Acute Kidney Injury: Diagnosis, Epidemiology and Treatment

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Conflicts of interest

✧ Consulting:
  ✧ Fresenius
  ✧ Gambro
  ✧ Baxter
  ✧ Astute Medical
  ✧ Alere
  ✧ Opsona
  ✧ Abbott
  ✧ AM Pharma
  ✧ BioAegis
  ✧ Roche

✧ Grant support:
  ✧ Baxter
  ✧ Gambro
  ✧ Astute Medical
  ✧ Alere

✧ Other:
  ✧ I’m an intensivist
Consider

- Millions of patients are admitted to Intensive care units.
  - As many as 2/3 will develop evidence of acute kidney injury (AKI)
  - Nearly half will be at increased risk of death because of AKI
  - 6% of critically ill patients world-wide will lose kidney function completely — 60% of these will die

- We have no real idea why AKI occurs, why the kidneys fail or why, despite hemodialysis, mortality is so high.

- Throughout the world ~2 million will die this year of a disease whose pathophysiology we do not understand and for which no effective treatment exists.
Definitions of ARF

\[ R^2 = 0.3962 \]
\[ p = 0.007 \]

Kellum et al. Current Opin in Crit Care 2002
RIFLE Criteria for Acute Kidney Injury

**Risk**
- Increased creatinine x1.5

**Injury**
- Increased creatinine x2
- Increased creatinine x3 or creatinine ≥4mg/dl (Acute rise of ≥0.5 mg/dl)

**Failure**
- UO < .5ml/kg/h x 6 hr
- UO < .5ml/kg/h x 12 hr
- UO < .3ml/kg/h x 24 hr or Anuria x 12 hrs
- UO < .5ml/kg/h x 6 hr

**Loss**
- Persistent ARF** = complete loss of renal function > 4 weeks
- End Stage Renal Disease

**ESRD**
- High Sensitivity
- High Specificity

Crit Care 2004, 8:R204-12
www.ADQI.net
Acute renal failure – definition, outcome measures, animal models, fluid therapy and information technology needs: the Second International Consensus Conference of the Acute Dialysis Quality Initiative (ADQI) Group

Rinaldo Bellomo, Claudio Ronco, John A Kellum, Ravindra L Mehta, Paul Palevsky, the ADQI workgroup

Critical Care 2004, 8:R204-R212 (24 May 2004)
RIFLE has been validated in >500,000 pts

- **Hospital and ICU based studies**
  - Recent studies
    - 120,123 patients in 57 ICUs in Australia (Bagshaw et al)
      - 36.1% developed AKI
      - Hosp Mortality: R:17.9%, I:27.7%, F:33.2%
    - 41,972 patients in 22 ICUs in Europe (Ostermann et al.)
      - 35.8% developed AKI
      - Hosp Mortality: R:20.9%, I:45.6%, F:56.8%

- **Population based studies**
  - Northern Scotland (pop 523,390) (Ali et al.)
    - AKI incidence 2147 pmp (16% CKD)
    - By comparison the incidence of acute MI in US is approximately 2667 pmp

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RIFLE max

No AKI
Risk
Injury
Failure

P<0.001 (Log Rank)

Days after hospital admission

Hoste et al. Crit Care 2006;10:R73
### RIFLEmax and mortality
(Covariate-adjusted Cox proportional hazard regression analysis).

<table>
<thead>
<tr>
<th></th>
<th>B (SE)</th>
<th>P</th>
<th>HR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>RIFLE\textsubscript{max}</strong></td>
<td></td>
<td>&lt;0.001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Risk</td>
<td>0.072 (0.207)</td>
<td>0.728</td>
<td>1.075</td>
<td>0.716-1.614</td>
</tr>
<tr>
<td>Injury</td>
<td>0.465 (0.147)</td>
<td>0.002</td>
<td>1.592</td>
<td>1.192-2.124</td>
</tr>
<tr>
<td>Failure</td>
<td>1.130 (0.132)</td>
<td>&lt;0.001</td>
<td>3.096</td>
<td>2.392-4.006</td>
</tr>
<tr>
<td>SOFA\textsubscript{non-renal (/point)}</td>
<td>0.092 (0.010)</td>
<td>&lt;0.001</td>
<td>1.096</td>
<td>1.075-1.117</td>
</tr>
<tr>
<td>Age (/10 yr)</td>
<td>0.151 (0.026)</td>
<td>&lt;0.001</td>
<td>1.163</td>
<td>1.106-1.223</td>
</tr>
</tbody>
</table>

Hoste et al. Crit Care 2006;10:R73
Recommendations for diagnosis and staging of Acute Kidney Injury

American College of Chest Physicians (ACCP), Acute Dialysis Quality Initiative (ADQI), Australian and New Zealand Intensive Care Society (ANZICS), Asia Pacific Association of Critical Care Medicine (APACCM), Asian Pacific Society of nephrology (APSN), American Society of Nephrology (ASN), American Society of Pediatric Nephrologists (ASPN), American Thoracic Society (ATS), Chinese Society of Nephrology (CSN), European Dialysis and Transplant Association-European Renal Association (EDTA-ERA), European Society of Intensive Care Medicine (ESICM), International Pediatric Nephrology Association (IPNA), Indian Society of Nephrology (ISN), International Society of Nephrology (ISN), National Kidney Foundation (NKF), Society of Critical Care Medicine (SCCM), Sociedade Latino-Americana de Nefrologia e Hipertensão (SLANH), Société de Réanimation de Langue Française (SRLF)
Modified RIFLE Criteria for AKI Staging

Increased creatinine x1.5
OR ≥ 0.3mg/dl

UO < .5ml/kg/h
x 6 hr

Increased creatinine x2

UO < .5ml/kg/h
x 12 hr

Increase creatinine x3
or creatinine ≥4mg/dl
(Acute rise of ≥0.5 mg/dl)

UO < .5ml/kg/h
x 24 hr

Anuria ≥12 hrs

RRT Started

Modifications proposed by AKIN
Amsterdam, 2005

Needs to occur of <48hrs
<table>
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<tr>
<th>AKIN</th>
<th>RIFLE</th>
<th>Total (AKIN)</th>
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<tr>
<td></td>
<td>non-AKI</td>
<td>10263 (15.9%)</td>
</tr>
<tr>
<td>n</td>
<td>8759</td>
<td></td>
</tr>
<tr>
<td>*</td>
<td>(12.9%)</td>
<td></td>
</tr>
<tr>
<td>Risk</td>
<td>781</td>
<td></td>
</tr>
<tr>
<td>(27.7%)</td>
<td>271</td>
<td></td>
</tr>
<tr>
<td>Injury</td>
<td>452</td>
<td>1077 (34.5%)</td>
</tr>
<tr>
<td>(37.4%)</td>
<td>95</td>
<td></td>
</tr>
<tr>
<td>Failure</td>
<td>271</td>
<td></td>
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<tr>
<td>(41.3%)</td>
<td>1077</td>
<td></td>
</tr>
<tr>
<td>Stage 1</td>
<td>457</td>
<td>1077 (34.5%)</td>
</tr>
<tr>
<td>n</td>
<td>1077</td>
<td></td>
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<tr>
<td>*</td>
<td>1077</td>
<td></td>
</tr>
<tr>
<td>Risk</td>
<td>282</td>
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<tr>
<td>(33.0%)</td>
<td>95</td>
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<tr>
<td>Injury</td>
<td>243</td>
<td></td>
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<tr>
<td>(44.0%)</td>
<td>1077</td>
<td></td>
</tr>
<tr>
<td>Failure</td>
<td>95</td>
<td>1077 (34.5%)</td>
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<tr>
<td>(60.0%)</td>
<td>1077</td>
<td></td>
</tr>
<tr>
<td>Stage 2</td>
<td>36</td>
<td>1033 (29.0%)</td>
</tr>
<tr>
<td>n</td>
<td>1033</td>
<td></td>
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<tr>
<td>*</td>
<td>1033</td>
<td></td>
</tr>
<tr>
<td>Risk</td>
<td>21</td>
<td></td>
</tr>
<tr>
<td>(47.6%)</td>
<td>91</td>
<td></td>
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<tr>
<td>Injury</td>
<td>885</td>
<td></td>
</tr>
<tr>
<td>(25.9%)</td>
<td>1033</td>
<td></td>
</tr>
<tr>
<td>Failure</td>
<td>91</td>
<td>1033 (29.0%)</td>
</tr>
<tr>
<td>(54.9%)</td>
<td>1033</td>
<td></td>
</tr>
<tr>
<td>Stage 3</td>
<td>11</td>
<td>1983 (41.2%)</td>
</tr>
<tr>
<td>n</td>
<td>1983</td>
<td></td>
</tr>
<tr>
<td>*</td>
<td>1983</td>
<td></td>
</tr>
<tr>
<td>Risk</td>
<td>8</td>
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</tr>
<tr>
<td>(12.5%)</td>
<td>1948</td>
<td></td>
</tr>
<tr>
<td>Injury</td>
<td>16</td>
<td></td>
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<tr>
<td>(62.5%)</td>
<td>1948</td>
<td></td>
</tr>
<tr>
<td>Failure</td>
<td>16</td>
<td>1983 (41.2%)</td>
</tr>
<tr>
<td>(41.3%)</td>
<td>1983</td>
<td></td>
</tr>
<tr>
<td>Total (RIFLE)</td>
<td>9263</td>
<td>14356 (21.7%)</td>
</tr>
<tr>
<td>n</td>
<td>14356</td>
<td></td>
</tr>
<tr>
<td>*</td>
<td>14356</td>
<td></td>
</tr>
<tr>
<td>Risk</td>
<td>1092</td>
<td></td>
</tr>
<tr>
<td>(29.2%)</td>
<td>2405</td>
<td></td>
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<tr>
<td>Injury</td>
<td>1596</td>
<td></td>
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<tr>
<td>(32.3%)</td>
<td>2405</td>
<td></td>
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<tr>
<td>Failure</td>
<td>2405</td>
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<tr>
<td>(42.6%)</td>
<td>2405</td>
<td></td>
</tr>
</tbody>
</table>

Number of patients classified into the respective stages of AKI by AKIN or RIFLE are cross-tabulated against each other. Hospital mortality of each group is given in brackets. Fields marked in yellow denote patients assigned to the same degree of AKI by both classification systems.

n number of patients

From Joannidis et al. (7), used with permission.
CHAPTER 2.1: DEFINITION AND CLASSIFICATION OF AKI

- 2.1.1: Acute kidney injury (AKI) is defined as any of the following (Not Graded):
  - Increase in SCr by ≥ 0.3 mg/dl within 48 hours; or
  - Increase in SCr to ≥ 1.5 times baseline, which is known or presumed to have occurred within prior 7 days; or
  - Urine volume <0.5 ml/kg/h for 6 hours.
Why is AKI so bad for you?
What do kidneys do?

- **Excretory**
  - Nitrogenous waste
  - Others

- **Regulatory**
  - Body water and circulating blood volume
  - Plasma sodium and potassium levels
  - Blood pH

- **Neuro-Endocrine**
  - Erythropoietin
  - Renin-Angiotensin system – blood pressure

- **Detoxification**
  - Major elimination pathway for many drugs and toxins
What happens when they don’t?

**CNS**
- Encephalopathy

**Fluid overload**
- Pulmonary edema, pleural effusions
- Skin breakdown, and delayed wound healing
- Atrial distension -- arrhythmias
- Gut mucosal edema (delayed nutrient and drug adsorption)

**Hematologic dysfunction**
- Anemia (loss of erythropoietin)
- Platelet dysfunction (vWF)
- White cell dysfunction (L-selectin etc)

**Acid-base and electrolyte imbalance**

“Dispharmacology”
AKI and Pneumonia

**l.p. Injection of 450mg/kg folic acid to induce AKI**

**Inhalation of P. aeruginosa (10^{14} CFU/ml aerosol)**

- **Sham (Saline Injection)**
- **Sham (Saline aerosol)**

Singbartl et al. Kidney Int. 2011 Sep;80(6):633-44
Pneumonia-AKI

AKI worsens oxygenation during Pneumonia (impaired lung recruitment)

Singbartl et al. Kidney Int. 2011 Sep;80(6):633-44
AKI impairs neutrophil function

Impaired PMN function

Decreased bacterial clearance
Guideline on Acute Kidney Injury

John Kellum and Norbert Lameire
Work Group Chairs
Stage-based management of AKI: Shading of boxes indicates priority of action—solid shading indicates actions that are equally appropriate at all stages whereas graded shading indicates increasing priority as intensity increases.
Not just an ICU disease

Murugan et al. Kidney Int Mar 2010
Specific Treatment

 Extracorporeal Kidney Support
 - Intensity
 - Modality
 - Membranes
 - Timing (initiation and discontinuation)
Intensity of Renal Support in Critically Ill Patients with Acute Kidney Injury

The VA/NIH Acute Renal Failure Trial Network*

Odds Ratio: 1.09
95% CI: 0.86-1.40
P=0.47
Intensity of Continuous Renal-Replacement Therapy in Critically Ill Patients

The RENAL Replacement Therapy Study Investigators*
Ronco et al (2000) 0.72 (0.60-0.88)
Bouman et al (2002) 0.91 (0.47-1.79)
Schiffl et al (2002) 0.60 (0.39-0.91)

Subtotal 0.71 (0.60-0.84) p=0.0001

Saudan et al (2006) 0.63 (0.48-0.82)
Tolwani et al (2008) 1.16 (0.87-1.55)
ATN Study (2008) 1.04 (0.93-1.16)
Faulhaber-Walter et al (2009) 1.15 (0.79-1.67)
RENAL Study (2009) 1.00 (0.89-1.12)

Subtotal 0.97 (0.83-1.14) p=0.730

Overall 0.89 (0.76-1.04) p=0.143
CHAPTER 5.8: DOSE OF RRT IN AKI

• 5.8.3: We recommend delivering a Kt/V of 3.9 per week when using intermittent or extended RRT in AKI. (1A)

• 5.8.4: We recommend delivering an effluent volume of 20-25 ml/kg/h for CRRT in AKI (1A). This will usually require a higher prescription of effluent volume. (Not Graded)
Dose response

Kellum and Ronco Nat Rev Nephrol 2010
Bagshaw et al. CCM 2008; 36:610-7

<table>
<thead>
<tr>
<th>Study</th>
<th>Odds ratio (95% CI)</th>
<th>No. of events CRRT</th>
<th>No. of events IRRT</th>
</tr>
</thead>
<tbody>
<tr>
<td>simpson (1993)</td>
<td>0.50 (0.21, 1.20)</td>
<td>43/65</td>
<td>48/58</td>
</tr>
<tr>
<td>kierdorf (1994)</td>
<td>0.81 (0.36, 1.82)</td>
<td>23/48</td>
<td>34/52</td>
</tr>
<tr>
<td>john (2001)</td>
<td>1.00 (0.19, 5.24)</td>
<td>14/20</td>
<td>7/10</td>
</tr>
<tr>
<td>mehta (2001)</td>
<td>1.89 (1.01, 3.52)</td>
<td>54/84</td>
<td>40/82</td>
</tr>
<tr>
<td>gasparovic (2003)</td>
<td>1.67 (0.74, 3.78)</td>
<td>37/52</td>
<td>31/52</td>
</tr>
<tr>
<td>augustine (2004)</td>
<td>0.89 (0.35, 2.29)</td>
<td>27/40</td>
<td>28/40</td>
</tr>
<tr>
<td>uehlinger (2005)</td>
<td>0.91 (0.45, 1.85)</td>
<td>34/70</td>
<td>28/55</td>
</tr>
<tr>
<td>vinsonneau (2006)</td>
<td>0.95 (0.61, 1.48)</td>
<td>118/175</td>
<td>126/184</td>
</tr>
<tr>
<td>lins (unpublished)</td>
<td>0.83 (0.53, 1.31)</td>
<td>100/172</td>
<td>90/144</td>
</tr>
<tr>
<td>Overall</td>
<td>0.99 (0.78, 1.26)</td>
<td>459/726</td>
<td>432/677</td>
</tr>
</tbody>
</table>
CHAPTER 5.6: MODALITY OF RRT FOR PATIENTS WITH AKI

• 5.6.2: We suggest using CRRT rather than standard intermittent RRT, for hemodynamically unstable patients. (2B)

• 5.6.3: We suggest using CRRT, rather than intermittent RRT, for AKI patients with acute brain injury or other causes of increased intracranial pressure or generalized brain edema. (2B)
### CLINICAL CHARACTERISTICS BY RIFLEmax

<table>
<thead>
<tr>
<th></th>
<th>All n=5383</th>
<th>Non AKI N=1766</th>
<th>Risk n=670</th>
<th>Injury n=1436</th>
<th>Failure n=1511</th>
</tr>
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<tbody>
<tr>
<td><strong>Baseline characteristics</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>100 %</td>
<td>32.8 %</td>
<td>12.4 %</td>
<td>26.7 %</td>
<td>28.1 %</td>
</tr>
<tr>
<td>Gender (male)</td>
<td>56.6 %</td>
<td>55.6 %</td>
<td>55.3 %</td>
<td>58.2 %</td>
<td>56.8 %</td>
</tr>
<tr>
<td>Age (yrs) *</td>
<td>60.5 (17.2)</td>
<td>56.7 (18.1)</td>
<td>63.3 (16.9)</td>
<td>62.5 (16.5)</td>
<td>61.7 (16.1)</td>
</tr>
<tr>
<td>APACHE III †</td>
<td>45 (33-59)</td>
<td>36 (26-47)</td>
<td>46 (35-57)</td>
<td>46 (36-59)</td>
<td>56 (41-74)</td>
</tr>
<tr>
<td>SOFA ‡</td>
<td>6.0 (4.3)</td>
<td>4.9 (3.6)</td>
<td>5.9 (4.1)</td>
<td>6.3 (4.3)</td>
<td>6.9 (4.8)</td>
</tr>
<tr>
<td>SOFA_{non-renal} *</td>
<td>4.9 (3.7)</td>
<td>4.3 (3.2)</td>
<td>5.0 (3.6)</td>
<td>5.2 (3.7)</td>
<td>5.3 (4.0)</td>
</tr>
<tr>
<td>In-hospital before ICU admission §</td>
<td>34.3 %</td>
<td>30.1 %</td>
<td>36.4 %</td>
<td>33.0 %</td>
<td>39.0 %</td>
</tr>
<tr>
<td>Pre-ICU LOS ¶</td>
<td>2 (1-5)</td>
<td>1 (1-4)</td>
<td>2 (1-4)</td>
<td>2 (1-5)</td>
<td>2 (1-6)</td>
</tr>
<tr>
<td><strong>Outcome:</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RRT §</td>
<td>4.1 %</td>
<td>0.1 %</td>
<td>0 %</td>
<td>0.3 %</td>
<td>14.2 %</td>
</tr>
<tr>
<td>LOS ICU (d) **</td>
<td>4 (2-10)</td>
<td>2.0 (2-4)</td>
<td>3 (2-6)</td>
<td>5 (3-10)</td>
<td>9 (4-21)</td>
</tr>
<tr>
<td>LOS Hospital (d) **</td>
<td>8 (4-17)</td>
<td>5 (3-10)</td>
<td>7 (4-13)</td>
<td>9 (5-17)</td>
<td>14 (7-28)</td>
</tr>
<tr>
<td>Mortality §</td>
<td>13.3 %</td>
<td>5.5 %</td>
<td>8.8 %</td>
<td>11.4 %</td>
<td>26.3 %</td>
</tr>
</tbody>
</table>
Are we waiting too long?

- **RIFLE-F (n=1511)**
  - 14.2% received renal support

- **Mortality**
  - Overall 26.3%
  - Renal support ~50%
  - No renal support ~23%
  - No AKI 5.5%
Long Interdialytic Interval and Mortality among Patients Receiving Hemodialysis
Robert N. Foley, M.B., David T. Gilbertson, Ph.D., Thomas Murray, M.S., and Allan J. Collins, M.D.

- 32,065 pts with ESRD
- 22.1 vs. 18.0 deaths per 100 person-years, P<0.001
  - cardiac (10.2 vs. 7.5, P<0.001)
  - infection (2.5 vs. 2.1, P=0.007)
Hospital Admissions

- myocardial infarction (6.3 vs. 3.9, P<0.001)
- congestive heart failure (29.9 vs. 16.9, P<0.001)
- stroke (4.7 vs. 3.1, P<0.001)
- dysrhythmia (20.9 vs. 11.0, P<0.001)
- any cardiovascular event (44.2 vs. 19.7, P<0.001)

Conclusions

- AKI is a disease of critical illness
  - Sepsis is the leading cause
  - AKI leads to MOF
  - AKI is in the causal pathway for mortality

- Intensivists need to direct the care of patients with AKI
  - Prevention
  - Fluid/electrolyte/nutrition management
  - Renal support
    - Timing
    - Intensity
    - Modality

- Patients with AKI are often not...
  - Going to ICU
  - Receiving renal support
    ...justifiably?