Acute Kidney Injury in the Hospitalized Patient

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Classification of Acute Kidney Injury
### RIFLE Classification for Acute Renal Failure

<table>
<thead>
<tr>
<th>Stage</th>
<th>GFR criteria</th>
<th>Urine output criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risk</td>
<td>$S_{Cr}$ increased 1.5-2 times baseline or GFR decreased &gt;25%</td>
<td>$UO &lt; 0.5 \text{ ml/kg/h} &lt; 6\text{h}$</td>
</tr>
<tr>
<td>Injury</td>
<td>$S_{Cr}$ increased 2-3 times baseline or GFR decreased &gt;50%</td>
<td>$UO &lt; 0.5 \text{ ml/kg/h} &gt; 12\text{h}$</td>
</tr>
<tr>
<td>Failure</td>
<td>$S_{Cr}$ increased &gt;3 times baseline or GFR decreased &gt;75% or $S_{Cr} \geq 4 \text{ mg/dl}$; acute rise $\geq 0.5 \text{ mg/dl}$</td>
<td>$UO &lt; 0.3 \text{ ml/kg/h} 24\text{h}$ or anuria 12 h</td>
</tr>
<tr>
<td>Loss of Function</td>
<td>Persistent acute renal failure: complete loss of kidney function &gt;4 wks</td>
<td></td>
</tr>
<tr>
<td>ESRD</td>
<td>Complete loss of kidney function &gt;3 months</td>
<td></td>
</tr>
</tbody>
</table>


### Acute Kidney Injury Network

- **Introduces term acute kidney injury (AKI)**
- **Classification**
  - Abrupt (within 48 h) reduction in kidney function: increase $S_{Cr}$ of 0.3 mg/dL or more ($\geq 26.4 \mu\text{mol/L}$) or
  - A percentage increase in $S_{Cr}$ of $>50\%$ or more (1.5-fold from baseline) or
  - A reduction in urine output (documented oliguria of $< 0.5 \text{ mL/kg/h}$ for $>6 \text{h}$)
- **Differences from RIFLE**
  - Changes within 48h vs 7d
  - Less severe injury
  - Avoids using GFR criteria

### Kidney Disease Global Outcomes Acute Kidney Injury (KDIGO) Classification

<table>
<thead>
<tr>
<th>Stage</th>
<th>S&lt;sub&gt;Cr&lt;/sub&gt; Criteria</th>
<th>Urine output criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1.5-1.9 times baseline or ≥0.3 mg/dl above baseline</td>
<td>&lt; 0.5 ml/kg/h for 6-12h</td>
</tr>
<tr>
<td>2</td>
<td>2.0-2.9 times baseline</td>
<td>&lt; 0.5 ml/kg/h &gt;12h</td>
</tr>
<tr>
<td>3</td>
<td>≥3 times baseline, ≥4.0 mg/dl, or initiation of renal replacement therapy</td>
<td>&lt; 0.3 ml/kg/h for ≥24h or anuria for ≥12 h</td>
</tr>
</tbody>
</table>


### Incidence of AKI is Increasing in Hospitalized Patients

Incidence of AKI by age, sex, and race over the years, showing a significant increase.

*J Am Soc Nephrol 17:1135-1142, 2006*
Risk Factors For AKI

• Advanced age
• Diabetes mellitus
• Black race
• Preexisting chronic kidney disease
  – Up to 10 times the risk vs absence of CKD

A Graded Relationship Between Increase in $S_{Cr}$ and Risk of CKD and Mortality


Post-op RF in Cardiac Surgical Patients Predicts In-Hospital Mortality and Long Term Survival

- Cardiac surgery in 843 patients, 145 with post-op AKI
- AKI (>25% change in S_{Cr}) associated with increased in hospital mortality and higher 5 year mortality
- This long term effect persisted even if S_{Cr} had returned to baseline at discharge

Case

- 71 year old women with stage 3 CKD, hypertension, and coronary artery disease is admitted with urosepsis. On admission she is hypotensive and is resuscitated with 4.2 L of NS and low-dose norepinephrine and started on broad spectrum antibiotics. One day later she is noted to have trace pedal edema and basilar crackles. Hemodynamics have improved. Urine output ranges from 600-750 ml/day.
Hospital Course

<table>
<thead>
<tr>
<th></th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum creatinine (mg/dl)</td>
<td>1.17</td>
<td>1.02</td>
<td>1.10</td>
<td>1.17</td>
<td>1.24</td>
<td>1.3</td>
</tr>
<tr>
<td>UA</td>
<td>Ni</td>
<td>1+ protein, 3-5 RTEC/hpf</td>
<td></td>
<td>1+ protein, 5-8 RTEC/hpf, 1-3 RTC casts/lpf</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weight</td>
<td>52 kg</td>
<td>55.5 kg</td>
<td></td>
<td>57.5 kg</td>
<td></td>
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By the KDIGO, serum creatinine and urine output criteria do not qualify as clinically defined AKI.

However, the proteinuria and renal tubular cells and casts suggest some degree of renal injury.
Continuum of Renal Injury

At risk kidney  Incipient AKI  Clinical AKI

Need For Biomarkers in AKI

- Lack of early biomarkers has impaired ability to initiate timely preventive and therapeutic measures
Neutrophil Gelatinase-Associated Lipocalin (NGAL): A Novel Early Biomarker of Renal Injury

- Neutrophil gelatinase-associated lipocalin (NGAL) is one of the maximally induced genes and proteins immediately after injury
- NGAL is easily detected in the urine very early after injury

Urine NGAL is Increased 2 Hours After CPB In Patients Who Later Develop AKI

Lancet 365:1231-38,2005
In Absence of Increased $S_{Cr}$ Neutrophil Gelatinase-Associated Lipocalcin (NGAL) Predicts Increased Risk for Adverse Outcomes

Outcome of NGAL Positive Patients with Subclinical AKI
Urinary Biomarkers of Nephron Injury Are Predictive of Adverse Outcomes During Hospitalization

![Graph A and B](image)

Multicenter prospective cohort study in of 1635 ER patients at time of admission

J Am Coll Cardiol 59:246-55, 2012

Need For Biomarkers in AKI

- Lack of early biomarkers has impaired ability to initiate timely preventive and therapeutic measures
- Early prediction of AKI can allow initiation of preventive and or therapeutic measures:
  - Avoid nephrotoxins
  - Ensure hemodynamic stability, maintain MAP of at least 65 mmHg
  - Closely monitor fluids, urine output, CVP
  - Reno-protective agents
Continuum of Renal Injury

At risk kidney  Incipient AKI  Clinical AKI

Early recognition and rapid renal recovery

Feasible Strategies to Minimize Further Kidney Injury

• Preferential use of balanced physiologic solutions for patients requiring fluid resuscitation
Types of Crystalloid Solutions

- Balanced
  - A physiologic mixture of electrolytes and buffers designed to approximate makeup of plasma
- Unbalanced
  - Typically contains NaCl and no other electrolytes or buffers

### Crystalloid Solutions

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<thead>
<tr>
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<th>Na⁺ (mEq/L)</th>
<th>K⁺ (mEq/L)</th>
<th>Ca²⁺ (mEq/L)</th>
<th>Mg²⁺ (mEq/L)</th>
<th>Cl⁻ (mEq/L)</th>
<th>Buffer (mEq/L)</th>
<th>Glucose (mg/dl)</th>
<th>pH</th>
<th>pOsm (mOsm/L)</th>
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<tr>
<td>Plasma</td>
<td>141</td>
<td>4.5</td>
<td>5</td>
<td>2</td>
<td>103</td>
<td>HCO₃</td>
<td>70-110</td>
<td>7.4</td>
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<tr>
<td><strong>Normal Saline</strong></td>
<td>154</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>154</td>
<td>-</td>
<td>6.0</td>
<td>308</td>
<td></td>
</tr>
<tr>
<td>Lactated Ringer’s solution</td>
<td>130</td>
<td>4</td>
<td>4</td>
<td>-</td>
<td>109</td>
<td>Lactate 28 (mEq/L)</td>
<td>-</td>
<td>6.5</td>
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<tr>
<td>Plasma-Lyte</td>
<td>140</td>
<td>5</td>
<td>-</td>
<td>3</td>
<td>98</td>
<td>Acetate 27 mEq/L, gluconate 23</td>
<td>7.4</td>
<td>294</td>
<td></td>
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**Normal Saline**

- Most commonly used crystalloid
- The term “normal saline” comes from in vitro study of RBC lysis performed by Dutch physiologist Hartog Hamburger in 1890’s
- His studies suggested 0.9% was concentration of salt in blood rather than true value of 0.6%
Normal Saline is an Unbalanced Crystalloid Solution

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Solution contains 154 mEq/L of Na⁺ and Cl⁻ making the osmolality (308 mOsm/L) of the solution (308 mOsm/L) > blood

However, osmotic coefficient of NaCl is about 0.93 making saline close to isotonic (0.154 × 1000 × 2 × .93 = 286.44 mOsm/L)

Potential Consequences of High Cl⁻ Concentration in Normal Saline

- Hyperchloremic metabolic acidosis
  - Dilution of extracellular fluid HCO₃ concentration
  - Volume expansion leading to decreased proximal HCO₃ reabsorption
  - Increased Cl⁻/HCO₃ exchange in β-intercalated cell (pendrin)
  - Plasma Cl⁻ increases to greater extent than Na⁺ narrowing strong ion difference thus causing increased H⁺ generation to aid in restoring charge equilibrium
Comparison of Rapidly Infused Crystalloids on Acid-base Status in Dehydrated Patients in ED

- Prospective DB randomized trial in 90 patients with diagnosis of dehydration of varying causes
- Blindly allocated to receive either normal saline, lactated Ringer’s, or Plasmalyte at 20 ml/kg/h for 2 hours

![Graph showing pH changes over time for different solutions: Normal Saline, Lactated Ringer’s, and Plasmalyte.](graph.png)

**Adverse Effects Attributed to Hyperchloremic Metabolic Acidosis**

- Immune dysfunction
  - Hyperchloremic acidosis increases lung and intestinal injury in normal rats
  - In experimental sepsis, resuscitation with NS vs RL is associated with decreased survival which is inversely correlated to increase in plasma [Cl⁻]
  - Circulating levels of IL-6, IL-10, and TNF increase to greater extent with NS vs RL

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1^J Lab Clin Med 138:270-276, 2001
2^Am J Respir Crit Care Med 159:397-402, 1999
3^Chest 125:243-248, 2004
4^Chest 130:962-967, 2006
Potential Consequences of High Cl⁻ Concentration in Normal Saline

- Hyperchloremic metabolic acidosis
- Increase in renal vascular resistance leading to renal dysfunction
  - Increased tubuloglomerular feedback
  - Potentiate vascular response to AII

J Clin invest 71:726-735, 1983
Br J Pharmacol 108:106-110, 1993

Comparison of NS and Plasma-Lyte on Renal Function in Normal Subjects

- Twelve subjects received 2-L intravenous infusion over one hour of 0.9 saline or Plasma-Lyte 148 in a randomized double blind fashion
- MRI scan used to measure renal artery flow velocity and renal cortical perfusion

Comparison of NS and Plasma-Lyte on Renal Function in Normal Subjects


Comparison of Cl⁻ Liberal vs Cl⁻ Restrictive Fluid Strategy on AKI in Critically Ill Adults

Prospective, open label sequential (6mo) period study

Control period: 760 ICU patients received standard IV fluids
Intervention period: 733 ICU patients received IV fluids restricted in Cl⁻
  • Hartmann solution
  • Plasma-Lyte 48
  • Cl⁻-poor 20% albumin

Cl⁻ use significantly decreased in restricted group

694 mmol/l to 496 mmol/l

JAMA 308:1566-1572, 2012
Comparison of Cl⁻ Liberal vs Cl⁻ Restrictive Fluid Strategy on AKI in Critically Ill Adults

Patients receiving NS/High Cl⁻ solutions had **double** the odds of RIFLE-defined AKI requiring dialysis after adjusting for covariates

Feasible Strategies to Minimize Further Kidney Injury

- Preferential use of balanced physiologic solutions for patients requiring fluid resuscitation
- Intelligent use of diuretics
Strategies to Overcome Diuretic Resistance

- Avoid reduction in GFR
- Add thiazide diuretic to loop diuretic
  - Long duration of action
  - Carbonic anhydrase inhibition
  - Inhibits transport in hypertrophied segments
- Continuous infusion (bolus dose should precede continuous infusion)

In the patient with decompensated CHF, what is the optimal way to administer loop diuretics?
Diuretic Strategies in Patients with Acute Decompensated CHF

- Observational studies have shown associations between high dose diuretics and adverse clinical outcomes to include renal failure, progression of heart failure, and death.
- High dose loop diuretics may be harmful secondary to activation of renin-angiotensin and sympathetic nervous system.

Potential Adverse Effects of Diuretics in CHF

- Loop diuretics:
  - ↑ Urine K⁺, Mg²⁺
  - ↑ Uric acid
  - ↑ PRA, AII, Aldosterone
  - ↑ SNS
  - ↑ AVP
  - ↓ EABV
  - Hypomagnesemia
  - Hypokalemia
  - ↑ Risk of arrhythmias
  - Long term adverse effects on cardiac remodeling
  - ↑ Urine Na⁺

- Long term adverse effects on cardiac remodeling:
  - ↑ Uric acid
  - Hypomagnesemia
  - Hypokalemia
  - ↑ Risk of arrhythmias

- Potential adverse effects of diuretics in CHF:

Am Heart J 147:331-8, 2004
Eur J Heart Fail 9:1064-9, 2007
Circulation 100:1311-5, 1999

Ann Intern Med 103:1-6, 1985
Diuretic Optimization Strategies Evaluation (DOSE) Trial

- 308 patients with decompensated CHF randomized to low dose (previous oral dose given IV) or high dose (2.5x), Q 12h vs continuous infusion
- High dose superior in:
  - Global assessment (p=0.06)
  - Net fluid loss
  - Dyspnea
  - ↓ NT-proBNP (p=0.06)
  - ↓ Adverse events

No significant difference at 72h or 60d

Diuretic Optimization Strategies Evaluation (DOSE) Trial

- High dose diuretics are safe and effective
  - No difference in low vs high with respect to the clinical composite of death, re-hospitalization, or ER visit
- In patients with decompensated CHF, no clear advantage of loop diuretics given as a bolus vs continuous infusion (no bolus)
- Not a study of diuretic resistant patients, no forced titration, no bolus preceding CI
Which is better in Acute Decompensated Congestive Heart Failure: Diuretics or Ultrafiltration

*Ultrafiltration* vs IV Diuretics for Patients Hospitalized for *Acute* Decompensated Congestive Heart Failure: *UNLOAD Trial*

- Prospective randomized clinical trial of 200 patients with ADHF with mean $S_{Cr}$ 1.5 mg/dl
- UF used exclusively for first 48 hrs at maximal rate of 500 ml/hr versus IV diuretics using twice daily admitting oral dose
- 90 day follow up

UNLOAD Trial: Primary Endpoint

- Weight loss at 48 hrs: $p=0.001$
- Change in dyspnea score at 48 hrs: $p=0.35$

UNLOAD Trial: Secondary Endpoints

- Rehospitalization for heart failure by 90 days: 43% reduction favoring UF, $p=0.037$
- Mean number of hospitalization days: 63% reduction favoring UF, $p=0.009$

**Cardiorenal Rescue Study in Acute Decompensated Heart Failure (CARESS-HF)**

- Prospective randomized trial of ADHF patients who developed CRS defined as $\uparrow S_{Cr}$ of $\geq 0.3$ mg/dl from baseline while demonstrating signs and symptoms of congestion
- Patients (188) randomized to UF (200 ml/hr) or stepped IV loop diuretics with target UOP of 3-5 L/d


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**CARESS-HF: Primary Endpoint**

Enrollment stopped early due to lack of treatment benefit and adverse events in the UF group

![Graph showing Mean Weight Change and Mean Creatinine Change from Baseline](image)

Mean Weight Change from Baseline (Lbs)  Mean Creatinine Change from Baseline (mg/dl)

CARESS-HF: 60 Day Event Rates

CARESS-HF: Summary

- Pharmacologic care was superior to ultrafiltration at 96 hours for preservation of renal function with similar weight loss
- Ultrafiltration, as administered in this study, had higher rates of adverse events and therefore offers no advantage to stepped pharmacologic care in patients with ADHF, worsened renal function, and persistent congestion
Feasible Strategies to Minimize Further Kidney Injury

- Preferential use of balanced physiologic solutions for patients requiring fluid resuscitation
- Intelligent use of diuretics
- Do not reflexively discontinue renin-angiotensin blockers

Continuum of Renal Injury

At Risk Kidney

- Reduced Oxygen Delivery
- P_{oc}

Incipient AKI

- Preserved Oxygen Delivery
- ACEI, ARB
- L_{P_{oc}}
- Ang II
AII Blockade Augments Renal Cortical Microvascular pO₂

Cortical microvascular pO₂ measured in Sprague-Dawley rats with and without enalaprilat


Change in RBF After ACEI, ARB or B₂ Blocker in Dogs Fed Low Na⁺ Diet

ICAT = icatibant

Am J Physiol Renal Physiol 279:F289-F293, 2000
Effect of ARB Pretreatment in Wistar Rat Model of Ischemic AKI

RAAS blockade ameliorates renal injury by improving peritubular capillary perfusion. Antioxidant and antiproliferative effects of these agents may also contribute to the reduction in renal injury.
Initial Change in eGFR and Long Term Renal Function

*Post Hoc* analysis of the Reduction of Endpoints in Non-Insulin-Dependent Diabetes Mellitus with the Angiotensin II Antagonist Losartan (RENAAL) trial

![Graph showing initial change in eGFR and long term renal function.](image)

Early Worsening of Renal Function After Initiation of ACEI in CHF

Studies of Left Ventricular Dysfunction (SOLVD) Trial

![Graph showing early worsening of renal function after initiation of ACEI.](image)
Summary

- AKI is common and ↑ in hospitalized patients
- Diagnostic staging systems exist for AKI
- Incipient AKI is renal injury manifested by new proteinuria and urine sediment activity in absence of clinical data that meet current diagnostic criteria
- Management considerations should consider:
  - Use of low chloride IV solutions
  - Use of diuretics to control intravascular volume
  - Continued use of RAAS blockers