Fluid Accumulation in Critical Illness: Less is More

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Division of Critical Care Medicine
Faculty of Medicine and Dentistry
University of Alberta

Critical Care Canada Forum
October 29, 2012
Disclosure Summary

• Sean M Bagshaw, MD, MSc
  – Nothing to disclose
Learning Objectives

• Review and Discuss:
  – Phases of Fluid Therapy
  – Impact of Fluid Accumulation
  – Fluid Removal (i.e. De-Resuscitation)
Fluid Balance Paradigm

I: Resuscitation
II: Maintenance/Homeostasis
III: Removal/Recovery

Time
Phase I of Fluid Paradigm

- Identification/diagnosis
- Therapeutic Monitoring
  - Individualized
- Early/Aggressive Initial Resuscitation
  - Hemodynamic stabilization
  - Shock reversal
  - Then:
    - REASSESS!!

Brierley et al CCM 2009
Phase II of Fluid Paradigm

- Maintenance of fluid balance homeostasis and/or prevention of worsening (+/- unnecessary) fluid overload
  - Assess need for all fluids (i.e. nutrition, medications, blood products)
  - Assess ability to maintain fluid balance
  - Assess patient’s current fluid accumulation status
Fluid resuscitation in septic shock: A positive fluid balance and elevated central venous pressure are associated with increased mortality*

John H. Boyd, MD, FRCP(C); Jason Forbes, MD; Taka-aki Nakada, MD, PhD; Keith R. Walley, MD, FRCP(C); James A. Russell, MD, FRCP(C)
The Importance of Fluid Management in Acute Lung Injury Secondary to Septic Shock

Claire V. Murphy, PharmD; Garrett E. Schramm, PharmD; Joshua A. Doherty, BS; Richard M. Reichley, RPh; Ognjen Gajic, MD, FCCP; Bekele Afessa, MD, FCCP; Scott T. Micek, PharmD; and Marin H. Kollef, MD, FCCP

• Retrospective cohort study (n=212) adult patients with ALI + septic shock

• Exposure:
  – Adequate Initial Fluid Resuscitation (AIFR)
    • ≥20 ml/kg bolus before vasopressors
    • CVP ≥8 mmHg after vasopressors within 6 hours
  – Conservative Late Fluid Management (CLFM)
    • Even to (-) fluid balance for at least 2 consecutive days in the first 7 days after sepsis onset

• Primary Outcome: hospital survival
# The Importance of Fluid Management in Acute Lung Injury Secondary to Septic Shock

Claire V. Murphy, PharmD; Garrett E. Schramm, PharmD; Joshua A. Doherty, BS; Richard M. Reichley, RPh; Ognjen Gajic, MD, FCCP; Bekele Afessa, MD, FCCP; Scott T. Micek, PharmD; and Marin H. Kollef, MD, FCCP

<table>
<thead>
<tr>
<th></th>
<th>Survivors</th>
<th>Non-Survivors</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fluid within 6 hr (mL/kg)</td>
<td>45.5</td>
<td>42.9</td>
<td>0.13</td>
</tr>
<tr>
<td>CVP measured (%)</td>
<td>92.0</td>
<td>70.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>AIFR (%)</td>
<td>79.2</td>
<td>54.0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>FB (7-day) (mL)</td>
<td>8,062</td>
<td>13,694</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CLFM (%)</td>
<td>72.8</td>
<td>34.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>FB (ICU) (%)</td>
<td>8,037</td>
<td>19,335</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>FB (Hospital) (%)</td>
<td>6,603</td>
<td>22,231</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>
The Importance of Fluid Management in Acute Lung Injury Secondary to Septic Shock

Claire V. Murphy, PharmD; Garrett E. Schramm, PharmD; Joshua A. Doherty, BS; Richard M. Reichley, RPh; Ognjen Gajic, MD, FCCP; Bekele Afessa, MD, FCCP; Scott T. Micek, PharmD; and Marin H. Kollef, MD, FCCP
Murphy et al. CHEST 2009

- AIFR not achieved ~ OR 4.94
- CLFM not achieved ~ OR 6.13

Hospital Mortality (%)
Decreased fluid volume to reduce organ damage: A new approach to burn shock resuscitation? A preliminary study

S. Arlati*, E. Storti, V. Pradella, L. Bucci, A. Vitolo, M. Pulici

Fluid Balance (24 hr) 7.5 L vs. 12.0 L, p<0.05
Decreased fluid volume to reduce organ damage: A new approach to burn shock resuscitation? A preliminary study

S. Arlati*, E. Storti, V. Pradella, L. Bucci, A. Vitolo, M. Pulici
Percent Fluid Overload (%FO)

\[
%FO = \frac{\sum [\text{FLUID IN} - \text{FLUID OUT}]}{[\text{Admission Weight (kg)}]} \times 100
\]
# Outcome in Children Receiving Continuous Venovenous Hemofiltration

Stuart L. Goldstein, MD*; Helen Currier, RN, CNN‡; Jeanine M. Graf, MD§; Carmen C. Cosio, MD§; Eileen D. Brewer, MD*; and Ramesh Sachdeva, MD§

<table>
<thead>
<tr>
<th>Clinical Variable</th>
<th>Survivors</th>
<th>Nonsurvivors</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td>8.0 ± 5.3</td>
<td>9.4 ± 7.1</td>
<td>.47</td>
</tr>
<tr>
<td>Weight at PICU admission (kg)</td>
<td>23.6 ± 16.5</td>
<td>31.9 ± 23.6</td>
<td>.32</td>
</tr>
<tr>
<td>PRISM at PICU admission</td>
<td>14.6 ± 7.1</td>
<td>12.6 ± 4.9</td>
<td>.69</td>
</tr>
<tr>
<td>PRISM at CVVH initiation</td>
<td>13.7 ± 10.3</td>
<td>16.5 ± 8.0</td>
<td>.31</td>
</tr>
<tr>
<td>GFR (mL/min/1.73 m²)</td>
<td>24.7 ± 25.9</td>
<td>24.3 ± 19.9</td>
<td>.95</td>
</tr>
<tr>
<td>Maximum pressor number</td>
<td>2.3 ± 1</td>
<td>2.4 ± 1</td>
<td>.64</td>
</tr>
<tr>
<td>P&lt;sub&gt;aw&lt;/sub&gt; change</td>
<td>−1.7 ± 3.4</td>
<td>−1.0 ± 3.4</td>
<td>.83</td>
</tr>
<tr>
<td>Percent fluid overload at CVVHD initiation</td>
<td>16.4 ± 13.8</td>
<td>34.0 ± 21.0</td>
<td>.03*</td>
</tr>
<tr>
<td>Percent accumulated fluid removed by CVVHD</td>
<td>15.3 ± 10.7</td>
<td>11.5 ± 30.6</td>
<td>.76</td>
</tr>
</tbody>
</table>
• “It is possible that in some cases CVVH/D may be a prevention, rather than a treatment, for worsening degrees of fluid overload.”

• “Early initiation of CVVH to allow for sufficient blood product and nutrition administration, while preventing fluid overload may improve patient survival…”
Fluid overload before continuous hemofiltration and survival in critically ill children: A retrospective analysis*

Jason A. Foland, MD; James D. Fortenberry, MD, FAAP, FCCM; Barry L. Warshaw, MD, FAAP; Robert Pettignano, MD, FAAP, FCCM; Robert K. Merritt, MA; Micheal L. Heard, RN; Kris Rogers, RN; Chris Reid, RRT; April J. Tanner, RN; Kirk A. Easley, MS
Fluid overload is associated with impaired oxygenation and morbidity in critically ill children*

Ayse A. Arikan, MD; Michael Zappitelli, MD, MSc; Stuart L. Goldstein, MD; Amrita Naipaul, NP; Larry S. Jefferson, MD; Laura L. Loftis, MD

Table 3. Relationship between total fluid overload percent and oxygenation index

<table>
<thead>
<tr>
<th>Total Fluid Overload %</th>
<th>Regression Coefficient</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.5%</td>
<td>0.05</td>
<td>.76</td>
</tr>
<tr>
<td>5%</td>
<td>0.05</td>
<td>.92</td>
</tr>
<tr>
<td>7.5%</td>
<td>0.05</td>
<td>.56</td>
</tr>
<tr>
<td>10%</td>
<td>0.08</td>
<td>.38</td>
</tr>
<tr>
<td>12.5%</td>
<td>0.10</td>
<td>.16</td>
</tr>
<tr>
<td>15%</td>
<td>0.12</td>
<td>.004</td>
</tr>
<tr>
<td>17.5%</td>
<td>0.20</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>20%</td>
<td>0.31</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>
Modified GDT for the Kidney

- **Volume Responsive AKI**
- **Volume Unresponsive AKI**

- High risk
  - Hypovolaemia
  - Euvolaemia
  - Hypervolaemia

- **Fluid Overload**

- Therapeutic Window
  - Sensitive Biomarkers
  - Traditional

- Kidney function
  - Mortality

Himmelfarb et al CJASN 2008
Clinical review: Volume of fluid resuscitation and the incidence of acute kidney injury - a systematic review

John R Prowle¹, Horng-Ruey Chua², Sean M Bagshaw³ and Rinaldo Bellomo⁴

No Greater Fluid Administration, Inotropes in GDT

<table>
<thead>
<tr>
<th>Study</th>
<th>Cases</th>
<th>Controls</th>
<th>Odds Ratio</th>
<th>95% CI</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benes, 2010</td>
<td>3</td>
<td>57</td>
<td>5.00</td>
<td>3.00</td>
<td>0.002</td>
</tr>
<tr>
<td>Mayer, 2010</td>
<td>1</td>
<td>29</td>
<td>5.00</td>
<td>3.00</td>
<td>0.002</td>
</tr>
<tr>
<td>Jhanji, 2010(SV+DPX)</td>
<td>4</td>
<td>41</td>
<td>10.00</td>
<td>6.00</td>
<td>0.003</td>
</tr>
<tr>
<td>Kapoor, 2008</td>
<td>1</td>
<td>29</td>
<td>5.00</td>
<td>3.00</td>
<td>0.002</td>
</tr>
<tr>
<td>Donati, 2007</td>
<td>2</td>
<td>66</td>
<td>7.00</td>
<td>4.00</td>
<td>0.003</td>
</tr>
<tr>
<td>Lobo, 2000</td>
<td>2</td>
<td>17</td>
<td>1.00</td>
<td>1.00</td>
<td>0.003</td>
</tr>
<tr>
<td>Polonen, 2000</td>
<td>1</td>
<td>195</td>
<td>3.00</td>
<td>2.00</td>
<td>0.003</td>
</tr>
<tr>
<td>Wilson, 1999</td>
<td>16</td>
<td>76</td>
<td>13.00</td>
<td>8.00</td>
<td>0.003</td>
</tr>
</tbody>
</table>

RE Model for Subgroup

RE Model for all: No Greater Fluid Administration

OR 0.46; 95% CI, 0.27-0.76, p=0.003
8 studies; n=1033
Fluid accumulation, recognition and staging of acute kidney injury in critically-ill patients

Etienne Macedo, Josée Bouchard, Sharon H Soroko, Glenn M Chertow, Jonathan Himmelfarb, T Alp Ikiizer, Emil P Paganini, Ravindra L Mehta for the Program to Improve Care in Acute Renal Disease (PICARD) study.

Kathleen D. Liu, MD; B. Taylor Thompson, MD; Marek Ancukiewicz; Jay S. Steingrub, MD; Ivor S. Douglas, MD; Michael A. Matthay, MD; Patrick Wright, MD; Michael W. Peterson, MD; Peter Rock, MD; Robert C. Hyzy, MD; Antonio Anzueto, MD; Jonathon D. Truwit, MD, MBA; for the National Institutes of Health National Heart, Lung and Blood Institute Acute Respiratory Distress Syndrome Network

<table>
<thead>
<tr>
<th>AKIN Stage</th>
<th>AKI - Unadjusted → Adjusted (delta)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Conservative</td>
</tr>
<tr>
<td>Stage I (%)</td>
<td>57 → 58 (1)</td>
</tr>
<tr>
<td>Stage II (%)</td>
<td>11 → 17 (6)</td>
</tr>
<tr>
<td>Stage III (%)</td>
<td>15 → 17 (2)</td>
</tr>
</tbody>
</table>

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<table>
<thead>
<tr>
<th>Group</th>
<th>AKI (unadj)</th>
<th>AKI (adj)</th>
<th>n (%)</th>
<th>Mortality (%)</th>
<th>Adj-OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>NO</td>
<td>NO</td>
<td>131 (13.1)</td>
<td>12</td>
<td>Reference</td>
</tr>
<tr>
<td>B</td>
<td>NO</td>
<td>YES</td>
<td>328 (32.8)</td>
<td>31</td>
<td>2.09 (1.19-3.67)</td>
</tr>
<tr>
<td>C</td>
<td>YES</td>
<td>NO</td>
<td>54 (5.4)</td>
<td>11</td>
<td>1.17 (0.45-3.02)</td>
</tr>
<tr>
<td>D</td>
<td>YES</td>
<td>YES</td>
<td>487 (48.7)</td>
<td>38</td>
<td>3.16 (2.04-4.87)</td>
</tr>
</tbody>
</table>
A positive fluid balance is associated with a worse outcome in patients with acute renal failure

Didier Payen¹, Anne Cornélie de Pont², Yasser Sakr³, Claudia Spies⁴, Konrad Reinhart³, Jean Louis Vincent⁵ for the Sepsis Occurrence in Acutely Ill Patients (SOAP) Investigators

Any ARF 36% (n=1120)

Early ARF 75% (n=842)

Late ARF 25% (n=278)

Mean fluid balance (L/24hr)

HR 1.21, 95%CI, 1.13-1.28, \( p < 0.001 \)

Late AKI

Early AKI

No AKI

CRRT 25% (n=278)

Late ARF 25% (n=278)
Adj-OR death for fluid overload at RRT initiation
2.07, 95%CI, 1.27-3.37
Volume-Related Weight Gain and Subsequent Mortality in Acute Renal Failure Patients Treated With Continuous Renal Replacement Therapy

TIBOR FÜLÖP, * MINESH B. PATHAK, † DARREN W. SCHMIDT, ‡ ZSOLT LENGVÁRSZKY, § JULIO P. JUNCOS, * CHRISTOPHER J. LEBRUN, ¶ HARJEET BRAR, ‖ AND LUIS A. JUNCOS* #

Oliguria (<20 mL/hr) – OR 2.71, p=0.04
Volume-Related Weight Gain ≥ 10% - OR 3.04, p=0.03
Fluid overload at initiation of renal replacement therapy is associated with lack of renal recovery in patients with acute kidney injury

Michael Heung\textsuperscript{1,*}, Dawn F. Wolfgram\textsuperscript{2,*}, Mallika Kommareddi\textsuperscript{1}, Youna Hu\textsuperscript{3}, Peter X. Song\textsuperscript{3} and Akinlolu O. Ojo\textsuperscript{1}

<table>
<thead>
<tr>
<th>Variable</th>
<th>Recovery (n=61)</th>
<th>Non-Recovery (n=109)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>% FO (%)</td>
<td>3.5</td>
<td>9.4</td>
<td>0.004</td>
</tr>
<tr>
<td>%FO &gt; 10% (%)</td>
<td>31.1</td>
<td>48.6</td>
<td>0.03</td>
</tr>
<tr>
<td>Comorbidity (%)</td>
<td>67.2</td>
<td>85.3</td>
<td>0.006</td>
</tr>
<tr>
<td>Albumin (g/L)</td>
<td>35 (30-38)</td>
<td>32 (28-35)</td>
<td>0.02</td>
</tr>
<tr>
<td>Vasopressors (%)</td>
<td>77.1</td>
<td>57.4</td>
<td>0.007</td>
</tr>
<tr>
<td>CRRT (%)</td>
<td>50.8</td>
<td>66.1</td>
<td>0.05</td>
</tr>
</tbody>
</table>

%FO (RRT) - HR 0.97; 95% CI, 0.95-1.00, p=0.02
What if the critically ill patient (with AKI) cannot tolerate the needed fluid volumes without developing worsening fluid accumulation?

A. Fluid restrict
B. Loop Diuretic
C. Early initiation of RRT renal replacement to maintain fluid homeostasis
for the treatment of AKI in the ICU. In our opinion, consideration should be given to the early initiation of CRRT—in advance of classic indications—if fluid balance cannot be adequately controlled with diuretic therapy. This approach anticipates and limits the extent of fluid over-load rather than treating its consequences. In addition, it permits adequate nutritional support without worsening fluid balance. Therefore, in a large proportion—perhaps the majority—of critically ill AKI patients, we believe that CRRT should be initiated within the first 24 h of ICU admission. Such earlier intervention with CRRT is now
Challenges…

• Currently available literature:
  – Small sample size/single center studies
  – Retrospective or Registry data

• Few data from INTERVENTIONAL trials:
  – Fluid management AFTER initial resuscitation
  – Focused on strategies for fluid management:
    • Volume: “Conservative” vs. “Liberal” (standard)
    • Type: Crystalloid or Colloid; Isotonic or Balanced
Effects of Intravenous Fluid Restriction on Postoperative Complications: Comparison of Two Perioperative Fluid Regimens

A Randomized Assessor-Blinded Multicenter Trial

Fluid administration

- Oral fluid
- Iv-Saline 0.9%
- Iv-Glucose 0.5%
- Iv-HAES 6%
- Iv-Other or unspecified

n=172
### Effects of Intravenous Fluid Restriction on Postoperative Complications: Comparison of Two Perioperative Fluid Regimens

*A Randomized Assessor-Blinded Multicenter Trial*

<table>
<thead>
<tr>
<th>Complication</th>
<th>Conservative (n=69)</th>
<th>Liberal (n=72)</th>
<th>( p )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pulmonary edema (%)</td>
<td>0</td>
<td>5.6</td>
<td>0.20</td>
</tr>
<tr>
<td>Pulmonary congestion (%)</td>
<td>2.9</td>
<td>11.1</td>
<td>0.09</td>
</tr>
<tr>
<td>Pneumonia (%)</td>
<td>4.3</td>
<td>12.5</td>
<td>0.13</td>
</tr>
<tr>
<td>Cardiac arrhythmia (%)</td>
<td>0</td>
<td>9.7</td>
<td>0.03</td>
</tr>
<tr>
<td>Cardiopulmonary* (%)</td>
<td>7.2</td>
<td>23.6</td>
<td>0.007</td>
</tr>
<tr>
<td>Tissue Healing (%)</td>
<td>15.9</td>
<td>30.6</td>
<td>0.04</td>
</tr>
</tbody>
</table>
## Comparison of Two Fluid-Management Strategies in Acute Lung Injury

The National Heart, Lung, and Blood Institute Acute Respiratory Distress Syndrome (ARDS) Clinical Trials Network*

<table>
<thead>
<tr>
<th>Variable</th>
<th>CON</th>
<th>LIB</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death (d 60) (%)</td>
<td>25.5</td>
<td>28.4</td>
<td>0.30</td>
</tr>
<tr>
<td>Ventilator-free days (d 1-28)</td>
<td>14.6</td>
<td>12.1</td>
<td>0.001</td>
</tr>
<tr>
<td>ICU-free days (d 1-28)</td>
<td>13.4</td>
<td>11.2</td>
<td>0.001</td>
</tr>
<tr>
<td>RRT (day 60) (%)</td>
<td>10</td>
<td>14</td>
<td>0.06</td>
</tr>
</tbody>
</table>

**Figure 3. Probability of Survival to Hospital Discharge and of Breathing without Assistance during the First 60 Days after Randomization.**
Comparison of Two Fluid-Management Strategies in Acute Lung Injury

The National Heart, Lung, and Blood Institute Acute Respiratory Distress Syndrome (ARDS) Clinical Trials Network*

Difference in fluid balance excluding initial resuscitation

---

FACTT - Wiedemann et al NEJM 2006
Fluid balance (per L/day) on 60-day mortality

**OR 1.61** (95% CI, 1.32-19.6, p<0.001)

**CONSERVATIVE GROUP**

- Less fluid!
- 0.9L vs. 2.2L per day, p<0.001
- 6.0L vs. 10.2L 6-day cumulative, p<0.001
Furosemide (per 100mg/d) on 60-d mortality
OR 0.48 (95% CI, 0.28-0.81, p=0.007)

CONSERVATIVE GROUP
• More furosemide!
• 80 mg vs. 23 mg per day, p<0.001
• 562 mg vs. 159 mg 6-day cumulative, p<0.001

Median Cumulative Furosemide by Group
Interquartile Range

Furosemide dose (mg)
0 300 600 900
Study day
0 1 2 3 4 5 6 7
Liberal Fluid Group
Restrictive Fluid Group

Grams et al CJASN 2011
Fluid balance in critically ill children with acute lung injury*

Stacey L. Valentine, MD, MPH; Anil Sapru, MD; Renee A. Higgerson, MD; Phillip C. Spinella, MD; Heidi R. Flori, MD; Dionne A. Graham, PhD; Molly Brett, BA; Maureen Convery, BS; LeeAnn M. Christie, RN; Laurie Karamessinis, CCRC; Adrienne G. Randolph, MD, MSc; on behalf of the Pediatric Acute Lung Injury and Sepsis Investigator’s (PALISI) Network and the Acute Respiratory Distress Syndrome Clinical Research Network (ARDSNet)

n=168
NGAL-Directed RRT Initiation

Use of Neutrophil Gelatinase-Associated Lipocalin (NGAL) to Optimize Fluid Dosing, Continuous Renal Replacement Therapy (CRRT) Initiation and Discontinuation in Critically Ill Children With Acute Kidney Injury (AKI)

ClinicalTrials.gov Identifier: NCT01416298

Available at: http://www.clinicaltrials.gov/ct2/show/NCT01416298?term=NCT01416298&rank=1
23 bags ≈ 9000 mg NaCl ≈
Next Steps…Phase III

• Body has not evolved a natural mechanism to remove excess ↑ Na⁺ and water

• “De-resuscitation” in MODS/AKI?
  – *When can fluid be ideally removed? Triggers?*
  – *How much fluid should/must be removed?*
  – *What is the timeline for active elimination?*
Summary

- **Fluid is a Drug** ~ considering its toxic cumulative effects to guide optimal dosing may improve outcome
- **Volume** and **Timing** of **Fluid** are critical
- (Excessive) **Fluid accumulation** is bad – *predictor of less favorable outcome*
- Need to better understand ideal strategies to (safely) mitigate and/or remove excess extravascular fluid
Thank You For Your Attention!

Acknowledgements
Stuart Goldstein

Questions?
bagshaw@ualberta.ca