AKI: The Kidney/Lung Connection and Fluid Management in COVID-19

Welcome & Opening Statements

ANITHA VIJAYAN, MD, FASN
Washington University
St. Louis, Missouri

@VijayanMD
Background-The Kidney/Lung Connection

Kathleen Liu, MD, PhD, FASN
University of California at San Francisco School of Medicine

Disclosures

• No relevant conflicts of interest
• Consultant for: BioMerieux, Durect, UptoDate
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Take Home Points

• The kidney-lung connection is bidirectional – there is organ crosstalk!
• At present, whether or not there are specific pathogenic mechanisms in the context of COVID-19 is unknown
• However, ARDS in the setting of COVID-19 is severe and prolonged ... so there is plenty of opportunity for crosstalk and impact on the kidney

Influence of the lung on the kidney: Focus on the acute respiratory distress syndrome

• Leading cause of hypoxemic respiratory failure
  • Defined by chest radiograph + PaO2/FiO2 < 300 on positive pressure ventilation
• Develops following certain clinical conditions, including COVID-19 infection
• No specific therapies
  • Ventilator and fluid management

Ranieri et al, JAMA 2012
What are the hemodynamic effects of positive pressure ventilation?

- Increased intrathoracic/right atrial pressure
  - Leads to decreased venous return
  - Exacerbated by intravascular volume depletion, higher airway pressures (PEEP); high PEEP is common in patients with COVID-19
- Increased PVR
  - Leads to decreased RV/LV output
- Vary depending on lung and chest wall compliance

Impact of lung injury on distal organ function: Role for soluble mediators?

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<thead>
<tr>
<th>MCP-1 (ng/mL)</th>
<th>Baseline</th>
<th>8 hours</th>
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<tbody>
<tr>
<td>Noninjurious</td>
<td>0.23 (0.09)</td>
<td>11.8 (2)</td>
</tr>
<tr>
<td>Injurious</td>
<td>0.29 (0.14)</td>
<td>2.2 (3)</td>
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<tr>
<th>IL-8 (ng/mL)</th>
<th>Baseline</th>
<th>8 hours</th>
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<tbody>
<tr>
<td>Noninjurious</td>
<td>0.08 (0.03)</td>
<td>0.23 (0.05)</td>
</tr>
<tr>
<td>Injurious</td>
<td>0.07 (0.02)</td>
<td>1.5 (0.34)</td>
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<tr>
<th>Cr (mg/dL)</th>
<th>Baseline</th>
<th>8 hours</th>
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<tr>
<td>Noninjurious</td>
<td>0.74 (0.02)</td>
<td>1.06 (0.04)</td>
</tr>
<tr>
<td>Injurious</td>
<td>0.72 (0.02)</td>
<td>1.3 (0.09)</td>
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Imai et al, JAMA 2003
Effects of lung injury on the kidney

**THE KIDNEY-LUNG CONNECTION**

**“Uninjured”**
1.9% TUNEL+

**“Injured” (+ALI)**
10.9%

Lung protective ventilation is associated with lower levels of pro-inflammatory cytokines

- In a multivariable analysis, IL-6 levels were independently associated with the development of AKI in this cohort (OR 1.31 [1.02-1.70], p=0.04)

**ARDN Network ARMA Study, NEJM 2000**
Endothelial injury biomarkers are increased in the kidney after VILI and sepsis

What is the impact of “adjunctive care” for ARDS on AKI?

• “Permissive hypercapnea” is component of low tidal volume ventilation algorithms
  • Since goal is low airway pressures, tidal volumes are reduced to a target of 6 cc/kg PBW, but sometimes as low as 4 cc/kg
  • Target pH 7.30-7.45
  • With normal renal function, develop compensatory metabolic alkalosis

• Although multiple animal studies suggest that hypercapneic acidosis is cytoprotective, it may enhance bacterial proliferation and thereby promote cellular injury
What is the impact of “adjunctive care” for ARDS on AKI?

**THE KIDNEY-LUNG CONNECTION**

- UOP < 0.5 ml/kg/h & CVP or PAOP low
- MAP < 60 Low flow by exam or CI <2.5

**Furosemide**

- CVP < 4
- PAOP < 8

Favors Dry LUNG


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**THE KIDNEY-LUNG CONNECTION**

**Graph:**

- Liberal
- Conservative
- ARMA 6 ml (1996-1999)
- ALVEOLI all (1999-2002)

FACTT Trial: Outcomes

- Trend towards less dialysis in the conservative arm compared to the liberal arm (10% vs 14%, p = 0.06)

**THE KIDNEY-LUNG CONNECTION**

Fluid overload in AKI may exacerbate lung function

- Complete recovery with fluid removal
- Partial recovery with fluid removal but failure to be quickly extubated
- Fluid removal does little to improve oxygenation

Faubel and Edelstein, Nat Rev Neph 2016
ARDS after AKI is mediated by IL-6

Impact of dialysis on inflammation

Klein et al, Kidney Int 2008

Altmann et al, Kidney Int 2017
Summary

- Multiple mechanisms may result in AKI after mechanical ventilation/ARDS (and vice versa)
- Low tidal volume ventilation is associated with lower levels of pro-inflammatory cytokines in large trials of patients with ARDS (non-COVID)
- Other supportive care interventions for patients with ARDS may affect AKI (permissive hypercapnia, fluid management)
- Volume overload is common in AKI; the impact of fluid removal may vary depending on mechanism of injury
- Pro-inflammatory cytokines may play an important role in ARDS in the context of AKI

Fluid Management in COVID-19

Michael Heung MD
University of Michigan
mheung@umich.edu
@keepingitrenal
Disclosures

• No relevant conflicts of interest

• Research funding from: VA, CDC, PCORI

The Quandary

Fluid Overload
• Contribution to cardiopulmonary edema
• Association with worse outcomes (mortality, kidney recovery)
• Venous congestion

Fluid Removal
• Exacerbation of shock, organ underperfusion
• Contribution to AKI

Key concept: fluid responsiveness
**Tools At Our Disposal**

- Physical exam: vital signs, perfusion
- Diagnostic maneuvers: passive straight-leg raise, IVF challenge
- Non-invasive monitoring: lung ultrasound, IVC ultrasound, PPV, SVV, RBV/Hct
- Invasive monitoring: CO, PAOP

*There remains no consensus approach*

**FLUID MANAGEMENT**

**Challenges in COVID-19**

- Minimizing physical contact and PPE use
- Validity of assessment tools in low tidal volume ventilation and in prone patients
- Limited resources in pandemic surge setting: disposables, advanced monitoring equipment, expertise
Literature: FACTT Trial

- RCT evaluating conservative vs liberal fluid strategies in ARDS (n=1000)
  - Achieved difference in fluid balance
- No difference in 60 day mortality
  - More ventilator-free and ICU-free days in conservative group
- No difference in pts requiring RRT (10 vs 14%, p=.06)

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<th>FLUID MANAGEMENT</th>
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<tr>
<td><strong>Conservative</strong></td>
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<tr>
<td>7d net balance (mL)</td>
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<tr>
<td>Shock</td>
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<td>Non-shock</td>
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Wiedemann, NEJM 2006;354:2564-75

Literature: Timing of Fluids

- Retrospective study (n=212)
- In patients with ALI and septic shock, adequate initial fluid resuscitation followed by conservative late fluid management was associated with lowest mortality

Murphy, Chest 2009;136:102-9
Literature: CRRT Fluid Management

- Pediatric patients requiring ECMO and CRRT (n=53)
- Fluid overload at CRRT initiation was most important predictor of outcome (mortality)
- In patients with significant fluid overload at RRT initiation, fluid removal was not associated with improved survival

Selewski Crit Care Med 2012;40:2694-9

Michigan COVID-19 Experience

FluId balance  PaO2/FIO2  PEEP

N=32  Unpublished data
**Principles/Take Home Advice**

- In general, a more conservative approach to fluid administration is suggested → Surviving Sepsis guidelines

- There is little evidence to guide RRT strategies in ARDS, but earlier initiation to manage fluid balance in patients at risk for fluid overload may be warranted

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**Round Table Discussion and Q & A Panelist**

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Summary and Closing Remarks

ANITHA VIJAYAN, MD, FASN
Washington University
St. Louis, Missouri

@VijayanMD 🐦