Fluid Balance in Acute Kidney Injury Patients on Dialysis

Jan O Friedrich, MD DPhil
Associate Professor of Medicine, University of Toronto
Medical Director, MSICU
St. Michael’s Hospital, Toronto, Canada
Critical Care Canada Forum – 27 October 2015
Conflicts of Interest

• None to report
I practiced my talk on these experts
They had no specific suggestions
Introduction

• Conceptually, fluid balance is important
  – Before patients develop acute kidney injury (AKI)
  – After developing AKI but before requiring dialysis
  – After AKI has progressed to dialysis
    • In theory, fluid balance most easily manipulated while on dialysis
    • This was meant be the focus of this presentation
    • Data are very limited
Contents

• Observational Data
• Randomized Controlled Trial Data
  – Diuretics (furosemide)
  – Conservative vs Liberal fluid management strategies
• Fluid Management in Dialysis
• Summary and Conclusions
RRT Initiation

• Based on Canadian practice
  – Observational: 3 centres, 6 ICUs, 234 patients

• RIFLE Cr criteria met for
  – Failure (tripling serum Cr): 77%
  – Injury (doubling serum Cr): 21%

• Ref: Bagshaw, Wald, Barton, Burns, Friedrich, House et al J Crit Care 2012; 27:268
Canadian practice on RRT timing

We don’t wait for classic indications in most cases

<table>
<thead>
<tr>
<th>Parameter – At RRT Initiation</th>
<th>n=234</th>
</tr>
</thead>
<tbody>
<tr>
<td>SOFA score (IQR)</td>
<td>14 (10-16)</td>
</tr>
<tr>
<td>Vasopressor (%)</td>
<td>147 (63%)</td>
</tr>
<tr>
<td>Mechanical ventilation (%)</td>
<td>199 (85%)</td>
</tr>
<tr>
<td>( \text{PaO}_2/\text{FiO}_2 ) (mmHg; mean ( \pm ) st dev)</td>
<td>206 (±167)</td>
</tr>
<tr>
<td>pH</td>
<td>7.28 (±0.11)</td>
</tr>
<tr>
<td>Potassium ( \geq 5.5 \text{ mM} )</td>
<td>38 (16%)</td>
</tr>
<tr>
<td>Bicarbonate ( \leq 15 \text{ mM} )</td>
<td>79 (34%)</td>
</tr>
<tr>
<td>sCr (( \mu \text{M} )) – baseline 92 (72-120)</td>
<td>331 (225-446)</td>
</tr>
<tr>
<td>Urea (mM)</td>
<td>23 (14-33)</td>
</tr>
<tr>
<td>Oligoanuria (&lt;400 mL/24h)</td>
<td>77 (33%)</td>
</tr>
<tr>
<td>% Fluid Overload &gt;10%</td>
<td>35 (18%)</td>
</tr>
<tr>
<td>Hospital admit to RRT (days)</td>
<td>3 (1-10)</td>
</tr>
<tr>
<td>ICU admit to RRT (days)</td>
<td>1 (0-4)</td>
</tr>
</tbody>
</table>

Fluid Overload Associated with Increased Mortality Pre-RRT

- Parameters associated with hospital mortality:
  - Non-renal organ failure >3
  - Time from ICU adm >4d to RRT
  - Urine Output <82 mL/d pre-RRT
  - Serum Cr <332 mM
  - Fluid balance >5% or >3L/24h
  - SOFA score >14
  - Δ Urea > 9 mM from ICU admit

Ref: Bagshaw et al J Crit Care 2012; 27:268
Fluid Overload Associated with Increased Mortality in AKI

• Sepsis Occurrence in Acutely-ill Patients (SOAP) Sub-Study
  – All* patients admitted May 1-15, 2002 from 198 European ICUs (n=3147)
    • 1120 (36%) had AKI (Cr>310 \( \mu \text{M}^+ \) or U/O <500 mL/d)
    • Higher 60d mortality vs non-AKI: 36% vs 16% (p<0.01)
    • Independent predictors of mortality included:
      – Age, SAPS II, medical (vs surgical), heart failure, cirrhosis, mechanical ventilation, \textbf{positive fluid balance}

• * Excluded routine post-operative monitoring patients
• Ref: Payen et al. Positive fluid balance is associated with a worse outcome in patients with acute renal failure. Crit Care 2008; 12: R74. \( ^+\) >3.5 g/dL
Fluid Overload Associated with Increased Mortality in Early AKI

- **SOAP Sub-Study**
  - Positive fluid balance only associated with higher mortality in early (≤2d post ICU admission) AKI

<table>
<thead>
<tr>
<th>Fluid Balance (L/d)</th>
<th>Survivors</th>
<th>Non-Survivors</th>
</tr>
</thead>
<tbody>
<tr>
<td>All AKI</td>
<td>0.1 ±1.1</td>
<td>1.0 ±1.5 (p&lt;0.001)</td>
</tr>
<tr>
<td>– Early AKI</td>
<td>0.1 ±1.1</td>
<td>1.2 ±1.5 (p&lt;0.001)</td>
</tr>
<tr>
<td>– Late AKI</td>
<td>0.1 ±1.0</td>
<td>0.4 ±1.4 (p=n.s.)</td>
</tr>
</tbody>
</table>

- Patients with early vs late AKI had similar mortality: 35% vs 37%

Fluid Overload Associated with Increased Mortality in Early AKI

• Early during resuscitation, it may be difficult to limit fluids
  – higher fluid balance may identify patients with higher need for resuscitation/acuity of illness

• The ability to limit fluids later in the ICU stay may have limited effect on outcomes

Fluid Overload Associated with Increased Mortality In CRRT

• RENAL Sub-Study
  – 1453/1508 patients randomized to high vs standard dose CVVHD in 35 ANZIC ICUs
  – Mean daily fluid balance lower in survivors:
    • −234 vs +560 mL/d (p<0.0001)
    • Independent predictor of survival
  – Negative fluid balance associated with
    • decreased death at 90d (OR 0.32, p<0.0001)
    • decreased ICU and hospital length of stay

• Ref: RENAL Investigators. CCM 2012; 40: 1753-60.
Fluid Overload Associated with Increased Mortality In CRRT

– Both survivors and non-survivors had positive fluid balances on Day 1 (resuscitation phase)

– Survivors had neutral mean fluid balance by Day 2

– Unclear whether this was due to less need for resuscitation or due to active fluid management by clinicians (presumably both groups managed similarly)
Fluid Overload Associated with Increased Mortality in AKI

- Program to Improve Care in Acute Kidney Disease (PICARD) in 5 U.S. ICUs 1999-2001
  - 618 patients referred to nephrologist with AKI (Cr rise of at least 44\* μM [0.5 mg/dL])
  - Compared patients with vs without fluid overload >10% body weight (BW)

- * increase of at least 88 μM if baseline Cr >133 μM
Fluid Overload Associated with Survival and Maintained Over 60 Days
Higher Mortality Proportional to Total Fluid Accumulation …
... and in patients who continued to be fluid overloaded during dialysis

- In patients starting dialysis with fluid overload >10% body weight,
  - those that ended dialysis with fluid overload >10% body weight had higher mortality
    - 65% vs 35% (p=0.0002)

Limitations: Observational Data

• Residual confounding
  – Fluid overload is strongly associated with higher acuity of illness
  – Only some patients tolerate fluid removal without significant hypotension
  – As patients conditions improve, they begin to spontaneously mobilize fluids

• Underestimation of AKI severity in fluid overloaded patients due to dilution of some traditional renal function markers (Cr, BUN)
Randomized Controlled Trial Data

• Unfortunately, RCT data is very limited
  (None comparing conservative to liberal fluid management strategies in patients with ARF)

• Diuretic RCTs

• Conservative vs liberal fluid management RCTs
  – Mild-moderate ARDS
  – Peri-operative elective surgery
Meta-Analyses of Furosemide RCTs (Used to Prevent or Treat AKI)

- *Furosemide treatment may reduce RRT duration but results in no improvement in clinical outcomes.*

<table>
<thead>
<tr>
<th>Meta-Analysis</th>
<th>Mortality</th>
<th>Need for RRT</th>
<th>RRT Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>9 RCTs/849 pts</td>
<td>RR 1.11</td>
<td>RR 0.99</td>
<td>-0.5 RRT Sessions</td>
</tr>
<tr>
<td></td>
<td>(0.92-1.33)</td>
<td>(0.80-1.22)</td>
<td>(-1.5 to 0.5)</td>
</tr>
<tr>
<td>5 RCTs/555 pts</td>
<td>OR 1.28</td>
<td>OR 0.50</td>
<td>-1.4 RRT days*</td>
</tr>
<tr>
<td></td>
<td>(0.89-1.84)</td>
<td>(0.23-1.10)</td>
<td>(-0.2 to -2.3)</td>
</tr>
</tbody>
</table>

*p=0.02

Largest Furosemide RCT (included in both meta-analyses)

- 338 patients from 13 ICUs and 10 nephrology wards with AKI requiring RRT
  - 8 improved without dialysis and excluded

• Randomization
  - Furosemide (mg/kg/d): 25 IV or 35 PO (max 2g/d)
    • tapered over 3 days post renal recovery
  - Blinded placebo

• Ref: Cantarovich et al AJKDz 2004; 44:402-9
## Largest Furosemide RCT

### Results

<table>
<thead>
<tr>
<th></th>
<th>Placebo (n=164)</th>
<th>Furosemide (n=166)</th>
<th>Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mortality</strong></td>
<td>30%</td>
<td>36%</td>
<td>+20% (p=0.36)</td>
</tr>
<tr>
<td><strong>RRT sessions</strong></td>
<td>6.9 ±5.3</td>
<td>6.5 ±5.4</td>
<td>-0.4 (p=0.37)</td>
</tr>
<tr>
<td><strong>Days</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>of RRT</td>
<td>12 ±9</td>
<td>11 ±9</td>
<td>-1 (p=0.21)</td>
</tr>
<tr>
<td>to U/O&gt;2 L/day</td>
<td>8 ±7</td>
<td>6 ±6</td>
<td>-2 (p=0.004)</td>
</tr>
<tr>
<td>to Cr &lt;200 μM</td>
<td>21.4 ±65</td>
<td>19.7 ±41</td>
<td>-1.7 (p=0.99)</td>
</tr>
</tbody>
</table>

### Ref:
- Cantarovich et al AJKDz 2004; 44:402-9
Summary of Furosemide RCTs

Furosemide

● Increases fluid removal
● May decrease duration of dialysis
● Results in no improvement in
  – renal function (serum Cr)
  – mortality
Lack of Response to Furosemide Predicts Worsening of AKI

- 77 patients with either
  - AKIN Stage 1
  - AKIN Stage 2
  - Not pre-renal treated with furosemide 1 mg/kg (Rx naive) or 1.5 mg/kg

- Outcome:
  - AKIN Stage 3 (RRT, > tripling Cr, or 24h u/o < 0.3 mL/kg) best predicted by
    - 2h u/o > 200 mL post furosemide
    - Sens 87% and Spec 84%

Furosemide Stress Test (FST) Predicts Worsening of AKI

- Hourly Urine Output in Non-Progressors (solid bars) and Progressors (striped bars) to AKIN Stage 3
Furosemide Stress Test (FST) Better Predictor than Other Biomarkers

- AUC for RRT 0.86
  - AUC for AKIN Stage 3 0.87
- better than other biomarkers
  - AUCs 0.52-0.62 for RRT
    - AUCs 0.54-0.75 for AKIN stage 3
  - Urine (or plasma) NGAL, IL-18, KIM-1, uromodulin, IGFBP-7, TIMP-2
  - Creatinine, albumin-to-creatinine ratio, FENa
- FST not sign. improved when biomarkers added
  - AUC 0.90-0.91

Why is the Furosemide Stress Test (FST) Such a Good Predictor?

- To increase urine output, furosemide requires two distinct tubular nephron segments to be functioning:
  1) As an organic acid, it is tightly bound to serum proteins and requires active secretion via the organic anion transporter in the proximal tubule
  2) Within the tubule it inhibits the Na-K-2Cl transporter in the thick ascending loop of Henle

- Postulated that this dual integrity requirement makes furosemide such a good physiological and clinical instrument to assess tubular function.

RCT of Conservative vs Liberal Fluid-Management Strategies in ARDS

- 1000 patients with ARDS (P/F < 300 mm Hg) randomized to conservative vs liberal fluid strategy (FACCT Trial)
- Comprehensive (but complex) algorithm based on
  - CVP (or PWP)
  - Blood Pressure
  - Urine Output
  - Ineffective vs effective circulating volume
  - (Targets were relaxed if patients were on vasopressors)
- Minimal renal dysfunction (mean Cr 110 μM [1.3 g/dL])

# RCT of Conservative vs Liberal Fluid-Management Strategies in ARDS

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Conservative</th>
<th>Liberal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Daily Fluid Balance/7d</td>
<td>–0.02 ±0.1</td>
<td>+1.0 ±0.1* L/d</td>
</tr>
<tr>
<td>VFD to Day 28</td>
<td>14.6 ±0.5</td>
<td>12.1 ±0.5*</td>
</tr>
<tr>
<td>Dialysis</td>
<td>10%</td>
<td>14% (p=0.06)</td>
</tr>
<tr>
<td>60d Mortality</td>
<td>26%</td>
<td>28% (p=0.3)</td>
</tr>
</tbody>
</table>

* *p<0.001

RCT of Peri-Operative Conservative vs Liberal Fluid-Management Strategies

• 142 colorectal resection patients (ASA 1-3) randomized to conservative vs liberal fluid strategy in 8 Danish hospitals with blinded assessment of complications

• Received less IVF:
  – Day of surgery: 2.7 vs 5.4 L (p<0.0005)
  – Post-op Day 1: 0.5 vs 1.5 L (p=0.003)

• Ref: Brandstrup et al Ann Surg 2003; 238: 641
RCT of Peri-Operative Conservative vs Liberal Fluid-Management Strategies

Conservative fluid management:

- Lower major, minor, tissue healing and cardiopulmonary complications (p=0.04 to <0.001)
- Renal differences only on day of surgery:
  - Lower urinary output: 1.1 vs 1.7 L (p<0.0005)
  - More oliguria (<0.5 mL/kg/h): 12% vs 3% (p=0.008)
  - Slightly Higher Cr: 86 vs 76 μM (p=0.002)
  - No cases of renal failure; 0 vs 4 deaths (p=0.12)

Fluid Management on Dialysis

- No published RCTs for guidance
  - Also, no pending RCTs on trial registration web sites
- On dialysis, fluid balance can be readily manipulated
- More aggressive fluid removal risks causing
  - Hypotension or
  - Increased vasopressor requirements
during (and often continuing post) dialysis

- How far should one increase vasopressors to achieve negative fluid balance?
Both Fluid Overload and Hypotension During Dialysis Associated with Increased Mortality

- Two University of Toronto Hospitals
  - Cohort of 492 patients with AKI requiring RRT for at least 2 days in ICU (2007-2012)
  - Collected fluid balance, fluid overload (>10% admission weight), hypotension (MAP<65 mm Hg or ≥20% decline) while receiving dialysis
  - Comorbidities, acuity of illness, and sequential organ failure (SOFA) score

Both Fluid Overload and Hypotension During Dialysis Associated with Increased Mortality

- Intradialytic hypotension extremely common: 87%

<table>
<thead>
<tr>
<th></th>
<th>Survivors</th>
<th>Non-Survivors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean daily balance/7d (L)</td>
<td>+0.4</td>
<td>+1.1 (p&lt;0.01)</td>
</tr>
</tbody>
</table>

- Independent predictors of mortality included both:
  - positive fluid balance,
  - intradialytic hypotension

Both Fluid Overload and Hypotension During Dialysis Associated with Increased Mortality

• This potentially causes a dilemma for clinicians:
  – Does one remove more fluid (to avoid fluid overload)? or
  – Does one remove less fluid (to avoid hypotension during dialysis)?

  since both are associated with mortality

• Which is more important?
# Causes and Avoidance of Intradialytic Hypotension

<table>
<thead>
<tr>
<th>Cause</th>
<th>Method to Minimize Impact</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intravascular volume depletion</td>
<td>Ultrafiltrate based on volume status (not dry weight)</td>
</tr>
<tr>
<td>Low blood osmolality</td>
<td>Lengthen or increase frequency of dialysis sessions</td>
</tr>
<tr>
<td>Myocardial contractility</td>
<td>Wrap extremities to increase hydrostatic pressures</td>
</tr>
<tr>
<td>Vascular reactivity</td>
<td>Increase [Na] (145-150 mM) in dialysate</td>
</tr>
<tr>
<td>Inflammatory cytokines</td>
<td>Lower blood flow rate</td>
</tr>
<tr>
<td></td>
<td>Increase [Ca] (∊1.75 mM) in dialysate</td>
</tr>
<tr>
<td></td>
<td>Use bicarbonate (not acetate) buffer</td>
</tr>
<tr>
<td></td>
<td>Cool dialysate (1-2 °C below body temperature)</td>
</tr>
<tr>
<td></td>
<td>Use most biocompatible membranes</td>
</tr>
</tbody>
</table>

Summary

• Observational data suggests a very strong relationship between positive fluid balance and poor clinical outcomes including higher mortality, but this data is confounded

• Randomized controlled trial data very limited
  – Diuretics in AKI: improved fluid removal and shortening of dialysis but no improvement in renal function or mortality
  – Conservative vs liberal fluid management (patients without AKI):
    • Shortened duration of ventilation in mild-moderate ARDS
    • Decreased (?fluid-related) peri-operative complications in elective surgery patients
    • No differences in mortality
Conclusions

- Patients (with or without AKI) likely benefit from aggressive removal of excessive fluids (especially after the early resuscitation phase)
- Achieving negative fluid balance requires vigilance
  - RCTs suggest fluids accumulate without a strict algorithm
- However, if achieving a negative fluid balance requires increasing vasopressors, higher vasopressor doses are likely more harmful than the smaller benefits from aggressive fluid removal
  - Highlights the importance of instituting methods to minimize hypotension during dialysis
The End -- Time to Wake Up

(Judging by how much the experts have aged, I may have gone a little over time ....)
Questions?