Why Quantify GFR in ACUTE KIDNEY INJURY? 
Advantages and Challenges 

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Why is mGFR at Point of Care Needed?

1. Serum creatinine is insensitive and slow to increase post injury.

2. Serum Creatinine and eGFR are unreliable due to altered release in AKI, and muscle wasting in 90 day value.

3. GFR is a proven measure of global kidney function.

4. Determination of GFR would allow for rapid diagnosis of AKI and stratification of patients by severity of injury.

5. GFR would allow for rapid determination of response to therapy such as a volume challenge.

6. mGFR would quantify loss of function following recovery of the acute event.
Why is GFR not Determined in AKI Now?

1. Multiple “Gold Standard” Techniques have been developed, YET

2. Sampling methods such as inulin, iohexol, or iothalimide clearance:
   - All require 6+ hours to administer test - multiple blood draws
   - Require samples to be sent for outside lab analysis, requiring days
   - Possible radiation exposure from injected marker
   - Based on ECF single compartment model
   - Too expensive, time consuming and cumbersome to be practical
   - GFR can change in time of study with AKI

3. Which GFR to quantify? Baseline (fasting), stimulated, average.
Developing a Progressive Proteinuric Chronic Kidney Disease Model Following Ischemic Injury

Note, SCr does not Correlate with GFR During Recovery
GFR and RBF are Chronically Reduced in Previously Healthy Patients with AKI

**Figure 1. Values for Inulin Clearance at Varying Intervals after the Onset of Acute Renal Failure.**

The dotted line indicates approximately normal values for this laboratory. The range is approximately $125 \pm 25$ ml. per minute per 1.73 square meters of body-surface area.

Finkenstaedt, JT and JP Merrill, NEJM 1956
Serum Creatinine Changes Associated with Critical Illness and Detection of Persistent Renal Dysfunction after AKI

Serum creatinine has many determinants

Muscle loss during hospitalization is a problem

With long term follow up eGFR increases even with AKI 3

How does one adjust for muscle loss?

Prowle JR et al, CJASN 2014
Creatinine is an Insensitive Marker of GFR Loss

Figure 3. Relationship of Serum Creatinine Level to Measured GFR in the Modification of Diet in Renal Disease Study. GFR was measured as the urinary clearance of $^{125}$Iiothalamate. Serum creatinine was measured with a Beckman Astra CX3 analyzer and a kinetic alkaline picrate assay.$^{32,33}$ Regression lines were computed from the relationship of the reciprocal of serum creatinine with GFR. When the GFR was 60 ml per minute per 1.73 m$^2$, the 95 percent confidence interval for the serum creatinine level was 1.3 to 1.5 mg per deciliter in white men (measured in 802) and in 1.4 to 1.8 in black men (measured in 113) (left panel) and 1.0 to 1.2 mg per deciliter in white women (measured in 502) and 1.1 to 1.4 mg per deciliter in black women (measured in 84) (right panel). These levels are close to the upper limit of the reference range. Confidence intervals for serum creatinine levels were wider at lower levels of GFR. To convert the values for serum creatinine to micromoles per liter, multiply by 88.4. Adapted from Levey et al.$^{32}$

Levy, A. NEJM
Which GFR should we Quantify?

Baseline GFR = Fasting GFR
Total GFR = Baseline + Renal Reserve
Glomular Filtration Rate

- Varies throughout the day
- 24 hr urine measures average daily CrCl
- Renal Reserve is the portion of GFR that can be stimulated above baseline
- When we loose GFR from injury do we first loose RR and then baseline GFR or do we loose them proportionally???
- Therefore, What GFR should we Quantify?
Pathophysiology of “Augmented Renal Clearance”

Udy AA, Clin Pharmacokinet 2010
<table>
<thead>
<tr>
<th>Variable</th>
<th>ARC (n = 183)</th>
<th>No ARC (n = 98)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yr, mean (95% CI)</td>
<td>49.1 (46.8–51.4)</td>
<td>64.4 (61.6–67.2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Gender, male, n (%)</td>
<td>124 (67.8)</td>
<td>54 (55.1)</td>
<td>0.036</td>
</tr>
<tr>
<td>Weight, kg, mean (95% CI)</td>
<td>73.3 (70.6–76.0)</td>
<td>70.6 (66.6–74.7)</td>
<td>0.266</td>
</tr>
<tr>
<td>Height, m, mean (95% CI)</td>
<td>1.67 (1.66–1.69)</td>
<td>1.65 (1.63–1.67)</td>
<td>0.077</td>
</tr>
<tr>
<td>Body mass index, kg/m², mean (95% CI)</td>
<td>26.0 (25.3–26.8)</td>
<td>25.8 (24.5–27.1)</td>
<td>0.750</td>
</tr>
<tr>
<td>Body surface area, m², mean (95% CI)</td>
<td>1.82 (1.78–1.85)</td>
<td>1.77 (1.72–1.81)</td>
<td>0.106</td>
</tr>
<tr>
<td>Acute Physiology and Chronic Health Evaluation II, mean (95% CI)</td>
<td>15.7 (14.7–16.6)</td>
<td>16.6 (15.3–17.8)</td>
<td>0.265</td>
</tr>
<tr>
<td>Modified Sequential Organ Failure Assessment score (max), median (IQR)</td>
<td>3 (2–6)</td>
<td>3 (2–6)</td>
<td>0.711</td>
</tr>
<tr>
<td>Mechanical ventilation (at any point), n (%)</td>
<td>150 (82.4)</td>
<td>56 (57.7)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Vasopressor/inotropes (at any point), n (%)</td>
<td>76 (41.5)</td>
<td>35 (35.7)</td>
<td>0.342</td>
</tr>
<tr>
<td>Norepinephrine (at any point), n (%)</td>
<td>66 (36.1)</td>
<td>30 (30.6)</td>
<td>0.358</td>
</tr>
<tr>
<td>Dopamine (at any point), n (%)</td>
<td>14 (7.7)</td>
<td>5 (5.1)</td>
<td>0.417</td>
</tr>
<tr>
<td>Admission category, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Elective</td>
<td>13 (7.1)</td>
<td>13 (13.3)</td>
<td>0.089</td>
</tr>
<tr>
<td>Emergency</td>
<td>54 (29.5)</td>
<td>39 (39.8)</td>
<td>0.081</td>
</tr>
<tr>
<td>Surgical emergency</td>
<td>86 (47.0)</td>
<td>40 (40.8)</td>
<td>0.321</td>
</tr>
<tr>
<td>Trauma</td>
<td>30 (16.4)</td>
<td>6 (6.1)</td>
<td>0.014</td>
</tr>
<tr>
<td>ICU length of stay (d), median (IQR)</td>
<td>5 (3–11)</td>
<td>3 (2–6)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>ICU mortality, n (%)</td>
<td>14 (7.7)</td>
<td>10 (10.2)</td>
<td>0.466</td>
</tr>
</tbody>
</table>

ARC = augmented renal clearance, IQR = interquartile range.

Udy AA, CCM Journal 2014
ICU CrCl over time in Patients w & w/o ARC

Udy AA, CCM Journal 2014
<table>
<thead>
<tr>
<th>Molecular Marker</th>
<th>Amount Injected</th>
<th>Sample Space</th>
<th>Detector Site</th>
<th>Test Time</th>
<th>Readout</th>
<th>Miscellaneous</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dextrans 150kDa-Rh</td>
<td>Rat 2.9mg / 100g BW&lt;br&gt;Dog 0.6mg / 100g BW&lt;br&gt;Man 0.2mg / 100g BW (3ml at 50mg/ml)</td>
<td>Vasculature</td>
<td>Venous</td>
<td>&lt;10 min/rat&lt;br&gt;&amp;&lt;60 min/dog&lt;br&gt;&amp;&lt;120 min Man</td>
<td>PV, GFR</td>
<td>FAST 2-compartment model&lt;br&gt;LED light source</td>
<td>Wang, E et al AJP: 2010; Wang et.al. Kidney Inter 2011</td>
</tr>
<tr>
<td>Sinistrin-FITC</td>
<td>63mg/100g BW</td>
<td>ECF</td>
<td>Skin</td>
<td>?</td>
<td>Decay Rate</td>
<td>HMKQ Quantitative Analytik</td>
<td>Schock-Kusch et al, Kidney Inter: 2011, Many others</td>
</tr>
<tr>
<td>99m Tc-DTPA</td>
<td>0.8μCi/Kg (56μCi/7.0Kg)</td>
<td>ECF</td>
<td>Arm</td>
<td>(30-60 min)*</td>
<td>Decay Rate</td>
<td>Can do renal scan also</td>
<td>Rabito, CA et al, Clin and Trans Res: 2010</td>
</tr>
<tr>
<td>Carbustyriyl 124-DTPA-Eu</td>
<td>10mg / 100g BW (14.4ml at 500mg/ml)</td>
<td>ECF</td>
<td>Skin</td>
<td>5 min/rat</td>
<td>Decay Rate</td>
<td>Laser 340nm</td>
<td>Rabito, CA et al, Applied Optics: 2005</td>
</tr>
<tr>
<td>PP-2338 / PEG-Pyrazine</td>
<td>ECF</td>
<td>Skin</td>
<td>120 min/rat</td>
<td>Decay Rate</td>
<td>Covidien Laser 445nm&lt;br&gt;MediBeacon</td>
<td>Poreddy et.al. Bioorg. and Med. Chem 2012</td>
<td></td>
</tr>
<tr>
<td>FITC – F10</td>
<td>ECF</td>
<td>Skin</td>
<td>?</td>
<td>Decay Rate</td>
<td>Roche, HMKQ Inulin derivative increased solubility</td>
<td>Schock-Kusch Abst; ASN 2010</td>
<td></td>
</tr>
</tbody>
</table>

*Estimate for man
Measured GFR, Cr-EDTA vs. CrCL

Variability unacceptable for measurement in AKI

Bragadottir G, Critical Care 2013
Measured GFR vs. Estimated GFR

eGFR on no value in AKI
Single Compartment GFR Determination

Advantages

- Straight forward
- Multiple compounds can be used
- Can determine ECF Fluorescence with external detector
- Can do continuous infusion and follow dynamically

Challenges

- Delayed timed samples needed, 4-6 hr
- Yields only a rate constant not GFR
- Need plasma volume or ePV to convert to GFR
- Large amount of compound to be infused
- Requires normal SQ perfusion, ? reliability in ICU
- Variability in skin thickness and readout
Dependence of Iohexol (one Compartment) GFR on Sample Time

Agarwal, R et al, CJASN 2009
Online feedback–controlled renal constant infusion clearances in rats


Table 2 | Summary of constant infusion clearance experiments

<table>
<thead>
<tr>
<th>Group</th>
<th>Blood sampling</th>
<th>MAP (mmHg)</th>
<th>GFR (ml/min/100 g/bw)</th>
<th>Absolute GFR (ml/min)</th>
<th>Fluorescence intensity % ref</th>
<th>Plasma FITC-S (mg/ml)</th>
<th>IFR (ml/min)</th>
<th>Equilibration (time in min)</th>
<th>Body wt (grams)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SD</td>
<td>BL</td>
<td>91.0±10.0</td>
<td>0.55±0.18</td>
<td>2.49±0.45</td>
<td>95±2</td>
<td>0.109±0.035</td>
<td>0.0248±0.0062</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>1 h</td>
<td>95.5±3.0</td>
<td>0.54±0.22</td>
<td>2.44±0.65</td>
<td>95±1</td>
<td>0.105±0.033</td>
<td>0.0241±0.0067</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>2 h</td>
<td>90.0±3.0</td>
<td>0.58±0.24</td>
<td>2.55±1.00</td>
<td>94±3</td>
<td>0.100±0.026</td>
<td>0.0232±0.0102</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>92.2±6.4</td>
<td>0.56±0.20</td>
<td>2.49±0.67</td>
<td>94±2</td>
<td>0.105±0.030</td>
<td>0.0240±0.0075</td>
<td>73±14</td>
<td>467±73</td>
<td></td>
</tr>
</tbody>
</table>
Multiple Compartment GFR Determination

**Advantages**
- Fast, 1-2 hours, can measure renal reserve (stimulate GFR)
- Small amount of compound given
- Second marker can measure true PV and time zero small maker concentration
- Yields GFR not rate constant

**Challenges**
- Invasive detection via intravascular probe or blood sample
- Intravascular probe needed for continuous study
mGFR and PV using Clearance of Intravenous Fluorescent Dextran

3ml IV injection of large & small fluorescent marker

Small marker filtered across glomerulus, large marker retained in vascular space
Quantifying Plasma Volume and GFR in Dogs using Fluorescent Dextrans

Two Compartment Analysis offers Rapid Determination of GFR:

- 35min = 3.54ml/min/kg
- 45min = 3.50ml/min/kg
- 55min = 3.53ml/min/kg
- 90min = 3.52ml/min/kg
- 2hr = 3.51ml/min/kg
- 4hr = 3.51ml/min/kg
- 24hr = 3.51ml/min/kg
Patient ID: 1009-013
Test Date: 2014-02-07

BSA GFR: 38.13 mL/min
Plasma Volume: 3661.99 mL

GFR: 46.03 mL/min
BSA GFR: 38.13 mL/min
Vascular Leakage: 123.72 mL/min
Plasma Volume: 3661.99 mL
Blood Volume: 6103.32 mL

R²: 1

Entered Values:

<table>
<thead>
<tr>
<th>Time (min)</th>
<th>FD001 (µg/mL)</th>
<th>FD003 (µg/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>15.36</td>
<td>7.414</td>
</tr>
<tr>
<td>15</td>
<td>8.718</td>
<td>7.414</td>
</tr>
<tr>
<td>30</td>
<td>6.2</td>
<td>7.205</td>
</tr>
<tr>
<td>60</td>
<td>4.517</td>
<td>7.231</td>
</tr>
<tr>
<td>120</td>
<td>3.137</td>
<td>7.18</td>
</tr>
<tr>
<td>180</td>
<td>2.369</td>
<td>7.008</td>
</tr>
<tr>
<td>320</td>
<td>1.387</td>
<td>6.948</td>
</tr>
<tr>
<td>500</td>
<td>1.22</td>
<td>6.909</td>
</tr>
<tr>
<td>720</td>
<td>0.622</td>
<td>6.634</td>
</tr>
<tr>
<td>1440</td>
<td>0.431</td>
<td>7.521</td>
</tr>
</tbody>
</table>

Columns Excluded from Calculations
Challenges for any Technique to Quantify GFR

Very little data on the effect of:

- Edema, Ascites
- Sepsis
- Vascular permeability changes

Likely will need a pre-injury GFR

Baseline or Maximal GFR?
SUMMARY

1. Individualization of Data is Critical in AKI
2. Serum Creatinine and eGFR are of Limited Value
3. Stratifying initial Injury and Quantifying late Response to Therapy in AKI are Important
4. Rapid progress is being made in measuring GFR
5. Single and Multi-Compartment models have their advantages and challenges
6. Studies in non-normal patients will be important