0.74). The occurrence of some adverse events, especially rare events such as myocardial infarction, which is in line with rates in previous studies or because of more reporting of the presence or absence of chronic hypertension, targeting a mean arterial pressure of 80 to 85 mm Hg, in patients with septic shock undergoing resuscitation did not result in

Results

The Surviving Sepsis Campaign recommends targeting a mean arterial pressure of 80 to 85 mm Hg, in patients with septic shock undergoing resuscitation did not result in reductions of 20 percentage points, as compared with 65 to 70 mm Hg (low-target group). However, given the small number of deaths reported in previous multicenter trials ranging from 25 to 57% were reported. Hence, the anticipated risk reduction in our study was close to the risk reductions tested in other studies, although it was in line with the results in the Surviving Sepsis Campaign..
High versus Low Blood-Pressure Target in Patients with Septic Shock

N Eng J Med 2014; 370:1583-1593
Pierre Asfar, M.D., Ph.D., Ferhat Meziani, M.D., Ph.D., Jean-François Hamel, M.D.,

**Figure**

High versus Low Blood-Pressure Target

Kaplan–Meier Survival (\%) for the high-target group required less renal-replacement therapy than did those in the low-target group. Among patients with chronic hypertension, those in the high-target group had a lower mortality rate than in the low-target group. There was no significant difference in mortality at 90 days, with 170 deaths (43.8%) and 164 deaths (42.4%) reported in 142 of 388 patients in the high-target group (36.6%) and 132 of 328 patients in the low-target group (40.3%), respectively. (Figs. 2 and 3; Table 1.)

Conclusion

The results of the SEPSISPAM trial suggest that targeting a mean arterial pressure of 80 to 85 mm Hg is as effective as a target of 65 to 70 mm Hg in reducing mortality in patients with septic shock. However, whether this blood-pressure target is more or less effective than a higher target (85 to 90 mm Hg) remains to be determined.

**References**


**Appendix**

The results are also available in the Supplementary Appendix.
High versus Low Blood-Pressure Target in Patients with Septic Shock

*The New England Journal of Medicine*

Pierre Asfar, M.D., Ph.D., Ferhat Meziani, M.D., Ph.D., Jean-François Hamel, M.D., Fabien Grelon, M.D., Bruno Megarbane, M.D., Ph.D., Nadia Anguel, M.D., Jean-Paul Mira, M.D., Ph.D., Pierre-François Dequin, M.D., Ph.D., Soizic Gergaud, M.D., Nicolas Weiss, M.D., Ph.D., François Legay, M.D., Yves Le Tulzo, M.D., Ph.D., Marie Conrad, M.D., René Robert, M.D., Ph.D., Frédéric Gonzalez, M.D., Christophe Guitton, M.D., Ph.D., Fabienne Tamion, M.D., Ph.D., Jean-Marie Tonnelier, M.D., Pierre Guezennec, M.D., Thierry Van Der Linden, M.D., Antoine Vieillard-Baron, M.D., Ph.D., Eric Mariotte, M.D., Gaël Pradel, M.D., Olivier Lesieur, M.D., Jean-Damien Ricard, M.D., Ph.D., Fabien Hervé, M.D., Damien Du Cheyron, M.D., Ph.D., Claude Guerin, M.D., Ph.D., Alain Mercat, M.D., Ph.D., Jean-Louis Teboul, M.D., Ph.D., and Peter Radermacher, M.D., Ph.D. for the SEPSISPAM Investigators*

The authors' affiliations are listed in the Appendix. Address reprint requests to Dr. Asfar at the Department of Medical Intensive Care and Hyperbaric Medicine, University Hospital of Angers, 4 rue Larrey, F-49933 Angers Cedex 9, France, or at piasfar@chu-angers.fr.

*Additional investigators in the Sepsis and Mean Arterial Pressure (SEPSISPAM) trial are listed in the Supplementary Appendix, available at NEJM.org.*

This article was published on March 18, 2014, at NEJM.org.

**DOI:** 10.1056/NEJMoa1312173

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**ABSTRACT**

**Background**

The Surviving Sepsis Campaign recommends targeting a mean arterial pressure of at least 65 mm Hg during initial resuscitation of patients with septic shock. However, whether this blood-pressure target is more or less effective than a higher target is unknown.

**Methods**

In a multicenter, open-label trial, we randomly assigned 776 patients with septic shock to undergo resuscitation with a mean arterial pressure target of either 80 to 85 mm Hg (high-target group) or 65 to 70 mm Hg (low-target group). The primary end point was mortality at day 28.

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At 28 days, there was no significant between-group difference in mortality, with deaths reported in 142 of 388 patients in the high-target group (36.6%) and 132 of 388 patients in the low-target group (34.0%) (hazard ratio in the high-target group, 1.07; 95% confidence interval [CI], 0.84 to 1.38; *P* = 0.57). There was also no significant difference in mortality at 90 days, with 170 deaths (43.8%) and 164 deaths (42.3%), respectively (hazard ratio, 1.04; 95% CI, 0.83 to 1.30; *P* = 0.74). The occurrence of serious adverse events did not differ significantly between the two groups (74 events [19.1%] and 69 events [17.8%], respectively; *P* = 0.64). However, the incidence of newly diagnosed atrial fibrillation was higher in the high-target group than in the low-target group. Among patients with chronic hypertension, those in the high-target group required less renal-replacement therapy than did those in the low-target group, but such therapy was not associated with a difference in mortality.

**Conclusions**

Targeting a mean arterial pressure of 80 to 85 mm Hg, as compared with 65 to 70 mm Hg, in patients with septic shock undergoing resuscitation did not result in significant differences in mortality at either 28 or 90 days. (Funded by the French Ministry of Health; SEPSISPAM ClinicalTrials.gov number, NCT01149278.)

---

**Doubling of serum creatinine level**

- **No chronic hypertension**
  - Low Target: 30%
  - High Target: 40%
  - *P* < 0.02

- **Chronic hypertension**
  - Low Target: 50%
  - High Target: 60%

---

*The New England Journal of Medicine*
High versus Low Blood-Pressure Target in Patients with Septic Shock


Pierre Asfar, M.D., Ph.D., Ferhat Meziani, M.D., Ph.D., Jean-François Hamel, M.D.,

Requirement for renal replacement therapy

![Bar chart showing requirement for renal replacement therapy](image)

- No Chronic Hypertension
  - Low Target: 30%
  - High Target: 35%

- Chronic Hypertension
  - Low Target: 45%
  - High Target: 40%

\[ P < 0.046 \]

Low Target
High Target

Copyright © 2014 Massachusetts Medical Society.
• No difference in mortality between treatment groups MAP 65-70 mmHg vs. 80-85 mmHg.
• No difference in renal outcomes in patients who did not have chronic hypertension.
• Higher incidence of AKI and RRT in chronically hypertensive patients titrated to lower MAP target.
The patient develops AKI on day 2 and rapidly progresses to oligoanuric AKI Stage 3. You decide to initiate RRT. What modality do you choose?

A. CRRT
B. IRRT (Intermittent)

Prolonged Intermittent RRT (PIRRT) is intermittent
## Controversy for 20+ years

<table>
<thead>
<tr>
<th>CRRT</th>
<th>IRRT</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Greater hemodynamic stability</td>
<td>• CHEAPER</td>
</tr>
<tr>
<td>• Continuous control of volume status</td>
<td>• Less resource intensive</td>
</tr>
<tr>
<td>• Avoid solute swings</td>
<td>• Avoids continuous anticoagulation</td>
</tr>
<tr>
<td>• Avoid cerebral edema</td>
<td>• Greater mobility</td>
</tr>
<tr>
<td></td>
<td>• No proven superiority of CRRT</td>
</tr>
<tr>
<td></td>
<td>• “If he doesn’t tolerate it, then let’s put him on CRRT”</td>
</tr>
</tbody>
</table>
Chapter 5.6: Modality of RRT for patients with AKI

5.6.1: Use continuous and intermittent RRT as complementary therapies in AKI patients. (Not Graded)

5.6.2: We suggest using CRRT, rather than standard intermittent RRT, for hemodynamically unstable patients. (2B)

5.6.3: We suggest using CRRT, rather than intermittent RRT, for AKI patients with acute brain injury or other causes of increased intracranial pressure or generalized brain edema. (2B)
Acute Kidney Injury and Chronic Kidney Disease as Interconnected Syndromes

Lakhmir S. Chawla, M.D., Paul W. Eggers, Ph.D., Robert A. Star, M.D., and Paul L. Kimmel, M.D.

- **Risk Factors**
  - Age
  - Race or ethnic group
  - Genetic factors
  - Hypertension
  - Diabetes mellitus
  - Metabolic syndrome

- **Acute Kidney Injury**

- **Disease Modifiers**
  - Severity of acute kidney injury
  - Stage of chronic kidney disease
  - No. of episodes
  - Duration of acute kidney injury
  - Proteinuria

- **Chronic Kidney Disease**

- **Outcomes**
  - Cardiovascular events
  - Kidney events
  - ESRD
  - Disability
  - Diminished quality of life
  - Death
CRRT vs IRRT debate is back!

CRRT!

IRRT!
ATN vs RENAL study

ATN (USA)
• CRRT/ SLEDD if hemodynamically unstable (cvSOFA 3-4)
• IHD if stable (cvSOFA 0-2)
• Patients can cross-over based on hemodynamic status
• Renal recovery at 28 days: 8%

RENAL (Australia-NZ)
• Exclusively CRRT
• Renal recovery at 28 days: 25.8%
### 1.1.1 Observational

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>IRRT Events</th>
<th>Total</th>
<th>CRRT Events</th>
<th>Total</th>
<th>Weight</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
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</thead>
<tbody>
<tr>
<td>Andrikos 2009</td>
<td>1</td>
<td>4</td>
<td>5</td>
<td>33</td>
<td>1.5%</td>
<td>1.65 [0.25, 10.81]</td>
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</tr>
<tr>
<td>Bagshaw 2006</td>
<td>15</td>
<td>42</td>
<td>12</td>
<td>54</td>
<td>7.0%</td>
<td>1.61 [0.84, 3.06]</td>
<td></td>
</tr>
<tr>
<td>Bell 2007</td>
<td>26</td>
<td>158</td>
<td>78</td>
<td>944</td>
<td>9.8%</td>
<td>1.99 [1.32, 3.00]</td>
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<tr>
<td>CartyCeba 2009</td>
<td>256</td>
<td>555</td>
<td>26</td>
<td>229</td>
<td>10.3%</td>
<td>4.06 [2.80, 5.90]</td>
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<tr>
<td>Chang 2004</td>
<td>4</td>
<td>44</td>
<td>1</td>
<td>11</td>
<td>1.3%</td>
<td>1.00 [0.12, 8.08]</td>
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<tr>
<td>Elsevier 2010</td>
<td>37</td>
<td>175</td>
<td>13</td>
<td>98</td>
<td>7.7%</td>
<td>1.59 [0.89, 2.85]</td>
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<tr>
<td>Garcia–Fernandes 2011</td>
<td>0</td>
<td>16</td>
<td>0</td>
<td>55</td>
<td>Not estimable</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gonwa 2001</td>
<td>1</td>
<td>6</td>
<td>4</td>
<td>25</td>
<td>1.4%</td>
<td>1.04 [0.14, 7.71]</td>
<td></td>
</tr>
<tr>
<td>Jacka 2005</td>
<td>9</td>
<td>14</td>
<td>3</td>
<td>24</td>
<td>3.5%</td>
<td>5.14 [1.66, 15.89]</td>
<td></td>
</tr>
<tr>
<td>Lin 2009</td>
<td>11</td>
<td>54</td>
<td>10</td>
<td>83</td>
<td>5.7%</td>
<td>1.69 [0.77, 3.71]</td>
<td></td>
</tr>
<tr>
<td>Lins 2006</td>
<td>9</td>
<td>37</td>
<td>1</td>
<td>4</td>
<td>1.6%</td>
<td>0.97 [0.16, 5.83]</td>
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<tr>
<td>Marshall 2012</td>
<td>5</td>
<td>56</td>
<td>2</td>
<td>16</td>
<td>2.1%</td>
<td>0.71 [0.13, 3.34]</td>
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</tr>
<tr>
<td>Park 2005</td>
<td>37</td>
<td>83</td>
<td>1</td>
<td>9</td>
<td>1.5%</td>
<td>4.01 [0.62, 25.86]</td>
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</tr>
<tr>
<td>Swartz 2005</td>
<td>24</td>
<td>110</td>
<td>10</td>
<td>64</td>
<td>6.7%</td>
<td>1.40 [0.71, 2.73]</td>
<td></td>
</tr>
<tr>
<td>Uchino 2007</td>
<td>37</td>
<td>110</td>
<td>52</td>
<td>360</td>
<td>10.5%</td>
<td>2.33 [1.62, 3.35]</td>
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<tr>
<td>Waldrop 2005</td>
<td>7</td>
<td>12</td>
<td>6</td>
<td>14</td>
<td>5.8%</td>
<td>1.36 [0.63, 2.94]</td>
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<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td><strong>1476</strong></td>
<td><strong>2023</strong></td>
<td><strong>76.4%</strong></td>
<td><strong>1.99 [1.53, 2.59]</strong></td>
<td></td>
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</tr>
</tbody>
</table>

Total events: 479

Heterogeneity: Tau² = 0.09; Chi² = 24.14, df = 14 (P = 0.04); I² = 42%

Test for overall effect: Z = 5.14 (P < 0.00001)

### 1.1.2 RCT

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>IRRT Events</th>
<th>Total</th>
<th>CRRT Events</th>
<th>Total</th>
<th>Weight</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
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</thead>
<tbody>
<tr>
<td>Abe 2010</td>
<td>2</td>
<td>25</td>
<td>3</td>
<td>19</td>
<td>1.8%</td>
<td>0.51 [0.09, 2.74]</td>
<td></td>
</tr>
<tr>
<td>Augustine 2004</td>
<td>8</td>
<td>12</td>
<td>8</td>
<td>13</td>
<td>7.6%</td>
<td>1.08 [0.60, 1.95]</td>
<td></td>
</tr>
<tr>
<td>Kumar 2004</td>
<td>3</td>
<td>12</td>
<td>1</td>
<td>8</td>
<td>1.3%</td>
<td>2.00 [0.25, 15.99]</td>
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</tr>
<tr>
<td>Lins 2009</td>
<td>15</td>
<td>60</td>
<td>11</td>
<td>65</td>
<td>6.5%</td>
<td>1.48 [0.74, 2.96]</td>
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<tr>
<td>Mehta 2011</td>
<td>3</td>
<td>43</td>
<td>4</td>
<td>29</td>
<td>2.4%</td>
<td>0.51 [0.12, 2.09]</td>
<td></td>
</tr>
<tr>
<td>Uehleriing 2005</td>
<td>1</td>
<td>27</td>
<td>1</td>
<td>37</td>
<td>0.8%</td>
<td>1.37 [0.09, 20.95]</td>
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<tr>
<td>Vinsonneau 2006</td>
<td>6</td>
<td>61</td>
<td>4</td>
<td>61</td>
<td>3.1%</td>
<td>1.50 [0.45, 5.05]</td>
<td></td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td><strong>240</strong></td>
<td><strong>232</strong></td>
<td><strong>23.6%</strong></td>
<td><strong>1.15 [0.78, 1.68]</strong></td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

Total events: 38

Heterogeneity: Tau² = 0.00; Chi² = 3.20, df = 6 (P = 0.78); I² = 0%

Test for overall effect: Z = 0.71 (P = 0.48)

**Total (95% CI)**

<table>
<thead>
<tr>
<th>IRRT</th>
<th>CRRT</th>
</tr>
</thead>
<tbody>
<tr>
<td>1716</td>
<td>2255</td>
</tr>
</tbody>
</table>

Total events: 517

Heterogeneity: Tau² = 0.12; Chi² = 37.19, df = 21 (P = 0.02); I² = 44%

Test for overall effect: Z = 4.36 (P < 0.0001)

Test for subgroup differences: Chi² = 5.45, df = 1 (P = 0.02), I² = 81.7%

---

**Fig. 2** Forest plot for dialysis dependence among survivors. Stratified by study design. *M–H* Mantel–Haenszel
The Association Between Renal Replacement Therapy Modality and Long-Term Outcomes Among Critically Ill Adults With Acute Kidney Injury: A Retrospective Cohort Study*


• Retrospective cohort study with propensity matching
  – Critically ill adults who initiated RRT for AKI

Matched cohort:
• 2004 pts CRRT as initial modality vs 2004 pts IHD as initial modality

Primary endpoints: Mortality (no difference) and chronic dialysis
The Association Between Renal Replacement Therapy Modality and Long-Term Outcomes Among Critically Ill Adults With Acute Kidney Injury: A Retrospective Cohort Study*


Cumulative risk of chronic dialysis among critically ill patients with acute kidney injury surviving to day 90
The Association Between Renal Replacement Therapy Modality and Long-Term Outcomes Among Critically Ill Adults With Acute Kidney Injury: A Retrospective Cohort Study*

• CONCLUSIONS: This study provides evidence of association, rather than causation, between receipt of CRRT as an initial therapy for severe AKI and a lower risk of chronic dialysis without an association with all-cause mortality.
Economics of dialysis dependence following renal replacement therapy for critically ill acute kidney injury patients

Olivier Ethgen\textsuperscript{1}, Antoine G. Schneider\textsuperscript{2}, Sean M. Bagshaw\textsuperscript{3}, Rinaldo Bellomo\textsuperscript{4} and John A. Kellum\textsuperscript{5}

\textit{Nephrol Dial Transplant} 2015;30: 54–61

- **OBJECTIVE:** To perform a cost-effectiveness analysis comparing IRRT with CRRT as initial therapy for AKI in the ICU.

- **METHODOLOGY:** Wald database of 2000 patients with AKI treated with CRRT and AKI. Study modeled life years gained, the QALYs and healthcare costs for a cohort of 1000 IRRT patients and a cohort of 1000 CRRT patients. 1-year, 5-year and a lifetime horizon were used.
• CRRT was associated with a marginally greater gain in QALY (Quality Adjusted Life Years) as compared with IRRT
  – 1.093 versus 1.078.
• Higher initial costs for CRRT in the ICU
  – $4,046 for CRRT versus $1,423 for IRRT
• 5-year total cost including the cost of dialysis dependence was lower for CRRT
  – $37,780 for CRRT versus $39,448 for IRRT
• CONCLUSIONS: Initial CRRT is cost-effective compared with initial IRRT by reducing the rate of long-term dialysis dependence among critically ill AKI survivors.
Chapter 5.6: Modality of RRT for patients with AKI

5.6.1: Use continuous and intermittent RRT as complementary therapies in AKI patients. (Not Graded)
CRRT first -> If patient tolerates it & fluid balance is well-controlled -> transition to IRRT
Summary

• Type of resuscitation fluid may matter (*Obs*)
  – Balanced solutions have been associated with lower incidence of AKI and lower mortality

• EGDT, as compared with usual resuscitation practice, did not decrease mortality among patients with early septic shock (*RCTs*) → *SSC guidelines have been revised*

• In septic shock patients with chronic hypertension, a higher incidence of AKI and RRT was seen with target MAP 65-70 mmHg vs. 80-85 mmHg (*RCT*)

• CRRT as initial modality in ICU-AKI is associated with lower incidence of ESRD (*Obs*)

• While initial costs of CRRT are higher, total 5-year cost is lower when considering the costs of chronic RRT (*Obs*)
Clinical case: Follow up

• PMX x 2 txs → BP improved, down to low dose NE, taken to OR: total abdominal colectomy, small bowel resection, and end ileostomy for bowel ischemia

• Off pressors on POD 2, transitioned to IHD on POD 4, extubated on POD 5, tx to floor on POD 6

• D/c alive after POD 19 on IHD

• To be continued...
Maraming salamat po!